資料３

平成１６年度第５回
運営委員会確認事項
（平成１６年９月１７日）

感染症定期報告に関する今後の対応について

１　基本的な方針

運営委員会に報告する資料においては、

(1) 文献報告は、同一報告に由来するものの重複を廃した一覧表を作成すること。

(2) ８月の運営委員会において、国内の輸血及び血漿分画製剤の使用した個別症例の感染症発生報告は、定期的にまとめた「感染症報告事例のまとめ」を運営委員会に提出する取扱いとされた。これにより、感染症定期報告に添付される過去の感染症発生症例報告よりも、直近の「感染症報告事例のまとめ」を主として利用することとすること。

２　具体的な方法

(1) 感染症定期報告の内容は、原則、すべて運営委員会委員に送付することとするが、次の資料概要を作成し、委員の資料の確認を効率的かつ効果的に行うことができるようにする。

① 研究報告は、同一文献による重複を廃した別紙のような形式の一覧表を作成し、当該一覧表に代表的なものの報告様式（別紙様式第２）及び該当文献を添付した「資料概要Ａ」を事務局が作成し、送付する。

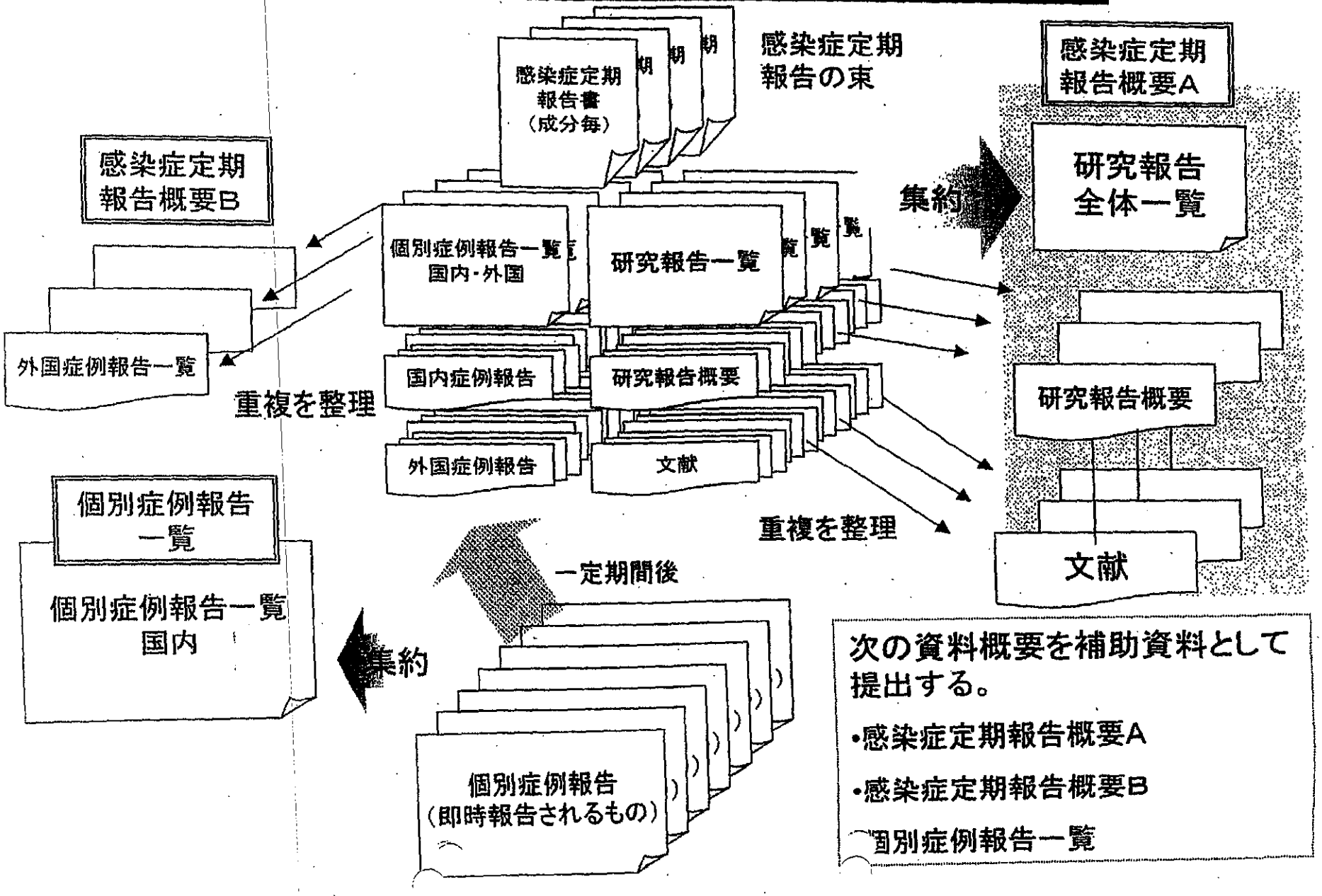
② 感染症発生症例報告のうち、発現国が「外国」の血漿分画製剤の使用による症例は、同一製品毎に報告期間を代表する感染症発生症例一覧（別紙様式第４）をまとめた「資料概要Ｂ」を事務局が作成し、送付する。

③ 感染症発生症例報告のうち、発現国が「国内」の輸血による症例及び血漿分画製剤の使用による感染症症例については、「感染症報告事例のまとめ」を提出することから、当該症例に係る「資料概要」は作成しないこととする。ただし、運営委員会委員から特段の議論が必要との指摘がなされたものについては、別途事務局が資料を作成する。

(2) 発現国が「外国」の感染症発生症例報告については、国内で使用しているロットと関係がないもの、使用時期が相当程度古いもの、因果関係についての詳細情報の入手が困難であるものが多く、必ずしも緊急性が高くないと考えられるものも少なくない。また、国内症例に比べて個別症例を分析・評価することが難しいものが多いため、緊急性があると考えられるものを除き、その安全対策への利用については、引き続き、検討を行う。

(3) 資料概要Ａ及びＢについては、平成１６年９月の運営委員会から試験的に作成し、以後「感染症定期報告について（目次）」資料は廃止することとする。

感染症定期報告・感染症個別症例報告の取り扱い



次の資料概要を補助資料として提出する。

- 感染症定期報告概要A
- 感染症定期報告概要B
- 個別症例報告一覧

資料３

感染症定期報告概要

（平成１９年５月２３日）

平成１８年１２月１日受理分以降

Ａ　研究報告概要
Ｂ　個別症例報告概要

Ａ　研究報告概要

○　一覧表（感染症種類毎）
○　感染症毎の主要研究報告概要
○　研究報告写

研究報告のまとめ方について

１　平成１８年１２月１日以降に報告された感染症定期報告に含まれる研究報告（論文等）について、重複している分を除いた報告概要一覧表を作成した。

２　一覧表においては、前回の運営委員会において報告したもの以降の研究報告について、一覧表の後に当該感染症の主要研究報告の内容を添付した。

感染症定期報告の報告状況(2006/12/1～2007/2/28)

血対ID	受理日	番号	感染症(PT)	出典	概要	
60184	2006/12/01	60745	A型肝炎	Epidemiol Infect 2006; 134: 87-93	1998年から1999年の韓国の血友病患者におけるHAV感染と血液凝固因子との因果関係を調べるため、比較対照試験と分子学的HAV検出を行った。疫学的調査およびHAV RNA配列検査から、凝固因子VIIIの1ロットがHAV感染に関与していたことが明らかになった。	
60184	2006/12/01	60745	BSE	ABC Newsletter 2006年9月22日 16ページ	欧州協議会は2005年の反芻動物(有蹄動物)における伝達性海綿状脳症(TSE)のモニタリングと検査に関する報告書を発表した。TSE検査を行った1千万頭以上のウシのうち、陽性となったのは561頭のみであった。2005年の調査結果は陽性例が引き続き減少していることを示している。	1
60184	2006/12/01	60745	B型肝炎	Transfusion 2006; 46: 1256-1258	ヨーロッパでのB型肝炎発生率は北西部が低く(1%以下)、南部が高い(5-15%)。北西部では抗HBcスクリーニングが導入され、南部ではHBV-NATが導入される傾向がある。B型肝炎ウイルス陽性となった供血者と血液の管理に関して、ヨーロッパではHBV DNA、HBc抗体陽性でHBs抗体レベルが100IU/L以上の場合は供血を続けることができるというリエントリー・アルゴリズムが検討されている。	
60184	2006/12/01	60745	B型肝炎	Vox Sang 2006; 91: 237-243	ドイツ赤十字血液センターの供血者10000名を、現行のPRISM® HBcおよび新規PRISM®Hbcore検査を用いたHBc抗体のスクリーニングを実施し、診断感度および特異性を調べた。両者とも約1.8%がHBc抗体陽性であることを示し、感度は同等であったが、特異性はPRISM® HBcoreの方が有意に高かった。この検査が陽性であった188検体について、さらに7種類の抗HBc検査、2種類の抗HBs検査、1種類の抗Hbe検査、3種類のHBV NAT検査を行って、検査結果を比較した。	2
60184	2006/12/01	60745	B型肝炎	日本輸血学会雑誌 52(2): 199 第54回日本輸血学会総会 2006年6月 9-11日	日本の献血者におけるHBV NAT陽性者について解析したところ、20歳代ではHBV感染初期、50歳代、60歳代では感染晩期の陽性例が多かった。陽性数の高い地域は千葉県から愛知県までの太平洋側と大阪府であった。HBV Genotype Aは101例(女性1例)検出され、全国に広がる傾向が見られた。	
60184	2006/12/01	60745	B型肝炎 C型肝炎	日本輸血学会雑誌 52(2): 234 第54回日本輸血学会総会 2006年6月 9-11日	2005年に全国の医療機関から日本赤十字社へ報告された輸血感染症(疑い症例を含む)の現況とその傾向についての報告である。2005年輸血感染症症例(疑い症例を含む)報告数は12月22日現在260例で、内訳は、HBV:127、HCV:71、HEV:2、HIV:2、CMV:3、ヒトパルボウイルスB19:3、細菌:52であった。この内、輸血との因果関係が高いと評価した症例は、HBV:10例、HCV:1例、HEV:1例、ヒトパルボウイルスB19:3例であった。	
60184	2006/12/01	60745	B型肝炎 C型肝炎	日本輸血学会雑誌 52(2): 198 第54回日本輸血学会総会 2006年6月 9-11日	医療機関において輸血後感染症の全数調査を実施したところ、輸血後陽転例はHBVで9例(0.9%)存在し、1例のみが輸血後B型肝炎と診断され、他の8例は感染晩期のHBVキャリアで再活性化が起こったと考えられた。HCVとHIVでは輸血後陽転例はみられなかった。	
60184	2006/12/01	60745	B型肝炎 C型肝炎	日本輸血学会雑誌 52(2): 197 第54回日本輸血学会総会 2006年6月 9-11日	輸血用血液製剤のHBV、HCV、HIVについて、2000年2月から2004年1月までの4年間の遡及調査を行った。調査は、主に複数回献血者において感染症マーカーが陽転した場合に前回の血液サンプルを個別NATで精査するもので、HBVについては50プールNAT, HBsAg, HBcAbのいずれかの陽転例約16000人について前回の保管検体を調べた。副作用報告による感染例を合せると、日本では輸血によるHBV感染が1年に約19例、HCV感染は4年に1例、HIV感染は2年に1例起こるものと推定された。	

血対ID	受理日	番号	感染症(PT)	出典	概要	
60184	2006/12/01	60745	C型肝炎	41st Annual Meeting of the European Association for the Study of the Liver 2006	スペインの肝臓及び消化器専門クリニック数施設における急性C型肝炎の全報告例についてレトロスペクティブ疫学解析を行った。1998年から2005年の急性C型肝炎患者103例を対象とした。大部分の症例で感染に関連する唯一の立証されたリスクファクターは入院であった。	
60198	2007/1/11	60790	E型肝炎	肝臓 2006; 47: 384-391	わが国のE型肝炎の実態を明らかにする目的で、全国から総数254例のE型肝炎ウイルス感染例を集め、これを解析した。その結果、以下の知見を得た。1)HEVは全国に浸透している。2)感染者の多くは中高年(平均年齢約50歳)で、男性に多い。3)我国に土着のHEVの遺伝型は3型と4型である。4)年齢と肝炎重症度に相関がある。5)遺伝型は4型が顕在化率も重症化率も高い。6)発症時期が無季節性である。7)感染経路は、動物由来食感染が約30%、輸入感染が8%、輸血感染が2%、不明が約60%であった。	3
60185	2006/12/14	60747	E型肝炎	肝臓 2006; 47(Suppl 1): A168	今回われわれは血液感染のハイリスクグループである血友病患者におけるHEV抗体の陽性頻度を調査した。その結果、調査した血友病患者80例の内の13例(16.3%)がHEV抗体陽性であった。過去の研究では日本人の供血者におけるHEV抗体の陽性率は3.7%、透析患者で9.4%と報告されており、血友病患者におけるHEV血液感染の可能性が示唆された。また、他のウイルスマーカーの陽性率については、HEV抗体陽性例と陰性例では差は見られなかったが、年齢が高い方がHEV抗体陽性例の割合が高かった。	
60185	2006/12/14	60747	E型肝炎	日本輸血学会誌 2006; 520: 231	北海道地区において試験研究的に献血時にHEV関連問診を追加するとともに、HEV NATスクリーニングを実施し、問診の有効性とHEV感染の実態を調査した。結果は、HEV問診に該当したのは765名(0.3%)で、その内の1名(0.1%)にHEV RNAが認められた。HEV NATスクリーニング陽性者は20名(HEV問診該当者1名を含む)で、陽性率は1/11,090であった。陽性者の多くはALT値が正常でHEV抗体は陰性であった。道内の献血者のHEV RNA陽性率は予想以上に高い。	
60186	2006/12/20	60760	HHV-8感染	N Engl J Med 2006; 355: 1331-1338	2000年12月から2001年10月に輸血を受けたウガンダのKampalaの患者1811例のうち、輸血前にヒトヘルペスウイルス8型(HHV-8)血清陰性であった患者991例について追跡調査を行った。そのうち43%(425例)にHHV-8血清陽性血が輸血された。991例中41例にHHV-8セロコンバージョンが起こったが、セロコンバージョンのリスクは陽性血を輸血された患者の方が陰性血を輸血された患者より有意に高かった。	4
60184	2006/12/01	60745	HIV	中日新聞 Chunichi Web Press 2006年9月4日	エイズウイルス(HIV)のうち、世界で感染が広がっている主流のHIV1型とは遺伝子タイプが異なる2型に日本人が初めて感染したことを、厚生労働省のエイズ研究班が確認したことが9月3日分かった。厚労省は、医療機関や保健所などが実施している検査で2型の感染を見逃さないよう、検査の徹底を求める通知を出した。HIV2型の感染が確認されたのは、過去に西アフリカで輸血を受けた経験がある男性である。同省は「滞在していた地域では2型が流行しており、現地での輸血が感染原因とみられる」としている。	5
60204	2007/01/26	60818	HIV	日刊薬業 第12105号 平成18年9月6日	日本人初のHIV-2感染者が確定された。男性は過去に西アフリカに渡航し、現地で輸血した経験があるため、これが感染経路と見られている。厚労省は、2型の検査も確実に行い、検査漏れがないよう、各都道府県に通知した。	
60184	2006/12/01	60745	HTLV	International Conference on Emerging Infectious Diseases 2006; Mar 19-22; Atlanta, Georgia. Abstracts #50	狩猟、屠殺、飼育を通して非ヒト霊長類(NHP)の血液と接触がある中央アフリカ人930名の血しょう検体を用いて、HTLV多様性を調べた。ウエスタンブロット法で陽性の13例から、PCRによりプロウイルスを増幅し、系統発生学的分析を行った。その結果、HTLV-3とHTLV-4と名づけた新しいウイルスの感染例(2例)が明らかになった。HTLV-3は、今までヒトでは見られなかったSTLV-3に属する。11例でマンドリル由来のものなど、多様なHTLV-1感染が見られた。	

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60184	2006/12/01	60745	パルボウィルス	J Infect Dis 2006; 194: 154-158	ヒトパルボウイルスB19DNA(1.6x10⁸IU/mL)を含むプール血漿の輸血後、B19 IgG陽性の患者では抗体価が19-39 IU/mLから50-100 IU/mLに上昇して再感染を防いだ。それに対し、陰性の患者では、1.6-2.2 x 10⁸IU/mLのB19DNAの存在下で、プール血漿のIgGレベルが59.5IU/mLではB19の伝播とセロコンバージョンを防ぐのは不十分であることがわかった。	
60198	2007/1/11	60790	パルボウィルス	Thromb Haemost 2004; 92: 838-845	今まで、凝固因子製剤のパルボウイルスB19遺伝子型2による汚染は報告されていないので、市販されている21製剤の202ロットを、パルボウイルスB19遺伝子型1と遺伝子型2のDNAについてPCRにより調べた。遺伝子型1のDNAが、現在投与されているロットの77/181(42.5%)に、1980年代初めまで使用されたロットの17/21(81%)に検出された。遺伝子型2のDNAは、5/202(2.5%)に見出され、その全てが遺伝子型1のDNAに汚染されていた。	
60184	2006/12/01	60745	パルボウィルス	Transfusion 2006; 46:1593-1600	パルボウイルスB19ジェノタイプ3流行地域であるガーナで、114組の成人供血者-小児受血者ペアにおける輸血によるB19の伝播および免疫学的特性について調べた。2例の供血がパルボウイルスB19DNAと特異的抗体を含有していたが、伝播は見られなかった。B19 IgG含有の全血がB19DNA陽性受血者14例に輸血されていたが、その内、輸血前にVP2に対する抗体が認められなかった10例ではウイルスが除去された。	10
60184	2006/12/01	60745	マラリア	AABB Weekly Report 2006年9月15日	2006年9月8日付けのKorea Timesによると、交通事故後に輸血を受け、その後マラリアと診断された患者が、疑わしい血液の流通を防ぐことができなかった韓国赤十字を批判している。韓国赤十字は状況を知りながら、何の行動も起こさず、その結果、不適切な血液製品が流通し続けたとのことである。輸血によるマラリア感染で既に1名の患者が死亡している。	
60184	2006/12/01	60745	マラリア	CDC 2006年6月30日	米国疾病対策予防センターは、バハマのグレートエグズーマ島におけるマラリア発生を確認し、旅行者に対して抗マラリア薬の使用を勧告した。2006年6月29日現在、患者数は合計18例で、うち4例が旅行者である。全員Plasmodium falciparumに感染していた。	
60184	2006/12/01	60745	マラリア	CDC/MMWR Weekly 2006; 55(37): 1013-1016	2006年9月19日、CDCは米国在住のグレートエグズーマ島渡航者向けの抗マラリア薬服用勧告を解除した。2006年5月～6月の間に合計19例のマラリア症例が確認されたが、3ヶ月間新規症例の報告がなかったためである。	11
60184	2006/12/01	60745	マラリア	ProMED-mail20060624.1758	キルギスタンの首都で79例のマラリア症例が登録された。予防手段を講じているにもかかわらず、流行が拡大中である。住民に問題を理解させるのが難しく、衛生疫学監視センターの職員は時々しか殺虫剤を散布できない。	
60186	2006/12/20	60760	マラリア	ProMED-mail20061004.2843	中国東部の安徽省でマラリア感染が拡大している。地元の保健当局によると、今年に入ってから2006年9月25日時点で17917例が報告されており、昨年の同時期と比較すると89.8%増加している。保健当局は緊急通告を出して、感染の監視を強化し、拡大防止のためにマラリア予防と治療に関する啓発を行うよう地元自治体に要請した。	12
60184	2006/12/01	60745	ムンプス	AABB Association Bulletin #06-04 2006年4月26日	アイオワ州では2005年12月以来、おたふくかぜが大流行中で、2006年4月20日時点で、疑い例も含め、1000例以上がアイオワ公衆衛生部に報告されている。おたふくかぜの輸血による伝播に関する現在の知見に基づき、AABBの輸血伝播病委員会およびFDAは、血液収集施設が行うべき予防的アプローチを承認した。	

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60184	2006/12/01	60745	ウイルス感染	Eurosurveillance 2006; 11(4): 060420	2005年4月1日から2006年2月28日の間に、フランスで307例のチクングンヤ輸入例が同定された。平均年齢は47歳(7-81歳)であった。月別の輸入例数はレユニオンでの発生状況と関連が見られた。自発例は2006年3月に1例発生したが、輸入例患者を看護した看護師で、インド洋への旅行歴はなく、血液の暴露による感染と考えられた。	
60184	2006/12/01	60745	ウイルス感染	Eurosurveillance 2006; 11(8): 060810	2005年12月以降、チクングンヤウイルス感染のアウトブレイクがインドの8つの州で続いており、拡大するおそれがある。最も被害の大きい5つの州では896500例以上の疑い例が報告されている。北部の州からは1例も報告されていない。ヨーロッパの多数の国で輸入症例が報告されている。感染の拡大防止ならびに特異的な抗ウイルス薬とワクチンの開発が急務である。	
60198	2007/1/11	60790	ウイルス感染	J Infect Dis 2006; 194: 1276-1282	ヒトボカウイルス感染の疫学的プロフィールおよび臨床的特徴を調べるため、2歳未満の小児のヒトボカウイルスを調査した。直接的免疫蛍光試験でRSV(respiratory syncytial virus)、パラインフルエンザウイルス(1-3型)、インフルエンザAおよびB、並びにアデノウイルスが陰性であった425名中22名(5.2%)がPCRでヒトボカウイルス陽性であり、無症候であった96名では陽性者はゼロであった。この試験期間中、2つの異なる遺伝型が見られた。	6
60200	2007/01/24	60812	ウイルス感染	Transfusion 2006; 46: 1352-1359	全血輸血により、サルfoamyウイルス(SFV)感染が起こるかをアカゲザルを用いて調べた。自然感染ザル2匹の全血を、各々、レトロウイルスを持たないサル2匹に輸血したところ、1匹のドナーからのレシピエントでは感染し、もう1匹のドナーからのレシピエントは感染しなかった。ヒトでのSFV輸血伝播の可能性が示された。	
60189	2006/12/26	60774	ウイルス感染	カナダ Public Health Agency of Canada 2006年5月26日	カナダ公衆衛生局は最近4例のカナダ人旅行者でチクングンヤ感染が原因と思われる疾患を確認した。これらの患者はレユニオン島などへ旅行し、2月から3月の初めに発症した。ヨーロッパでも帰国者による輸入例が報告されている。インド洋南西諸島で2005年3月から2006年4月22日までの間に公式に報告されたチクングンヤ感染例は3877例であるが、実際には255000例に達すると思われる。インドでは2005年12月以来、チクングンヤウイルスのアウトブレイクが報告され、2006年4月20日現在、153324例に達する。	
60186	2006/12/20	60760	クロイツフェルト・ヤコブ病	Vox Sang 2006; 91(Suppl 3): 68-69	米国で供血後に古典的CJDを発症した個人を特定し、受血者の追跡調査を行った。2006年2月までに、古典的CJDで死亡した供血者31名が試験に登録され、384名の受血者が特定された。追跡を行ったところ、古典的CJDが輸血を介して受血者に伝播したという証拠は示されなかった。本研究は、1995年に米国の大規模血液供給システムと疾病対策予防センター(CDC)により開始され、継続中である。	7
60184	2006/12/01	60745	トリパノソーマ症	CDC/MMWR Weekly 2006; 55(29); 798-800	ロサンジェルスの心臓移植患者2名で、臓器移植によるシャーガス病伝播が見られた。1例は拒絶反応による合併症で死亡し、もう1例は心不全で死亡した。両例ともドナーがTrypanosoma cruzi感染者であったことが明らかとなった。米国における固形臓器移植によるT. cruzi伝播としては4例目と5例目になる。	8
60186	2006/12/20	60760	トリパノソーマ症	Vox Sang 2006; 91(Suppl 3): 98	フランスでリスクのある供血者に対し、シャーガス病スクリーニング検査を行うこととなり、Bioelisa Chagas、Chagatek、Ortho T.cruzi ELISA Test System ‘1、ELISA Cruzi の4種類のTrypanaosoma cruzi ELISAキットの感受性、再現性、特異性を評価した。感受性に関しては4種類の検査法で正確に検出された。再現性は24コピーのS/CO値の平均の変動係数によって示され、各々、6.30%、9.30%、15.7%、22.40%であった。	9

血対ID	受理日	番号	感染症(PT)	出典	概要	
60184	2006/12/01	60745	リンパ性脈絡髄膜炎	N Engl J Med 2006; 354: 2235-2249	2003年12月及び2005年4月に固形臓器の移植を受けた2つの患者群の感染症について調べた。レシピエント全員(8名)の検体からリンパ性脈絡髄膜炎ウイルス(LCMV)が検出されたが、ドナー(2名)からは検出されなかった。2005年群のドナーはLCMVに感染したハムスターをペットとして飼っていたが、2003年群の感染源は不明であった。レシピエント8例中7例は移植後9日から76日で死亡した。	
60184	2006/12/01	60745	異型クロイツフェルト・ヤコブ病	AABB Weekly Report 2006年7月21日	アイルランド輸血サービスは、CJDの病因となるプリオンを供血血液から除去するために開発された新しい装置を1年間使用した後、試用の中止を決定した。血液サービスは昨年、そのフィルター装置を購入したが、十分な効果が得られず、CJDプリオンは捕捉されずに通過し、供血中に混入する可能性があるためである。	
60184	2006/12/01	60745	異型クロイツフェルト・ヤコブ病	ABC Newsletter 2006 Sep 1; 16	外科用器具には殺菌後も依然としてクロイツフェルトヤコブ病(CJD)が残存する可能性が明らかとなった。エジンバラ大学研究チームは、タンパク質による平均汚染量が器具1mm2あたり0.2μgであり、ヒトへの感染に必要な量をかなり上回る数値であることを認めた。最大量は、扁桃腺(プリオンが分布することが知られている組織のひとつ)の切除に用いた器具で認められた。同チームは、保健省に対し、同チームが開発したガスプラズマ滅菌の広範な導入を推奨している。	13
60184	2006/12/01	60745	異型クロイツフェルト・ヤコブ病	Blood 2006; 107: 3907-3911	PrPcは全身の多数の組織に存在し、血小板に大量に存在する。静止血小板ではα顆粒膜上に存在することが知られているが、その生理学的機能は不明である。血小板中のPrPcの局在を調べたところ、血小板が活性化すると、血小板表面上にPrPcが一時的に発現し、続いて、微小胞およびエキソソーム上への放出が起こることが明らかとなった。血小板由来エキソソーム上にPrPcが存在するということは、血中でのPrPc輸送および細胞間伝播におけるメカニズムを示唆する。	
60184	2006/12/01	60745	異型クロイツフェルト・ヤコブ病	BMJ 2006; 332: 1186-1188	1996年から1999年に、手術時に20-29歳であった患者から得られた虫垂および扁桃12674検体のうち、病原体プリオンに陽性染色であった3例(虫垂)について、プリオン蛋白の遺伝子型分析を行った。3検体中2例で分析が可能であり、両者ともプリオン蛋白遺伝子(PRNP)コドン129のValがホモ接合体であった。今まで、vCJD患者は、Met/Valのヘテロである医原性の1例を除いて全て、PRNPのコドン129がMetのホモ接合体であり、Valホモ接合体がvCJDに対し感受性があることが初めて示された。	
60198	2007/1/11	60790	異型クロイツフェルト・ヤコブ病	FDA/CBER 2006年10月15日 FDA/TSEAC Meeting 2006年12月15日	FDAは、米国で認可されたヒト血漿由来第VIII凝固因子製剤(pdFVIII)の使用に係る潜在的vCJDリスク評価草案を作成した。FDAの評価モデルの結果は、血友病Aおよびフォンウィルブランド病患者に使用されるpdFVIII製剤の、vCJD感染リスクは非常に低いが、ゼロではないかもしれないことを示唆した。またTSEAC(TSE Advisory Committee)は、pdFVIII製品中のTSE除去の適切な閾値について議論した。TSE除去レベルにより、vCJD感染リスクは大きく変動することが示された。	14
60185	2006/12/14	60747	異型クロイツフェルト・ヤコブ病	Future Virol 2006; 1: 659-674	血液製剤の製造工程におけるプリオンの除去に関する総説である。プリオン除去のための個々の製造工程は、実際の製造条件を実験室での条件にスケールダウンさせ、確立されているスクレイピー株をモデル系として用いて通常は評価されている。しかしながら、血液中のプリオンタンパクの存在形態が不明なので、評価実験のためのスパイク材料としてのプリオンの調製方法は注意深く考慮しなければならない。現在のところ、エタノール分画、PEG 分画、カラムクロマトグラフィー、ウイルス除去膜およびデプスフィルターでの濾過が有効とされている。	

血対ID	受理日	番号	感染症(PT)	出典	概要	
60198	2007/1/11	60790	異型クロイツフェルト・ヤコブ病	Guidance for Industry (DRAFT GUIDANCE) FDA/CBER August 2006	古典的CJDの潜伏期間は38.5年であり、vCJDの潜伏期間も非常に長いことが示唆されている。また、未確認ではあるが恐らくかなりの数の血液ドナーが、欧州におけるBSE激増中にフランスで感染した可能性がある。これらのことから、FDAは1980年以降フランスで血液又は血液成分の輸血を受けた者からの供血を無期限に停止するという予防策の導入をガイダンス案として発表した。	
60198	2007/1/11	60790	異型クロイツフェルト・ヤコブ病	Lancet 2006; 367: 2068-2074	1996年7月から2004年6月までに11人のクールー病患者を確認したが、全員がSouth Foreに住んでいた。患者は全員、1950年代後半に食人習慣が中止される前に生れていた。推定された潜伏期間は、最小で34年から41年の範囲であったが、男性における潜伏期間は39年から56年の範囲と考えられ、更に最長で7年長かった可能性もある。プリオン遺伝子の分析によって、殆どのクールー病の患者は、潜伏期間の延長とプリオン病への耐性に関係する遺伝子型であるコドン129がヘテロ接合体であることが明らかとなった。	
60198	2007/1/11	60790	異型クロイツフェルト・ヤコブ病	PLoS Pathogens 2006; 2: 956-963	最近、大規模なスクリーニングによって、従来とは異なるPrPresがウシにおいて発見された。これらもまた別のプリオン株を代表するかを調べるため、H型と呼ばれる高分子量のウシの単離体を、ウシまたはヒツジの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、感染性プリオンの新規の株であることが示された。この病原体は、BSE病原体およびヒツジスクレイピー病原体とは明らかに異なる特有の神経病理学的特徴を示した。	15
60184	2006/12/01	60745	異型クロイツフェルト・ヤコブ病	Science 2006; 313: 92-94	TSEの前兆期に、スクレイピーに感染させたハムスターの血液中のPrPScをPMCA (protein misfolding cyclic amplification)法を用いて生化学的に検出した。潜伏期間の初期には、おそらく血液中に検出されたPrPScは末梢でのプリオンの複製に由来していると思われる。感染しているが発症していない動物の血液中のプリオンを生化学的に検出することができるということは、TSEの非侵襲的早期診断を期待させる。	
60186	2006/12/20	60760	異型クロイツフェルト・ヤコブ病	Science 2006; 314: 133-136	慢性消耗病(CWD)非感染シカをCWD陽性のシカの唾液、血液または尿・糞に曝露させた。その結果、CWDを伝播しうる感染性プリオンが唾液および血液中に認められた。CWDはシカ科の動物に容易に伝播すると言える。プリオン感染では体液との接触に関する注意が払われるべきである。	16
60184	2006/12/01	60745	異型クロイツフェルト・ヤコブ病	The Guardian 2006年5月2日	英国は、1990年代に輸出された英国製の血液製剤からのvCJD感染の危険性について、輸出先の14ヵ国に連絡を行った。輸血を介したvCJD感染は英国では3例報告されており、未発症の感染者からの供血により引き起こされる災害の「第二の波」が懸念される。最も危険性の高いブラジルとトルコや、ブルネイ、アラブ首長国連邦、インド、ヨルダン、オマーン、シンガポールに予防措置をとるよう勧告した。	
60186	2006/12/20	60760	異型クロイツフェルト・ヤコブ病	Vox Sang 2006; 91(Suppl 3): 70	PRDT(Pathogen Removal and Diagnostics Technologies)は、全血、RBCまたは血漿存在下で脳由来プリオンタンパク質およびTSE感染物と強く結合する高親和性リガンドを得るため、何百万もの化合物をスクリーニングした。その結果、PRDTのリード樹脂は赤血球存在下でも高濃度のTSE感染物を吸着し、低濃度の内因性TSE感染物を除去した。この樹脂を使用したMacoPharma P-Capt(TM)フィルターを用いることにより、輸血によるvCJD伝播リスクを軽減できる。	17
60204	2007/01/26	60818	異型クロイツフェルト・ヤコブ病	厚生労働省 平成18年8月24日	平成18年8月23日に開催された薬事・食品衛生審議会血液事業部会安全技術調査会において、ヒト胎盤エキス(プラセンタ)注射剤使用者に対する献血制限措置を日本赤十字社が実施することが了承された。	

血対ID	受理日	番号	感染症(PT)	出典	概要	
60184	2006/12/01	60745	肝炎	J Infect Dis 2006; 193: 1089-1097	非特異的PCRを行った後、染色体由来配列を除去することにより、非A-E肝炎患者の血清から、外来DNA断片が得られた。これらの内の一つをNV-Fと名づけたが、部分的オープンリーディングフレームを含み、非A-E肝炎患者69例中17例(24.6%)に検出された。NV-F陽性患者65例中49例(75.4%)の血清中に抗NV-F抗体が検出された。また免疫蛍光分析により、抗原は患者の肝細胞に存在することが明らかとなった。NV-Fはヒト肝炎に関連する新規の1本鎖DNA断片である。	
60199	2007/01/12	60802	結核	WHO 2006年9月5日	WHOは病原性が強く、致死性の結核の世界的な拡大防止の強化および措置を求めた。6クラスの第2選択薬の3クラス以上に耐性のある多剤耐性結核(XDR-TB)は世界の様々な地域で確認されており、特に旧ソビエト連邦やアジアで多い。また南アフリカではXDR-TBでHIV陽性である患者群で極めて高い死亡率が確認されている。	
60184	2006/12/01	60745	鳥インフルエンザ	Emerg Infect Dis 2006; 12: 1041-1043	タイで2005年11月28日にトリインフルエンザを発病し、12月7日に死亡した5歳の少年の血液検体を調べた。RT-PCRにより、血漿はH5N1インフルエンザウイルス陽性であった。ウイルスを分離し、遺伝子配列を決定したところ、A/Thailand/NK165/05 accession no. DQ372591-8であった。ヘムアグルチニンとノイラミニダーゼ遺伝子について系統遺伝学的分析を行ったところ、2004年初めにタイで発生した野鳥のインフルエンザウイルスの特徴と同じであった。	

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
				2006. 9. 26	該当なし	
一般的名称	解凍人赤血球濃厚液		研究報告の公表状況	ABC Newsletter. 2006 Sep 22; 16.	公表国 EU	
販売名(企業名)	解凍赤血球濃厚液「日赤」(日本赤十字社) 照射解凍赤血球濃厚液「日赤」(日本赤十字社)					

研究報告の概要	使用上の注意記載状況・その他参考事項等
○欧州協議会が伝達性海綿状脳症に関する報告書を発行 欧州協議会は2005年の反芻動物(有蹄動物)における伝達性海綿状脳症(TSE)のモニタリングと検査に関する報告書を発表した。TSE検査を行った1千万頭以上のウシ亜科動物のうち、陽性となったのは561頭のみと報告されている。2005年の調査結果は陽性例が引き続き減少していることを示している。TSE年次報告は、1990年代の食物安全危機を受けて、牛海綿状脳症モニタリングプログラムの一環として行われている。2001年以降5,100万頭のウシがこのプログラムによって検査されている。報告書はECのウェブサイト上で公開されている。	解凍赤血球濃厚液「日赤」 照射解凍赤血球濃厚液「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
欧州協議会が伝達性海綿状脳症に関する報告書を発表し、1千万頭のうち561頭がTSE陽性であったとの報告である。	日本赤十字社は、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1980年～1996年に1日以上の英国滞在歴のある方からの献血を制限している。今後も、CJD等プリオン病に関する内外の新たな知見及び情報の収集に努める。

INFECTIOUS DISEASE UPDATES

A high school science teacher in Salina, Kansas this week was suspended for allowing students to reuse the same instrument to draw blood from their fingers as part of a class project. Carol Pitts, spokeswoman for the Salina school district, said students in two science classes at Salina High School South were allowed to use the same lancet, or small pin, to prick their fingers for an experiment on Monday. She said about 50 students might have been involved. Ms. Pitts said there was additional concern that some of the students might have come in contact with blood when they washed the science experiment slides. She said it was unclear what experiment the classes were doing, but they may have been checking blood glucose levels. The school district is working with the Saline County Health Department to ensure that the students are tested for diseases such as HIV and hepatitis, both of which can be spread by using a shared instrument to draw blood. "Our recommendation is that the kids get tested now as a baseline for HIV and Hepatitis B and C and have it repeated two or three times," said health department director, Yvonne Gibbons, MD. But she said there likely was little cause for concern. "This is minimal risk," Dr. Gibbons said. "I don't think there is any reason to panic, but we're cautioning the school to take the best possible course they can, and that would be to have the kids tested." (Source: Associated Press, 9/19/06)

vCJD

The European Commission this week released its 2005 report on the monitoring and testing of ruminants (hoofed animals) for the presence of Transmissible Spongiform Encephalopathy (TSE) in the EU. Out of over 10 million bovine animals tested for TSE in 2005, only 561 were positive, EC reports. The 2005 results show a continuous decline in the number of positive tests. The annual TSE report is produced as part of the monitoring program on Bovine Spongiform Encephalopathy (BSE), following the food safety crisis of the 1990s. Since 2001, 51 million cattle have been tested through the program. The report is available on the EC Web site at: ec.europa.eu/food/food/biosafety/bse/-annual_report_tse2005_en.pdf ♦

PEOPLE:

Maria Elena Geyer, vice president of Donor Services at Puget Sound Blood Center, this week was honored as a Women In Science at the *Northwest Asian Weekly's* Women of Color Empowered Luncheon. Ms. Geyer is one of several women being honored for their work in the field of science. *Northwest Asian Weekly* is an English language newspaper published by Assunta Ng, publisher of the *Seattle Chinese Post.* Ms. Ng started the Women of Color Empowered luncheons in 1996 as a networking group and as a way to recognize the accomplishments of women from diverse ethnic backgrounds. Ms. Geyer was also named recipient of the AABB's Chapman Franzmeier Memorial Award. The award was made in recognition of her exceptional leadership in the area of donor recruitment.

Jennifer Taggart is the new chief financial officer for Florida's Blood Centers. Ms. Taggart, whose background is in finance and management, will oversee finances, procurement and employee relations. She previously was vice president and general manager for Orlando Harley Davidson – where she managed revenue growth that went from less than $20 million in 2000 to $48 million in 2005, and year-to-year net income growth of more than 50 percent every year since 2001, including some years of triple-digit growth. She also oversaw the opening of five new retail stores and laid the groundwork for two future sites.

(continued on page 17)

医薬品 研究報告 調査報告書

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研究報告の概要

○供血者のHBc抗体スクリーニング:HBc抗体検査9種の比較
【背景および目的】ドイツ赤十字社におけるB型肝炎ウイルス(HBV)に対するミニプール核酸増幅検査(NAT)導入以降、輸血関連HBV感染の残存リスクは1:500,000と推定されているが、これはヒト免疫不全ウイルス(HIV)あるいはC型肝炎ウイルス(HCV)の10倍である。このリスクの高さは、B型肝炎コア抗原に対する抗体(HBc抗体)の慢性陽性、B型肝炎表面抗原(HBsAg)の陰性、ならびにウイルス量が少なくポリメラーゼ連鎖反応(PCR)で陰性を示す供血者が主な原因である。【対象および方法】血液センターの供血者10,000名を対象に、現行のPRISM®HBcおよび新規PRISM®HBcore検査を用いたHBc抗体のスクリーニングを実施し、これらの検査の診断感度および特異性を調べた。PRISM® HBcまたはPRISM® HBcoreで陽性だった検体については、別のHBc抗体検査7種、B型肝炎表面抗原抗体(HBs抗体)検査2種、B型肝炎エンベロープ抗原抗体(HBe抗体)検査1種、およびHBV NAT検査3種を用いて、さらに分析を行った。【結果】合計10,000名の供血者のうち、PRISM® HBc およびPRISM® HBcoreの一方のみに陽性反応を示したのは、それぞれ9および14検体であったが、2つのHBc抗体検査ともに陽性だった検体は165であった。HBc抗体検査が陽性であったこの188検体について、計9種類の抗HBc検査による分析をさらに実施したところ、162(86.2%)検体で一致した結果が得られた。HBc抗体のみ陽性だった検体のHBc抗体のカット・オフ値は、HBs抗体またはHBe抗体も陽性だった検体と比較して、有意に低かった($p < 0.01$)。【結論】PRISM HBc抗体検査はいずれも、ドイツのプレスクリーニング未実施供血者の約1.8%がHBc抗体陽性であることを示した。両PRISMテストの感度は同等であったが、特異性はPRISM® HBcoreの方が有意に高かった。HBc抗体のカット・オフ値が高い検体では、その他のHBVパラメータが陽性であり、9種類のHBc抗体検査結果が一致することが示された。HBc抗体のみ陽性およびHBc抗体/HBs抗体陽性の輸血によるそれぞれの感染リスクを推定するためには遡及調査が必要である。

使用上の注意記載状況・その他参考事項等

解凍赤血球濃厚液「日赤」
照射解凍赤血球濃厚液「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
現行のPRISM®HBcおよび新規PRISM®Hbcore検査を用いたHBc抗体のスクリーニングを実施し、診断感度および特異性を調べたところ、感度は同等であったが、特異性はPRISM® HBcoreの方が有意に高かった。HBc抗体のカット・オフ値が高い検体では、その他のHBVパラメータが陽性であり、9種類のHBc抗体検査結果が一致することが示されたとの報告である。	日本赤十字社では、HBs抗原検査及びHBc抗体検査を実施することに加えて、HBVについて20プールでスクリーニングNATを行い、陽性血液を排除している。HBV感染に関する新たな知見等について今後も情報の収集に努める。また、これまでの凝集法と比べて、より感度の高い化学発光酵素免疫測定法(CLEIA)の導入を予定している。

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Anti-HBc screening of blood donors: a comparison of nine anti-HBc tests

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Vox Sanguinis

Background and Objectives Since voluntary introduction of hepatitis B virus (HBV) minipool nucleic acid amplification technology (NAT) at the German Red Cross, the expected residual risk of a transfusion-associated HBV infection has been estimated to be 1 : 500 000 – about 10 times higher than for human immunodeficiency virus (HIV) or hepatitis C virus (HCV) infection. Donors demonstrating chronic positivity for antibody to hepatitis B core antigen (anti-HBc), negativity for hepatitis B surface antigen (HBsAg) and polymerase chain reaction (PCR)-negative with a low virus load are a major cause of this increased risk.

Materials and Methods Ten-thousand blood donors from our blood-donation centre were screened for anti-HBc using the current PRISM® HBc and the new PRISM® HBcore assay to evaluate the diagnostic sensitivity and specificity of these tests. PRISM® HBc- or PRISM® HBcore-reactive samples were further analysed using seven additional tests for anti-HBc, two tests for antibody to hepatitis B surface antigen (anti-HBs), one test for antibody to hepatitis B envelope antigen (anti-HBe) and three HBV NAT assays.

Results From a total of 10 000 donors, nine and 14 samples were reactive only in the PRISM® HBc and the PRISM® HBcore, respectively, whereas 165 samples were reactive in both anti-HBc assays. Further analysis of these 188 anti-HBc-reactive specimens in a total of nine different anti-HBc assays revealed concordant results for 162 (86·2%) specimens. Sample cut-off values for anti-HBc were significantly ($P < 0{\cdot}01$) lower for anti-HBc-only reactive samples compared with specimens that were also reactive for anti-HBs or anti-HBe.

Conclusions Both PRISM anti-HBc assays revealed that ≈ 1·8% of non-prescreened blood donors from Germany were reactive for anti-HBc. Although sensitivity was comparable between both assays, specificity was increased significantly with the PRISM® HBcore. High anti-HBc sample cut-off values were indicative for reactivity in other HBV parameters and for concordant results in the nine different anti-HBc assays. Look-back investigations are necessary to estimate the infection risk both of anti-HBc-only positive and of anti-HBc/anti-HBs-positive blood transfusions.

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Key words: anti-HBc assays, anti-HBs, blood screening, HBV DNA.

Introduction

Hepatitis B virus (HBV) infection is a serious global health problem affecting two billion people worldwide, and 350 million people suffer from chronic HBV infection [1]. In Germany, ≈ 5–8% of the population has a history of HBV infection, and

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0·4–0·7% are chronic HBV carriers [2]. To provide a safe blood supply, minipool nucleic acid amplification technology (MP-NAT) for hepatitis C virus (HCV), human immunodeficiency virus 1 (HIV-1) and HBV was implemented on a voluntary basis in 1997 at most German Red Cross Blood Donor Services, and subsequently NAT became mandatory in Germany for HCV RNA (in 1999) and for HIV-1 RNA (in 2004) [3–5]. With the introduction of NAT testing, the risk of transfusion-transmitted viral infections was significantly reduced [5]. For Germany the risk of receiving an infectious blood donation is calculated at 1 in 5 540 000 for HIV-1 and 1 in 4 400 000 for HCV. In contrast, the transfusion-associated risk of HBV is estimated at 1 in 620 000 by using MP-NAT and 1 in 820 000 by using individual-donation (ID) NAT [6].

This relatively high risk for HBV in part can be attributed to chronic HBV-infected blood donors with low-level viraemia. The likelihood of chronicity after an acute hepatitis B infection varies with age. Infection at birth is associated with a clinically silent acute infection with a 90% probability of chronic infection, while infection during adulthood is typically associated with clinically apparent acute hepatitis and a low risk of chronicity (≈ 1%) [7].

Heptatitis B surface antigen (HBsAg) [8] assays have been available for blood donor screening since 1971. However, despite the introduction of HBsAg- and MP-NAT testing, cases of HBV transmission via HBsAg-negative blood donations have been reported [9]. This indicates that both screening tests (HBsAg and MP-HBV-NAT) might have limitations for the diagnosis of chronic HBV infections, as the viral load may be below the detection limit of NAT, and that HBsAg may become undetectable only a few months after infection.

Seroconversion to antibody to hepatitis B core antigen (anti-HBc) occurs within the first 1–2 weeks [9] after the appearance of HBsAg and precedes detectable levels of antibody to hepatitis B surface antigen (anti-HBs) by weeks to months. High anti-HBs levels of > 100 IU/l in a donor are currently assumed to be putatively protective against transmission of HBV to a recipient of blood transfusion. However, HBV infections may occur without detectable anti-HBs or with disappearance of anti-HBs, sometimes associated with late-phase reactivation of HBV. Additional screening for anti-HBc could therefore both close the diagnostic gap between the disappearance of HBsAg and the appearance of anti-HBs and detect late-phase HBV infection with potential low-level viraemia.

Isolated anti-HBc does not necessarily indicate active virus replication, as most cases of isolated anti-HBc denote resolved hepatitis B infections of the past [10]. HBV-infected blood donors with a low-level viraemia and without anti-HBs, however, are assumed to be infectious to recipients, and probably contribute to the relatively high residual infection risk compared with HCV or HIV [5,11].

Anti-HBc screening of blood donors is performed in some countries (e.g. the USA, France and Japan) and will become mandatory in Germany from July 2006. Currently available anti-HBc assays, however, are reported to be unsatisfactorily non-specific, with unconfirmed reactive results in ≈ 32% of initially anti-HBc reactives [12–14]. The unnecessary deferral of a high number of non-specific anti-HBc reactive, but otherwise healthy, blood donors could lead to an undersupply of essential blood products.

The objectives of this study were to document the prevalence of anti-HBc reactives in HBsAg-negative donations made to our blood transfusion service and to compare two commercially available anti-HBc assays (PRISM® HBc and PRISM® HBcore) for their diagnostic and analytical specificity and sensitivity. In addition, all 188 samples, which were either PRISM® HBc or PRISM® HBcore reactive, were analysed by comparative testing in a total of nine different anti-HBc tests and by analysis of the HBV parameters anti-HBs, antibody to hepatitis B envelope antigen (anti-HBe) and HBV DNA.

Materials and methods

Blood donors

Whole-blood samples were collected from 10 000 unpaid blood donors at the German Red Cross Institute Frankfurt between January and February 2004. Of these, 10·5% were first-time donors (50·4% female, mean age 36·1 ± 12·4 years; 49·6% male, mean age 37·9 ± 12·8 years) and 89·5% were repeat donors (38·8% female, mean age 44·6 ± 12·5 years; 61·2% male, mean age 46·7 ± 12·3 years). The donor population had not been previously screened for anti-HBc. The study was approved by the ethics committee of the Johann Wolfgang Goethe University, Frankfurt am Main.

Sample preparation and test algorithm

Samples were centrifuged at 3000 *g* for 10 min, and EDTA-plasma was separated within 24 h. Samples involved were tested by the current PRISM® HBc and the new PRISM® HBcore (Fig. 1). Reactive samples were analysed using a total of nine commercially available anti-HBc assays (including the two used for screening), as well as with two anti-HBs assays, an anti-HBe assay and three different NAT assays. Samples with a positive test result in one anti-HBc assay were initially defined as anti-HBc reactive until the results of further testing were available. Samples where the initial anti-HBc result was confirmed by an additional HBV parameter (such as anti-HBs without vaccination, anti-HBe or HBV DNA) were defined as anti-HBc positive. Samples that were anti-HBc-only reactive, or vaccinated donors who were anti-HBc and anti-HBs reactive, were termed anti-HBc indeterminate. The donors were queried about their vaccination status if anti-HBs was the only additional marker.

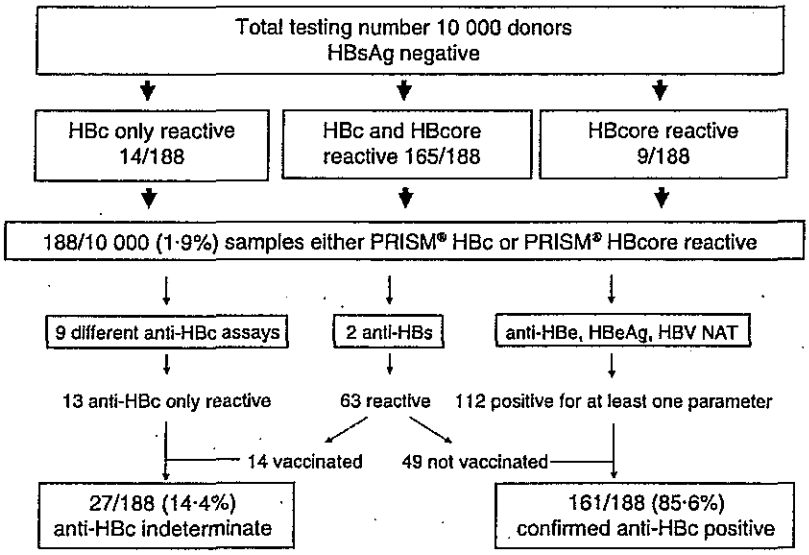

Fig. 1 Testing procedure. A total of 10 000 hepatitis B surface antigen (HBsAg)-negative donors were screened with PRISM® HBc and PRISM® HBcore. Reactive samples were analysed by nine different tests for antibody to hepatitis B core antigen (anti-HBc) and tested for antibody to hepatitis B surface antigen (anti-HBs), antibody to hepatitis B envelope antigen (anti-HBe) and hepatitis B virus by nucleic acid amplification technology (HBV NAT). Samples that were also positive for anti-HBe, hepatitis B e antigen (HBeAg), HBV NAT or anti-HBs without vaccination were interpreted as confirmed anti-HBc positive. Samples that were anti-HBc-only reactive or anti-HBs with vaccination were interpreted as anti-HBc indeterminate.

HBV NAT

Samples diagnosed as anti-HBc reactive by PRISM® HBc or PRISM® HBcore were tested using an in-house real-time HBV DNA polymerase chain reaction (PCR) assay with primers targeted to the surface (S) gene (nucleotides 338–430) [15]. To increase sensitivity of the in-house NAT, we performed enrichment of viruses from 9·6 ml of single-donor plasma by centrifugation at 58 000 *g* for 1 h before extraction (single-sample enrichment PCR). After centrifugation, supernatants were decanted and the pellets were subjected to nucleic acid extraction using the QIAamp DNA blood mini kit (Qiagen, Hilden, Germany). Nucleic acids were eluted from the Qiagen columns in a final volume of 50 µl. Aliquots of 20 µl were subjected to amplification by HBV PCR in duplicate. Single-sample enrichment PCR was independently repeated at least four times. The analytical sensitivity (95% detection limit) of the single-sample enrichment PCR was 1·86 IU/ml, based on the World Health Organization (WHO) International Standard for HBV DNA (NIBSC Code 97/746). Furthermore, all anti-HBc-reactive specimens were tested in two commercially available HBV DNA screening NAT assays by ID-NAT, HBV Cobas AmpliScreen (Roche Molecular Systems, Pleasanton, CA, USA) and TMA Ultrio (Chiron, Emeryville, CA, USA), according to the manufacturers' instructions. The test systems HBV Cobas AmpliScreen and TMA Ultrio yield a sensitivity of 6·7 IU/ml [16] and 11 IU/ml [17], respectively.

Serological testing

A total of 10 000 blood donors were screened with PRISM® HBc, as well as with PRISM® HBcore. Samples that were positive in at least one of the assays were additionally tested in the following seven anti-HBc assays: AxSym Core™ (Abbott, Wiesbaden, Germany); Immulite® 2000 Anti-HBc (DPC, Bad Naunheim, Germany); Enzygnost® Anti-HBc Monoclonal (Dade Behring, Marburg, Germany); Ortho™ HBc ELISA (Ortho Clinical Diagnostic, Neckargemuend, Germany); Cobas® Anti-HBc (Roche Diagnostics, Mannheim, Germany); Murex® Anti-HBc (Abbott/Murex Biotech Ltd, Dartford, Great Britain); and ADVIA Centaur HBc® (Bayer Health Care, Tarrytown, NY, USA). To determine HBsAg, hepatitis B envelope antigen (HBeAg), anti-HBs and anti-HBe, the following tests were used: PRISM HBsAg®, AxSYM HBe 2·0®, AxSYM AUSAB®, and AxSYM anti-HBe 2·0®, respectively (all Abbott); ADVIA Centaur Anti-HBs (Bayer Health Care); and Architect Anti-HBe (Abbott). All serological tests were conducted strictly in accordance with the manufacturers' instructions. All anti-HBc assays were competitive tests, with the exception of ADVIA Centaur HBc® and Ortho™ HBc ELISA, which were non-competitive anti-HBc assays.

Statistical analysis

The standard deviation (SD) and coefficient of variation (CV) of the antibody assays were calculated with Excel 2000. The Student's unpaired *t*-test was performed with the data from sample cut-off (S/Co) values. Fisher's test was performed for sensitivity, specificity, positive and negative predictive value between PRISM® HBc and PRISM® HBcore. Statistical significance was considered if the *P*-value was < 0·05. Results were highly significant if the *P*-value was < 0·01.

Results

Prevalence of anti-HBc in the German Red Cross donor population

A total of 10 000 HBsAg-negative donors from our blood donation service were screened, in parallel, with PRISM® HBc

Table 1 Characterization of 188 antibody to hepatitis B core antigen (anti-HBc)-reactive samples by nine different anti-HBc assays

		Anti-HBc reactivity in nine different assays		
		Class A (9 assays)	Class B (5–8 assays)	Class C (1–4 assays)
Group 1				
Anti-HBc only	13	0	8	5
Group 2[a]				
Anti-HBc + anti-HBs	63	50	11	2
Anti-HBc + anti-HBe	7	7	0	0
Group 3[b]				
Anti-HBc + anti-HBs + anti-HBe	105	105	0	0
Total	188	162 (86·2%)	19 (10·1%)	7 (3·7%)
	[168 (89·4%) anti-HBs positive]			

[a]One second marker positive.
[b]Both second markers positive.
All 188 samples reactive by PRISM® HBc and/or by PRISM® HBcore were re-analysed by seven additional assays for anti-HBc. Samples were categorized into three groups [1 = anti-HBc-only reactives; 2 = one second marker positive for antibody to hepatitis B surface antigen or antibody to hepatitis B envelope antigen (anti-HBs or anti-HBe); 3 = samples reactive for anti-HBc and anti-HBe + anti-HBs). The samples were further classified into three classes (class A = reactive in all nine anti-HBc assays; class B = reactive in five to eight anti-HBc tests; class C = reactive in four or fewer anti-HBc tests).

and PRISM® HBcore (Fig. 1). One-hundred and eighty eight of 10 000 (1·88%) samples were either PRISM® HBc or PRISM® HBcore reactive. The majority of these samples were additionally positive for anti-HBs (168/188, 89·4%) or for anti-HBe (112/188 59·6%) (Table 1). All of these anti HBc-reactive samples were HBeAg negative. Only one sample, which was anti-HBc reactive in all nine assays, negative for anti-HBs and positive for anti-HBe, was HBV DNA positive by single-sample enrichment NAT. Quantification yielded a virus load of 2·5 IU/l. However, both commercial HBV NAT systems designed for NAT blood screening (Cobas Ampliscreen and TMA Ultrio) gave negative results after triplicate testing of the individual plasma.

Sensitivity and specificity of PRISM® HBc and PRISM® HBcore assays

One-hundred and sixty five of 188 samples were reactive in both anti-HBc screening assays, whereas 14 and nine samples were only PRISM® HBc and PRISM® HBcore reactive, respectively. Ten of 14 PRISM® HBc-only reactive samples were not confirmed by other HBV parameters. The remaining four samples were positive for anti-HBs. Three of nine PRISM® HBcore-reactive samples were not confirmed by other HBV parameters. The remaining six samples were positive for anti-HBs.

Diagnostic sensitivity is defined as the ratio of positive tested samples divided by all positive samples, whereas diagnostic specificity is defined as the ratio of negative tested samples divided by all negative samples. Based on 'anti-HBc-positive' samples (samples that were also positive for an additional HBV parameter after exclusion of vaccination), diagnostic sensitivity was equal for both screening assays (96·9% and 99·4% for PRISM® HBc and PRISM® HBcore, respectively; not significant $P = 0·5$; 159/161 samples reactive for PRISM® HBc and 160/161 samples reactive for PRISM® HBcore). In contrast, diagnostic specificity was significantly higher for PRISM® HBcore (9812/9822 samples negative for PRISM® HBc and 9812/9815 samples negative for PRISM® HBcore; $P = 0·046$) and the positive predictive value was also significantly increased for PRISM® HBcore (159/169 samples positive for PRISM® HBc and 160/163 samples positive for PRISM® HBcore; $P = 0·049$).

Detailed investigation of 188 anti-HBc reactive samples

Samples that were either PRISM® HBc or PRISM® HBcore reactive were tested in parallel with seven additional anti-HBc assays, two anti-HBs tests and three NAT assays. Arbitrary confirmation of anti-HBc reactivity was either decided on the basis of additional detection of anti-HBs, anti-HBe or HBV-DNA, or in conjunction with the frequency of reactivity in the total of nine different anti-HBc assays. As shown in Table 1, the samples were categorized into three groups in regard to the presence of additional serological HBV markers. The first group represented anti-HBc-only reactive samples (no additional serological HBV marker), the second group consisted of samples that had exclusively anti-HBs or anti-HBe as a second HBV marker, and the third group was made up of anti-HBe- and additional anti-HBs-reactive samples.

To address the theoretical possibility that the reactive anti-HBc screening result might be non-specific (false-positive) and the anti-HBs reactivity caused by an HBV vaccination with recombinant HBsAg vaccine, we interviewed 63 of the

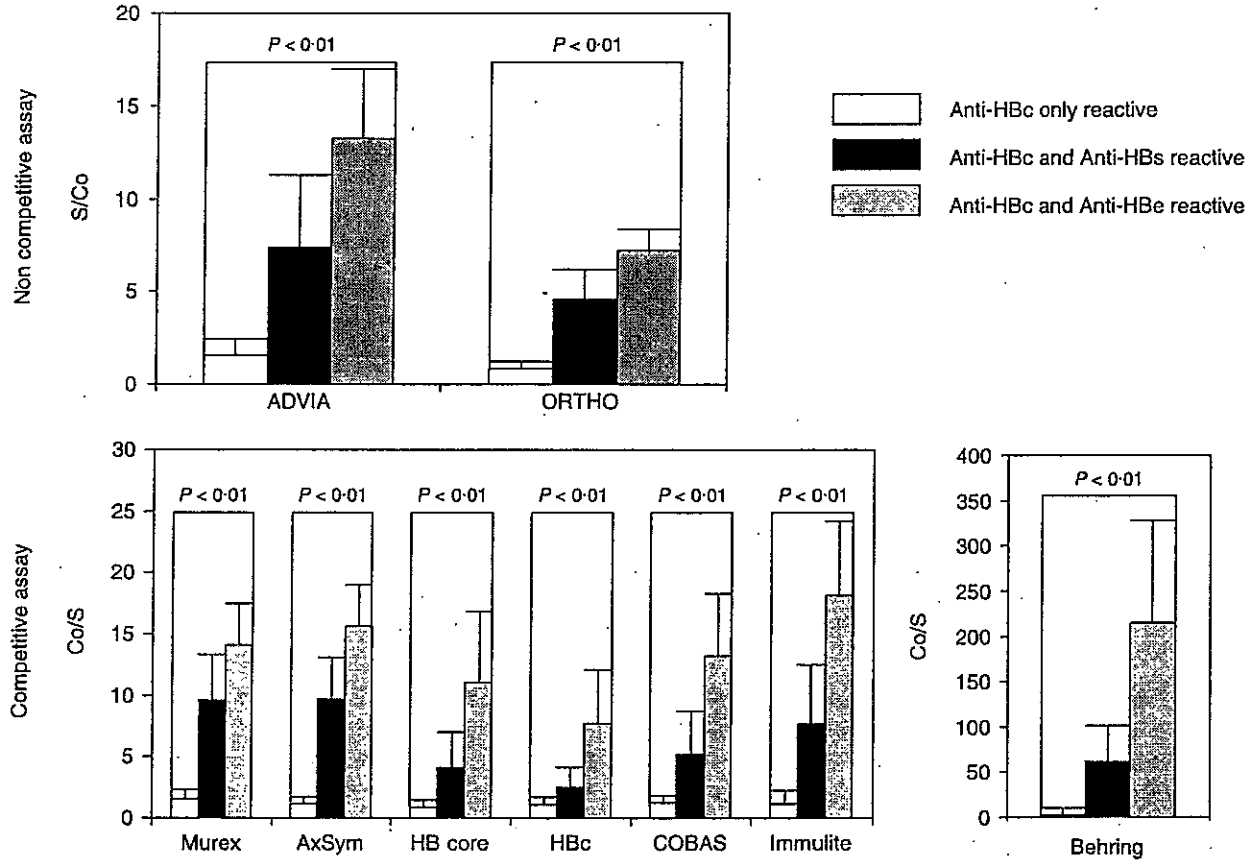

Fig. 2 Analysis of 188 antibody to hepatitis B core antigen (anti-HBc)-reactive samples: comparison between nine anti-HBc assays. Anti-HBc assays were divided into competitive (Murex, AxSYM, PRISM® HBcore, PRISM® HBc, COBAS Immulite and Behring) and non-competitive (ADVIA and Ortho) assays. Sample cut-off values (S/Co) differed significantly between anti-HBc-only reactive samples and anti-HBc + antibody to hepatitis B envelope antigen (anti-HBe)-reactive samples.

anti-HBc/anti-HBs dual-reactive donors about their vaccination history: 14 (22·2%) reported having had an HBV vaccination in the past.

All 112 anti-HBe-reactive samples were also concordantly reactive in the nine anti-HBc assays, providing strong evidence for anti-HBe as the most specific marker for a past HBV infection. Figure 2 shows S/Co values for each group according to the different anti-HBc assays. One might also consider the S/Co ratio of anti-HBc results as an indication of distinguished true and false-positive anti-HBc results: significantly lower anti-HBc signals were obtained with the anti-HBs- and/or anti-HBe-negative samples compared with anti-HBs- and/or anti-HBe-reactive samples (Fig. 2, $P < 0{\cdot}01$). The student's unpaired *t*-test was performed for the S/Co values between these groups of samples and differed significantly ($P < 0{\cdot}05$) in all nine anti-HBc tests.

Discussion

Blood donors chronically infected with HBV, but without detectable HBsAg, contribute to the residual risk of transfusion-transmitted HBV infections, which is higher for HBV than for HIV or HCV [6]. Blood donor screening with HBsAg assays and HBV MP or single-donation NAT may fail to detect chronic HBV-infected persons, because the low virus burden may remain undetected by these assays. However, a significant proportion of these HBV infections might be detected by testing for anti-HBc.

In this study we first compared two anti-HBc assays (PRISM® HBc and PRISM® HBcore) with each other. One-hundred and sixty one of 188 anti-HBc-reactive samples were confirmed by other HBV markers. This corresponds to a prevalence of 1·61% of confirmed anti-HBc-positive donors in our population. The diagnostic sensitivity was comparable between both assays, whereas the diagnostic specificity was significantly enhanced for the PRISM® HBcore. Based on these data, we suggest the use of the PRISM® HBcore for blood donor screening in order to enhance the specificity of the anti-HBc assay without compromising sensitivity.

Screening for anti-HBc is considered a potential measure to improve blood safety further. However, because of presumed non-specificity of assays, the implementation of anti-HBc as

a screening marker for blood donors is the subject of controversial discussion. A golden rule for the confirmation of anti-HBc reactivity as an indicator of a past HBV infection has not yet been established. It is likely that anti-HBc reactivity, in conjunction with both anti-HBs and anti-HBe, indicate a past HBV infection. In our study, 105/188 (55·9%) of the donors showed this. Anti-HBe as the only second marker also suggests a past HBV infection. This conclusion is supported by the fact that all anti-HBe-reactive samples, with or without anti-HBs coreactivity, were clearly anti-HBc reactive in all nine anti-HBc assays used in this study.

Under this premise, 112/188 (59·6%) anti-HBc-reactive samples were truly anti-HBc positive. At first glance, one might also consider anti-HBs as the only second marker as a confirmation for anti-HBc positivity (group 2). However, both the reactivity of some of these specimens in only a few anti-HBc assays, and the low anti-HBc S/Co values combined with very high anti-HBs titres, raised some doubts. Indeed, in interviews, 14/63 donors confirmed that past HBV vaccinations with recombinant HBsAg were presumably responsible for the high anti-HBs titres. Therefore, we cannot retrospectively differentiate between vaccinated donors who comprise non-specific anti-HBc reactivity and vaccinated donors with anti-HBc as a marker of past HBV infection. Both constellations seemed to be represented in our population. After exclusion of all anti-HBs-positive donors with a vaccination history (including most of the weak anti-HBc reactives), probably 49/63, both anti-HBs and truly anti-HBc-positive donors remain. Altogether, 27/188 (14·4%) of anti-HBc-reactive samples remain as probably non-specific anti-HBc reactive (false-positive), and 161/188 (85·6%) of anti-HBc-reactive samples appear to be truly positive.

A total of 160/161 and 159/161 of these samples were reactive with PRISM® HBcore and PRISM® HBc, respectively. This low percentage of unconfirmed anti-HBc results contrasts previous reports [12,14] and may be explained, in part, by the use of modern, more specific, assays for our blood donor screening.

In an attempt to classify the anti-HBc status by the S/Co values, the samples were classified into three groups according to the level of the S/Co values. The highest S/Co values were found for samples that were at least anti-HBc and anti-HBe reactive, followed by samples that were anti-HBc and anti-HBs reactive (Fig. 2). S/Co values for anti-HBc-only reactive samples were higher for those detected by five to nine assays than those which were reactive in only one to four tests. Therefore, the analysis of the S/Co values enabled us to define confidence intervals for each anti-HBc test in order to classify unknown samples to be potentially confirmed, indeterminate, or potentially negative. There were, however, two samples that could not be classified in this manner because they were both anti-HBc weak and anti-HBs highly reactive. The weak anti-HBc result could be a non-specific finding in donors recently vaccinated for HBV. These preliminary conclusions, however, should be challenged by studies that use a larger number of samples.

In this study, only one anti-HBc-positive donation was found to be positive for HBV DNA in one of the three NAT tests, and again only in three of four respective test runs. Clearly, HBV DNA in this plasma would have hardly been detected with state-of-the-art NATs, even when performed on a single-donation basis. The donor was a repeat donor who had previously donated 18 times, with a normal alanine aminotransferase (ALT) value obtained at each time point. HBV infection has not occurred in the recipients (six of 18 were retested by antibody screening and ultrasensitive NAT; 12 were already dead at the time of the look-back). In a previous study, Roth *et al.* [5] reported on seven HBV-positive samples among 729 HBsAg-negative, anti-HBc-positive donors. Six of these seven donors were also positive for anti-HBs. Kleinman and colleagues [13] found four HBV DNA-positive samples by testing 395 anti-HBc-positive samples with anti-HBs titres of < 100 IU/l. The risk associated with transfusion of those low-level viraemic donations is difficult to assess. Look-back examinations could eventually offer some clarification of this issue.

Based on the data presented, all anti-HBc assays tested were suitable for blood donor screening. However, we prefer a highly sensitive and specific screening test, such as PRISM® HBcore. Confirmation with a second anti-HBc test might be one strategy to identify non-specific reactivity, but we must bear in mind that many assays use the same antigens for testing. Therefore, a sample that could be confirmed with a second assay might well be a result of the non-specificity of both tests. In this study, confidence intervals for S/Co values were defined for each assay, allowing differentiation between truly anti-HBc-positive samples and anti-HBc-indeterminate samples. In very rare cases, however, anti-HBc-only reactive samples with a very weak S/Co value may represent a past HBV infection where anti-HBs and anti-HBe disappeared and anti-HBc waned to low levels. These cases might be outside the confidence intervals for the S/Co values defined in this study. Currently, there were no data, based on look-back examinations, that these donors were infectious.

In summary, ≈ 1·88% of our blood donors were initially reactive for anti-HBc, as determined by screening with PRISM® HBc and PRISM® HBcore, and, in 161/188 donors, anti-HBc reactivity was confirmed by additional HBV parameters. The diagnostic specificity and positive predictive value of PRISM® were significantly enhanced for PRISM HBcore® when compared with the PRISM® HBc. The approach to define confidence intervals for anti-HBc S/Co values might be useful for classifying an unknown sample as anti-HBc positive or anti-HBc indeterminate. The infection risk resulting from anti-HBc-positive donors is under examination in a separate study by the German Red Cross Research Foundation in which ≈ 1300 look-back analyses are being conducted. Results of

these look-back examinations are eagerly awaited and may allow us to assess the impact of donors, chronically infected with HBV, on blood safety more accurately.

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研究報告の概要	使用上の注意記載状況・その他参考事項等
わが国の E 型肝炎の実態を明らかにする目的で、全国から総数 254 例の E 型肝炎ウイルス感染例を集め、これを解析した。 その結果、以下の知見を得た。 1)HEV は全国に浸透している。 2)感染者の多くは中高年（平均年齢約 50 歳）で、男性に多い(男女比約 3.5 対 1)。 3)我国に土着の HEV の遺伝型は 3 型と 4 型であり、後者は北海道に多い。 4)年齢と肝炎重症度との間に相関がある。 5)遺伝型 3 型に比べて、4 型は顕在化率も重症化率も高い。 6)発症時期は無季節性である。 7)感染経路は、動物由来食感染が約 30%、輸入感染が 8%、輸血感染が 2%、不明が約 60%であった。	2. 重要な基本的注意 (1) 本剤の原材料となる献血者の血液については、HBs 抗原、抗 HCV 抗体、抗 HIV-1 抗体、抗 HIV-2 抗体、抗 HTLV-Ⅰ抗体陰性で、かつ ALT(GPT)値でスクリーニングを実施している。更に、プールした試験血漿については、HIV-1、HBV 及び HCV について核酸増幅検査(NAT)を実施し、適合した血漿を本剤の製造に使用しているが、当該 NAT の検出限界以下のウイルスが混入している可能性が常に存在する。本剤は、以上の検査に適合した血漿を原料として、Cohn の低温エタノール分画で得た画分から人ハプトグロビンを濃縮・精製した製剤であり、ウイルス不活化・除去を目的として、製造工程において 60℃、10 時間の液状加熱処理及び濾過膜処理(ナノフィルトレーション)を施しているが、投与に際しては、次の点に十分注意すること。

報告企業の意見	今後の対応
日本におけるE型肝炎ウイルス感染の統計学的･疫学的･ウイルス学的特徴を求めた調査の解析結果報告である。 万一原料血漿にHEVが混入したとしても、EMCをモデルウイルスとしたウイルスバリデーション試験成績から、本剤の製造工程において十分に不活化・除去されると考えている。	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。

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研究報告の概要

○ヒトヘルペスウイルス8型の輸血伝播
背景:ヒトヘルペスウイルス8型(HHV-8)が輸血によって伝播するかどうかについては明らかにされていない。HHV-8の流行地域であるウガンダにおいてHHV-8の輸血伝播のリスクを検討した。
方法: ウガンダのKampalaで、2000年12月～2001年10月に輸血を受けた患者を登録した。HHV-8抗体について輸血前の血液検体と複数の輸血後検体(6ヶ月の期間中で最高9回行われた来院調査時に採取)を検査した。HHV-8血清反応陰性血液の受血者と比較した、HHV-8血清反応陽性血液受血者におけるセロコンバージョンの超過リスクを経時的に算出した。
結果:登録した受血者1811名のうち、輸血前のHHV-8血清反応が陰性で、必要な追跡調査を完了した患者は991名であった。991名のうち、43%はHHV-8血清反応陽性の血液の輸血を、57%はHHV-8血清反応陰性の血液の輸血を受けた。HHV-8セロコンバージョンは991名中41名に発現した。HHV-8血清反応陽性血液受血者の方が、HHV-8血清反応陰性血液受血者よりも、セロコンバージョンのリスクが有意に高く(超過リスク2.8%; P<0.05)、また、リスクの増加は、主に輸血3～10週後にセロコンバージョンを起こした患者に認められ(超過リスク2.7%; P=0.005)、このウイルスの輸血による感染に合致する結果であった。保存期間が4日を越える血液製剤と比較して、保存期間が4日以内の血液製剤では、セロコンバージョンの頻度が高かった(超過リスク4.2%; P<0.05)。
結論:本試験は、HHV-8が輸血によって伝播する強力なエビデンスを示す。伝染リスクは、血液の保存期間が長くなるほど低下する可能性がある。

使用上の注意記載状況・その他参考事項等

赤血球M・A・P「日赤」
照射赤血球M・A・P「日赤」
赤血球濃厚液-LR「日赤」
照射赤血球濃厚液-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
ヒトヘルペスウイルス8型が輸血によって伝播する疫学的証拠が示されたとの報告である。	今後も引き続き情報の収集に努める。

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Transmission of Human Herpesvirus 8 by Blood Transfusion

Wolfgang Hladik, M.D., Sheila C. Dollard, Ph.D., Jonathan Mermin, M.D., Ashley L. Fowlkes, M.P.H., Robert Downing, Ph.D., Minal M. Amin, M.S., Flora Banage, M.B., Ch.B., Esau Nzaro, M.B., Ch.B., Peter Kataaha, M.B., Ch.B., Timothy J. Dondero, M.D., Philip E. Pellett, Ph.D., and Eve M. Lackritz, M.D.

ABSTRACT

BACKGROUND

Whether human herpesvirus 8 (HHV-8) is transmissible by blood transfusion remains undetermined. We evaluated the risk of HHV-8 transmission by blood transfusion in Uganda, where HHV-8 is endemic.

METHODS

We enrolled patients in Kampala, Uganda, who had received blood transfusions between December 2000 and October 2001. Pretransfusion and multiple post-transfusion blood specimens from up to nine visits over a 6-month period were tested for HHV-8 antibody. We calculated the excess risk of seroconversion over time among recipients of HHV-8–seropositive blood as compared with recipients of seronegative blood.

RESULTS

Of the 1811 transfusion recipients enrolled, 991 were HHV-8–seronegative before transfusion and completed the requisite follow-up, 43% of whom received HHV-8–seropositive blood and 57% of whom received seronegative blood. HHV-8 seroconversion occurred in 41 of the 991 recipients. The risk of seroconversion was significantly higher among recipients of HHV-8–seropositive blood than among recipients of seronegative blood (excess risk, 2.8%; $P<0.05$), and the increase in risk was seen mainly among patients in whom seroconversion occurred 3 to 10 weeks after transfusion (excess risk, 2.7%; $P=0.005$), a result consistent with the transmission of the virus by transfusion. Blood units stored for up to 4 days were more often associated with seroconversion than those stored for more than 4 days (excess risk, 4.2%; $P<0.05$).

CONCLUSIONS

This study provides strong evidence that HHV-8 is transmitted by blood transfusion. The risk may be diminished as the period of blood storage increases.

From the Global Acquired Immunodeficiency Syndrome Program, National Center for Human Immunodeficiency Virus, Sexually Transmitted Diseases, and Tuberculosis Prevention, Centers for Disease Control and Prevention, Entebbe, Uganda (W.H., J.M., R.D., F.B.), and Atlanta (T.J.D.); the Division of Viral Diseases, National Center for Infectious Diseases (S.C.D., A.L.F., M.M.A.), and the Division of Reproductive Health, National Center for Chronic Disease Prevention and Health Promotion (E.M.L.), Centers for Disease Control and Prevention, Atlanta; Mulago Hospital (E.N.) and Nakasero Blood Bank (P.K.) — both in Kampala, Uganda; and the Department of Molecular Genetics, Lerner Research Institute, Cleveland Clinic Foundation, Cleveland (P.E.P.). Address reprint requests to Dr. Dollard at the Centers for Disease Control and Prevention, Mailstop G-18, 1600 Clifton Rd., Atlanta, GA 30333, or at sgd5@cdc.gov.

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KAPOSI'S SARCOMA IS THE MOST COMmon cancer associated with the acquired immunodeficiency syndrome (AIDS) worldwide, and human herpesvirus 8 (HHV-8), also known as Kaposi's sarcoma–associated herpesvirus, was identified a decade ago as the causative agent of Kaposi's sarcoma.[1] The burden of Kaposi's sarcoma in Africa is high; in Uganda, Kaposi's sarcoma accounts for half of all reported cancers.[2] In industrialized countries, the seroprevalence of HHV-8 is relatively low (2 to 8%),[3] whereas in sub-Saharan Africa, the seroprevalence of HHV-8 can exceed 50%. The modes of transmission of HHV-8 in Africa remain poorly understood. Studies indicate that the seroprevalence increases throughout childhood and reaches a plateau by adolescence, suggesting that transmission occurs mainly in the community, probably through saliva or other nonsexual routes.[3]

Whether HHV-8 is transmitted by blood transfusion remains controversial.[4] Transmissibility of the virus by this route may be limited by the cell-associated nature of the virus and the low frequency of circulating virus in asymptomatic seropositive persons.[5] Previous studies that did not find evidence of transfusion-transmitted infection enrolled small numbers of patients, most of whom received leukocyte-reduced or acellular blood components.[6-8]

The potential for blood-borne transmission of HHV-8 has been supported by the results of a number of studies. The transmission of HHV-8 has been associated with the use of injection drugs[9,10] and transplantation of infected organs.[11,12] HHV-8 infection has been seen among U.S. patients undergoing cardiac surgery who received multiple units of non–leukocyte-reduced blood.[13] Several case reports of Kaposi's sarcoma have described an association with blood transfusions.[14-17] Infectious HHV-8 has been recovered from a U.S. blood donor,[18] and viral DNA has been detected in blood donors in Africa.[19] The seroprevalence of HHV-8 has increased with increasing numbers of blood transfusions among patients with sickle cell anemia in Uganda.[20]

To evaluate the risk of the transmission of HHV-8 by blood transfusion, we conducted a prospective observational cohort study of transfusion recipients in Uganda, where the seroprevalence among blood donors was 40%,[21] leukocyte reduction was not used, and blood storage time was usually short. If transmission of HHV-8 by transfusion occurs, it is likely to be detected in such a setting.

METHODS

BLOOD DONATIONS

All volunteers who donated blood to the national blood-transfusion service in central Uganda between November 2000 and September 2001 were invited to participate in the study. A sample of blood from each consenting donor was stored for HHV-8 serologic testing. The samples were screened at the Nakasero Blood Bank in Kampala, Uganda, for human immunodeficiency virus (HIV), hepatitis B surface antigen, and *Treponema pallidum* and stored at 4° to 8°C according to routine procedures. Blood units were transfused as whole blood or separated into packed red cells and plasma. Some units were split into pediatric blood packs for use in young children. Leukocyte-reduction filters were not used; the buffy coat was partially removed in packed-cell units.

TRANSFUSION RECIPIENTS

Enrollment and follow-up of transfusion recipients took place between December 2000 and October 2001 at Mulago Hospital, Kampala. Transfusion recipients were eligible for enrollment if their pretransfusion specimen (left over from blood typing and cross-matching) was available and their transfusion could be linked to an identified blood unit. Patients who had received transfusions within the previous 6 months were not eligible. Follow-up visits were scheduled 1, 2, and 4 weeks after transfusion and monthly thereafter for up to 6 months; unscheduled visits also occurred. At enrollment and at each follow-up visit, blood was drawn, demographic data were recorded, and information was obtained about any repeated transfusions.

Transfusion recipients were included in the analysis if their pretransfusion specimen was seronegative for HHV-8 and they completed at least 2 months of follow-up. Patients who received more than one transfusion during the first 7 days of enrollment remained in the analysis, and their transfusion date was considered to be the midpoint between the first and last transfusions. The follow-up period for analysis began on day 10 after transfusion to exclude the earliest seroconversions, which were probably the result of community-acquired infections. Follow-up ended at the

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time of the last visit, death, seroconversion, or receipt of an additional transfusion that was either HHV-8–seropositive or had equivocal results (more than 2 months after transfusion). Transfusions that were repeatedly HHV-8–seronegative were allowed throughout follow-up and did not lead to censoring of data.

LABORATORY PROCEDURES

Specimens were transported daily from Mulago Hospital to the Centers for Disease Control and Prevention (CDC) laboratory at the Uganda Virus Research Institute in Entebbe. The recipient's pretransfusion plasma was tested for antibodies against HIV, and reactivity was confirmed by polymerase-chain-reaction assay for recipients who were 24 months of age or younger.

Testing for HHV-8 antibody was performed at the CDC in Atlanta. Three serologic assays were used: two peptide enzyme immunoassays based on epitopes in the open reading frames 65 and K8.1[22,23] and an immunofluorescence assay based on lytic HHV-8 antigens.[24] The immunofluorescence assay was performed as described previously,[24] except that plasma was diluted to 1:40 for screening and 1:80 for confirmation. Specimens that showed reactivity in two or more tests (with the immunofluorescence assays performed at two different dilutions counted as separate tests) were categorized as positive. Results were categorized as equivocal when more than one of the individual assays showed equivocal reactivity or when the test results were conflicting or incomplete because of depletion of the specimen. For all recipients, the pretransfusion specimen and the linked specimen from the blood donor were tested for antibodies against HHV-8. For recipients who were HHV-8–seronegative before transfusion, the last two follow-up specimens were tested, and if either was positive, all follow-up specimens were tested. The laboratory staff was unaware of the recipient–donor linkages.

For the purpose of analysis, patients who had received a transfusion of any HHV-8–seropositive blood products were categorized as exposed, regardless of the serologic status of additional units. Patients who had received transfusions of HHV-8–seronegative blood alone were categorized as unexposed. Patients who had received blood with equivocal serologic status or a combination of seronegative blood and blood with equivocal serologic status were excluded from the analysis.

STATISTICAL ANALYSIS

The data were double-entered with the use of Epi Info software (version 6.04) and analyzed with the use of Stata software (version 8.0) and SAS software. The primary data analysis evaluated whether the risk of HHV-8 seroconversion was higher among recipients of HHV-8–seropositive blood than among those who received seronegative blood. To allow sufficient time for HHV-8 antibodies to develop in the event of an infection and for any passive HHV-8 antibodies from the donor to be cleared, seroconversion was defined as two or more consecutive HHV-8–seropositive results obtained at least 25 days after transfusion. The date of seroconversion was defined as the midpoint between the last seronegative and the first seropositive visit.

For each recipient, we analyzed the variables of sex, number of children in the household, HIV status, hemoglobin concentration, admission diagnosis, number of transfusions, volume and component (whole blood, packed cells, or plasma) of blood transfused, and duration of blood storage, according to the recipient's exposure status and risk of seroconversion. Continuous variables with a normal distribution were analyzed by Student's t-test, and those with a non-normal distribution were analyzed by the Wilcoxon rank-sum test. Categorical variables were analyzed by Fisher's exact test.

Using survival analysis, we compared the risk of HHV-8 seroconversion over time in the exposed and unexposed groups. We calculated the excess risk of seroconversion as the difference between the Kaplan–Meier survival functions for time to seroconversion in exposed and unexposed recipients, both for the full follow-up period and for the 3-to-10-week period after transfusion that is most likely to be associated with transfusion-transmitted infection. We used Greenwood's formula (SAS software) to calculate the variance of the excess risk as the sum of the variance of the Kaplan–Meier estimates. Confidence intervals were calculated by using a normal approximation. We evaluated recipients' age, the number of blood units transfused, and the duration of blood storage for confounding and an interaction with exposure status. All comparisons were two-sided, and a P value of less than 0.05 was considered to indicate statistical significance.

The study was approved by the Uganda National Council for Science and Technology and

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the institutional review board of the CDC and the Uganda Virus Research Institute. Written informed consent was obtained from all adults and from the parents of children less than 18 years old.

RESULTS

STUDY POPULATION

A total of 6533 patients had pretransfusion specimens and were evaluated for enrollment (Fig. 1). Of these, 72.3% were not enrolled because they did not receive a transfusion, were too ill, declined participation, lived too far away, died, or were discharged before enrollment. The remaining 1811 recipients were enrolled and followed for an average of 4.6 months. The seroprevalence of HHV-8 among the 1761 linked blood donations was 36.2%. The seroprevalence of HHV-8 was 14.5% overall among the enrolled patients before transfusion and increased with age; the seroprevalence was 11.4% among those 2 years of age, 14.9% among those 5 years of age, 21.2% among those 10 years of age, 27.8% among those 20 years of age, and 32.4% among those 30 years of age or older.

Of the 1811 transfusion recipients who were enrolled, 820 were excluded from seroconversion analysis: 266 were seropositive for HHV-8 before transfusion, 17 had equivocal serologic results before transfusion, 101 had received blood from unlinked donors, 362 had insufficient follow-up, 62 had an additional transfusion with a positive or equivocal HHV-8 test result 8 days to 2 months after the first transfusion, and 12 had other reasons for exclusion (Fig. 1). The characteristics of the 991 recipients included in the seroconversion analysis are summarized in Table 1. The recipients tended to be young (median age, 1.5 years; interquartile range, 0.1 to 4.6), and most had received one transfusion (range, one to eight). The majority (79.2%) had received packed red cells, 14.6% had received whole blood, 0.2% had received plasma, and 6.0% had received units of undetermined type. On the average, a recipient had 7 follow-up visits (range, 3 to 12) and was observed for 144 days (Table 1).

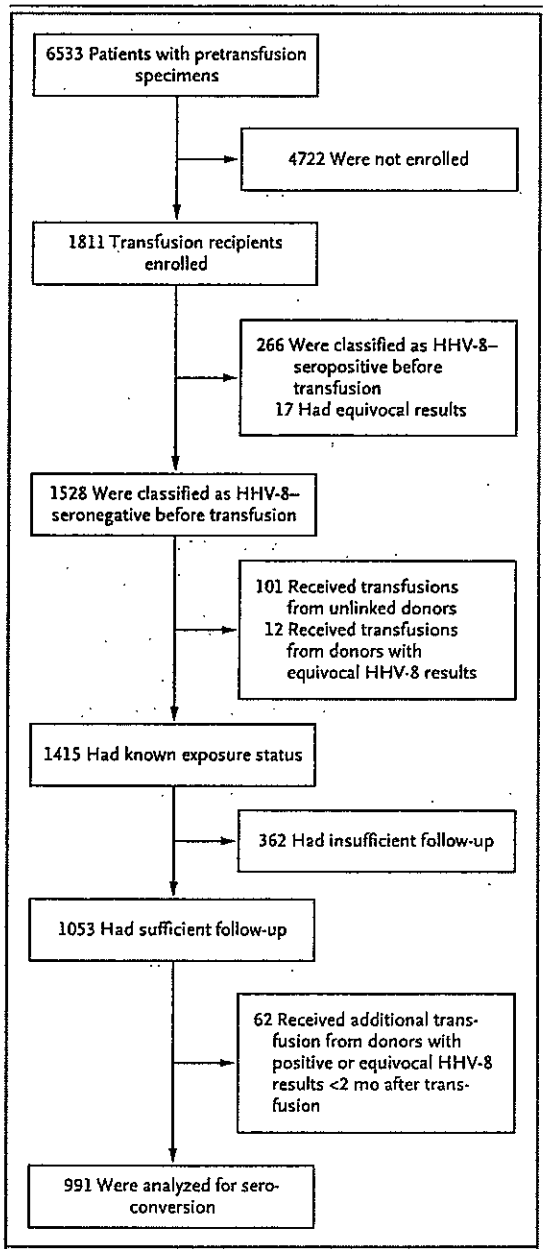

Figure 1. Enrollment and Outcomes.

HHV-8 SEROCONVERSION

Of the 991 patients included in the analysis, 425 (42.9%) received HHV-8–seropositive units and 566 (57.1%) received only HHV-8–seronegative units. Forty-one recipients (4.1%) met the case definition for HHV-8 seroconversion. The excess risk of seroconversion after transfusion with HHV-8–seropositive blood during the 24-week follow-up period was 2.8% (Table 2), suggesting that an estimated 12 of the 425 patients who received HHV-8–seropositive blood were infected by transfusion. The seroconversion risks for various periods after transfusion are presented in Table 2. At week 3, there was no significant difference in risk between exposed recipients and unexposed recipients; however, by week 10, the excess risk of

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Table 1. Characteristics of the Study Patients According to Whether They Were Exposed to HHV-8–Seropositive Blood during Transfusion.*

Characteristic	All Patients (N=991)	Exposed Patients (N=425)	Unexposed Patients (N=566)	Odds Ratio†	P Value
Female sex — no. (%)	515 (52.0)	234 (55.1)	281 (49.6)	1.24	0.09
Median age — yr	1.5	1.6	1.5	—	0.14
Age ≥2 yr — no. (%)	400 (40.4)	188 (44.2)	212 (37.5)	1.32	0.03
HIV-infected — no./total no. (%)	76/758 (10.0)	28/319 (8.8)	48/439 (10.9)	0.78	0.33
Reason for transfusion — no./total no. (%)					
Malaria	828/988 (83.8)	344/423 (81.3)	484/565 (85.7)	0.73	0.07
Obstetrical or gynecologic procedure	46/988 (4.7)	19/423 (4.5)	27/565 (4.8)	0.94	0.83
Sickle cell anemia	48/988 (4.9)	21/423 (5.0)	27/565 (4.8)	1.04	0.89
Hemorrhage	20/988 (2.0)	11/423 (2.6)	9/565 (1.6)	1.65	0.27
Cancer	4/988 (0.4)	1/423 (0.2)	3/565 (0.5)	0.44	0.47
Unknown	42/988 (4.3)	27/423 (6.4)	15/565 (2.7)	2.50	0.004
Median duration of blood storage — days	5.0	5.0	5.0	—	0.73
Median observation time — days	144	144	144	—	0.92
Mean no. of follow-up visits	7.3	7.1	7.3	—	0.17
Mean no. of transfusions per recipient	1.3	1.4	1.2	—	0.001

* Patients who had received a transfusion of any HHV-8–seropositive blood products were categorized as exposed, regardless of the serologic status of additional units. Patients who had received transfusions of HHV-8–seronegative blood alone were categorized as unexposed.
† Odds ratios are for seroconversion in the exposed patients as compared with the unexposed patients.

Table 2. Kaplan–Meier Estimates of Cumulative Risk of HHV-8 Seroconversion after Blood Transfusion.*

Observation Period	Study Population		Patients with Seroconversion		Risk of Seroconversion		Excess Risk (95% CI)†	P Value
	Exposed Patients	Unexposed Patients	Exposed Patients	Unexposed Patients	Exposed Patients	Unexposed Patients		
	number				*percent*			
Wk 1–3	425	566	4	7	0.9	1.2	−0.3 (−1.6 to 1.0)	0.69
Wk 1–10	425	566	18	11	4.2	1.9	2.3 (0.1 to 4.6)	0.04
Wk 1–24	425	566	24	17	5.9	3.1	2.8 (0.1 to 5.5)	<0.05
Wk 3–10	421	559	14	4	3.4	0.7	2.7 (0.8 to 4.6)	0.005
Blood storage‡								
≤4 days	156	—	9	—	5.9	—	4.2 (0.1 to 8.3)	<0.05
>4 days	240	—	4	—	1.7	—		

* Patients who had received a transfusion of any HHV-8–seropositive blood products were categorized as exposed, regardless of the serologic status of additional units. Patients who had received transfusions of HHV-8–seronegative blood alone were categorized as unexposed.
† Confidence intervals (CIs) that do not cross zero indicate statistical significance.
‡ For the analysis of the effect of the duration of blood storage, the total number of exposed recipients was reduced to 396, because recipients who had multiple storage records or conflicting or missing data were not included.

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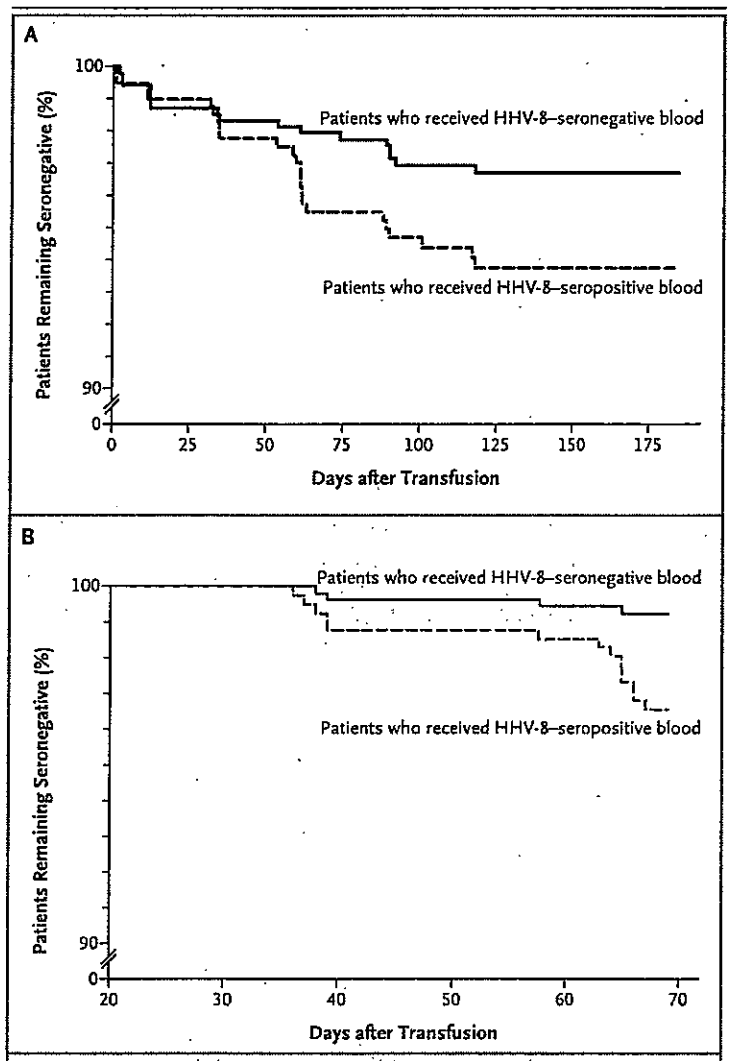

Figure 2. Kaplan–Meier Analysis of the Percentage of Transfusion Recipients Who Remained Seronegative for the Entire 6-Month Follow-up Period (Panel A) and from Week 3 to 10 after Transfusion (Panel B), According to Whether They Were Exposed to HHV-8–Seronegative or HHV-8–Seropositive Blood.

Patients who had received a transfusion of any HHV-8–seropositive blood products were categorized as exposed, regardless of the serologic status of additional units. Patients who had received transfusions of HHV-8–seronegative blood alone were categorized as unexposed. During the entire 6-month follow-up period, there were 24 seroconversions among exposed recipients, as compared with 17 among unexposed recipients ($P<0.05$) (Panel A). During the first 3 to 10 weeks after transfusion, there were 14 seroconversions among exposed recipients, as compared with 4 among unexposed recipients ($P=0.005$) (Panel B).

seroconversion for exposed recipients rose to 2.3% ($P=0.04$). The excess risk among exposed recipients was 2.8% ($P<0.05$) through week 24 and 2.7% for the period from week 3 to week 10 ($P=0.005$) (Table 2 and Fig. 2). Figure 3A shows the time to seroconversion after transfusion for the 41 recipients with conversion and highlights the proportionately greater number of seroconversions among exposed recipients 3 to 10 weeks after transfusion. Figure 3B shows the numbers of exposed and unexposed transfusion recipients according to age group.

The relation between the duration of blood storage and seroconversion was also evaluated for the recipients of HHV-8–seropositive blood. An excess risk of 4.2% was observed among patients who received blood stored for up to 4 days, as compared with those who received blood stored for more than 4 days (Table 2). The risk of seroconversion was not associated with the number of HHV-8–seropositive units transfused, the volume of blood transfused, the type of blood component, the sex or HIV status of the recipient, or the number of children in the recipient's household.

All 41 recipients with seroconversion had been found to be seronegative for HHV-8 when examined on visits before seroconversion. Reversion to seronegative status was not observed, although one patient had equivocal reactivity at the last follow-up visit after having had four visits with seropositive results. Seroconversion did not occur in 12 patients who received seropositive units from donations linked to persons with seroconversion (split donations); however, on follow-up visits, some of them had seroreactivity on one test or were seropositive at one visit and therefore did not meet the criteria for seropositivity or seroconversion.

DISCUSSION

We conducted a prospective cohort study assessing the risk of transfusion-associated HHV-8 infection in a large population of linked blood donors and transfusion recipients. Patients who received HHV-8–seropositive blood were significantly more likely to become infected than were recipients of seronegative blood. The increased risk associated with receiving HHV-8–seropositive blood was most striking among recipients in whom seroconversion occurred 3 to 10 weeks after transfusion, an interval that is similar to the timing of the immune response for other transfusion-transmitted herpesviruses.[25] The risk of seroconversion was also higher among recipients of seropositive units that had been stored with shorter storage times than among recipients of blood that had been stored for more than 4 days

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(excess risk, 4.2%), as has been found with other herpesviruses.[25] Together, these results provide compelling evidence of the transmission of HHV-8 by blood transfusion.

Previous studies have not detected transfusion-associated HHV-8 infection,[6-8,26] probably because of small samples, low seroprevalence of HHV-8 in the donor pool, low[27-29] or intermittent[30] viremia among antibody-positive donors, and deferral of donors at risk for infectious diseases. The design and setting of our study — with a large study population, high seroprevalence of HHV-8 in the community, short duration of blood storage before transfusion, and absence of leukocyte reduction — optimized our ability to detect transfusion-associated transmission of HHV-8 even in the context of a high rate of incident infection, especially in our young study population, who had early and relatively rapid acquisition of HHV-8 (with a seroprevalence of 15% by the age of 5 years).

To account for the fact that HHV-8 serologic assays are not standardized, we used stringent criteria for seropositivity and seroconversion, which provided greater specificity but probably lowered our testing sensitivity and estimates of risk. In this setting, we estimated that 2.8 infections occurred for every 100 seronegative recipients of HHV-8–seropositive blood. A retrospective, cross-sectional study of children with sickle cell disease in the same hospital[20,31] estimated a similar risk of infection. The Nakasero Blood Bank released 52,512 blood units for use in 2001. By extrapolating the findings of our study (and adjusting the seroprevalence of HHV-8 in the patient population to 21% according to age), we estimated that these transfusions may have resulted in approximately 300 HHV-8 infections in 2001.

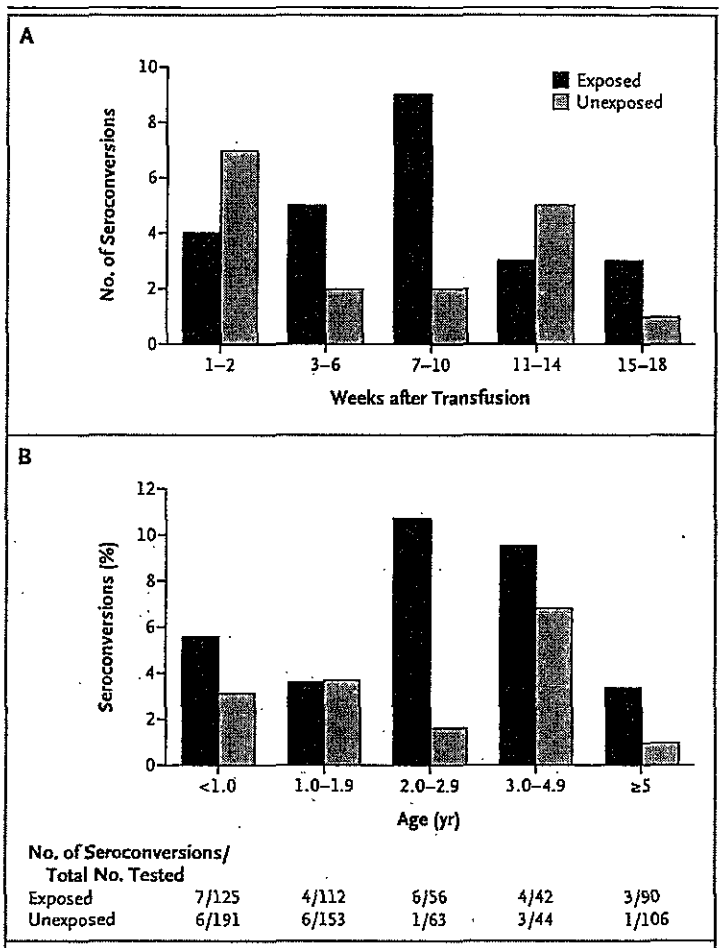

Figure 3. Seroconversion among Patients Who Received HHV-8–Seronegative Blood and Those Who Received HHV-8–Seropositive Blood, According to the Interval between Transfusion and Seroconversion (Panel A) and the Recipient's Age (Panel B).

Patients who had received a transfusion of any HHV-8–seropositive blood products were categorized as exposed, regardless of the serologic status of additional units. Patients who had received transfusions of HHV-8–seronegative blood alone were categorized as unexposed. In Panel A, from 3 to 10 weeks after transfusion, seroconversion was proportionately more common among exposed recipients than among unexposed recipients.

The policy implications of our findings warrant careful consideration. High-throughput serologic assays suitable for blood-bank screening do not yet exist for HHV-8. Nucleic acid testing would not be effective, since most seropositive blood donors tested to date have had very low or undetectable HHV-8 viral loads. Having enough blood available for transfusion is an ongoing public health challenge throughout sub-Saharan Africa; availability would be jeopardized by efforts to eliminate donations from HHV-8–positive donors in high-prevalence areas. Further studies are needed to determine whether leukocyte reduction, longer storage time, or other techniques could reduce the risk of transmission of HHV-8. However, the cost and logistics of leukocyte reduction would probably be substantial barriers in most African countries, and longer storage times might increase the risk of bacterial infection and other adverse events.[32]

The relevance of our findings with respect to the U.S. blood supply may be different from that in Uganda, since the seroprevalence of HHV-8 among blood donors in the United States is low (3.5%).[5] Most blood products in the United States are leukocyte reduced, but the efficacy of this tech-

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nique for reducing the risk of HHV-8 infection has not been evaluated. The risk of transfusion-associated Kaposi's sarcoma would be highest among HIV-infected and other immunocompromised recipients. Selective screening of blood products for immunocompromised populations may be warranted if this approach is found to be effective.

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No potential conflict of interest relevant to this article was reported.

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Department of Health and Human Services.

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医薬品 研究報告 調査報告書

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販売名(企業名)	解凍赤血球濃厚液「日赤」(日本赤十字社) 照射解凍赤血球濃厚液「日赤」(日本赤十字社)					

研究報告の概要	使用上の注意記載状況・その他参考事項等
○日本人でHIV2型の感染初確認　西アフリカで輸血 エイズウイルス(HIV)のうち、世界で感染が広がっている主流のHIV1型とは遺伝子タイプが異なる2型に日本人が感染したことを、厚生労働省のエイズ研究班が確認したことが9月3日分かった。国内滞在中の外国籍の感染者は過去に報告があるが、日本人感染者の確認は初めてである。厚労省は、医療機関や保健所などが実施している検査で2型の感染を見逃さないよう、検査の徹底を求める通知を出した。 HIV2型の感染が確認されたのは、過去に西アフリカで輸血を受けた経験がある男性である。同省は「滞在していた地域では2型が流行しており、現地での輸血が感染原因とみられる」としている。 男性は気管支ぜんそくの症状で国内の医療機関に入院した。治療を受け回復し、既に退院している。入院時の1次検査でHIV感染の疑いが分かり、確認検査で2型と分かった。エイズ研究班を通じ8月に厚労省に情報提供された。 日本での2型の感染確認はこれまで、検査のため来日した韓国籍の男性や、定住者のアフリカ出身の男性ら計3例の報告がある。 厚労省によると、保健所や医療機関で実施されているHIVの1次検査では、1型、2型を問わず感染の疑いを判別する。その後に実施される確認検査では、1型と2型を別々に調べる必要がある。同省は「通常は両方とも調べており緊急対応が必要な状況ではないが、感染がまれな2型の検査が抜け落ちると見逃す恐れがあり、検査の徹底が必要」として、都道府県などに通知を出し、管内の保健所や医療機関に対し注意喚起するよう求めた。	解凍赤血球濃厚液「日赤」 照射解凍赤血球濃厚液「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
HIV2型に西アフリカで輸血を受けたことがある日本人が感染したことが初めて確認されたとの報告である。	日本赤十字社では、輸血感染症防止のため国内外を問わず輸血歴のあるドナーを無期限に献血延期としている。また、国内のHIV感染、AIDS発生の動向について、引き続き情報の収集に努めるとともに、次期NAT試薬についても評価する。

5

別紙1

朋夕刊の記事
:治｜経済｜国際
:会｜運動｜訃報
地域の記事
:知｜岐阜｜三重
:賀｜長野｜福井
:岡｜石川｜富山
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:集ライブラリー

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:ごやデパート情報
:阜スポット情報
:EW商品

:海エリア
地震情報
:災／人災

:コラム
:説
:日春秋
:歩道
:集局デスク
:済人ナウ(口遊録)
:界の街から

:聞音読
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社会

日本人でHIV2型の感染初確認

西アフリカで輸血

エイズウイルス(HIV)のうち、世界で感染が広がっている主流のHIV1型とは遺伝子タイプが異なる2型に日本人が感染したことを、厚生労働省のエイズ研究班が確認したことが3日、分かった。

同省によると、国内滞在中の外国籍の感染者は過去に報告があるが、日本人感染者の確認は初めて。

厚労省は、医療機関や保健所などが実施している検査で2型の感染を見逃さないよう、検査の徹底を求める通知を出した。

同省によると、HIV2型の感染が確認されたのは、過去に西アフリカで輸血を受けた経験がある男性。同省は「滞在していた地域では2型が流行しており、現地での輸血が感染原因とみられる」としている。

男性は気管支ぜんそくの症状で国内の医療機関に入院。治療を受け回復し、既に退院している。入院時の1次検査でHIV感染の疑いが分かり、確認検査で2型と分かった。エイズ研究班を通じ8月に厚労省に情報提供された。

日本での2型の感染確認はこれまで、検査のため来日した韓国籍の男性や、定住者のアフリカ出身の男性ら計3例の報告がある。

厚労省によると、保健所や医療機関で実施されているHIVの1次検査では、1型、2型を問わず感染の疑いを判別。その後に実施される確認検査では、1型と2型を別々に調べる必要がある。

同省は「通常は両方とも調べており緊急対応が必要な状況ではないが、感染がまれな2型の検査が抜け落ちると見逃す恐れがあり、検査の徹底が必要」として、都道府県などに通知を出し、管内の保健所や医療機関に対し注意喚起するよう求めた。

◇徹底検査に尽きる　吉倉広・元国立感染症研究所所長の話

さまざまな国とこれだけ人の行き来がある中で、エイズウイルス(HIV)2型への日本人の感染は当然予想されたものというべきで、保健所や医療機関の検査で見落とさないようにすることに尽きる。2型の今後の広がりを把握するため、HIV感染の監視制度の在り方についても、コストの点を考慮しながら検討を進めていく必要があるだろう。

＜エイズウイルス(HIV)2型＞　世界的に感染の主流となっている1型に対し、遺伝子のタイプが異なり、感染力が比較的弱いとされる。主に西アフリカ地域で流行。フランスやインドなどでも報告例がある。感染しても潜伏期間が長く、症状の進行も遅いとされている。

医薬品
医薬部外品　研究報告　調査報告書
化粧品

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研究報告の概要

＜背景＞
ヒトボカウイルスは、新たに確認されたヒトパルボウイルスで、元々呼吸器疾患の子供の呼吸器分泌物において確認された。ヒトボカウイルス感染の疫学的プロフィールおよび臨床的特徴をさらに調査するため、我々は、幼児および 2 歳未満の子供のヒトボカウイルスを調査した。
＜方法＞
検査機関へ提出された呼吸器検体が RS ウイルス、パラインフルエンザウイルス（1-3 型）、A 型および B 型インフルエンザウイルス、アデノウイルスに対して陰性であった子供について、無症候の子供と合わせ、PCR を用いたヒトボカウイルスのスクリーニングを実施した。呼吸器検体は、2004 年 1 月 1 日から 2004 年 12 月 31 日までに子供から採取した。
＜結果＞
呼吸器検体が検査機関に提出された 425 人の子供のうちの 22 人（5.2%）がヒトボカウイルスの PCR に陽性であり、無症候であった 96 人では陽性者はゼロであった。ヒトボカウイルス陽性の子供の 50%以上に、発熱、鼻漏、咳、喘鳴が観察された。胸部 X 線撮影をした 17 人の子供のうち、12 人（70.6%）が異常所見を示した。ヌクレオチド多型がウイルスカプシド蛋白 1 あるいは 2 の遺伝子に検出された。この試験期間中、2 つの異なるヒトボカウイルス遺伝型が見られた。
＜結論。
ヒトボカウイルスは米国に流行し、幼児と小児において上気道疾患と下気道疾患の両者に関係している。

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) 本剤の原材料となる献血者の血液については、HBs 抗原、抗 HCV 抗体、抗 HIV-1 抗体、抗 HIV-2 抗体、抗 HTLV-Ⅰ抗体陰性で、かつ ALT(GPT)値でスクリーニングを実施している。更に、プールした試験血漿については、HIV-1、HBV 及び HCV について核酸増幅検査(NAT)を実施し、適合した血漿を本剤の製造に使用しているが、当該 NAT の検出限界以下のウイルスが混入している可能性が常に存在する。本剤は、以上の検査に適合した血漿を原料として、Cohn の低温エタノール分画で得た画分から人ハプトグロビンを濃縮・精製した製剤であり、ウイルス不活化・除去を目的として、製造工程において 60℃、10 時間の液状加熱処理及び濾過膜処理(ナノフィルトレーション)を施しているが、投与に際しては、次の点に十分注意すること。

報告企業の意見	今後の対応
新たに確認された呼吸器ウイルスであるボカウイルスの遺伝学的特徴、疫学プロフィールおよび臨床的特徴を紹介した報告である。 ボカウイルスはパルボウイルス科に属するウイルスである。これまで血漿分画製剤によってボカウイルスが伝播したとの報告はないが、原料血漿にボカウイルスは混入し得るのか否か、混入する場合どの程度混入し得るのか等の情報が得られていないため、現時点では安全性評価は困難である。	ボカウイルスに関連する情報については、今後も注視することとする。

6

MAJOR ARTICLE

Human Bocavirus Infection in Young Children in the United States: Molecular Epidemiological Profile and Clinical Characteristics of a Newly Emerging Respiratory Virus

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(See the editorial commentary by McIntosh, on pages 1197–9, and the major article by Manning et al., on pages 1283–90.)

Background. Human bocavirus (HBoV) is a newly identified human parvovirus that was originally identified in the respiratory secretions of children with respiratory tract disease. To further investigate the epidemiological profile and clinical characteristics of HBoV infection, we screened infants and children <2 years of age (hereafter referred to as "children") for HBoV.

Methods. Children for whom respiratory specimens submitted to a diagnostic laboratory tested negative for respiratory syncytial virus, parainfluenza viruses (types 1–3), influenza A and B viruses, and adenovirus, as well as asymptomatic children, underwent screening for HBoV by use of polymerase chain reaction (PCR). Respiratory specimens were obtained from the children from 1 January 2004 through 31 December 2004.

Results. Twenty-two (5.2%) of the 425 children who had a respiratory specimen submitted to the diagnostic laboratory and 0 of the 96 asymptomatic children were found to be positive for HBoV by PCR ($P = .02$). Fever, rhinorrhea, cough, and wheezing were observed in ≥50% of the HBoV-positive children. Of the 17 children who had chest radiography performed, 12 (70.6%) had abnormal findings. HBoV appeared to have a seasonal distribution. Nucleotide polymorphisms were detected in the viral capsid protein (VP) 1/VP2 genes. Two distinct HBoV genotypes circulated during the study period.

Conclusions. HBoV is circulating in the United States and is associated with both upper and lower respiratory tract disease in infants and young children.

Among children, respiratory tract infections are a leading cause of morbidity and mortality worldwide [1]. Respiratory syncytial virus (RSV), influenza viruses, parainfluenza viruses, adenoviruses, rhinoviruses, coronaviruses, and the recently discovered human metapneumovirus likely account for a majority of respiratory tract illnesses. However, for a substantial proportion of respiratory tract illnesses in children, a pathogen cannot be identified, even when sensitive detection methods, such as polymerase chain reaction (PCR), are used [2–4]. This finding suggests that unidentified pathogens may be circulating and causing disease in children.

In 2005, Allander et al. [5] discovered a previously unidentified human parvovirus in respiratory secretions obtained from individuals with clinical features of respiratory tract illness. This novel virus was discovered with a technique that included viral purification (with filtration and ultracentrifugation), PCR amplification of purified viral DNA with primers containing random hexamer-binding sites, and subsequent cloning and sequencing of the amplified DNA products.

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Sequence and phylogenetic analyses demonstrated that this new virus was a parvovirus and was closely related to, although distinct from, bovine parvovirus and minute virus of canines, which are members of the genus *Bocavirus* of the family Parvoviridae, subfamily Parvovirinae. This new virus was designated "human bocavirus" (HBoV).

Parvoviruses are nonenveloped, single-stranded DNA viruses that are among the smallest viruses. The family Parvoviridae contains 2 subfamilies: the Densovirinae subfamily, which infects insects, and the Parvovirinae subfamily, which infects vertebrates [6]. Within the subfamily Parvovirinae are the genus *Erythrovirus* (which contains parvovirus B19, which was previously thought to be the only human pathogenic parvovirus), the genus *Dependovirus*, and the genus *Bocavirus* [7]. Within the genus *Bocavirus*, HBoV is clearly distinct from both bovine parvovirus and minute virus of canines, having only ~42% amino acid identity within the major open reading frames with the 2 viruses [5].

The complete genomic sequences of 2 strains of HBoV have been elucidated. The 5217-base viral genome contains 3 open reading frames encoding (in the 5′–3′ orientation) NS1 (a gene encoding a nonstructural protein), NP-1 (the function of which is unknown), and the viral capsid protein (VP) 1/VP2 overlapping genes, which likely encode the structural proteins of the HBoV virion. Overall, there is relatively little heterogeneity in the HBoV genome of the 2 isolates studied to date, although most of the nucleotide polymorphisms appear to be in the VP1/VP2 genes [5].

Overall, Allander et al. [5] found that 17 (3.1%) of 540 respiratory specimens tested positive for HBoV. These specimens were collected from November 2003 through October 2004 and were obtained from children hospitalized on a pediatric infectious diseases ward at Karolinska University Hospital in Stockholm, Sweden. No other respiratory virus was detected in specimens obtained from 14 of these children. A majority of these children had fever, and, of the 7 children who had chest radiography performed, 6 had abnormal findings [5]. HBoV has been detected in Australia and Japan. Of 324 Australian children with acute respiratory tract infection who had respiratory specimens submitted to a diagnostic laboratory, 18 (5.6%) tested positive for HBoV. These specimens were collected from May through August (i.e., autumn and winter in the Southern Hemisphere) in 2004 [8]. Eighteen (5.7%) of 318 Japanese children with lower respiratory tract infection tested positive for HBoV [9]. The findings of the aforementioned studies suggested that HBoV may be a common human virus; however, because none of these initial studies included a control group of asymptomatic children, it is difficult to draw any conclusions about causation. To determine whether HBoV circulated in New Haven, Connecticut, and to further define the epidemiological profile and clinical characteristics associated with HBoV in young children, we screened respiratory specimens obtained from both symptomatic and asymptomatic infants and children (hereafter referred to as "children") for HBoV.

MATERIALS AND METHODS

Clinical specimens. All respiratory specimens that were screened for HBoV were obtained from children <2 years of age. Two groups of children were screened for HBoV. The first group of children had respiratory specimens submitted to the Clinical Virology Laboratory, Yale–New Haven Hospital (New Haven, Connecticut). These respiratory specimens (nasal swabs, respiratory secretions, and bronchoalveolar lavage fluid samples) were submitted to the Clinical Virology Laboratory from 1 January 2004 through 31 December 2004 and were stored at −20°C after the addition of an equal volume of "viral freezing media" (2× Dulbecco's modified Eagle medium, 200 mmol/L $MgSO_4$, and 100 mmol/L HEPES [pH 7.5]). Specimens originated from children seen in the emergency department, inpatient wards, intensive care units, and the hospital-affiliated outpatient urgent care clinic and were submitted at the discretion of the medical teams. These specimens tested negative for RSV, parainfluenza viruses (types 1–3), influenza A and B viruses, and adenovirus by means of direct immunofluorescence assay (DFA). The second group of children was comprised of asymptomatic control subjects who were seen at the Yale–New Haven Hospital Pediatric Primary Care Center for routine well-child visits. Nasal wash specimens, obtained after the parent or guardian of the child provided written, informed consent, were collected according to standard protocols [10] and were stored at −20°C after the addition of an equal volume of viral freezing media.

Nucleic acid purification and PCR screening. Nucleic acids from each respiratory specimen were extracted by use of QIAamp nucleic acid purification kits (Qiagen), according to the manufacturer's protocol. DNA was subsequently screened for the presence of HBoV by means of PCR performed with HotStar *Taq* polymerase (Qiagen), according to the manufacturer's specification. The primers used in the screening of the respiratory specimens were identical to those described elsewhere by Allander et al. [5]. The forward primer 5′-GACCTCT-GTAAGTACTATTAC-3′ and the reverse primer 5′-CTCTGTG-TTGACTGAATACAG-3′ target a portion of the HBoV NP-1 gene and produce a 354-bp amplicon that corresponds to nt 2351–2704 of the HBoV genome (GenBank accession number DQ000495). PCR amplification cycles were performed at 95°C for 15 min, followed by 35 cycles at 94°C for 1 min, 54°C for 1 min, and 72°C for 2 min, and then by a final extension cycle at 72°C for 10 min [5]. Each set of PCRs contained appropriate negative controls. The authenticity of each amplicon was confirmed by DNA sequencing. For phylogenetic analysis, regions

of the VP1/VP2 genes were amplified and sequenced. The forward primer 5′-GGACCACAGTCATCAGAC-3′ and the reverse primer 5′-CCACTACCATCGGGCTG-3′ target nt 4370–4387 and nt 5172–5189, respectively, of the HBoV genome, and PCR amplification yields a predicted amplicon of 819 bases. The PCR amplification cycle that was used is the same as the one outlined above. Each HBoV-positive specimen was screened for human metapneumovirus by reverse-transcriptase PCR [11].

DNA sequencing and phylogenetic analysis. Sequencing was performed using an Applied Biosystems 3730 XL DNA Analyzer at the W. M. Keck Biotechnology Resource Laboratory, Yale University School of Medicine. Each nucleotide polymorphism that was present in only 1 strain of HBoV was confirmed by sequencing of an amplicon product from an independent PCR. Phylogenetic analysis was performed using Lasergene MegAlign software (version 5.05; DNAstar), with use of the Clustal W alignment method.

Clinical data. The medical records of all HBoV-positive children were reviewed. The demographic and clinical characteristics of each HBoV-positive child were recorded on a standard collection form. Each HBoV-positive specimen was assigned a numerical code, and none of the data presented in the current study includes protected health information. Specimen collection and collection of clinical data were approved by the Yale University Human Investigation Committee.

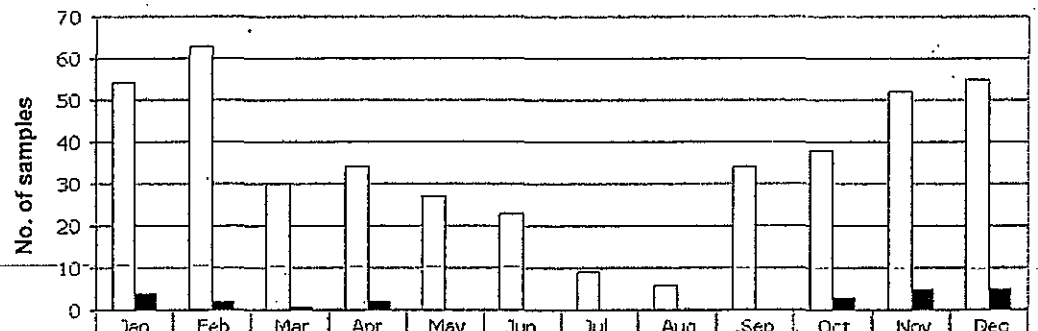
Statistical analysis. Fisher's exact test was used to determine whether the difference in the percentage of HBoV-positive specimens between the 2 groups was statistically significant.

RESULTS

Overall, 1271 DFA-negative respiratory specimens collected from children <2 years of age were obtained from the Clinical Virology Laboratory. We screened every third sample for HBoV. Twenty-two (5.2%) of 425 samples tested positive for HBoV. None of the 96 respiratory specimens obtained from asymptomatic children tested positive for HBoV; this difference between the 2 groups was statistically significant ($P = .02$). Each of the HBoV-positive specimens tested positive for both the NP-1 gene and the VP1/VP2 genes by PCR. None of these HBoV-positive specimens tested positive for human metapneumovirus.

The monthly distribution of HBoV-positive specimens is displayed in figure 1. HBoV was detected in January–April and in October–December. No HBoV-positive specimens were obtained in May–August. During the months in which HBoV was detected, the range of the percentage of HBoV-positive specimens was 3.3% (in March) to 9.6% (in November). Overall, 79 (82.3%) of the 96 specimens collected from asymptomatic children were obtained during months in which HBoV was detected in specimens obtained from symptomatic patients. The age distribution of HBoV-positive children is shown in figure 2. In general, the presence of HBoV was not limited to a specific subpopulation (e.g., young infants) among the children <2 years of age who had screening performed. The youngest HBoV-positive individual was 40 days of age at the time that the respiratory specimen was obtained.

The clinical characteristics of 20 of the 22 HBoV-positive children are shown in table 1. Medical records were available for 21 of the 22 HBoV-positive children. One child whose respiratory specimen was subsequently found to be culture positive for adenovirus was not included in the analysis of clinical characteristics of HBoV infection. Nearly two-thirds of the HBoV-positive children were males. Rhinorrhea (in 18 [90%] of 20 children), fever (in 14 [70%] of 20 children), cough (in 14 [70%] of 20 children), and wheezing (in 10 [50%] of 20



	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
□ Total screened	54	63	30	34	27	23	9	6	34	38	52	55
■ HBoV positive	4	2	1	2	0	0	0	0	0	3	5	5
% positive	7.4	3.2	3.3	5.8	0	0	0	0	0	7.9	9.6	9.1

2004

Figure 1. Distribution of human bocavirus (HBoV)–positive specimens in 2004, by month. The no. of respiratory specimens submitted to the Clinical Virology Laboratory at Yale–New Haven Hospital (New Haven, Connecticut) *(white bars)*, the no. of HBoV-positive specimens *(black bars)*, and the percentage of HBoV-positive specimens collected in each month are shown.

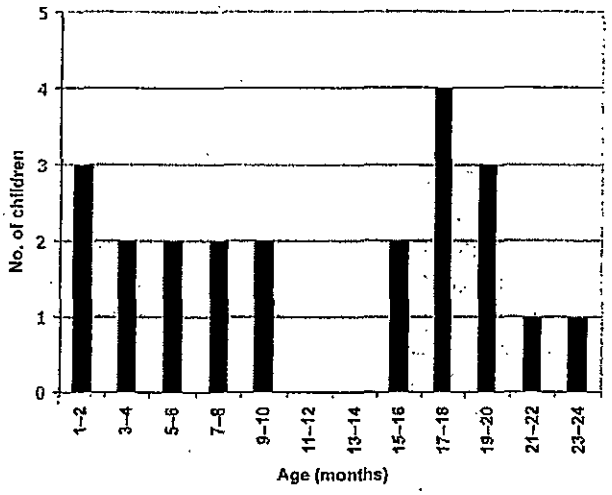


Figure 2. Distribution of human bocavirus–positive children, by age

children) were present in ≥50% of the children. Six (30%) of 20 children had hypoxia (SaO_2, <90%). Of the 17 children who had chest radiography performed, 12 (70.6%) had abnormal findings. Eight of these children had radiographic findings consistent with lung hyperinflation, peribronchial cuffing, or atelectasis; 4 children had evidence of lobar infiltrates, and 1 child had evidence of pleural effusion. Fifteen (75%) of the 20 children had comorbidities, and 12 (80%) of these 15 patients had a history of prematurity or underlying lung disease or both. Complete blood counts were performed for 15 of the 20 children. The mean WBC count was 11,700 cells/μL (range, 7700–15,800 cells/μL), and the mean platelet count was 449,000 cells/μL (range, 245,000–680,000 cells/μL). Bacterial cultures of blood or of blood and urine were obtained for 2 patients (patients 3141 and 4176, respectively). All culture results were negative. Rashes were not reported for any patient.

Five children had diarrhea, and 3 of these children (patients 3429, 3503, and 3559) ultimately had "viral gastroenteritis" diagnosed. For 2 of the 3 children who had viral gastroenteritis diagnosed (patients 3429 and 3503), a stool specimen tested negative for rotavirus antigen. A stool specimen obtained from patient 4168 tested positive for *Clostridium difficile* toxin.

Nosocomial infection occurred in at least 3 children. These children (patients 2879, 4527, and 4549), who were 1, 4, and 6 months of age at the time that their HBoV-positive specimen was obtained, had been hospitalized since birth. The HBoV-positive specimens obtained from the child who was 4 months of age (patient 4527) and the child who was 6 months of age (patient 4549) were collected 4 days apart, and both specimens were collected in late December of 2004. These children received care in separate rooms in the same respiratory care unit, although they received care from the same medical and nursing personnel.

Rare nucleotide polymorphisms were observed in the amplified 354-base portion of the NP-1 gene of the New Haven HBoV isolates (a map of the HBoV genome is shown in figure 3*A*) (GenBank accession numbers DQ652146–DQ652167). The maximum number of nucleotide changes observed for any given sequence, compared with the sequences of the reference HBoV genome (reference strain ST1 [GenBank accession number DQ000495]), was 1. Three strains contained a G→A change at nt 2471, and 4 strains contained a G→A change at nt 2516 (data not shown). Single-nucleotide polymorphisms, which occurred in single-isolate sequences, were observed at nt 2585 and nt 2638 of the HBoV genome. None of these nucleotide changes resulted in changes in the predicted amino acid sequence.

Sequence analysis of the VP1/VP2 genes of nearly one-half of the HBoV-positive specimens revealed that the greatest frequency of nucleotide polymorphism occurred in the 3′ third of the gene. Therefore, the sequences of the 3′ third of the VP1/VP2 gene of all HBoV-positive specimens were obtained (nt 4370–5189 of the HBoV genome) (GenBank accession numbers DQ652168–DQ652182). Phylogenetic analysis of these sequences, which is shown in figure 3*B*, revealed that at least 2 distinct genotypes circulated during the study period. The nucleotide sequences of viruses of one genotype were either identical or nearly identical to those of ST1, which is 1 of the 2 HBoV isolates identified by Allander et al. [5]. Likewise, nucleotide sequences of viruses of the second genotype were either identical to or nearly identical to those of ST2 (GenBank accession number DQ000496), the second HBoV isolate identified by Allander et al. [5]. The majority of the nucleotide polymorphisms did not translate into changes in the predicted amino acid sequences. HBoV isolates ST1 and ST2 differ at nt 4823, resulting in either a serine or threonine in the predicted amino acid sequence. The polymorphism at nt 4823 was noted in the New Haven isolates. For the 2 children with nosocomial infection whose samples were obtained 4 days apart, the nucleotide sequences were identical in both NP1 and VP1/VP2 (figure 3*B*, *arrows*). The sequences of these 2 isolates were also identical to those of other isolates that circulated during the same time of year and to those of isolates that circulated earlier in the year.

DISCUSSION

HBoV was detected in 5.2% of children who were <2 years of age and for whom a respiratory specimen submitted to a diagnostic virology laboratory was found to have DFA results that were negative for RSV, parainfluenza viruses (types 1–3), influenza A and B viruses, and adenovirus. The percentage of HBoV-positive specimens was similar to that noted in the limited numbers of clinical studies of HBoV infection [5, 8, 9]. It is unlikely that our findings were the result of PCR contami-

Table 1. Clinical characteristics associated with human bocavirus (HBoV) infection in children <2 years of age.

Patient[a]	Date when HBoV+ specimen was obtained	Age in months, sex	Fever[b]	Chest radiography finding(s)	Diarrhea	Wheeze	Cough	Rhinorrhea	Hospitalization[c] (duration, in days)	Hypoxia[d]	Comorbidity
2864	2 Jan 2004	17, F	+	A (RUL)/cuff	−	+	+	+	+ (5)	+	Rec bronch/atopia
2879	3 Jan 2004	2, F	−	Negative	−	−	−	+	+ (40)	−	Prem/BPD
2908	6 Jan 2004	20, M	+	I (RML)/hyp	−	+	+	+	+ (2)	−	Seizure/asthma
2942	10 Jan 2004	2, F	+	Cuff	−	−	+	+	−	−	CF
3141	5 Feb 2004	4, F	+	Negative	−	+	+	+	+ (3)	+	None
3429	15 Mar 2004	15, F	+	Cuff	+	−	+	+	+ (6)	−	MRCP/OSA/HepC
3503	11 Apr 2004	2, M	+	NP	+	−	−	+	+ (2)	−	None
3559	23 Apr 2004	7, M	+	Hyp	−	−	+	+	−	−	None
3963	1 Oct 2004	19, M	+	NP	−	+	+	+	−	−	Prem/BPD/RAD
4032	16 Oct 2004	19, M	+	A (Ling, LLL, RUL)	−	+	+	+	+ (17)	+	VCD/MRCP/Prem
4080	24 Oct 2004	17, M	−	Hyp	+	+	+	+	+ (2)	+	None
4164	6 Nov 2004	18, M	+	Negative	−	−	+	+	−	−	CHD
4168	7 Nov 2004	15, M	+	Cuff	+	−	−	+	+ (3)	−	None
4176	8 Nov 2004	22, F	+	I (RUL)	−	+	+	+	+ (1)	+	Eczema/recurrent skin abscess
4290	25 Nov 2004	10, M	+	I (RUL, perihilar)	+	+	+	+	+ (1)	−	Asthma
4362	4 Dec 2004	24, F	−	Negative	−	+	+	−	+ (3)	+	AOM, asthma
4411	9 Dec 2004	9, M	+	NP	−	−	−	+	−	−	Eczema
4419	9 Dec 2004	7, M	+	I (perihilar)/hyp	−	+	+	+	+ (1)	NP	None
4527	27 Dec 2004	4, F	−	Negative	−	−	−	−	+ (136)	−	Prem/BPD/trach
4549	31 Dec 2004	6, M	−	Effusion, A (RUL, LUL)	−	−	−	+	+ (221)	−	Prem/BPD/trach

NOTE. Patients are sorted by the date when the HBoV specimen was collected. The medical record for 1 of the 22 HBoV-positive children was not available. Adenovirus was cultured from the respiratory specimens obtained from 1 child, and this child was not included in the analysis. A, atelectasis (with the location of atelectasis shown in parentheses); AOM, acute otitis media; BPD, bronchopulmonary dysplasia; CF, cystic fibrosis; CHD, congenital heart disease; cuff, peribronchial cuffing; I, infiltrate (with the location of the infiltrate shown in parentheses); HBoV+, human bocavirus positive; HepC, hepatitis C virus positive; Hyp, hyperinflation; Ling, lingual; LLL, left lower lobe; effusion, pleural effusion; MRCP, mental retardation and cerebral palsy; NP, not performed; OSA, obstructive sleep apnea; Prem, history of premature birth; RAD, reactive airways disease; rec bronch, recurrent bronchiolitis; RML, right middle lobe; RUL, right upper lobe; trach, tracheostomy; VCD, vocal cord dysfunction; +, present; −, absent.

[a] Patient nos. also appear in the phylogenetic analysis in figure 3.
[b] Temperature >38°C.
[c] Patients 2879, 4527, and 4549 had been hospitalized since birth.
[d] SaO_2, <90%.

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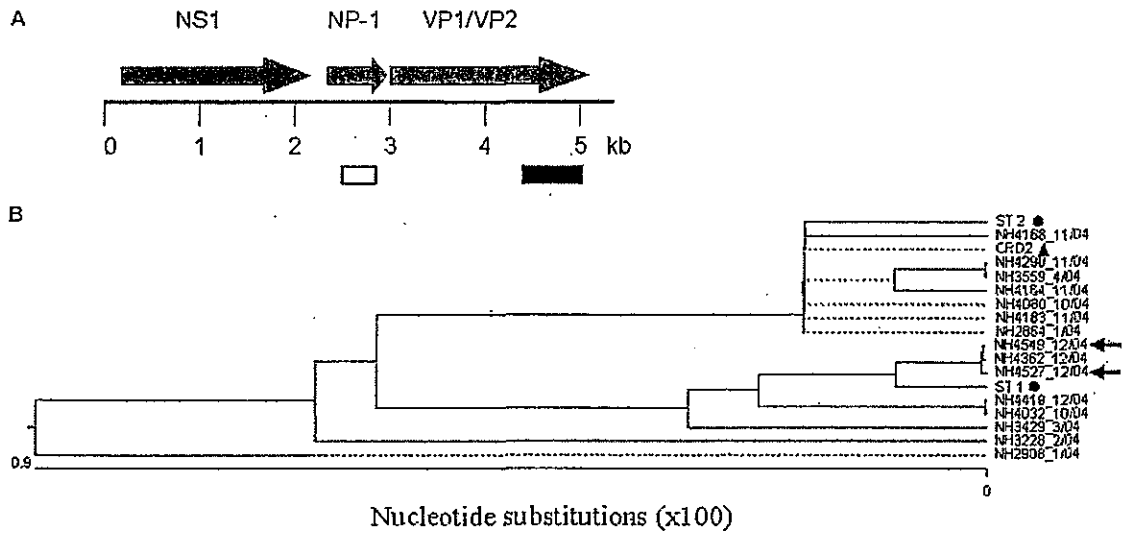

Figure 3. *A,* Map of the human bocavirus (HBoV) genome. The putative open reading frames of the HBoV genome are shown above the map. A portion of the NP-1 gene *(white box)* was targeted during screening for HBoV in respiratory specimens. Phylogenetic analysis was based on sequences of the 3′ third of the viral capsid protein (VP) 1/VP2 genes (nt 4370–5189 of the HBoV genome) *(black box). B,* Phylogenetic analysis of HBoV isolates. The sequences of the New Haven (NH) isolates, the patient nos., and the month of acquisition of each HBoV-positive specimen (month/year) are shown. HBoV isolates recovered from 2 children with nosocomial infection whose respiratory specimens were collected 4 days apart are denoted by arrows. •, Initial strains of HBoV (ST1 and ST2) identified by Allander et al. [5]; ▲, HBoV isolate from St Louis, Missouri (CRD2). For figure clarity, not all New Haven isolates were included in the phylogenetic analysis. The HBoV sequences that were omitted were identical to at least one of the strains shown in the figure.

nation. Each HBoV-positive specimen tested positive at least twice by use of independent PCR primers and reactions. Furthermore, each set of PCRs included appropriate negative controls.

Several lines of evidence indicate that HBoV was the agent responsible for the disease observed in HBoV-positive children. All but one of the 22 HBoV-positive children tested negative for other respiratory viruses. Although the DFA and PCR screening tests that were used do not screen for all known respiratory viruses (such common viruses as rhinoviruses and coronaviruses were not included in the screening), and although the sensitivity of DFA for adenovirus is only 70% (one child whose respiratory specimen ultimately tested positive for adenovirus in cell culture was found to be negative for adenovirus by DFA), it is unlikely that another respiratory virus was present in 21 HBoV-positive specimens. Furthermore, none of the 96 asymptomatic children who had screening performed tested positive for HBoV. One potential explanation for the absence of HBoV in the asymptomatic children was that those children were selected and underwent screening during months (May to September) of the year-long study period in which HBoV apparently was not circulating. However, this was not the case. The respiratory specimens of 82.3% of asymptomatic children were collected in January–April and in October–December, the months during which HBoV was detected in specimens collected from symptomatic children.

The screening of respiratory specimens submitted to a diagnostic laboratory has potential shortcomings, not the least of which is that there are no specific criteria used for sample collection. However, there are potential benefits to this approach. Screening is not limited to hospitalized children, as has been the case in other studies of HBoV infection [5]. Because respiratory specimens are often collected and screened for reasons other than the detection of respiratory tract disease (e.g., for the identification of the source of a fever), other manifestations of HBoV-associated disease not limited to the respiratory tract may be detected. Indeed, 5 of the HBoV-positive children had diarrhea, and 3 of these 5 children (2 children were hospitalized) had viral gastroenteritis diagnosed. Our study was not designed to evaluate the potential role of HBoV in gastrointestinal disease. However, both bovine parvovirus and minute virus of canines, the other 2 members of the genus *Bocavirus* (HBoV is the third member of this genus), cause enteric disease in their natural host [12, 13]. The potential role of HBoV in enteric disease will require further investigation.

Our data suggest that HBoV may have a seasonal distribution. All of the HBoV-positive specimens were collected in fall, winter, and early spring (although only a relatively few specimens obtained in July and August were screened, and, therefore, it is not possible to draw any conclusions about seasonality from our data). Nonetheless, this finding is in agreement with the findings of other studies of HBoV. In the 1-year study by

Allander et al. [5], 16 of the 17 HBoV-positive specimens were collected from December 2003 through April 2004. Of the 18 HBoV-positive specimens identified in a Japanese study, 17 were collected from January through May [9]. Likewise, HBoV was detected in Australian children during the fall and winter months [8]. Erythema infectiosum (i.e., fifth disease), caused by parvovirus B19 (which, before the discovery of HBoV, was the only known human parvovirus to be associated with a specific disease), is also seasonal, although occurrence of the disease peaks in the spring and summer [14].

Nosocomial infection was observed in at least 3 children who had been hospitalized since birth. Two of these children, whose HBoV-positive specimens were obtained 4 days apart, were apparently infected with the same strain of virus. This strain was detected in other children in the same and in different periods of the year. These children were hospitalized on the same hospital ward at the same time. Because the mode of transmission of HBoV is unknown, it is impossible to determine, at this point, how these children became infected with HBoV.

Our initial sequencing efforts focused on a portion of the NP-1 gene of the New Haven isolates of HBoV. Rare nucleotide changes were observed in NP-1, and none of these polymorphisms resulted in amino acid changes. On the basis of the sequencing of 2 isolates, Allander et al. [5] found that nucleotide polymorphisms were most common in the VP1/VP2 gene of HBoV. Therefore, we hypothesized that sequencing of the VP1/VP2 gene of the New Haven isolates would allow for the most robust phylogenetic analysis. We sequenced the VP1/VP2 gene of ~50% of the isolates and found that the majority of nucleotide changes occurred in the 3′ third of the VP1/VP2 cassette. Therefore, we sequenced the 3′ third of the VP1/VP2 gene of all New Haven isolates. Although nucleotide polymorphisms were infrequent, there appeared to be at least 2 strains of HBoV circulating. A polymorphism in VP1/VP2 was observed at nt 4823 in the HBoV genome. This polymorphism resulted in either a serine or a threonine in the predicted amino acid sequence. This polymorphism was also present in ST1 and ST2, the original isolates identified by Allander et al. [5]. Our findings indicate that the 2 genotypes of HBoV identified in New Haven are remarkably similar to the genotypes of the initial strains of HBoV identified in Sweden, and this suggests that the nucleotide sequences (of the NP-1 and VP1/VP2 genes, at least) are highly conserved among viruses circulating in different locations.

In conclusion, our data demonstrate that HBoV is circulating in the United States. Furthermore, our data suggest that HBoV is the etiological agent responsible for both upper and lower respiratory tract disease in infants and young children. Additional studies are required to completely define the epidemiological profile of this newly recognized pathogen.

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医薬品 研究報告 調査報告書

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研究報告の概要	使用上の注意記載状況・その他参考事項等
○クロイツフェルトヤコブ病の遡及調査:最新報告 背景:英国は輸血により感染したと考えられる変異型クロイツフェルト・ヤコブ病(vCJD)を3例報告しており、一番最近の症例は2006年に発症している。本試験は、1995年に米国の大規模血液供給システムならびに米国血液センターと共同でCJD供血者・受血者の特定を行っている米国疾病対策予防センター(CDC)により開始された。 目的:本試験の目的は、血液製剤の輸血による古典的CJDの伝播リスクの分析および特定を支援することである。 方法:米国血液センターや家族からの報告により、供血後に古典的CJDを発症した個人を特定した。血液センターは血液成分を受領した病院を探し出し、該当病院は血液成分の受血者を特定した。受血者は、国民の死亡索引(National Death Index、NDI)および必要であれば他のデータベースを用いて追跡を行った。受血者のフォローアップ調査は年1回ベースで行い、死亡(特にCJD関連死)についてNDIデータベースを検索し、死亡証明書の調査もいくつか行った。 結果:2006年2月までに、古典的CJDで死亡した供血者31名が試験に登録された。384名の受血者が特定され、合計1790人年の追跡を行った。1790人年の内訳は、生存者100名が1150人年、死亡者273名が606人年、追跡不能者11名が34 人年であった。輸血を受けてから5年以上生存した受血者は138名であった。これらの長期生存者の追跡は、計1569人年であった。138名中93名は最新報告時も生存し(1142人年)、42名は死亡(404人年)、3名は追跡不能であった(23人年)。長期生存者138名のうち7名は輸血後21年以上生存した。NDI調査によれば、2003年まではCJD発症患者はいない。さらに2名CJDの供血者が報告され、調査中である。 結論:現在実施中である本試験は、古典的CJDが輸血を介して受血者に伝播したという証拠を示さなかった。	人全血液CPD「日赤」 照射人全血液CPD「日赤」 人全血液-LR「日赤」 照射人全血液-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
供血後に古典的CJDを発症した個人を特定し、受血者の追跡調査を行ったところ、古典的CJDが輸血を介して受血者に伝播したという証拠は示されなかったとの報告である。	今後も引き続き、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。

Results: In a total of 1728 blood samples from university or technical school students, 14 samples (0.8%) were found positive for HBsAg, whereas 75 samples (4.34%) were positive for anti-HBc. 15 (20%) out of these anti-HBc positive samples contained very low titre of anti-HBs (<100mIU/ml) and 14 serum samples (18.67%) had no protective antibodies against HBV and were characterized 'anti-HBc-only'. From the group of immigrants, 3 donors were HBsAg positive and totally 37 serum samples tested positive for anti-HBc. 12 samples out of the 37 anti-HBc positive (32.43%) were described as 'anti-HBc-only', since they had no anti-HBs antibodies. All blood components having the 'anti-HBc-only' profile were discarded.
Conclusions: It has previously been described that HBV can be transmitted by anti-HBc-only blood components or organs. Preliminary data of this study suggest that the percentage of anti-HBc-only donors in Greece appears to be increased, especially among the group of immigrants, signifying that immigration from less to more developed countries could contribute to reemergence of a number of infectious diseases. Experiments are underway to determine the presence of HBV DNA in these serum samples, verifying the infectivity of the blood components.

01.3 Blood Safety - TTD - TSEs

P-086
HIGH RATE OF VCJD TRANSMISSION IN MICE BY INTRAVENOUS INOCULATION OF WHOLE BLOOD

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Background: Variant Creutzfeldt-Jakob disease (vCJD), a newly emerged disease resulting from animal-to-human transmission though dietary exposure to bovine spongiform encepahlopathy, belongs to the group of transmissible spongiform encephalopathies (TSE)/prion diseases. Patients with vCJD accumulate TSE infectivity and disease-associated prion protein (PrPd) in lymphoreticular tissues more extensively than patients with classical CJD. These findings indicate that blood may also carry higher levels of infectivity. Recently, three cases of possible iatrogenic transmission of vCJD through blood transfusion have been reported in the UK, increasing the concern about safety of blood.
Aims: The present study is designed to elucidate the transmission of vCJD by intravenous (i.v.) inoculation of whole blood using a mouse model.
Methods: Swiss mice were inoculated intracerebrally (i.c.) with mouse-adapted vCJD agent. When mice developed clinical disease, they were euthanized and their blood was collected, pooled and inoculated i.v. (0.1 ml per mouse) into an experimental group of 19 mice. A sample of that blood was also diluted 1:4 in physiological saline and inoculated i.c. (30 ul per mouse) into 7 additional mice. Appropriate controls received i.v. blood from healthy animals. Brains and spleens of deceased and euthanized animals were examined for the presence of PrPd using western blotting.
Results: In the group of mice that received i.v. blood from vCJD infected animals, eight out of 19 mice were confirmed to be positive for infection by western blotting: five mice developed clinical signs of the diseases after 260 days and three died earlier from other causes. None of the mice in the i.c. inoculated group or control group developed clinical disease even after being followed up for more than 2 years after inoculation.
Summary and Conclusion: We previously have shown that at the clinical phase of the disease, blood of mice i.c. inoculated with vCJD contains low levels of TSE infectivity, which is present in buffy coat and plasma but not in RBC. We also showed that infection is efficiently transmitted by the i.c. route and the i.v. route both for buffy coat and for platelet poor plasma. In this study using a mouse model of vCJD, we showed that the disease is transmitted at a high rate by i.v. inoculation of whole blood from animals infected with vCJD. Absence of infections in a small group of animals inoculated i.c. with the same but diluted blood sample points to the limitations of an animal model when small numbers of animals are used in bioassay of samples with low levels of infectivity.

P-087
PERFORMANCE CHARACTERISTICS OF PALLS ENHANCED LEUKOTRAP AFFINITY PRION REDUCTION FILTER

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Background and Objectives: Three recent probable cases of transmission of a variant of human Creutzfeldt-Jakob Disease (vCJD) through blood transfusion suggest that the disease can be transmitted through transfusion of blood components from pre-symptomatic blood donors. In the present study, we investigated the performance of a new filter for reducing the levels of infectious prions (PrPSc) in red cell concentrates (RCC).
Materials and Methods: Endogenous Infectivity: A pool of 500mL of whole blood was collected from 263K-strain scrapie-infected hamsters into CPD anticoagulant, processed into either leucocyte-reduced (LR-RCC) or non-leucoreduced RCC (NL-RCC), and then passed through a prion reduction filter. Pre- and post-filtration samples were tested for PrPSc by Western blot and infectivity by inoculation of healthy hamsters Exogenous (Spiking)
Study: Different preparations of scrapie infected hamster brain homogenates containing PrPSc (clarified suspension, microsomal and pure forms) were added to human RCC and then filtered. Levels of PrPSc were determined by Western blot assay. The effects of different red cell preparative procedures on prion removal efficiency of the filter were evaluated. In addition, the effect of prior leucodepletion of 'spiked' RCC on PrPSc removal by the prion removal filter was also assessed.
Results: In the exogenous (spiking) study, the levels of all the different forms of PrPres were significantly reduced in RCC by about 2.5 to 3.7 logs, $p<0.05$. Prior leucodepletion of the RCC with a leucoreduction filter did not significantly reduce the concentration of exogenously spiked PrPSc, $p>0.05$.
Conclusion: The use of this new prion reduction filter should reduce the risk of vCJD transmission through transfusion of RCC, the most widely transfused blood component.

P-088
CREUTZFELDT-JAKOB DISEASE LOOK-BACK STUDY: AN UPDATE

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Background: The UK has reported three cases of probable transfusion-transmission of variant Creutzfeldt-Jacob disease (vCJD), the most recent case occurring earlier this year (2006). The present study was initiated in 1995 by a large US blood supply system and the Centers for Disease Control and Prevention (CDC), who work in collaboration with US blood centers to locate and identify CJD blood donors and

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their recipients.
Aims: The aim of this study is to help assess and define the potential risk of transmission of classic CJD by transfusion of blood products.
Methods: Individuals who donated blood and subsequently developed classic CJD were identified by reports from US blood centers and family members. Blood centers located the hospitals that received the blood components and the hospital identified the recipients of those components. Tracking of these recipients is carried out by using the National Death Index (NDI) and, if necessary, other databases. Follow-up of the recipients occurs on an annual basis by querying the NDI database for deaths, particularly CJD-related deaths, and reviewing some death certificates.
Results: By February 2006, 31 blood donors who died of classic CJD were enrolled in the study. A total of 384 recipients were identified and followed for a total of 1,790 person-years (py). Of the latter, 1,150 py were from 100 survivors, 606 py were from 273 deceased recipients, and 34 py were from 11 recipients who were lost to follow up. 138 recipients survived 5 or more years after their transfusion. These long-term survivors were followed for a total of 1,569 py. Ninety-three of these 138 persons were still alive at last report and accounted for 1142 py, 42 were deceased (404 py) and 3 were lost to follow up (23 py). Seven of these 138 long term survivors lived 21 years or more after their transfusion. (Table 1) Through 2003, based on the NDI search, none of the recipients developed CJD. Two additional CJD blood donors were reported and are under investigation
Conclusions: This ongoing study shows no evidence that classic CJD was transmitted to the recipients through blood transfusion.

Table 1: Summary of Long-Term Survivors

Recipients	Deceased	Survivors	Lost to Follow Up	Total
5-10 Years	34	41	3	78
11-15 Years	4	37	0	41
16-20 Years	3	9	0	12
21+ Years	1	6	0	7
Total	42	93	3	138
Person-Years	403.5	1142.25	23.25	1569

P-089
ABILITY OF THE MACOPHARMA PRION CAPTURE (P-CAPT™) FILTER TO REMOVE BRAIN PRPRES IN LEUKOREDUCED HUMAN RBC

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Background: Transmissible spongiform encephalopathy (TSE) diseases, also known as prion diseases, are neurodegenerative illnesses that can be transmitted by the transfusion of infected blood and blood products. Blood-borne TSE infectivity can harbor undetected for years in the blood of an asymptomatic variant Creutzfeldt-Jakob disease (vCJD) patient who, during this period, could donate blood. Precautionary measures against the spreading of TSE through the blood supply have been implemented, but alone those measures are not sufficient.
TSE pathogen removal is probably one of the most achievable options to date to better safeguard the blood supply. Pathogen Removal and Diagnostic Technologies Inc. (PRDT) developed a strategy in which resins that best adsorbed the TSE causative agent from blood were selected. One resin was shown to capture brain PrPres in red blood cell concentrate (RBC), whole blood, and plasma. The same resin also reduced brain-derived scrapie infectivity by approximately 4 log(10) and more recently we have demonstrated that the resin captured all detectable endogenous infectivity from hamster whole blood as measured by the bioassay. The resin was incorporated into membrane layers that were developed by MacoPharma into a prion capture filter termed P-CAPT™.
Aim: To investigate the performance of the P-CAPT(TM) filter to capture PrPres from scrapie infected hamster brain homogenate mixed in leukoreduced human RBC as assessed by Western blot analysis.
Methods: Hamster brain homogenate infected with the 263K strain of scrapie was added to a unit of leukoreduced (LST1 MacoPharma whole blood filter) human RBC. The unit bag was sterile docked to a P-CAPT™ kit containing an in-line P-CAPT(TM) filter and a transfer bag to collect the treated RBC. The spiked RBC was applied to the P-CAPT™ filter by gravity at ambient temperature according to the manufacturer's instructions. At the end of the run, the filter was extensively washed until most of the red blood cells were removed. The proteins captured by the filter were eluted for Western blot analysis using 3F4 antibody to specifically detect PrP. In some studies, two P-CAPT(TM) filters in series were tested to investigate the level of PrPres removal provided by the filter. Other parameters such as reproducibility of binding and filtration time were also analyzed.
Results: Western blot analysis of the filter-bound proteins indicated that the P-CAPT(TM) filter captured brain PrPres from a unit of human leukoreduced RBC. The binding was reproducible within the experimental variability of the Western blot signal and the filtration time was also reproducible. Additional studies also indicated that the input PrPres was not detected adsorbed in a second, in series filter.
Conclusions: P-CAPT(TM) filters contain a resin that, when tested in column format, captured brain PrPres and brain-derived infectivity as well as endogenous hamster blood infectivity. The studies here investigated whether the same resin incorporated into a filter was still capable of capturing brain PrPres. The results indicated that the resin maintained those properties under the current new format. Furthermore, one P-CAPT™ filter removed all PrP input to the limit of detection of the Western blot.

P-090
IN VITRO EVALUATION OF RED CELL CONCENTRATES AFTER FILTRATION OVER THE NEW COMPOSAFE PR SYSTEM (SYSTEM FOR PRION REDUCTION FROM LEUKOCYTE DEPLETED RCC)

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Background: Although the risk for contamination of RCC with prions is unknown, several companies are developing filters for prion reduction of blood components. The prion filter for RCC recently developed by Pall (LAPRF), was combined with leukodepletion in a Fresenius whole blood system and tested for the in vitro quality of RCC during storage for up to 42 days.
Methods: Whole blood was collected in standard Fresenius in line systems with integrated whole blood filter. The whole blood was either leukoreduced after overnight storage at 22°C (group I; n=8) or within 4 h (group II; n=8) and subsequently separated into plasma and RCC in SAGM. For group I the RCC units were immediately filtered over the prion filter (Composafe Pr) and for group II the RCC were filtered over the prion filter after overnight storage at 4°C. After filtration over the prion filter all RCC were stored at 4°C and sampled at various time points during storage.
Results: The CompoSafe Pr filter had no effect on the total amount of protein in the supernatant of the RCC, but removed factor IX from the supernatant (before 0.14 IE/ml, after < 0.01 IE/ml) which has been indicated as a pseudomarker for prion removal. The RCC in both groups contained 54 ± 4 g Hb (mean±SD), with a combined loss due

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販売名(企業名)	解凍赤血球濃厚液「日赤」(日本赤十字社) 照射解凍赤血球濃厚液「日赤」(日本赤十字社)					

研究報告の概要	使用上の注意記載状況・その他参考事項等
○臓器移植後のシャーガス病ーロスアンジェルス、カリフォルニア、2006年 ロスアンジェルスの心臓移植患者2名で、今年の初めに臓器移植によるシャーガス病伝播が見られた。米国における固形臓器移植によるTrypanosoma cruzi伝播としては4例目と5例目になる。 症例1:2005年12月、64歳の男性が心臓移植を受け、1月に拒絶反応を疑われて強い免疫抑制療法を受けた。2月に食欲不振、発熱、下痢で再入院した。血液培養ではT. cruzi陽性となり、心内膜心筋の生検では無鞭毛型が検出された。血清学検査はT. cruzi抗体陰性、PCRではDNA陽性であり、最近感染したことが示された。治療によって寄生虫血症は解消されたが、移植臓器の拒絶反応で4月に死亡した。遡及調査を行ったところ、臓器ドナーは米国生まれだがメキシコのT. cruzi汚染地域に渡航したことがあった。血清学検査の結果は、RIPAでT. cruzi抗体陽性、IFAで弱陽性だった。これに加えて3人の患者が肝臓と両腎臓を移植されていた。これらの患者はT. cruzi血清陰性でPCRでも寄生虫血症は確認されなかった。 症例2:2006年1月、73歳の男性が心臓移植を受け、2月に発熱、倦怠感、腹部の発疹で再入院した。血液検査ではT. cruzi陽性だった。患者は6月に死亡した。主な死因は心不全で、剖検は行われなかった。他の3人の臓器移植患者では血清学検査陰性でPCRで寄生虫血症は確認されなかった。ドナーはエルサルバドル生まれで死亡時はカリフォルニア在住であり、血清学検査はRIPAで陽性、IFAで陰性だった。いずれのドナーも供血の記録は確認されなかった。	解凍赤血球濃厚液「日赤」 照射解凍赤血球濃厚液「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
ロスアンジェルスの心臓移植患者2名で、今年の初めに臓器移植によるシャーガス病伝播が見られたとの報告である。	日本赤十字社は、輸血感染症対策として献血時に海外渡航歴の有無を確認し、帰国後4週間は献血不適としている。また、シャーガス病の既往がある場合には献血不適としている。今後も引き続き情報の収集に努める。

MMWR Weekly
July 28, 2006 / 55(29);798-800

Chagas Disease After Organ Transplantation --- Los Angeles, California, 2006

Chagas disease is an infection caused by the parasite *Trypanosoma cruzi*. Reduviids (i.e., "kissing bugs") transmit the parasite through infected feces. *T. cruzi* also can be transmitted congenitally and through blood transfusion or organ transplantation. The infection is lifelong if left untreated; the majority of infected persons are asymptomatic, and their disease remains undiagnosed. Although routine serologic testing of organ and blood donors is performed in areas of Latin America where Chagas disease is endemic, no *T. cruzi* screening test is licensed in the United States. However, seroprevalence studies using research tests have documented the presence of *T. cruzi* antibodies in U.S. blood (*1*) and organ donor populations (*2*). This report describes two cases of acute Chagas disease in heart transplant recipients reported by two Los Angeles County hospitals in February 2006. In the United States, one previous report documented *T. cruzi* transmission through solid organ transplantation, in which three organ recipients were infected (*3*).

Case Reports

Case 1. In December 2005, a man aged 64 years with idiopathic cardiomyopathy received a heart transplant. In January 2006, he was treated with enhanced immunosuppression for suspected organ rejection. In February 2006, he was readmitted to the hospital with anorexia, fever, and diarrhea of 2 weeks' duration. A peripheral blood smear revealed *T. cruzi* trypomastigotes, blood cultures were positive for *T. cruzi*, and endomyocardial biopsy specimens contained amastigotes. The patient was interviewed about natural exposures, and organ procurement and transplantation records were reviewed. He had no identifiable risk factors for *T. cruzi* infection (e.g., travel to a country endemic for Chagas disease). He was seronegative for *T. cruzi* antibodies but positive for *T. cruzi* DNA by polymerase chain reaction (PCR), indicating recent infection. After initiation of nifurtimox therapy, his parasitemia rapidly cleared. However, in April 2006, the patient died from complications attributed to acute infection of the transplanted organ.

To identify the source of infection, a traceback was conducted on all blood products transfused to the heart donor and recipient. All available blood donors tested negative for *T. cruzi* antibodies by immunofluorescence assay (IFA) and radioimmunoprecipitation assay (RIPA). However, blood from the organ donor tested seropositive for *T. cruzi* antibodies by RIPA and tested borderline-positive by IFA. The organ donor had been born in the United States but had traveled to a *T. cruzi*--endemic area of Mexico.

Three additional patients received a liver and both kidneys from the same donor. These patients are *T. cruzi*--seronegative by IFA and have no evidence of parasitemia by PCR. They continue to be monitored.

Case 2. In January 2006, a man aged 73 years with ischemic cardiomyopathy received a heart transplant. The patient was readmitted to the hospital in February 2006 with fever, fatigue, and an abdominal rash. A thin blood smear revealed *T. cruzi* trypomastigotes, and blood cultures were positive for *T. cruzi*. Organ procurement and transplantation records were reviewed. The patient had no identifiable risk factors for *T. cruzi* infection. He was seronegative but PCR-positive for *T. cruzi*, indicating recent infection.

The patient's rash and parasitemia resolved after 10 days of nifurtimox treatment. Serial endomyocardial biopsies did not reveal trypanosomes, and he remained seronegative by IFA for *T. cruzi*. The patient died in June 2006. The primary cause of death was cardiac failure; no autopsy was performed.

he source of infection was investigated with the same methods used for case 1. All available blood donors tested eronegative for *T. cruzi*. The organ donor, who had been born in El Salvador and was residing in Los Angeles at ie time of his death, tested positive for *T. cruzi* antibodies by RIPA but had a negative IFA. Three other patients eceived solid organs from the same donor. These patients are *T. cruzi*-seronegative by IFA and have no evidence f parasitemia by PCR. They continue to be monitored. No record of previous blood donations by either organ onor was found.

eported by: *L Mascola, MD, Acute Communicable Disease Control Program, Los Angeles Dept of Health Svcs; Kubak, MD, Univ of California; S Radhakrishna, MD, Univ of Southern California; T Mone, One Legacy, Los ngeles; R Hunter, California Dept of Health Svcs. DA Leiby, PhD, American Red Cross, Rockville, Maryland. M uehnert, MD, Div of Healthcare Quality Promotion, National Center for Infectious Diseases; A Moore, MD, F teurer, MS, G Lawrence, MPH, Div of Parasitic Diseases, National Center for Preparedness, Detection, and ontrol of Infectious Diseases (proposed); H Kun, ScD, EIS Officer, CDC.*

ditorial Note:

he two cases described in this report are the fourth and fifth cases of reported *T. cruzi* transmission through solid gan transplantation in the United States. The prevalence of infection with *T. cruzi* in the United States varies by gion and might now be higher than previously thought, especially in geographic areas such as Los Angeles ounty, where a substantial proportion of blood and organ donors have emigrated from Chagas-endemic countries ecause organ donors frequently receive blood transfusions, infection can be transmitted to recipients either by ansfusion or transplant. Currently, no policies recommend laboratory screening for *T. cruzi*. Diagnostic tests vailable for research studies have variable sensitivities and specificities, and no licensed screening test exists.

hysicians and laboratorians should maintain a high index of suspicion for *T. cruzi* infection in transplant and ansfusion recipients who exhibit complications of an unknown etiology when more common sources have been cluded. Acute Chagas disease in severely immunocompromised patients is of special concern because the inical course is often severe and rapidly progressive. If Chagas is suspected, manual microscopic examination of eripheral blood smears should be performed. Patients with acute Chagas disease should be treated as early as ossible in the course of the infection. Available treatments include nifurtimox (available from CDC Drug Service, lephone 404-639-3670) or benznidazole (only distributed outside of the United States).

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研究報告の概要

○フランス人供血者におけるシャーガス病スクリーニング検査の実施
背景:仏領ギアナにおけるシャーガス病の有病率増加が判明し、当地における採血中止が決定された。その後、リスクのある供血者を対象に、Trypanosoma cruziスクリーニング検査を行うことが決定された。
目的:4種類のELISA及び1種類のIFA検査の検出能を評価し、リスクのある供血者の適格性基準を定めること。
方法:Bioelisa Chagas、Chagatek、Ortho T.cruzi ELISA Test System ' 1、ELISA Cruzi の4種類のELISAキットの感受性、再現性、特異性を評価した。感受性は15検体の商用パネルと、サンパウロ血液銀行(ブラジル)で3種類の検査法で陽性となった36検体のパネルを使用して評価した。再現性は低いS/CO ratioの陽性検体(8コピー/1日、異なる3日間)を検査することで評価した。特異性は南米への渡航歴のないフランス人供血者で評価した。
結果:感受性に関しては、商用パネルの陽性14検体全て及び陰性1検体が4種類の検査法で正確に検出された。ブラジルの供血者パネルでは12検体が陰性となり、ブラジルの検査結果と同じであった。20検体はブラジルの検査及び4種類の検査法で連続して陽性となった。残りの4検体は判定不一致となった。ブラジルの検査結果と比較すると4種類の検査法の感受性は100%で偽陽性検体は認められなかった。2検体はBiokit ELISA及びELISA Cruziで陰性となった。再現性は24コピーのS/CO値の平均の変動係数によって示され、Bioelisa Chagas、Chagatek、Ortho Elisa、Elisa Cruziでそれぞれ6.30%、9.30%、15.7%、22.40%だった。特異性に関しては、これまでの供血者500人の検査では偽陽性検体は発見されていない。特異性の評価は継続中であり、各検査法で2000人を検査するまで行う予定である。
結論:評価対象の4種類のELISAはT. cruziのスクリーニングに適している。フランスの供血者スクリーニングは、生の抗原を使用するものとリコンビナント抗原を使用するものの2種類のELISAを併用し、リスクのある供血者(流行地で出生あるいは母親が流行地で出生した供血者、期間によらず南米への渡航歴のある供血者)に対して実施する。陽性検体と判定不一致の検体はIFAで確認検査を行う。

使用上の注意記載状況・その他参考事項等

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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
Bioelisa Chagas、Chagatek、Ortho T.cruzi ELISA Test System ' 1、ELISA Cruzi の4種類のELISAキットの感受性、再現性、特異性を評価したところ、T. cruziのスクリーニングに適していると認められたとの報告である。	日本赤十字社は、輸血感染症対策として献血時に海外渡航歴の有無を確認し、帰国後4週間は献血不適としている。また、シャーガス病の既往がある場合には献血不適としている。今後も引き続き情報の収集に努める。

P-159
DEATH AFTER TRANSFUSION OF PLATELET CONCENTRATE CONTAMINATED WITH KLEBSIELLA PNEUMONIAE

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Background and Objectives: Platelet concentrates (PCs) are the most common source of transfusion-related sepsis. Approximately 1 in 2,000 to 1 in 3,000 units of PCs are contaminated with bacteria originating from the donor's skin or bloodstream. The risk of acquiring a bacterial infection through transfusion is currently 100 to 1,000 times higher than that of transfusion-associated viral infections.
Study Design and Methods: A 58-year-old patient was transfused with an apheresis platelet concentrate (APC) after bone marrow transplantation. Only five minutes into transfusion, the patient was seized with shivering fits. His temperature rose to 39.8°C and blood pressure fell to 60/40 mmHg. The patient went into septic shock, was intubated and treated in an emergency care unit. He eventually died of multiple organ failure 24 days after infection. Bacterial cultures were taken from the recipient's blood samples and also from samples of the original platelet bags.
Results: Klebsiella pneumoniae subspecies pneumoniae were detected in blood samples, as well as in the original PCs. DNA fingerprints authenticated the identity. Capsule type was determined as K62. The bacterial number exceeded 108 CFU/ml 24 hours after spiking with an inoculum of 1-10 CFU/ml, which demonstrated very rapid growth kinetics. LPS concentration also increased to 1 µg/mL. The bacterial strain was neither resistant to common antibiotics nor 70% isopropyl alcohol.
Conclusion: Bacterial infection remains a risk in transfusion medicine. Screening methods or pathogen inactivation methods should add significantly to blood safety.

01.8. Blood Safety - TTD - Parasites

P-160
IMPLEMENTATION OF CHAGAS DISEASE SCREENING IN FRENCH BLOOD DONORS

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Background: Chagas disease is endemic in Latin America. A French government survey showed an increase in the prevalence of the disease in the French Guyana and led to the decision of halting blood collection in this French overseas territory. Thereafter the decision was made to implement trypanosoma cruzi screening in the French blood donors in a targeted at risk population.
Aims: Evaluate the analytical performances of 4 ELISA and an IFA assays and define the criteria of at risk donor eligibility.
Methods: We evaluated the analytical sensitivity, reproducibility and specificity of 4 ELISA kits: Bioclisa Chagas (Biokit, Spain), Chagatek (Lemos, Argentina), Ortho T.cruzi ELISA Test System ' 1 (Ortho, USA) and ELISA Cruzi (BioM rieux, France). The samples were dispensed with an automated pipetting instrument (Microlab AT, Hamilton) and the assays processed according to the manufacturer's instructions, on a microplate processing automated instrument (Summit, Ortho, France). The sensitivity was evaluated with a set of panels: a commercial panel of 15 samples (14 positives and one negative, BBI, USA) collected over 5 countries of Southern America and a 36-sample panel selected from a larger set of positive samples tested with 3 assays by the Sau Paulo blood bank (Brazil): ELISA Bioschile, Abbott, IHA, Biolab Brazil, and IFA Imunocruzi, Biolab Brazil. Reproducibility was assessed by testing a positive sample with a low S/CO ratio (8 replicates per day, during 3 different days). The specificity is evaluated on French blood donors who never had been in Southern America before.
Results: Regarding clinical sensitivity all the positive samples of the BBI panel (14/15) as well as the negative sample were accurately detected by the 4 assays . With regard to the Brazilian donors panel, 12 samples were found non reactive by the 4 assays, as well as the Brazilian assays. Twenty samples were consistently reactive with both Brazilian assays and the 4 evaluated assays. The results of the 4 remaining samples were discrepant. Based on Brazilian results, the sensitivity of the 4 assays is 100 %, no false negative sample was found. Two equivocal samples were found negative by both Biokit ELISA and ELISA Cruzi.The reproducibility was expressed by coefficient of variation on the average of S/CO values of the 24 replicates. It was 6.30 %, 9.30 %, 15.7 % and 22.40 % for Bioelisa Chagas, Chagatek, Ortho Elisa and Elisa Cruzi, respectively. As for the specificity, no false positive sample was found on the first 500 donors tested with the 4 assays. The specificity evaluation is still ongoing, up to 2000 donors tested with each assay.
Conclusions: The 4 evaluated ELISA are suitable for T. cruzi screening. Blood donor screening in France will be performed with 2 simultaneous ELISA tests, one with crude antigens and the other one with recombinant antigens. Positive samples will be confirmed with IFA as well as discrepant samples. Screening will be performed in at risk donors: people born in or from mother born in an endemic area and donors traveling to Southern America, regardless the stay lasting.

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CORRELATION BETWEEN THE SPECIFIC SERUM IMMUNOGLUBULINES (IGE,IGG) WITH EOSINOPHILIA IN CYSTIC HYDATIDOSIS PATIENTS

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Introduction: Cystic hydatidosis is recognized as one of world,s zoonosis. This is caused by an infection with the metacestode stage of Echinococcus granulosus parasite . Diagnosis of this disease is important from both healthy and economical point of view . Therefore , This study was evaluated correlation between the specific Igs (IgE and IgG)with eosinophilia in cystic echinococusis patients who were candidated for surgery .
Materials and Methods: In an analytical correlation from study , the blood samples were obtained from 43 hydatidosis patients who were uder operation . The serum of samples were kept in at ' 20 0c. In orther to detection of eosinophilia percent , the peripheral blood samples were prepared from patients and stained with Wright ' Gimssa . The IFA method was carried out for detection of specific antibodies (IgE and IgG) titer . Correlation between specific immunoglubines (IgE and IgG) with eosinophilia , number and location of cysts removed and existence of germinal layer were recorded from each patients and were analyzed by using Spss.
Results: The increasing of specific antibodies (IgE , IgG) titer were observed in all patients sera but , increasing higher in IgE titeration . Results also indicated that specific antibodies titers were higher than in patients with liver cysts in comparison with lungs and liver kidney

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研究報告の概要	使用上の注意記載状況・その他参考事項等
○ジェノタイプ3流行地のヒトエリスロウイルス(パルボウイルス)B19感受性またはB19感染小児受血者に対する輸血の影響 【背景】ヒトエリスロウイルスB19は、血液、血液成分、血漿分画製剤の輸血によって感染し、ほとんどのウイルス不活化法に抵抗性を示す。B19ジェノタイプ3はガーナで蔓延しているが、これに関連した臨床情報は得られていない。 【実験デザインおよび方法】B19ジェノタイプ3の輸血による感染、ならびにウイルス血症を呈した受血者における輸血されたB19抗体の潜在的な影響について評価した。主に急性マラリア性貧血のために輸血を受けた小児を対象に、B19ジェノタイプ3の免疫学的特性を調べた。ジェノタイプ3用に分子学的、血清学的方法を開発し、使用した。 【結果】ガーナの供血者-受血者ペア114組のうち、2件の供血血液にB19 DNAおよび特異的抗体が含まれていたが、感染の証拠は認められなかった。B19免疫グロブリンG(IgG)を含んだ全血は、14名のB19 DNA陽性受血者に輸血された。検出可能レベルのB19IgGを認めた受血者3名は、輸血1～2.3ヵ月後のウイルス血症を排除できなかった。輸血前にVP2に対するIgGを認めなかった受血者10名は、ウイルスを排除できたが、輸血後1～2ヵ月の間B19に対する免疫反応が発現しなかった。検出可能な抗体を生じたのは、少量の特異的IgGを輸血された1名のみであった。 【結論】特異的IgGを伴う低レベルのB19ジェノタイプ3 DNAは、輸血により感染しない。ウイルス排除とB19に対する免疫反応の明らかなダウン・レギュレーションは、輸血された抗体および(または)輸血の免疫変調作用によるウイルス抗原の除去に関連する可能性がある。	解凍赤血球濃厚液「日赤」 照射解凍赤血球濃厚液「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
特異的IgGを伴う低レベルのヒトエリスロウイルス(パルボウイルス)B19ジェノタイプ3 DNAは、輸血により感染せず、ウイルス排除とB19に対する免疫反応の明らかなダウン・レギュレーションは、輸血された抗体および(または)輸血の免疫変調作用によるウイルス抗原の除去に関連する可能性があるとの報告である。	今後も引き続き、ヒトパルボウイルスB19に関する新たな知見及び情報の収集に努める。

Effects of transfusion on human erythrovirus B19-susceptible or -infected pediatric recipients in a genotype 3–endemic area

Armen Parsyan, Emmanuel Addo-Yobo, Shirley Owusu-Ofori, Henrietta Akpene, Francis Sarkodie, and Jean-Pierre Allain

BACKGROUND: Human erythrovirus (parvovirus) B19 is transmitted by transfusion of blood, blood components, and plasma derivatives and is resistant to most viral inactivation methods. B19 genotype 3 is prevalent in Ghana, and no related clinical information is available.
STUDY DESIGN AND METHODS: This study assessed the transmission of B19 genotype 3 by transfusion and the potential effect of transfused B19 antibodies in viremic recipients. Immunological aspects of B19 genotype 3 infection in children mainly transfused for acute malarial anemia were examined. Molecular and serologic methods adapted to genotype 3 were developed and used.
RESULTS: Among 114 donor-recipient pairs from Ghana, two donations contained B19 DNA and specific antibodies, and no evidence of transmission was found. B19 immunoglobulin G (IgG)–containing whole blood was transfused to 14 B19 DNA–positive recipients. Three recipients with detectable levels of IgG to B19 failed to clear viremia 1 to 2.3 months after transfusion. Ten recipients without IgG to VP2 before transfusion cleared the virus but failed to develop an immune response to B19 within 1 to 2 months after transfusion. Only 1 patient who received little specific IgG by transfusion produced detectable antibodies.
CONCLUSION: Low levels of B19 genotype 3 DNA associated with specific IgG are not infectious by transfusion. Viral clearance and apparent down regulation of immune response to B19 may be related to removal of the viral antigens by transfused antibodies and/or immunomodulatory effect of transfusion.

Human erythrovirus (parvovirus) B19 (called B19 in this report) is a 19- to 23-nm-diameter nonenveloped single-stranded DNA virus.[1,2] Its capsid consists of VP2 and VP1 proteins, which are identical, except VP1 has a 227-amino-acid N-terminal extension: the VP1 unique (VP1u) region.[3] Until recently B19 was thought highly genetically conserved but two new genotypes (2 and 3) considered rare were described.[4-7] Far from being rare, genotype 3 was found endemic in Ghana, West Africa.[8] Infection with B19 is common among children, who acquire the infection mainly through personal contact via aerosol or respiratory secretions and develop fifth disease.[9-11] B19 also causes other conditions, such as hydrops fetalis and various forms of anemia (reviewed in Young and Brown[12]).

B19 is transmissible by transfusion of blood, blood components, and plasma derivatives and resistant to most viral inactivation methods.[13-17] Although the seroprevalence of B19 in adult blood donors ranges between 40 and 92 percent depending on age, DNA is detectable in 0.003 to 1.3 percent of donors.[8,14,18-23] The broad range of DNA

ABBREVIATIONS: PBST = phosphate-buffered saline with 0.05 percent Tween 20; S/CO = sample-to-cutoff ratio.

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prevalence reported in the literature might be related to the variations in sensitivity of detection or study populations. Whether or not the association of viral DNA and immunoglobulin G (IgG) prevents infectivity in the transfused blood is a matter of debate. Some data suggest that the low incidence of infection among recipients transfused with B19 DNA–positive components is related to the presence of neutralizing antibodies.[14] Products derived from specific IgG-positive plasma pools containing less than 10^4 geq per mL of B19 DNA were shown to be noninfectious.[13] The potential infectivity of blood components containing concomitant B19 DNA and IgG, however, needs further investigation. This is particularly important, because blood products with viral load below 4×10^3 (geq/mL or IU/mL) but without specific IgG were found infectious.[15,16] In addition, data on transmission, pathogenicity, and immune response to genotypes 2 and 3 are not available.

The present study aimed at assessing the transmission of B19 genotype 3 by blood transfusion and the effect of passive immunity acquired by transfusion on recent B19 infection in young, severely anemic recipients carrying viral DNA. This study was undertaken in a Ghanaian population of pediatric recipients of whole blood collected in an area endemic for B19 genotype 3.

MATERIALS AND METHODS

Study design and sample collection

A prospective study of donor-recipient pairs (n = 114) was conducted from November 2003 to March 2005. The study was approved by the Ethics and Publication Committee of the School of Medical Sciences, Kwame Nkrumah University of Science and Technology, Kumasi, Ghana. Participants or their relatives (when applicable) were informed, and informed consent was obtained. Study population included adult donors and children recipients below 6 years of age, admitted to the Pediatric Emergency Unit of the Komfo Anokye Hospital.

The predominant indication for hospitalization and transfusion was severe anemia related to malaria (93%). At the time of transfusion, hemoglobin levels ranged between 2.8 and 7 g per dL. Each recipient was transfused once with 100 to 200 mL of whole blood negative for antibody to human immunodeficiency virus, hepatitis C virus, and hepatitis B surface antigen[24] according to patient body weight. Posttransfusion samples were collected at home or follow-up visits a mean of 42.5 days after transfusion. Six recipients had a second posttransfusion sample collected approximately 3 months after transfusion.

Detection, quantification, and molecular analysis B19 DNA

Viral DNA was isolated from individual samples as previously described.[8] Detection and quantification of B19 DNA were performed according to a previously described quantitative polymerase chain reaction (PCR).[8] Positive samples or samples reactive in only one replicate were retested in duplicate and confirmed with in-house seminested PCR with a detection limit comparable to the one of the qualitative PCR. The seminested PCR targeted the C-terminal part of the VP1u region and used a PCR system (Expand High Fidelity^{PLUS} PCR system, Roche, Lewes, UK). The first round was performed in 50 µL of reaction with 10 µL of the extracted DNA and 5× reaction buffer with 7.5 mmol per L $MgCl_2$, 200 µmol per L dNTP, 2.5 U of High Fidelity^{PLUS} enzyme blend, 0.4 µmol per L forward, GAPS (5′-ATGGACAGTTATCTGACCACCCCC-3′), and reverse, USTO (5′-GCTGGGGTATTTTTCCGAGGCGT-3′), primers. The second round was performed with the same concentrations of reagents but with 5 µL of the first-round reaction and another forward primer, GAPSi (5′-AGTATTATCTAGTGAAGACTTACACAAGCCTGGG-3′). The cycling conditions for both rounds were denaturation for 5 minutes at 95°C, followed by 35 cycles at 95°C for 30 seconds, 57°C for 40 seconds, and 72°C for 50 seconds, followed by final extension at 72°C for 7 minutes. Only samples positive by seminested PCR were considered confirmed positive. GenBank Accession Numbers of sequenced seminested PCR products are DQ234769, DQ234771, and DQ234774-DQ234789.

Recombinant genotype 3 proteins and immunoassays

IgM to B19 in donors and recipients were tested with parvovirus B19 IgM enzyme immunoassay (EIA; Biotrin International, Dublin, Ireland) according to the manufacturer's instructions.

B19 DNA of genotype 3 (GenBank Accession Number AY582124) previously isolated from a Ghanaian blood donor was used for cloning and expression of B19 genotype 3 proteins in a baculovirus system. The detailed protocol for amplification of VP1 from this sample was described by Parsyan and colleagues.[25] The VP1u region was cloned to baculovirus transfer pBlueBac4.5/V5-His-TOPO vector (Invitrogen, Paisley, UK) and expressed with C-terminal V5/6×His tags in Bac-N-Blue with Sf9 insect cells (Invitrogen), according to the manufacturer's instructions. VP1u was purified by HisTrap HP kit (Amersham Biosciences, Chalfont St. Giles, UK) according to the manufacturer's instructions. VP2 capsids were essentially purified by previously described techniques.[26] In-house EIA with genotype 3 VP2 was developed and used to screen for IgG against nondenatured VP2 capsids (hereafter referred as native VP2). A quantity of 2.5 µg per mL VP2 protein in 100 µL of carbonate-bicarbonate buffer, pH 9.6 (Sigma-Aldrich, St. Louis, MO), was coated on plates (MaxiSorp, Nunc, Roskilde, Denmark) overnight at 4°C. After five washes with 300 µL of phosphate-buffered saline

(PBS), pH 7.4, 0.05 percent Tween 20 (PBST), wells were blocked with 100 μL of PBST plus 4 percent bovine serum albumin (BSA; Sigma-Aldrich) for 2 hours at 37°C. Plates were washed and incubated for 1 hour at 37°C with test plasma diluted 1:100 in PBST plus 1 percent BSA. Following washing as above, plates were incubated at 37°C for 30 minutes with 1:40,000 rabbit anti-human IgG-horseradish peroxidase conjugate (Sigma-Aldrich). After washing, 100 μL of substrate (1-Step Ultra TMB-ELISA, Perbio Science, Cramlington, UK) was added. After 9 minutes, the reaction was stopped by adding 100 μL of 2 mol per L H_2SO_4. Reading was done at 450 nm with a 630-nm reference filter.

Forty Ghanaian children samples previously confirmed negative on repeated testing with the commercial B19 IgG kit (Biotrin International) were used in single well in each plate to determine the assay cutoff, which was defined as the mean OD + 3 standard deviations. Results are expressed as sample-to-cutoff ratio (S/CO). Samples with S/CO of less than 0.9 were considered negative, greater than 1.1 positive, and otherwise equivocal/indeterminate. Averaged S/CO of replicates was used for analysis. Retested samples initially negative or equivocal then equivocal or negative were considered negative. Otherwise, if discrepant with initial test, the retested samples were considered equivocal. Antibody titration was performed with twofold serial dilutions of the sera against NIBSC/WHO international standard for anti-parvovirus B19 (01/602, National Institute for Biological Standards and Control, Potters Bar, UK) calibrated at 77 IU per mL.

For detection of antibodies against denatured (linear epitopes) VP2 and VP1u, in-house Western blotting was developed. Proteins were separated under denaturing conditions by sodium dodecyl sulfate-polyacrylamide gel electrophoresis (10% for VP2 and 12% for VP1u) and transferred to a nitrocellulose membrane. After blocking with the 10× blocking buffer (Sigma-Aldrich) the membrane was washed three times for 10 minutes with Tris-buffered saline, pH 7.4, and 0.05 percent Tween 20. Strips were incubated for 1 hour with 1:100 (for VP2 WB) or 1:50 (for VP1u WB) dilutions of test samples (the optimal dilution was assessed by a dilution series), washed as above, and incubated for 1 hour with goat anti-human IgG Fc fragment antibodies conjugated to alkaline phosphatase (Sigma-Aldrich). After washing, substrate (5-bromo-4-chloro-3-indolylphosphate/nitroblue tetrazolium, Sigma-Aldrich) was added for 6 to 10 minutes. International standard for B19 antibodies (see above) and IgG-positive and negative-plasma samples from Ghanaian blood donors were used as controls. A recombinant extracellular domain of human platelet glycoprotein VI tagged with V5/6×His or calmodulin were used as negative control for reactivity with V5/6×His tag.

TABLE 1. Epidemiologic data of the donor and recipient populations

Variable	Donors	Recipient children, before transfusion
Number of samples	113*	114
DNA-positive†	2 (1.8)	15 (13.2)
Genotype	3	3
IgG-positive	93 (82.3)	9 (7.9)
IgG-negative	15 (13.3)	104 (91.2)
IgG-indeterminate	5 (4.4)	1 (0.9)
Male/female	1.8‡	1.1 (59/55)
Age range	16-59 years‡	0.13-66 months

* One donation was transfused to two recipients.
† Data are reported as number (%).
‡ Extrapolation from general donor population.[27]

RESULTS

Description of study population

This study included complete sets of 114 donor-recipient pairs with 113 donors and 114 recipients (1 blood unit was transfused to two recipients in the study). The epidemiologic details are shown in Table 1. The mean time interval between pretransfusion and first posttransfusion follow-up samples was 42.5 days (range, 10-86 days).

The prevalence of B19 markers in donated blood was 82.3 percent for IgG and 1.8 percent for viral DNA. The two viremic samples identified also contained B19 antibodies. In contrast, B19 IgG prevalence in children was 7.9 percent (n = 9), with four seropositive samples also containing viral DNA. The prevalence of B19 DNA was 13.2 percent. A majority of viremic samples did not contain IgG to native VP2, but 7 contained IgM. The viral load ranged 9.1×10^1 to 1.7×10^6 IU per mL. All 17 B19 DNA–positive strains were of genotype 3. The sample collection dates of 15 pretransfusion viremic recipients were clustered between December and April 2003 to 2004 or 2004 to 2005 (Fig. 2).

Transfusion of B19 DNA–positive blood

B19 DNA was present in two donations (1.8%). Donation 251 contained 5.8×10^2 IU per mL viral DNA, specific IgG to denatured, and native VP2 but no IgM or anti-VP1u IgG (Table 2). Approximately 200 mL of whole blood from this donor was transfused to a 3-year-old boy without viral or serologic B19 markers. No clinical or laboratory evidence of B19 infection was recorded 33 and 94 days after transfusion.

Donation 1599 contained 2.3×10^5 IU per mL B19 DNA and VP2-specific IgM and IgG (Table 2). Blood was transfused to an 18-month-old girl who had evidence of recent B19 infection. Her plasma contained 8.1×10^2 IU per mL viral DNA and IgM but no VP2- or VP1u-specific

TABLE 2. Summary of donor-recipient pairs that contained human erythrovirus B19 DNA

Donor							Recipient before transfusion							
ID	Age (years)	VL*	IgM*	IgG 1-VP2†	IgG 1-VP2‡	IgG 1-VP1u§	Age (months)	Sex	Diagnosis¶	VL	IgM	IgG n-VP2	IgG 1-VP2	IgG 1-VP1u
251	30	5.6×10^2	–	3.05	3+	–	36	M	MA	–	–	0.37	–	–
1599	28	2.3×10^5	+	1.51	2+	±	18	F	MA	8.1×10^2	+	0.32	–	–
227	17	–	–	3.28	3+	±	24	M	MA	2.9×10^5	+	3.32	2+	–
1579	31	–	±	2.33	2+	–	30	M	MA	9.6×10^3	–	3.84	2+	2+
416	52	–	–	1.56	2+	–	36	F	MA	1.7×10^6	+	5.60	3+	3+
748	23	–	–	3.20	3+	±	60	F	MA	1.2×10^6	+	4.24	3+	–
1589	44	–	–	3.18	–	–	5	M	MA	1.7×10^2	+	0.57	–	–
1598	28	–	–	1.85	2+	–	4	F	MA	1.9×10^3	+	0.52	–	–
223	45	–	–	1.30	1+	1+	18	F	MA	6.0×10^5	+	0.37	–	–
1471	19	–	–	1.21	2+	–	60	M	MA	9.1×10^1	±	0.89	1+	–
1597	25	–	–	2.63	3+	–	36	M	SC	8.0×10^3	–	0.92	3+	–
1621	19	–	–	2.83	3+	1+	9	M	MA	2.1×10^5	–	0.44	2+	–
1623	20	–	–	3.80	3+	–	36	M	MA	5.2×10^2	–	0.23	–	–
693	35	–	–	2.64	3+	±	9	M	BL	1.3×10^4	–	0.21	–	–
234	20	–	–	1.92	2+	3+	9	F	MA	4.6×10^4	–	0.25	–	–
1604	18	–	–	0.74	1+	±	30	F	MA	4.5×10^2	–	0.67	–	–

* Viral load expressed in IU/mL.
† IgG n-VP2 = IgG against VP2 by EIA (native conformation); samples with S/CO below 0.9 are considered negative, over 1.1 positive, and 0.9 to 1.1 indeterminate.
‡ IgG l-VP2 = IgG against VP2 by Western blotting (denatured, linear epitopes); for Western blotting 1+ = weak/medium reactivity, 2+ = strong, 3+ = very strong, ± = equivocal.
§ IgG l-VP1u = IgG against VP1u by Western blotting (denatured, linear epitopes).
MA = malaria; SC = sickle cell disease; BL = bleeding disorder of unknown etiology.
¶ PT2 was available in four recipients.
NA = not available; + = positive; ± = equivocal/indeterminate; – = negative.

IgG. Seventy-two days after transfusion, no B19 DNA or specific IgM was detectable but strong IgG response to VP2 and VP1u was found.

Transfusion of B19 IgG–containing blood to B19 DNA–positive recipients

Before transfusion, 15 recipients had detectable B19 DNA in plasma (Table 2). Seven of these children samples contained specific IgM and 3 of them were also positive for B19 IgG. Thus at least 7 of 15 children had evidence of recent B19 infection indicated by the association of viral DNA and specific IgM. Four recipients (1623, 693, 234, and 1604) carried only viral DNA without serologic markers of B19 infection before transfusion. IgG to denatured and native VP2 was detectable in 12 of 14 donor samples. Specific IgG titers in 10 donors in this group ranged between 35 and 76 IU per mL. At a mean of 1.5 months after transfusion, three recipients remained viremic, although at lower levels, and the other 11 cleared B19 DNA (Table 2).

The blood received by the three recipients who remained viremic after transfusion (227, 416, and 1579) contained comparable IgG reactivity to B19 (Table 2). After transfusion, viremia slightly decreased, and all patients either further developed or maintained IgG reactivity to VP1u. IgG response to native VP2 was also retained, but reactivity to denatured VP2 either decreased or became undetectable.

The second group of 11 recipients who were viremic before transfusion no longer carried B19 DNA in the post-transfusion samples. One recipient (748) had high viral load, specific IgM, and relatively strong IgG reactivity to denatured and native VP2. Seven recipients had no IgG to B19 and 3 carried only IgG to denatured VP2. After transfusion, no evidence of development of a specific antibody response to B19 was observed, except for Recipient 1604 who produced significant levels of all types of IgG to VP2. The blood transfused to this patient contained very low levels of IgG to denatured but not to native VP2. In two recipients (234 and 223), who had a second sampling 3 months after transfusion, the serologic pattern remained unchanged. In three recipients (748, 1621, and 1597), who had IgG to VP2 pretransfusion, the reactivity either decreased or became undetectable.

Serology in B19 DNA–negative pairs

Ninety-eight donor-recipient pairs who were B19 DNA–negative in both donor and pretransfusion recipient samples were screened for the presence of anti-B19 IgG by EIA to study the passive transfer of B19 antibodies in the absence of B19 DNA. IgG to VP2 was present in 78 of 97 donors (80.4%) and 5 of 98 children (5.1%) before transfusion. After transfusion, all of anti-B19 IgG–negative recipients transfused with the anti-B19–positive blood remained negative, suggesting that on average 1.3 months

Recipient after transfusion 1 (PT1)						Recipient after transfusion 2 (PT2)					
Days PT1	VL	IgM	IgG n-VP2	IgG 1-VP2	IgG 1-VP1u	Days PT2	VL	IgM	IgG n-VP2	IgG	IgG 1-VP1u
33	–	–	0.19	–	–	94	–	–	0.25	–	–
72	–	–	2.22	2+	2+						
37	4.5×10^3	+	3.98	1+	±	69	6.9×10^3	–	4.27	1+	3+
35	5.1×10^2	–	3.79	–	2+						
35	1.5×10^4	–	4.49	2+	3+						
51	–	–	0.38	±	–						
NA	–	–	0.39	–	–						
47	–	–	0.24	–	–						
38	–	–	0.36	–	–	99	–	–	0.33	–	–
65	–	–	0.30	1+	–						
49	–	–	0.73	2+	–						
NA	–	–	0.49	–	–						
62	–	–	0.25	–	–						
54	–	–	0.38	–	–						
37	–	–	0.24	–	±	97	–	–	0.23	–	–
68	–	–	2.25	2+	±						

after transfusion, passively transfused IgG to B19 was undetectable. This result did not differ from data obtained in DNA-positive pairs (Table 2). To test the hypothesis that relatively low antibody titer and antibody $t_{1/2}$ were responsible for this observation, four medium to high IgG S/CO samples from DNA-negative and -positive recipients before transfusion were matched by age and S/CO and titrated by limiting dilution. Considering the $t_{1/2}$ of transfused specific IgG in samples tested on average 1.3 months after transfusion, and the dilution factor in the recipients' blood stream (4-8 times), a negative result was predicted and observed.

DISCUSSION

This study examined the effects of transfusion on B19 infection in a genotype 3–endemic area. Based on the sequence analysis of the seminested GAPSi-USTO products, it confirms previous data indicating that B19 genotype 3 was prevalent in Ghana (Fig. 1).[8] The vast majority of children received transfusion for treatment of severe anemia related to malaria, a major indication of pediatric transfusion in Africa.[26,29] Both malaria and B19 are etiologic agents of anemia as they target erythroid cells (reviewed Young and Brown[12] and Menendez et al.[30]), and their coexistence might exacerbate anemia, as previously suggested.[31,32] The possibility that this exacerbation could have increased the likelihood that patients sought medical care because of such association has been examined. In one study, a hospital-based control group of children with median age 10.1 years (range, 2 months-16 years) had 7 percent prevalence of B19 DNA.[33] In our population with a median age of 18 months, 13.2 percent of patients were viremic and more than 90 percent had acute malaria. Some degree of malnutrition is usually observed in approximately one-third of the pediatric transfusion recipients in Kumasi. It is possible, if not likely, that the association of primary infection with both B19 and malarial parasites accompanied by malnutrition increased the severity of anemia and the likelihood of hospitalization.

In temperate countries B19 genotype 1 infection is seasonally distributed with the peak of outbreaks ranging from winter to spring.[9-11,18,20] B19 genotype 3 DNA was detected in Ghana between December and April (Fig. 2), which corresponds to the dry season, during which transmissions by aerosol might be increased by a high level of dust particles and resulting coughing. Clustering of young children as in day care settings or domestic playgroups may contribute to spread.

In the adult donor population, 82.3 percent carried B19 IgG indicating recovered infection. Reported seroprevalence in donors ranges between 40 and 92 percent depending on age and country.[8,18-22] The 1.8 percent prevalence of B19 genotype 3 DNA is consistent with previously reported data from Ghanaian blood donors (Table 1).[8] No transfusion-related infection was documented after transfusion of 200 mL blood containing 580 IU per mL B19 DNA and IgG (Table 2). This anecdotal case is consistent with previous reports suggesting that, in the presence of neutralizing antibodies, the risk of transmission by transfusion of blood products containing relatively low level of viral DNA is negligible.[13,14] This conclusion seems applicable to this case of genotype 3 infection. The response of B19 viremic children who received a transfusion from donors carrying IgG antibodies to this virus was heterogeneous. The major feature of a first group of three recipients was the presence of IgG to both denatured and native VP2 at the time of transfusion and the absence of viral clearance approximately 1 or 2 months after transfusion. Despite the presence of spe-

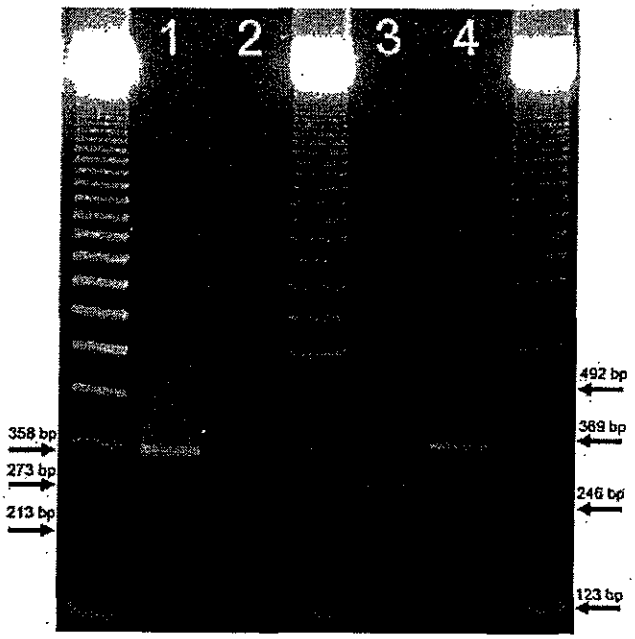

Fig. 1. VP1u amplicons (358 bp) were subjected to *DraI* restriction endonuclease (New England Biolabs, Hitchin, UK) digestion and electrophoresed on 1 to 1.5 percent agarose gels. The expected sizes of digested fragments for genotype 1 are of 213, 85, and 60 bp and for the genotypes 2 and 3 are 273 and 85 bp. To distinguish between G2 and G3, amplicons were sequenced. Lanes 1 and 4 = 358-bp second-round undigested PCR products for B19 genotypes 1 and 3, respectively; Lane 2 = restriction digest of B19 genotype 1 (NIBSC/WHO International Standard), 213-bp product; Lane 3 = restriction digest of B19 genotype 3 (Recipient 416 after transfusion), 273-bp product. The molecular weight of restriction digest fragments are indicated by arrows on the left and of molecular weight markers (123-bp DNA ladder [Invitrogen]) on the right-hand side.

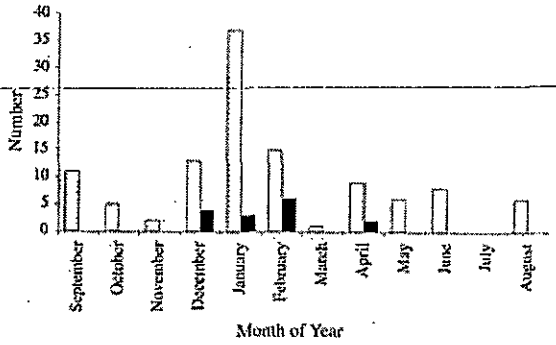

Fig. 2. The month of collection of B19 DNA–negative samples is shown in open bars (n = 113). (■) Time of collection of samples from B19-positive (presumably recently infected) recipients (n = 15).

cific IgG in the recipient and the transfusion of IgG to B19, viremia persisted. This unexpected outcome might be explained by a competition between recipients' and donors' antibodies for the viral antigens. It is hypothesized that at the initial stages of infection with B19 (when viremia is not yet cleared) the neutralizing capacity of antibodies, particularly when produced by young children, might not be very efficient, despite their ability to bind to antigens at the viral surface. Antibodies with binding but poor neutralizing properties were described.[34-36] In this situation, antibodies provided by donor plasma with presumably higher neutralizing capacity might not be able to access neutralizing epitopes on the virions already complexed with host IgG.

The second group of 11 viremic recipients who received specific IgG from transfused blood cleared the virus after transfusion. Clearance of viremia and apparent down regulation of the patients' immune response could be explained by passively transferred immunity to B19. The mechanical clearance of viral particles and antigens from circulation by the passively transfused donor antibodies may have aborted further development of the immune response. The dose of IgG received in 100 to 200 mL of transfused Ghanaian whole blood is considerable, because Ghanaian donors carry 12 to 30 mg per mL IgG (Candotti et al.[8] and unpublished data), ranging between 0.1 and 0.6 g per kg. The role of neutralizing donor IgG in the observed clearance of viremia is indirectly supported by data from Recipient 1604 who, while receiving blood containing no IgG against native VP2 and the lowest reactivity of IgG to denatured VP2, cleared the virus almost 2 months after transfusion and developed a strong IgG response against VP2.

There are, however, alternative or contributing (to the antigen clearance) mechanisms that could be potentially involved in down regulation of the immune response to B19, such as a down regulatory effect of transfusion through a modulatory effect of transfused IgG[37] or other factors present in transfused blood;[38] massive malarial hemolysis and anemia causing temporary blockade or dysregulation of the immune system due to release of cytokines and increased reticuloendothelial activity.[30,39,40] We did not observe clearance of viremia associated to the presence of anti-VP1u, which are considered by some authors the major source of neutralizing activity.[36,41] The presence of neutralizing epitopes in VP2 has been described[34,42] and is corroborated by observations in this study suggesting that anti-VP2 response alone might be sufficient to clear viremia. The significance of antibodies to linear or to native VP2 epitopes deserves some attention. The presence of IgG to linear epitopes of VP2 is considered an indicator of active, recent, or persistent infection.[43-45] The data presented here in children are compatible with this suggestion and support findings indicating that responses to linear epitopes decrease or

disappear when recent infection subsides.[43,45] The prevalence of IgG to denatured VP2 in the adult donors higher than reported might be a reflection of a younger age, increased reexposure, or tissue persistence.[21,43,44]

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医薬品 研究報告 調査報告書

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研究報告の概要	使用上の注意記載状況・その他参考事項等
○マラリア－バハマ、グレートエグズーマ島、2006年5月～6月 カリブ地域においてマラリアはヒスパニオラ島(ハイチ及びドミニカ共和国)を除くすべての島で根絶されていた。しかしながら、マラリアが蔓延していないにもかかわらず、カリブ海の島々は、熱帯性の気候、媒介動物の存在、近接するマラリア汚染国などによりマラリア再侵入の危機にさらされてきた。この懸念は最近のバハマ、グレートエグズーマ島におけるマラリアの流行によって裏付けられた。2006年5月～6月の間に合計19例のマラリア症例が確認された。このうち4例は北米及び欧州からの渡航者のものである。このような輸入症例は、渡航先の国におけるマラリアの問題の存在を明らかにし、現地保健当局の調査の一助となる。3ヶ月間新規症例の報告がなかったため、2006年9月19日、CDCは米国在住の渡航者向けの抗マラリア薬服用勧告を解除した。	解凍赤血球濃厚液「日赤」 照射解凍赤血球濃厚液「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
2006年9月19日、CDCは米国在住のグレートエグズーマ島渡航者向けの抗マラリア薬服用勧告を解除したとの報告である。	日本赤十字社は、8月1日以降、バハマに滞在した場合は帰国(入国)から1年間献血延期としている(帰国(入国)後にマラリアを思わせる症状があった場合は、マラリア感染が否定されるまで)。また、今後も引き続き、マラリア感染に関する新たな知見及び情報の収集に努める。

MMWR Weekly
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Malaria --- Great Exuma, Bahamas, May--June 2006

Malaria in humans is caused by four distinct protozoan species of the genus *Plasmodium* (*P. falciparum, P. vivax, P. ovale*, and *P. malariae*). These parasites are transmitted by the bite of an infective female *Anopheles* mosquito (*1*). In the Caribbean region, malaria has been eliminated from all islands except Hispaniola, the island consisting of Haiti and the Dominican Republic. Elimination of malaria elsewhere resulted from a combination of integrated control measures, socioeconomic development, and close public health surveillance. However, even Caribbean islands where malaria is no longer endemic remain at constant risk for reintroduction of the disease because of their tropical climate, presence of competent malaria vectors, and proximity to other countries where malaria is endemic. This susceptibility was underscored by the recent outbreak of malaria on the island of Great Exuma in the Bahamas; during May--June 2006, a total of 19 malaria cases were identified. Four of the cases, in travelers from North America and Europe, are described in this report; such cases of imported malaria can signal the presence of a malaria problem in the country visited and thus assist local health authorities in their investigations. On September 19, after 3 months with no report of new cases, CDC rescinded its previous recommendation that U.S.-based travelers take preventive doses of the antimalarial drug chloroquine before, during, and after travel to Great Exuma.*

Case 1. On May 24, 2006, a man aged 33 years from the United States received a diagnosis of malaria in a hospital emergency department in Virginia. The patient had intermittent fever, sweats, abdominal discomfort, nausea, and vomiting, which had begun during a May 4--7 visit to Great Exuma, where the patient had stayed in a resort hotel. The patient had no history of exposure to malaria. Blood smears on May 24 indicated *P. falciparum*. After outpatient treatment with chloroquine, changed later to quinine and doxycycline, the patient recovered uneventfully.

Case 2. On June 6, a woman aged 29 years from Germany received a diagnosis of *P. falciparum* malaria in a hospital in Germany. She had experienced fever, headache, nausea, and vomiting since May 30, near the end of a May 18--31 visit to Great Exuma. After her return to Germany, the woman was treated initially with antibiotics for suspected sinusitis. However, her illness persisted, and she was hospitalized on June 6 with high fever and neck stiffness. Diagnostic tests included magnetic resonance imaging of her head, a lumbar puncture to exclude meningitis, and a blood smear that revealed *P. falciparum*. She was treated with artemether-lumefantrine and recovered.

Case 3. On June 16, a man aged 20 years from Canada had *P. falciparum* malaria diagnosed. The man had been born in the Bahamas and had visited friends and relatives there during April 19--June 11, spending most of his time in Georgetown, the most populous city on Great Exuma. On June 14, the man experienced fever and chills and went to an emergency department for evaluation after learning that his cousin had been treated recently for malaria on Great Exuma. The diagnosis of *P. falciparum* malaria was confirmed by blood smear on June 16. He was treated on an outpatient basis with chloroquine followed by atovaquone-proguanil and recovered uneventfully.

Case 4. A man aged 66 years from the United States, who lived on a boat, received a diagnosis of *P. falciparum* malaria on June 19. The man, who had not recently visited any area that was endemic for malaria, stayed in Great Exuma from late April to late May. In early May, he began experiencing fever, chills, sweats, headaches, and fatigue but did not seek medical care; he left Great Exuma to sail to other Bahamian islands. On June 18, on his return to Great Exuma, the patient learned of the outbreak and went the next day to the district medical clinic, where he received a diagnosis of *P. falciparum* malaria. He was treated with chloroquine and primaquine and recovered uneventfully.

fter report of the first case in Virginia, the Bahamian Ministry of Health (MOH) initiated epidemiologic and ıtomologic investigations with the technical assistance of the Pan American Health Organization. MOH also ɜightened mosquito-control activities that were already being conducted on Great Exuma in conjunction with the ahamian Department of Environmental Health Services.

ctive case detection was conducted on Great Exuma during June 6--30; however, no case of malaria was agnosed later than the June 19 diagnosis in case 4. Persons examined at primary-care clinics who had a history ; fever and a temperature of ≥99.0°F (≥37.2°C) and contacts of persons who received diagnoses of malaria were ;reened using thick and thin blood smears stained with Wright's stain. On Great Exuma, 15 persons were ɜtermined infected with *P. falciparum*. Ages ranged from 16 to 66 years (median: 36 years); 84% were males. lost of these patients were residents of the Bahamas, clustered around the areas of Georgetown and Bahama ɔund, and living in close proximity to a community of immigrants from Haiti; most said they had not recently aveled to Haiti or any other area endemic for malaria. All patients were initially treated with chloroquine and ɔxycyline; the latter was subsequently replaced by primaquine to eliminate gametocytes and thus prevent further ansmission. All 15 patients recovered.

parasite prevalence survey was conducted on Great Exuma in a community of immigrants from Haiti, from hich anecdotal reports of illness had been received. Of 159 persons who consented to testing, 29 adults were ɜtermined infected with *P. falciparum*. This finding prompted mass treatment with chloroquine and primaquine ; 203 persons within that community.

ıtomologic surveys were conducted in multiple sites near bodies of fresh water identified by ground and air ırveys in Great Exuma. Human bait and CDC light-trap collections yielded large populations of mosquitoes, of hich only five were adult *Anopheles albimanus*. Surveys of potential breeding sites indicated few areas favorable r breeding of *An. albimanus* larvae, with five confirmed *An. albimanus* larvae collected from three breeding tes. Mosquito-control interventions were intensified beginning May 30. These measures included spraying 1) at l potential breeding sites, 2) within a quarter-mile radius of patients with confirmed cases, and 3) within a half-ile radius of patients detected through contact tracing, initially with a water-based pyrethroid insecticide, and ter with malathion 96.5%. In addition, all bodies of fresh water on Great Exuma, neighboring Little Exuma, and rrounding cays (reefs) were treated with temephos to eliminate larvae.

s of September 19, no additional cases of malaria had been identified on Great Exuma or any other island in the ahamas, despite intense epidemiologic surveillance. Mosquito-control measures were being continued roughout the Bahamas.

eported by: *M Dahl-Regis, MD, Ministry of Health, Bahamas. C Frederickson, PhD, Caribbean Epidemiology ɜntre; K Carter, MD, Y Gebre, MD, Pan American Health Organization, World Health Organization. B ınanan, Arlington County Dept of Human Svcs, Arlington, Virginia. C Mueller-Thomas, MD, Klinikum rechst ;r Isar, Munich, Germany. AE McCarthy, MD, Ottawa Hospital--General Campus, Ottawa; M Bodie-Collins, ıblic Health Agency of Canada. P Nguyen-Dinh, MD, Div of Parasitic Diseases, National Center for Zoonotic, ;ctor-Borne, and Enteric Diseases (proposed), CDC.*

ditorial Note:

ıe Bahamas is an archipelagic nation in the northern Caribbean Sea, consisting of approximately 700 islands and 400 cays stretching between Florida and Haiti (Figure). Persons from Hispaniola and other countries have ıigrated to the Bahamas, where malaria is not endemic and only one imported case was reported in 2005. ɔwever, because of frequent travel and relocation among countries, health-care providers in the Bahamas and her countries where malaria is not endemic should remain alert to the risk for this disease, especially in travelers d immigrants. Introduced malaria is much less common than imported malaria but of greater epidemiologic ɜnificance. Imported malaria usually occurs when travelers acquire the infection while visiting areas where alaria is endemic. Introduced malaria typically occurs when infected travelers return home and transmit the fection to local *Anopheles* mosquitoes, which subsequently transmit it to local residents. Left unchecked, this ocess can result in reestablishment of endemic malaria in countries that have previously eliminated the disease cause these areas have climatic conditions favorable to transmission and *Anopheles* species that are receptive to alaria parasites. In the United States, 1,320 cases of imported malaria were reported in 2004 (1), and 63 episodes introduced malaria were detected from 1957 to 2003, the year when the latest episode occurred in Florida (2--

4).

Available evidence indicates that during May--June 2006, Great Exuma experienced an outbreak of introduced malaria that was successfully contained and terminated. The observations that all cases were caused by *P. falciparum* and a substantial proportion of patients were immigrants from Haiti suggest that malaria was introduced by those immigrants. All patients treated with chloroquine responded to the treatment, which is a further suggestion that the parasites originated from Haiti, where *P. falciparum* has remained sensitive to chloroquine. *P. falciparum* causes 99% of malaria cases in Haiti and the Dominican Republic (MD Milord, Ministry of Public Health and Population, Haiti, and JM Puello, National Center for Control of Tropical Diseases, Dominican Republic, personal communication, 2006), which share the only Caribbean island still endemic for malaria. Conversely, *P. vivax* causes 94% of cases in Mexico and Central America (5).

The successful containment of this malaria outbreak is attributable to several factors. The first identified case, detected in a foreign tourist returning from the Bahamas, was promptly reported to the Bahamian MOH, which responded with several complementary interventions, including identification and treatment of patients and asymptomatic parasite carriers and institution of mosquito-control measures. Fewer than 30 days elapsed between diagnosis of the first identified case in Virginia and diagnosis of the last case on Great Exuma. Since June 19, no additional cases have been noted, despite intensive ongoing surveillance among febrile patients.

In view of these findings, CDC has rescinded recommendations made on June 16, 2006, that travelers take preventive doses of chloroquine before, during, and after travel to Great Exuma. As of September 19, CDC no longer recommends that travelers to Great Exuma take antimalarial prophylaxis.

This malaria outbreak illustrates the importance of vigilance by health-care providers and rapid response by public health authorities for successful containment (2) and also might provide incentive for measures to eliminate malaria from all Caribbean islands, including Hispaniola. Recently, the International Task Force for Disease Eradication recommended that Haiti and the Dominican Republic work jointly to eliminate from Hispaniola both malaria and lymphatic filariasis, two vectorborne parasitic diseases that have been eliminated from all other Caribbean islands (6). Agreements reached in July 2006 between the ministries of health of Haiti and the Dominican Republic represent a first step toward achieving this goal.

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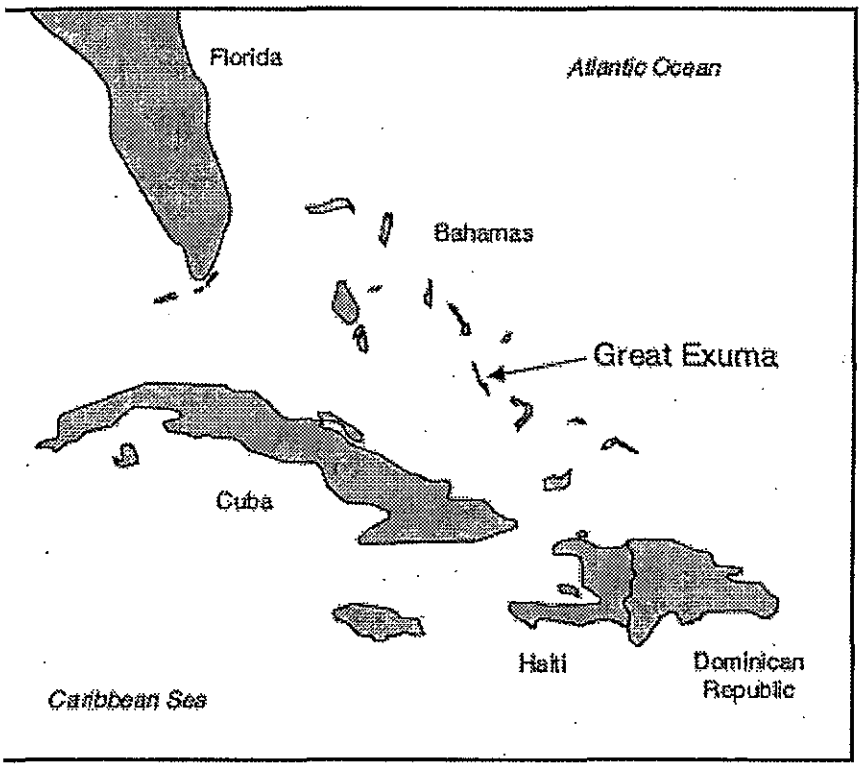
* Available at http://www.cdc.gov/travel/other/2006/malaria_bahamas.htm.

Figure

FIGURE. Nineteen cases of malaria, including four among travelers, were reported as acquired on the island of Great Exuma in the Bahamas during May–June 2006



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研究報告の概要	使用上の注意記載状況・その他参考事項等
○中国東部でマラリアが拡大 中国東部の安徽省でマラリア感染が拡大している。地元の保健当局によると、今年に入ってから2006年9月25日時点で17917例が報告されており、昨年の同時期と比較すると89.8%増加している。報告が多いのは、亳州、淮北、蘇州、蚌埠、富陽である。当局によると、2000年からマラリア感染が増え始めている。保健当局は緊急通告を出して、感染の監視を強化し、拡大防止のためにマラリア予防と治療に関する啓発を行うよう地元自治体に要請した。マラリアの予防と抑止の視察を10月の最初の20日間に行うと通告では伝えている。感染拡大を招くことになった監督の甘い担当者には厳しい処分が行われるだろうとのことである。保健省によると、中国全土では2005年に39656例のマラリア症例が発生し、うち45名が死亡している。	人全血液CPD「日赤」 照射人全血液CPD「日赤」 人全血液-LR「日赤」 照射人全血液-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
中国東部の安徽省でマラリア感染が拡大しているとの報告である。	日本赤十字社では、輸血感染症対策として問診時に海外渡航歴の有無を確認し、帰国後4週間は献血不適としている。また、安徽省をはじめとする中国南部をマラリア流行地(B地域)として、旅行者または居住経験者の供血を一定期間延期している(1～3年の延期を行うとともに、帰国後マラリアを思わせる症状があった場合は、感染が否定されるまでの間についても献血を見合わせる)。今後も引き続き、マラリア感染に関する新たな知見及び情報の収集、対応に努める。

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Malaria spreads in east China province

Malaria is spreading in east China's Anhui Province, which reported 17 917 cases by 25 Sep 2006 (this year), according to the provincial health department. The malaria cases increased by 89.8 percent from the same period last year, said the department. The cases were mainly reported in Bozhou, Huaibei, Suzhou, Bengbu and Fuyang in the north of the province.

Malaria cases have been on the rise since 2000 in these areas, according to the department. The department has issued an emergency notice asking local government authorities to strengthen the monitoring of the epidemic and promote the prevention and treatment knowledge among people to curb its spread

A check on malaria prevention and control in the disease-hit areas will be carried out in the 1st 20 days of this month [October 2006], said the notice. Those officials whose lax supervision caused a spread of the disease will be severely punished, according to the department. China reported 39 656 malaria cases in 2005, 45 of whom died, according to the Ministry of Health.

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[Anhui province is regarded as a low risk area for malaria in China. We presume that all cases are _Plasmodium vivax_. It is a cause for concern that malaria is returning to an area previously regarded as very low risk. The CDC does not recommend malaria prophylaxis to visitors to Anhui Province <http://www.cdc.gov/travel/regionalmalaria/eastasia.htm#malariarisk>, and more information is needed before recommendations to travelers might be changed.

A map of malaria in China for 2001 can be found at
<http://www.actmalaria.org/downloads/pdf/info/2004/China.pdf#search=%22Malaria 20%2BChina%22>;
it shows Anhui Province as having 0 to less than 1 case per 100 000 inhabitants. ProMED will be happy to publish newer data if available. - Mod.EP

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医薬品 研究報告 調査報告書

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一般的名称	解凍人赤血球濃厚液		研究報告の公表状況	ABC Newsletter. 2006 Sep 1; 16.	公表国 英国	
販売名(企業名)	解凍赤血球濃厚液「日赤」(日本赤十字社) 照射解凍赤血球濃厚液「日赤」(日本赤十字社)					

研究報告の概要	使用上の注意記載状況・その他参考事項等
○新規試験により外科用器具には殺菌後も依然としてクロイツフェルトヤコブ病(CJD)が残存する可能性が認められた エジンバラ大学の研究者らは、検査を実施した全器具に、感染をもたらす危険性がある量の残留タンパク質の汚染があることを認めた。研究者らは、5つの国立病院の委託滅菌サービス部門(trust sterile service departments)からランダムに入手した器具の検査を行った。英国保健省の出資による当該試験の結果は、先月のJournal of Hospital Infectionに掲載された。変性致死性脳疾患であるCJDは、変異したタンパク質(プリオン)により生じると考えられている。この立体構造が変化したタンパク質は、外科用器具の表面に固着し、洗浄や過熱等を使用した標準的な除染工程では除去が大変困難であることが分かっている。手術時の汚染器具によって数人の患者がCJDに感染している。エジンバラチームは、タンパク質による平均汚染量が器具1mm^{2}あたり0.2μgであり、ヒトへの感染に必要な量をかなり上回る数値であることを認めた。最大量は、扁桃腺(プリオンが分布することが知られている組織のひとつ)の切除に用いた器具で認められた。筆頭著者である同大学化学学部のBob Baxter博士は、「何かを100%完全に除去することは不可能だが、これ程のタンパク質が残存していたことは意外だった」と語った。ある患者がCJDに感染している危険性が高いことが分かっている場合には、外科用器具を区別する措置を取るべきだと述べた。この研究チームは、ラジオ波を用いて無害ガスの分子を励起し、器具表面を効果的に洗浄するイオンおよびラジカルを産生するガスプラズマ滅菌と呼ばれる技法を用いた有効性の高い器具殺菌法を開発した。Baxter博士は、保健省に対し、ガスプラズマ滅菌の広範な導入を推奨している。	解凍赤血球濃厚液「日赤」 照射解凍赤血球濃厚液「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
エジンバラ大学の研究者らは、検査を実施した全ての手術器具に、CJD感染をもたらす危険性がある量の残留タンパク質の汚染があることを認めたとの報告である。	今後も引き続き、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。

GLOBAL NEWS: (continued from page 15)

Scientists hope to be able to use stem cells, the earliest form of cells, to regenerate the organs and tissues of patients with disabling injuries. One Premier League footballer, playing in the northwest of England, said: "We decided to store our new baby's stem cells for possible future therapeutic reasons, both for our children and possibly for myself." The player, who declined to be named, added: "As a footballer, if you're prone to injury, it can mean the end of your career, so having your stem cells – a repair kit, if you like – on hand makes sense." He is one of five professional footballers who have frozen their children's stem cells with Liverpool-based CryoGenesis International (CGI), one of about seven commercial stem cell "banks" in Britain. In the past five years, more than 11,000 British parents have paid up to £1500 ($3.700) to store their babies' stem cells in the banks in order to grow tissue, should their children become ill. One professional footballer known to have stored stem cells for his children's future use is the Frenchman Thierry Henry, the Arsenal and France striker. There is no indication that he intended them for his own use. (Source: *London Sunday Times*, 8/27/06) ♦

INFECTIOUS DISEASE UPDATES:

BSE/CJD/vCJD

A new study has found that surgical instruments still have the potential to harbor Creutzfeldt-Jakob disease (CJD) even after sterilization. Edinburgh University researchers found every instrument they tested was contaminated with enough protein residue to pose a potential infection risk. The researchers tested instruments taken at random from five National Health Service hospital trust sterile service departments. Results of the study, financed by the Department of Health, appeared last month in the *Journal of Hospital Infection*. CJD, a degenerative and fatal brain disease, is thought to be caused by mutated proteins called prions. These twisted proteins are known to be able to cling to the surface of surgical instruments, and are remarkably difficult to remove by standard decontamination processes, which involve the use of detergents and super-heating. A number of patients have contracted CJD from contaminated instruments during surgery. The Edinburgh team found an average level of protein contamination of 0.2 micrograms per square millimeter of instrument, much higher than the dose needed to cause infection in humans. The highest doses were found on instruments used to remove tonsils – one of the tissues known to harbor prions. Lead researcher Bob Baxter, PhD, from the University's chemistry department, said, "You can never get something 100 percent clean, but we were surprised at how much protein there was." Dr. Baxter said hospitals take measures to quarantine surgical instruments if a patient is known to be at high risk of carrying CJD. The Edinburgh team has developed a more effective way to sterilize instruments with a technique called gas plasma sterilization using radio waves to excite the molecules of harmless gases, creating charged atoms called ions and radicals which effectively scour the surface of the instruments. Dr. Baxter has recommended the widespread introduction of gas plasma cleaning to the Department of Health. (Source: BBC News, 8/24/06) **Citation:** Baxter RL, *et al.* Quantitative analysis of residual protein contamination on reprocessed surgical instruments. J Hosp Infect. 2006;63(4):439-44.

Researchers exploring the likelihood that variant Creutzfeldt-Jakob (vCJD) disease might be spread via the reuse of surgical instruments have called for more data in order to allay fears over the possible transmission of the deadly infection. Their study was published in the online edition of the *Journal of the Royal Society Interface*. Scientists based at both the London School of Hygiene & Tropical Medicine and the National Creutzfeldt-Jakob Disease Surveillance Unit at Western General Hospital in Edinburgh report that key factors determining the scale of any epidemic are the number of

(continued on page 17)

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	新医薬品等の区分	厚生労働省処理欄
				2006年11月29日	該当なし	
一般的名称	人ハプトグロビン	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）	ハプトグロビン注ーヨシトミ(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病原体暴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

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の考えられる対応案が示されている。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。

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..

Since 2003, three presumptive transfusion transmitted cases of vCJD have been reported in the UK. Two of the transfusion recipients died of vCJD, whereas the third had vCJD infection detected after death from an unrelated cause. Each had received transfusions of red blood cells from individuals who were asymptomatic at the time of donation, but who later died from vCJD. The strong likelihood that transmission of vCJD occurred via transfusion of red blood cells in the UK increased the concern that products manufactured from the plasma portion of human blood might also pose a risk of vCJD transmission. Note, however, there have been no reported cases of vCJD in any recipients of plasma derived products in the UK, where risk is considered greatest, or anywhere else in the world. In the fall of 2004 UK authorities notified recipients of a number of plasma derivatives that they might be at increased risk of vCJD. These products included coagulation factors VIII, IX, and XI, as well as antithrombin III, and intravenous immune globulins.

Because BSE occurs at an extremely low level in US cattle (only three reported cases: two in US born cattle and one in a cow imported from Canada), and there have been no human cases of vCJD acquired in the US, any risk of plasma donors acquiring vCJD by consuming domestically produced beef is thought to be extremely low. However, it is possible that a small population of US donors may have been exposed to the BSE agent during travel or residence in the UK, France, or other countries of Europe and may therefore be at some risk for vCJD. Some of these donors may have been unknowingly infected with vCJD through dietary exposure and then contributed donations to plasma pools used to manufacture pdFVIII in the U.S. The donor deferral policy likely removes most of the vCJD risk; however, there may be residual risk in the US donor population for persons who do not meet criteria for donor deferral, or who meet those criteria, but fail to be deferred due to limitations of the donor screening process.

FDA has developed a computer-based simulation model to try to estimate the potential risk and understand factors involved in determining and potentially reducing the degree of risk. The model and various risk estimate results and uncertainties are presented in the document "A 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" provided as a separate attachment. The results are estimates of the probability and level of exposure to the vCJD agent and the possible risk of vCJD infection in patients with severe hemophilia A (HA) and the severe form of von Willebrand disease (vWD) (Type 3) who have used human pdFVIII product manufactured in the US.

The parameters used in this risk assessment were derived after receiving recommendations from the TSEAC about another risk assessment, the "Draft Risk Assessment: Potential Exposure to the vCJD agent in United States Recipients of Factor XI Coagulation Product Manufactured in the United Kingdom" at the February 8, 2005 meeting; from discussion at a meeting of the TSEAC on October 31, 2005 on several risk assessment model inputs for plasma derivatives and potential vCJD risks specifically related to pdFVIII; and from peer review by non-FDA experts in risk assessment.

The ranges of uncertainty and variability in the input parameters of the risk assessment are great, resulting in very large uncertainty in the model's outputs that estimate potential risk. Additionally, because scientific data on the level of exposure to the vCJD agent and the

likelihood of certain human health outcomes, such as infection and illness, are lacking, estimates for the infectious risk generated in the risk assessment may not be accurate. For these reasons, it is not possible to provide an actual estimate of the vCJD risk to individual patients potentially exposed to the vCJD agent through plasma-derived products. Additionally, the absence of any reported cases of vCJD in repeatedly exposed recipients of plasma derivatives in the UK, where risk is thought to have been greatest, or anywhere else in the world, further suggests that the actual risk of vCJD from pdFVIII is likely to be very low.

Nevertheless, FDA believes it is appropriate to share both the findings of and the uncertainties in our risk assessment for pdFVIII with physicians, patients, and the general public since it is possible that the risk is not zero. Advice will be sought from the TSEAC in December concerning communication of the findings of the risk assessment and its interpretation, given the very wide range of uncertainty in the estimate of vCJD risk. Advice will also be sought on potential steps that may help to better understand as well as to further reduce any risks.

DISCUSSION:

A. Risk Assessment and Interpretation

The FDA risk assessment estimates the risk of vCJD infection as a function of product exposure for different assumed levels of vCJD infectious agent clearance in manufacturing of pdFVIII and under two assumed levels of vCJD prevalence in the UK. The risk assessment utilizes a probability-based statistical sampling model that evaluates successively the impact on vCJD risk of individual processes used in the production of human pdFVIII beginning with plasma donation, extending through manufacturing steps, and finally, addressing utilization by various representative patient subpopulations. Input data for parameters used in the model such as clearance, vCJD prevalence, and pdFVIII usage are represented as statistical distributions that express the underlying uncertainty and variability. Each run of the model randomly samples one number from the distribution for each parameter; this is done thousands of times to generate a single distribution representing the final risk estimate that expresses, where possible, the accompanying uncertainty of these risk estimates. A sensitivity analysis, conducted by varying values of key parameters within the input range of the model and observing the effect on the predicted outcomes, determined that three major factors in the model greatly influenced potential vCJD risk: reduction of the infectious agent by the manufacturing process, intensity of pdFVIII utilization by the patient, and differing estimates of disease prevalence in the UK.

One of the most influential risk assessment parameters for vCJD risk is the manufacturing process, which may reduce or eliminate the amount of the vCJD agent in the final product. Because of the uncertainty and variability in the levels of vCJD clearance afforded during the manufacturing process for any pdFVIII product, the model evaluated three separate categories of reduction in infectivity that the product may have undergone during manufacturing including 2-3 $\log_{10}$, 4-6 $\log_{10}$, and 7-9 $\log_{10}$ reduction. These three categories are meant to span the possible range of uncertainty and variability in reduction of vCJD agent for marketed pdFVIII products. Based on currently available experimental studies, FDA believes that all US licensed pdFVIII products probably achieve at least a 4 $\log_{10}$ of vCJD level of clearance during manufacture.

Another major variable affecting potential risk is the quantity of product used by patients in different treatment groups. For purposes of this model only patients with severe HA were considered because their higher use of product would put them at higher risk than patients with mild or moderate forms of the disease. Severe HA patients account for approximately 50% of the total HA population. Approximately 25% of all HA patients use pdFVIII products, while most others use recombinant FVIII. Data from a CDC sponsored epidemiological study on HA patients were used to generate the statistical distribution of pdFVIII usage by patients. Using these estimates, the risk assessment evaluated different treatment regimens including patients on prophylaxis, prophylaxis plus inhibitor, prophylaxis plus inhibitor plus immune tolerance, episodic treatment, and episodic treatment plus inhibitor. It also evaluated the potential of patients with severe von Willebrand disease (vWD) to be exposed to the risk of infection with vCJD through the use of pdFVIII. These patients must use plasma-derived sources of FVIII/von Willebrand factor because there is presently no recombinant von Willebrand factor.

The prevalence of vCJD in the United Kingdom population was used to estimate vCJD exposure and therefore prevalence in US donors who traveled to the UK, France and other European countries. For purposes of the risk assessment, we used two different estimates of vCJD prevalence in the UK. One estimate is based on epidemiological modeling of actual reported cases and an estimate of future vCJD cases in the UK. The other estimate is based on testing for prion protein in a relatively small tissue (tonsil and appendix) surveillance study. At present it is not possible to know which of the two estimates of vCJD prevalence in the UK provides a better estimate of the true prevalence.

The vCJD case prevalence based on epidemiological modeling of actual reported cases and an estimate of future vCJD cases in the UK yielded an estimate of approximately 1.8 vCJD cases per million. There are a number of limitations to this estimate based on simplifying assumptions that contribute to considerable uncertainty in the final case estimates. These assumptions include the intensity of human exposure to the BSE agent, the length of the incubation period, and how a person's age and genetic background could influence exposure, disease susceptibility, and incubation period. However, it is possible that the prevalence of vCJD in the UK is higher than this estimate if there are people infected who never develop the disease (but can still spread the infection) or if some individuals take an extremely long time to become ill. Therefore, we also used a second approach to estimate vCJD infection prevalence based on testing for prion protein in a relatively small tissue (tonsil and appendix) surveillance study. This approach yielded an estimate of 1 in 4,225 (237 infections per million). Limitations to this study that contribute to uncertainty include the fact that this study was not controlled using tissues from a non-BSE exposed population and false positive findings cannot be ruled out. It is also not known whether this finding of prion protein in tissues is a reliable marker for vCJD pre-clinical infection or for an individual's capability to transmit the infection through blood donation.

After accounting for the age distribution, incubation period, country, year and duration of travel, these two different prevalence estimates have been used to predict the number of vCJD donations that could be present in variably sized pools of US donated plasma.

Results

See Risk Assessment, including the Executive Summary, and especially Tables I.A and II.A in the Executive Summary and attached here in an Appendix.

Interpretation

Results from the FDA pdFVIII risk assessment model suggest that the risk of vCJD infection from US manufactured pdFVIII generally appears likely to be very low, but may not be zero. For US plasma donors, the major source of vCJD risk is dietary exposure during travel and/or residency in the UK, France, or other countries in Europe since 1980. Donor deferral criteria in place since 1999 have reduced the risk of donation by exposed persons.

Manufacturing processes for human pdFVIII products likely reduce the quantity of vCJD agent, if present, but the level of reduction through manufacturing steps is not precisely known. Clearance of TSE agents in manufacturing appears to vary among products, but has not been measured in standardized studies which might allow more meaningful direct comparisons. Based on currently available experimental studies, it is estimated that pdFVIII products potentially have 4 $\log_{10}$ (or 10,000 fold) or greater manufacturing process reduction of the vCJD agent. Assuming a 4-6 $\log_{10}$ manufacturing process reduction, the modeling predicts that the potential risk per person per year for patients with severe HA using pdFVIII ranges from 1 in 15,000 for the higher vCJD prevalence estimate and high product usage, to 1 in 9.4 million for the lower vCJD prevalence estimate and low product usage. While higher levels of clearance are likely to reduce risk, it is not possible at this time to determine with certainty if a specific product may be less or more safe than another due to the wide range of methods used for clearance studies currently available, the results themselves, and gaps in information. Although results of the model suggest that exposure to vCJD agent could occur, and that there is a potential risk of infection that is likely to be generally very low, it is not possible for the model to provide a precise estimate of the vCJD risk in general, or of the actual risk to individual patients. Despite the uncertainties in the model, we believe this is information that patients and physicians might consider when making treatment decisions.

B. <u>Risk Management Strategy, Key Message Points, and Communication Strategy</u>

Risk Management Strategy

FDA's current risk management strategy for vCJD has evolved in response to emerging epidemiologic findings and basic scientific developments pertinent to the epidemic. The overall risk management strategy for vCJD includes:

- Deferral of donors at increased risk of vCJD based on epidemiological data, and withdrawal of products at increased vCJD risk
    - Donor deferrals: Guidance since August 1999 (most recently updated in January 2002) to defer donors with "geographic risk," e.g. that visited or resided in countries where BSE prevalence is higher; deferral of donors that used UK-sourced bovine insulin; deferral of donors transfused in the UK since 1980 (note also draft guidance published in August 2006 for deferral of donors transfused in France since 1980).
    - Withdrawal of implicated blood components and plasma derivatives is recommended if a donor is diagnosed with vCJD

- Facilitating development, validation, and information sharing (including product labeling) regarding the performance of manufacturing processes in clearance of TSE agents from blood products.
    - FDA reviews requests for TSE clearance labeling claims which may be approved if detailed, validated TSE clearance study data are provided
    - On September 18, 2006, FDA discussed with TSEAC the feasibility and scientific value of standardized assessments of TSE clearance in the manufacturing processes for pdFVIII. The topic will be addressed again at this meeting
- Facilitating development of candidate donor screening and diagnostic tests for vCJD and other TSEs
    - FDA has held meetings with candidate test kit manufacturers to discuss developmental pathways
    - A public discussion of validation for donor screening tests for vCJD and other TSEs was discussed with the TSEAC on September 19, 2006
- Risk assessment and communication to inform patients and physicians about the current scientific understanding regarding vCJD risk from blood products and to help in informing treatment decisions
    - FDA has engaged in periodic reassessment of TSE epidemiology and pathogenesis to determine whether guidance/policies need to be revisited in light of new information
    - FDA performed risk assessments for potential exposure to vCJD in investigational pdFXI made from plasma donated in the UK, and for pdFVIII made from plasma donated in the US

The risk assessments that FDA has performed for potential exposure to vCJD from licensed pdFVIII made from US plasma has led us to consider further actions. Based on the finding that, despite very large uncertainties in the risk assessment models and generally low risk estimates, the risk of vCJD exposure from these products may not be zero, and we are taking the following steps:

- The risk assessment model has indicated that the level of TSE agent clearance during product manufacturing is one of the most important parameters for vCJD risk. For this reason, FDA seeks to improve our understanding of the actual prion clearance in manufacturing by encouraging standardized clearance studies of the different pdFVIII products, and, potentially, by setting minimum standards for TSE agent clearance.
- Although the risk of vCJD exposure from US pdFVIII products is likely to be very low, and it may not be zero, and FDA is encouraging physicians and patients to consider this risk in making treatment decisions.

DRAFT Risk Communication Messages

Based on the findings of the risk assessment FDA has developed key message points and additional, background information about the risk of vCJD in pdFVIII made from US donor plasma. They include the following:

Key Messages

vCJD (variant Creutzfeldt Jakob Disease, the agent which causes the human form of "Mad Cow Disease") is rare, even in the UK. Infection is not known to have been acquired in the US and there is no evidence that any US plasma donor has had vCJD. FDA has put steps in place to reduce the risk of transmission by deferring plasma donation from individuals with the most potential risk of exposure, those who lived in affected areas for significant time periods. Exposure to vCJD through pdFVIII could still potentially occur if someone traveled or resided briefly in the UK or another area where TSE is present, and became infected without knowing it from eating infected meat, and then donated plasma. While blood transfusion has transmitted vCJD in the UK, pdFVIII products go through additional manufacturing steps likely to help remove the agent and reduce or eliminate the risk of transmitting the disease.

FDA used a computer risk assessment model to help estimate any remaining potential risk to US pdFVIII recipients. While there are still many uncertainties, and it is not possible to estimate risk for specific individuals, the model suggests that any potential risk to the health of most US pdFVIII recipients is likely to be very low. Also, no cases of vCJD have yet been reported in patients receiving such products either in the UK, where the risk is highest, or anywhere else in the world.

Because so much is unknown about vCJD and its incidence, the risk assessment performed by FDA has a lot of uncertainty, making it impossible to precisely estimate any risk. However, we wanted to provide information about the risk assessment so that patients and health care providers can consider the matter, where appropriate, in their treatment decisions.

Additional Information

vCJD is a very rare, fatal disease that can infect a person for many years before making people sick by destroying cells in the brain.

Most cases of vCJD have occurred in the UK and individuals there are thought to be at higher risk for the disease than individuals elsewhere.

Beef products contaminated with the infectious agent of BSE are the main cause of vCJD. As of August 2006, world-wide, 195 cases have been reported, 162 of them in the UK. Food risk in the US blood donor population is expected to be very low as there have been only three cases of BSE found in US cattle (two US born, and one imported from Canada) and safeguards are in place to prevent infected beef products, if present, from entering human food.

While most vCJD is due to eating infected beef products, there is convincing evidence that the disease has also been transmitted by red blood cell transfusion. In

the UK, three people who became infected with the vCJD agent had received blood from donors who later developed vCJD

Plasma is the liquid part of blood, after the cells are removed, that is used for manufacture of plasma-derived products such as pdFVIII. Animal studies show that when blood carries this infection, so does the unprocessed plasma.

Manufacturing steps used in making most pdFVIII products appear likely to be effective in removing the agent and may reduce or eliminate most risk even if a vCJD infected donor contributed plasma.

Because so much is unknown about vCJD and its incidence, the risk assessment performed by FDA has a lot of uncertainty, making it impossible to precisely estimate any risk. The risk assessment model suggests that important contributors to risk are how common vCJD is in the donor population, the degree to which the manufacturing process can remove the agent from the products, and the quantity of product that individuals use.

The Public Health Service believes the risk of developing vCJD infection from pdFVIII is likely to be very low, given both the results of the risk assessment and the lack of any reported cases of vCJD in plasma-derived blood products following decades of use, including in the UK, where the risk is considered greatest. For example, for the most common pattern of use (i.e. episodic, no inhibitor) of a pdFVIII product made using processes with a level of clearance believed to be achieved by most manufacturing processes, the model suggests a possible estimated risk of from 1/105,000 to 1/9.4 million infections per person per year, depending on which prevalence estimate is assumed, or a possible total of 1 case in the population of severe HA patients using such products every 35 to 3,077 years. However, there is a great deal of uncertainty in the model, including how effective clearance may be, and it is also possible that not enough time has passed for some people receiving plasma products that contained the vCJD agent to have developed signs of infection. Therefore, while the risk is estimated to be very low, it may not be zero.

While there is no proof of a significant risk at this time, patients and physicians utilizing pdFVIII should be aware of the possibility and consider both the potential risks and benefits of their treatment.

Efforts to better understand and reduce any potential risk of transmission of vCJD by plasma products are ongoing. PHS will provide additional information as it becomes available.

Communication Strategy

Subject to further input from the PHS agencies and possible revisions, the Key Messages and Additional Information cited above are the messages that the FDA, in cooperation with other components of the Public Health Service would utilize for communications with the patient community and health care providers, through various media presentations including government web sites, press, and communications with Hemophilia Treatment Centers and consumer organizations.

APPENDIX

Table I.A. Model Results for all Severe Hemophilia A Patients who use a Hypothetical Plasma-derived FVIII Product with 4-6 log_{10} Manufacture Process Reduction of vCJD Agent: *Predicted mean potential per person annual vCJD risk using two different UK vCJD prevalence estimates.*

				4 - 6 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)*
Treatment Regimen	Inhibitor Status	Est. Total Number patients in US	Mean quantity FVIII used per person per year (5th - 95th perc)[b]	Mean potential vCJD risk per person per year[a] (5th - 95th perc)[b]	Mean potential vCJD risk per person per year[a] (5th - 95th perc)[b]
Prophylaxis	No Inhibitor	578	157949 IU[c] (21242 , 382316)	1 in 4.0 million (0-0)[d]	1 in 54,000 (0 - 1 in 12,000)
	With Inhibitor – No Immune Tolerance	63	190523 IU[c] (26956 , 447639)	1 in 4.8 million (0-0)[d]	1 in 41,000 (0 - 1 in 9,000)
	With Inhibitor – With Immune Tolerance	62	558700 IU[c] (33235, 1592943)	1 in 1.3 million (0-0)[d]	1 in 15,000 (0 - 1 in 3,700)
Episodic	No Inhibitor	946	85270 IU[c] (4633, 244656)	1 in 9.4 million (0-0)[d]	1 in 105,000 (0 - 1 in 24,000)
	With Inhibitor	151	160458 IU[c] (5314 , 488906)	1 in 8.0 million (0-0)[d]	1 in 48,000 (0 - 1 in 12,000)

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

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

[c] IU - represents international units of Factor VIII and may be expressed using the term "unit" or "units" in this document.

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

Table II.A. Model Results for von Willebrand Disease (vWD) Patients[a] with Severe Disease: Predicted Potential Annual vCJD Risk:

- Assuming a reduction from manufacturing of 4-6 $\log_{10}$, and
- Two different UK vCJD prevalence estimates.

YOUNG vWD (≤ 15 yrs of age)				
			4 - 6 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)*
	Est. Total Number patients in US	Mean quantity product used per person per year	Mean vCJD risk per person per year[b] (5th - 95th perc)[c]	Mean vCJD risk per person per year[b] (5th - 95th perc)[c]
Prophylaxis	39	165,713 IU[d] (9876, 454306)	1 in 4.7 million (0-0)[e]	1 in 52,000 (0 - 1 in 13,000)
Episodic	60	11,045 IU[d] (1025, 34352)	1 in 48 million (0-0)[e]	1 in 971,000 (0 - 1 in 293,000)
ADULT vWD (> 15 yrs of age)				
Prophylaxis	73	186,880 IU[d] (16910, 539877)	1 in 4.1 million (0-0)[e]	1 in 46,300 (0 - 1 in 11,000)
Episodic	78	86,923 IU[d] (2182, 240338)	1 in 10 million (0-0)[e]	1 in 1 million (0 - 1 in 24,000)

[a] Number (percent) patients in a CDC sponsored study with 6 states to survey treatment of hemophilia A and B conducted 1993 - 1998. Our analysis included 14 patients (<15yrs) and 28 patients (≥15yrs) (total = 42) on prophylaxis or episodic treatment with Humate P only and no record of inhibitor.

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

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

[d] IU - represents international units of Factor VIII and may be expressed using the term "unit" or "units" in this document.

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

DRAFT

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

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EXECUTIVE SUMMARY

Variant Creutzfeldt-Jakob disease (vCJD) is a fatal neurodegenerative disease attributed to human infection with the agent of bovine spongiform encephalopathy (BSE) and is most often transmitted by the consumption of beef products from infected cattle. Cases of vCJD were first reported in humans in the U.K. in 1996 – and as of August 2006, 195 cases have been reported worldwide, with 162 cases in the U.K. Since December 2003, there have also been three reports in the United Kingdom (U.K.) of probable variant Creutzfeldt-Jakob disease (vCJD) transmission by red blood cell transfusions. The donors were healthy at the time of donation, but later developed vCJD. Of the three red blood cell recipients who probably became infected with the vCJD agent after transfusion, two developed vCJD and died from the disease. The third died of an unrelated illness.

The probable transmission of vCJD via red blood cell transfusions raised the possibility that plasma derivatives might also pose a risk of vCJD transmission, although there have as of yet been no reported cases of vCJD in any recipients of plasma derivatives in the U.K., where the risk is considered greatest, or elsewhere in the world. U.K. authorities have notified physicians in the U.K. and their patients who received plasma derivatives made from plasma from U.K. donors about the potential for risk of vCJD from these products. These products included coagulation factors VIII, IX, and XI, as well as antithrombin III, and intravenous immune globulins.

This document "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" quantitatively estimates the probability and level of exposure to the vCJD agent and the possible risk of vCJD infection in patients with severe hemophilia A (HA) and von Willebrand disease (vWD) patients with severe disease who have used human plasma-derived Factor VIII (pdFVIII) product manufactured in the US. Because BSE occurs at an extremely low level in US cattle (2 native born cows and 1 cow imported from Canada), the risk of plasma donors acquiring vCJD by consuming domestically produced beef is thought to be very low. Because of concerns about potential exposure to the BSE agent in US blood donors who traveled to or lived in the UK and other at risk European countries, FDA implemented donor deferral policies beginning in 1999. The policies are believed likely to reduce the possible risk from blood donors potentially exposed to BSE agent by ~ 90%. However, it is possible that a small number of non-deferred US donors may have been exposed to the BSE agent during extended travel or residence in the UK, France or other European countries and may be at risk for vCJD. Some of these donors may have been unknowingly infected with vCJD through eating beef from BSE-infected cattle and then contributed donations to plasma pools used to manufacture pdFVIII in the US.

The FDA risk assessment utilizes a computer-based simulation model that evaluates successively the impact on vCJD risk of individual processes used in the production of human pdFVIII starting with plasma donation, extending through manufacturing steps, and finally, addressing utilization by various patient subpopulations. Risk for these products was estimated for the baseline year of 2002 but the results and conclusions also are likely to reflect the current vCJD risk for recipients of pdFVIII. A few major elements of the model greatly influence vCJD risk. The most influential of these are manufacturing processes, which may reduce or eliminate the amount of vCJD agent in the final product. The amount of product used by patients in different clinical scenarios also has a significant impact on risk. Additionally, the risk estimate is significantly affected by the prevalence

of vCJD in the United Kingdom population, which is used to estimate vCJD prevalence in US donors who resided in or traveled to the UK and other countries of Europe. The risk assessment model estimates the potential for vCJD exposure and the potential risk of vCJD infection for patients receiving pdFVIII from plasma collected in the US and the accompanying uncertainty of these estimates. Because scientific data on the level of exposure to vCJD agent and the likelihood of certain human health outcomes, such as infection and illness, are lacking, the estimates generated may not be accurate. As a result of these and other large uncertainties, it is not possible to provide a precise estimate of the vCJD risk to patients potentially exposed to the agent through plasma-derived products.

Patients with hemophilia A (HA) have an inherited, recessive, sex-linked bleeding disorder that affects approximately 14,000 individuals in the United States (Soucie et al 1998). FDA estimated that there are approximately 1,800 patients in the US with severe disease who use plasma-derived products. The blood of affected individuals contains functionally abnormal or abnormally low concentrations of FVIII. FVIII is a glycoprotein circulating in blood plasma that is part of the blood coagulation pathway and is critical for the normal clotting of blood. In the case of severe disease, FVIII is <1% of normal. Among severely affected persons, spontaneous bleeding or bleeding at the site of an injury or within a joint is common and can lead to severe disability or death without treatment. The complications of HA can be prevented by appropriate clinical management and treatment with pdFVIII or recombinant FVIII products.

Patients with vWD (Type 3) have an inherited, non-sex linked bleeding disorder associated with abnormal platelet adhesion caused by deficiency in von Willebrand Factor (vWF) activity. FDA estimated that there are approximately 250 patients in the US with severe vWD who use plasma-derived products. Mucosal bleeding is common in patients with vWD due to the platelet adhesion disorder. In some cases there may be a deficiency in FVIII coagulant activity (anti-hemophilic factor) as well. Patients with severe vWD can experience persistent bleeding into joints resulting in pain, degeneration of joints, swelling and loss of range of motion similar to patients with HA. Mild forms of vWD are often treated successfully with desmopressin but more severe forms of the disease usually require treatment with coagulation factor concentrates that contain both vWF and FVIII. Patients who need vWF must use plasma-derived sources of FVIII which contain vWF. No recombinant vWF is currently available.

Results from the Model

An important, yet also highly uncertain parameter in driving the risk assessment results is the estimate used for vCJD prevalence in the UK. The prevalence of vCJD in the UK population was estimated in the model using two different approaches. The first approach to estimating vCJD prevalence in the UK was from a study based on epidemiological modeling that was derived using actual reported vCJD cases in the UK combined with an estimate of future vCJD cases (Clarke and Ghani, 2005). Several factors used in epidemiologic modeling approaches are difficult to quantify and add uncertainty to the final estimated number of future vCJD cases. These factors include: the intensity of human exposure to the BSE agent, incubation period, time of infection, and whether illness will develop in individuals who are not homozygous for methionine at codon 129 of PrP. All cases of vCJD to date have occurred in individuals who are homozygous for methionine at this location. Our calculations, based on the Clarke and Ghani study (2005) and diagnosed cases in 2002 and 2003, yielded a prevalence estimate of approximately 1.8 vCJD cases per million in the UK.

Running the model with this vCJD case prevalence estimate (~1.8 per million) produces an estimate suggesting that, on average, there was a 0.027% likelihood that a plasma pool, which then undergoes manufacturing, will contain at least one donation from an individual whose blood contains the vCJD agent. Therefore, on average, more than 99% of the time the model predicts the product as administered will contain no vCJD agent and this is reflected in the (0 – 0) values for the 5th and 95th percentiles shown for the lower prevalence estimate results in Table I.A. (below).

However, it is possible that the prevalence of vCJD in the UK is higher than that estimated above. This could happen if there are people infected who never develop the disease (but can still spread the infection) or if some individuals take extremely long to become ill. Therefore, a second approach to estimating vCJD infection prevalence was used based on a relatively small tissue surveillance study by Hilton, *et al* (2004), which tested stored tonsil and appendix tissues from the UK for accumulation of abnormal prion protein. It yielded a much higher prevalence estimate of 1 in 4,225 (237 infections per million). This study was not controlled using tissues from a non-BSE exposed population and false positive findings cannot be ruled out. It is also not known whether this staining of appendiceal tissues is a reliable marker for vCJD pre-clinical infection or for an individual's capability to transmit the infection through blood donation. However, while unconfirmed, the findings from this study provide a higher prevalence estimate that may be relevant to transfusion risk and therefore should also be considered. Use of these data as the basis for a vCJD infection prevalence estimate which is then used in the model produces a significantly higher estimate suggesting that, on average, if it were correct, there could be a 2.41% likelihood that a plasma pool, which then undergoes manufacturing, may contain at least one donation from an individual whose blood contains the vCJD agent.

Estimated annual potential vCJD risk associated with human pdFVIII used to treat severe Hemophilia A

Results from the model indicate that it is possible that a donor unknowingly infected with vCJD may have donated plasma used in the manufacture of pdFVIII in the US. Output from the model using the lower UK vCJD prevalence estimate (~1.8 in 1 million) indicated that, on average, there is a 0.027% (95% CI: 0 % - 0 %) likelihood that a plasma pool may contain at least one donation from an individual with the vCJD agent in their blood. Readers may notice that the 5th and 95th percentile intervals for all of the model outputs are from 0 to 0, meaning that the chance of an infected donor donating to a plasma pool would be an infrequent event. This means that at least ninety five percent of the time the model estimates the risk to be zero because vCJD agent was not present in pdFVIII product used during treatment. Again, actual model predictions indicated that, at the lower prevalence, 0.027% of the time the exposure to vCJD may be greater than zero. When the model was run using the higher UK vCJD prevalence estimate (1 in 4,225) to derive an estimate for vCJD prevalence in US plasma donors, the FDA model predicted that, on average, there is an approximately 2.41% (95% CI: 0 % - 10 %) likelihood that a plasma pool will contain at least one donation from an individual with the vCJD agent in their blood. For either set of results, the model assumes that if vCJD agent were present, the amount in a plasma pool would likely be reduced or possibly eliminated by processing steps used during the manufacture of pdFVIII product.

Individuals with HA vary in their degree of FVIII deficiency. For simplicity, the model results and this executive summary specifically address potential vCJD exposure and risk for persons with severe HA. FDA estimates that among the total population of 14,000 HA patients in the United States, approximately 1,800 (Table I.A.) have severe disease and use pdFVIII products. FDA obtained data

on FVIII utilization from the Centers for Disease Control (CDC). The data were generated as part of a collaborative effort between CDC and six states in a study conducted from 1993 –1998.. Treatment regimens for HA are administered either as prophylaxis to prevent the occurrence of bleeding episodes or on an episodic basis to control bleeding when it occurs. Additionally, inhibitors may be treated with very high doses of pdFVIII to induce immune tolerance. Assuming these patients are treated with a pdFVIII product that has a 4-6 $\log_{10}$ manufacturing process reduction of vCJD agent, Table I.A. displays model outcomes for patients treated using either prophylaxis or episodic treatment, and with respect to their inhibitor status.

Table I.A. Model Results for all Severe Hemophilia A Patients who use a Hypothetical Plasma-derived FVIII Product with 4-6 $\log_{10}$ Manufacture Process Reduction of vCJD Agent: *Predicted mean potential per person annual vCJD risk using two different UK vCJD prevalence estimates.*

				4 - 6 $\log_{10}$ 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)*
Treatment Regimen	**Inhibitor Status**	**Est. Total Number patients in US**	**Mean quantity FVIII used per person per year (5th - 95th perc)[b]**	**Mean potential vCJD risk per person per year[a] (5th - 95th perc)[b]**	**Mean potential vCJD risk per person per year[a] (5th - 95th perc)[b]**
Prophylaxis	No Inhibitor	**578**	**157949 IU[c]** (21242 , 382316)	1 in 4.0 million (0-0)[d]	1 in 54,000 (0 - 1 in 12,000)
	With Inhibitor – No Immune Tolerance	**63**	**190523 IU[c]** (26956 , 447639)	1 in 4.8 million (0-0)[d]	1 in 41,000 (0 - 1 in 9,000)
	With Inhibitor – With Immune Tolerance	**62**	**558700 IU[c]** (33235, 1592943)	1 in 1.3 million (0-0)[d]	1 in 15,000 (0 - 1 in 3,700)
Episodic	No Inhibitor	**946**	**85270 IU[c]** (4633, 244656)	1 in 9.4 million (0-0)[d]	1 in 105,000 (0 - 1 in 24,000)
	With Inhibitor	**151**	**160458 IU[c]** (5314 , 488906)	1 in 8.0 million (0-0)[d]	1 in 48,000 (0 - 1 in 12,000)

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

[b] The 5th - 95th perc (percentiles) are the minimum and maximum numbers that define the range of values constituting the 90% confidence interval. Accordingly, the mean risk estimates generated by the model should fall within this defined interval at least 90% of the time.
[c] IU - represents International units of Factor VIII and may be expressed using the term "unit" or "units" in this document.
[d] For a 5th and 95th percentile interval of 0 and 0, respectively, the model estimates that for at least 90% of FVIII recipients the risk is zero. At low vCJD prevalence, donation by a vCJD infected donor to a FVIII plasma pool would be rare and more than 90% of FVIII product lots (of vials) would not be predicted to contain vCJD agent.

The risk estimate for the entire severe HA population of 1,800 in the US who use pdFVIII, obtained by summing the total annual exposure and vCJD risk, is shown in Table I.B. Variant CJD risk for US donors with a history of travel to the UK, France or other countries in Europe since 1980 is further adjusted to account for donor age, country, duration and year of travel. Using the lower UK prevalence estimate as a starting point, the model estimates that the total patient population may be exposed to a potential population-based vCJD risk of 1 case observed in 3,077 years of treatment. If the higher vCJD prevalence estimate is used, the model estimates that the total patient population may be exposed to a potential population-based vCJD risk of 1 case observed in 35 years of treatment.

Table I.B. Model Results for Mean Total Population-based Potential vCJD Risk for all Hemophilia A Patients who use a Hypothetical Plasma-derived FVIII Product with 4-6 $\log_{10}$ Manufacture Process Reduction of vCJD Agent. Risk estimates were calculated for patients with severe disease, using two different UK vCJD prevalence estimates.

			4 - 6 $\log_{10}$ 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)*
	Est. Total Number severe HA patients in US	**Mean Total quantity FVIII used by all patients per year (5th - 95th perc)[c]**	**Mean population –based potential vCJD risk[a] (5th - 95th perc)[b]**	**Mean population –based potential vCJD risk[a] (5th - 95th perc)[b]**
Mean Total cumulative annual exposure and population risk	**1,800**	**243 million IU[c]**	1 in 3,077 years (0-0)[d]	1 in 35 years (0 - 1 in 8)

[a] Mean population-based potential annual vCJD risk – the risk of potential vCJD infection for the entire population of 1,800 based on animal model dose-response information.
[b] The 5th - 95th perc (percentiles) are the minimum and maximum numbers that define the range of values constituting the 90% confidence interval. Accordingly, the mean risk estimates generated by the model should fall within this defined interval at least 90% of the time.
[c] IU - represents International units of Factor VIII and may be expressed using the term "unit" or "units" in this document.
[d] For a 5th and 95th percentile interval of 0 and 0, respectively, the model estimates that for at least 90% of FVIII recipients the risk is zero. At low vCJD prevalence, donation by a vCJD infected donor to a FVIII plasma pool would be rare and more than 90% of FVIII product lots (of vials) would not be predicted to contain vCJD agent.

Estimated annual potential vCJD risk associated with human pdFVIII used to treat severe von Willebrand disease (vWD)

Individuals with vWD have varying severities of disease; those with Type 3 disease have the severest form of the disease. This executive summary specifically addresses potential vCJD exposure and risk for persons with severe vWD (Type 3) who are assumed to use larger amounts of pdFVIII product and thus, may be at higher risk. FDA estimates that approximately 250 vWD patients have severe vWD disease in the United States and use human pdFVIII products to control their disease (Table II.A.). Results from the risk assessment model for young vWD patients and adult vWD patients treated with pdFVIII product that is assumed to have a 4-6 $\log_{10}$ manufacturing process reduction of vCJD agent are shown in Table II.A. Generally results from the model are expressed for patients with vWD for two groups, either Prophylaxis or Episodic treatment. FDA obtained data on FVIII utilization from the Centers for Disease Control (CDC). The data were generated as part of a collaborative effort between CDC and six states; the study was conducted from 1993 –1998. Annual usage of product by vWD patients was estimated based on an assumption that this patient class largely uses Humate-P®. Totaling the model results for the lower prevalence estimate of ~1.8 per million reveals that the 250 severe vWD patients in the US (Table II.B.) are predicted to have an average potential vCJD infection risk for the population of 1 infection in 28,450 years. At the higher prevalence estimate, the average potential vCJD infection risk for this population is 1 infection in 405 years

Table II.A. Model Results for von Willebrand Disease (vWD) Patients[a] with Severe Disease: Predicted Potential Annual vCJD Risk:

- Assuming a reduction from manufacturing of 4-6 $\log_{10}$, and
- Two different UK vCJD prevalence estimates.

YOUNG vWD (≤ 15 yrs of age)				
			4 - 6 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)*
	Est. Total Number patients in US	**Mean quantity product used per person per year**	**Mean vCJD risk per person per year[b] (5th - 95th perc)[c]**	**Mean vCJD risk per person per year[b] (5th - 95th perc)[c]**
Prophylaxis	**39**	**165,713 IU[d]** (9876, 454306)	1 in 4.7 million (0-0)[e]	1 in 52,000 (0 - 1 in 13,000)
Episodic	**60**	**11,045 IU[d]** (1025, 34352)	1 in 48 million (0-0)[e]	1 in 971,000 (0 - 1 in 293,000)
ADULT vWD (> 15 yrs of age)				

Prophylaxis	73	186,880 IU[d] (16910, 539877)	1 in 4.1 million (0-0)[e]	1 in 46,300 (0 - 1 in 11,000)
Episodic	78	86,923 IU[d] (2182, 240338)	1 in 10 million (0-0)[e]	1 in 1 million (0 - 1 in 24,000)

[a] Number (percent) patients in a CDC sponsored study with 6 states to survey treatment of hemophilia A and B conducted 1993 - 1998. Our analysis included 14 patients (<15yrs) and 28 patients (≥15yrs) (total = 42) on prophylaxis or episodic treatment with Humate P only and no record of inhibitor.
[b] Mean potential annual vCJD risk – the risk of potential vCJD infection based on animal model dose-response information.
[c] The 5th - 95th perc (percentiles) are the minimum and maximum numbers that define the range of values constituting the 90% confidence interval. Accordingly, the mean risk estimates generated by the model should fall within this defined interval at least 90% of the time.
[d] IU - represents international units of Factor VIII and may be expressed using the term "unit" or "units" in this document.
[e] For a 5th and 95th percentile interval of 0 and 0, respectively, the model estimates that for at least 90% of FVIII recipients the risk is zero. At low vCJD prevalence, donation by a vCJD infected donor to a FVIII plasma pool would be rare and more than 90% of FVIII product lots (of vials) would not be predicted to contain vCJD agent.

Table II.B. Von Willebrand Disease (vWD) patients[a] with Severe Disease: Predicted Total Population-based Potential vCJD Risk:

- *Assuming a reduction from manufacturing of 4-6 log $_{10}$, and*
- *Two different UK vCJD prevalence estimates.*

			4 - 6 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)*
	Est. Total Number severe vWD patients in US	**Mean Total quantity FVIII used by all patients per year (5th - 95th perc)[c]**	**Mean[b] population –based Potential vCJD risk (5th - 95th perc)[c]**	**Mean[b] population –based Potential vCJD risk (5th - 95th perc)[c]**
Mean total annual exposure and population risk	**250**	**29.9 million IU[d]** (3013, 311745)	**1 in 28,450 years** (0 - 0)[e]	**1 in 405 years** (0 - 1 in 76)

[a] Number (percent) patients in a CDC sponsored study with 6 states to survey treatment of Hemophilia A and B conducted 1993 - 1998. Our analysis included 14 patients (<15yrs) and 28 patients (≥15yrs) (total = 42) on prophylaxis or sodic treatment with Humate P only and no record of inhibitor.
[b] Mean potential annual vCJD risk – the risk of potential vCJD infection based on animal model dose-response information.
[c] The 5th - 95th perc (percentiles) are the minimum and maximum numbers that define the range of values constituting the 90% confidence interval. Accordingly, the mean risk estimates generated by the model should fall within this defined interval at least 90% of the time.
[d] IU - represents international units of Factor VIII and may be expressed using the term "unit" or "units" in this document.
[e] For a 5th and 95th percentile interval of 0 and 0, respectively, the model estimates that for at least 90% of FVIII recipients the risk is zero. At low vCJD prevalence, donation by a vCJD infected donor to a FVIII plasma pool would be rare and more than 90% of FVIII product lots (of vials) would not be predicted to contain vCJD agent.

Conclusions

Results from the FDA pdFVIII risk assessment model suggest that the risk of vCJD infection from US manufactured pdFVIII generally appears likely to be very low, but may not be zero. For US plasma donors, the major source of vCJD risk is dietary exposure during travel and/or residency in the UK, France, or other countries in Europe since 1980. Although donor deferral criteria in place

since 1999 have reduced the risk of donation by exposed persons, some are not deferred and potentially may donate plasma that contains the vCJD agent. However, the model suggests that the likelihood of a vCJD contaminated plasma pool is low.

Manufacturing processes for human pdFVIII products likely reduce the quantity of vCJD agent, if present, but the level of reduction through manufacturing steps is not precisely known. Clearance of TSE agents in manufacturing appears to vary among products, but has not been measured in standardized studies which might allow more meaningful direct comparisons. Based on currently available experimental studies, it is estimated that pdFVIII products potentially have 4 $\log_{10}$ (or 10,000 fold) or greater manufacturing process reduction of the vCJD agent. Assuming a 4-6 $\log_{10}$ manufacturing process reduction, the model predicts that the potential risk per person per year for patients with severe HA using pdFVIII ranges from1 in 15,000 for the higher vCJD prevalence estimate and high product usage to 1 in 9.4 million for the lower vCJD prevalence estimate and low product usage. Due to the wide range of methods used for currently available clearance studies, the results themselves, and gaps in information, it is not possible at this time to determine with any certainty if a specific product may be less or more safe than another.

Although results of the model suggest exposure to vCJD agent is possible, and there is a potential risk of infection that is likely to be very low, it is not possible for the model to provide a *precise* estimate of the vCJD risk in general, or of the actual risk to individual patients. Although the actual risk is highly uncertain, the risk assessment model indicates that the most important factors affecting risk are the clearance of the vCJD agent though manufacturing steps, how much product individuals used, and the vCJD prevalence in the UK donor population.

In considering the results of the risk assessment it is important to note that to date we are not aware of any cases of vCJD having been reported worldwide in patients receiving plasma-derived products, including pdFVIII. This includes patients receiving large amounts of plasma-derived products manufactured from UK plasma donations over a long period of time. This observation also suggests that the actual risk of vCJD infection from pdFVIII is likely to be very low. The absence of cases does not rule out the possibility of exposure that could potentially result in illness in some recipients at some future point in time.

RISK ASSESSMENT

I. INTRODUCTION

Variant Creutzfeldt-Jakob disease (vCJD) is a fatal neurodegenerative disease attributed to human infection with the agent of bovine spongiform encephalopathy (BSE) and is most often transmitted by the consumption of beef products from infected cattle. Cases of vCJD were first reported in humans in the UK in 1996 – and as of August 2006, 195 cases have been reported worldwide, with 162 cases in the UK. Since December 2003, there have also been three reports in the United Kingdom (UK) of probable variant Creutzfeldt-Jakob disease (vCJD) transmission by red blood cell transfusions. The donors were healthy at the time of donation, but later developed vCJD. Of the three red blood cell recipients who probably became infected with the vCJD agent after transfusion, two developed vCJD and died from the disease. The third died of an unrelated illness.

The probable transmission of vCJD via red blood cell transfusions raised the possibility that plasma derivatives might also pose a risk of vCJD transmission, although there have as of yet been no reported cases of vCJD in any recipients of plasma derivatives in the UK, where the risk is considered greatest, or elsewhere in the world. UK authorities have notified physicians in the UK and their patients who received plasma derivatives made from plasma from UK donors about the potential for risk of vCJD from these products. These products included coagulation factors VIII, IX, and XI, as well as antithrombin III, and intravenous immune globulins.

Because only 3 cases of BSE (2 that originated in the US, 1 in Canada) have been reported in the US, the US vCJD risk from domestic beef is thought to be very low. However, some US residents (including blood and plasma donors) traveled to the UK, France and other countries in Europe since 1980 and may have been exposed to the BSE agent, and some of these donors may unknowingly be infected with vCJD. The UK had the largest epidemic of BSE among its cattle population and the largest human epidemic of vCJD, which as of August, 2006, reported 162 cases. The UK instituted strong food chain control measures to prevent the entry of high risk cattle tissues into its food supply in 1996; so risk after that time likely decreased considerably. France is considered to rank second in the world for risk for vCJD at this time, albeit at a much lower level than the UK, but higher than many other countries in Europe. As of August 2006 France has reported 20 cases of vCJD. Current US blood and plasma donation policies defer donors with a history of travel or residence to: the UK for a period of three months or longer (1980 – 1996); France, for a period of five years or longer (1980 - present); and other countries in Europe (blood donation only) for 5 years or longer (1980 – present). The CJD geographic donor deferral policy likely removes most of the vCJD risk; however, there may be residual risk in the US donor population for persons who do not meet criteria for donor deferral, or who meet those criteria, but fail to be deferred due to limitations of the donor screening process.

FDA initiated a draft risk assessment of the potential vCJD risk for US manufactured pdFVIII in late 2004. A preliminary draft concept risk assessment model assessing the potential vCJD risks for US manufactured pdFVIII was presented at the February 8, 2005 meeting of the Transmissible Spongiform Encephalopathies Advisory Committee (TSEAC) for review and comment. The committee largely agreed with the proposed approach. On October 31, 2005, FDA sought advice and

discussion on several risk assessment model inputs to be used in a risk assessment for US manufactured pdFVIII and potential vCJD risks. FDA has incorporated staff, peer reviewer comments, and technical advice provided by the TSEAC at the February 8, 2005 and October 31, 2005 meetings to develop this document "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".

This document quantitatively estimates the probability and level of exposure to the vCJD agent and the possible risk of vCJD infection in patients with severe hemophilia A (HA) and von Willebrand disease (vWD) patients with severe (Type 3) disease who have used human pdFVIII product manufactured in the US. Because BSE occurs at an extremely low level in US cattle (2 native born cows and 1 cow imported from Canada), the risk of plasma donors acquiring vCJD by consuming domestically produced beef is thought to be very low. Because of concerns about potential exposure to the BSE agent in US blood donors who traveled to or lived in the UK and other at risk European countries, FDA implemented donor deferral policies beginning in 1999. The policies are believed likely to reduce the possible risk from blood donors potentially exposed to BSE agent by ~ 90%. However, it is possible that a small number of non-deferred US donors may still have been exposed to the BSE agent during extended travel or residence in the UK, France or countries of Europe and may be at risk for vCJD. Some of these donors may have been unknowingly infected with vCJD through eating beef from BSE-infected cattle and then contributed donations to plasma pools used to manufacture pdFVIII in the US.

Scope of the risk assessment

The scope of this FDA risk assessment evaluates the annual potential exposure to the vCJD agent and risk of vCJD infection through human plasma-derived Factor VIII (pdFVIII) product manufactured in the US. Risk for these products was estimated for the baseline year of 2002 but the results and conclusions also are likely to reflect the current vCJD risk for recipients of pdFVIII. The FDA risk assessment specifically addresses pdFVIII used to treat patients with severe HA and severe vWD.

The FDA risk assessment utilizes a computer-based simulation model that evaluates successively the impact on vCJD risk of individual processes used in the production of human pdFVIII starting with plasma donation, extending through manufacturing steps, and finally, addressing utilization by various patient subpopulations. A few major elements of the model greatly influence vCJD risk. The most influential are manufacturing processes, which may reduce or eliminate the amount of vCJD agent in the final product. The amount of product used by patients in different clinical scenarios also has a significant impact on risk. Additionally, the prevalence of vCJD in the United Kingdom population, which is used to estimate vCJD prevalence in US donors who resided in or traveled to the UK and other countries of Europe, has a significant effect on the risk estimate.

The risk assessment model estimates the potential for vCJD exposure and the potential risk of vCJD infection for patients receiving pdFVIII from plasma collected in the US and the accompanying uncertainty of these estimates. Because scientific data on the level of exposure to vCJD agent and the likelihood of certain human health outcomes, such as infection and illness, are lacking, the estimates generated may not be accurate. As a result of these and other large uncertainties, it is not possible to

provide a precise estimate of the vCJD risk to patients potentially exposed to the agent through plasma-derived products.

Background

Hemophilia and Factor VIII

Patients with HA have an inherited, recessive, sex-linked bleeding disorder that affects approximately 14,000 individuals in the United States (Soucie et al 1998). FDA estimated that there are approximately 1,800 patients in the US with severe disease who use plasma-derived products. The blood of affected individuals contains functionally abnormal or abnormally low concentrations of FVIII. FVIII is a protein in blood plasma that is part of the blood coagulation pathway and is critical for the normal clotting of blood. In the case of severe disease, FVIII is <1% of normal. Among severely affected persons, spontaneous bleeding or bleeding at the site of an injury or a joint is common and can lead to severe disability or death without treatment. The complications of HA can be prevented by appropriate clinical management and treatment with pdFVIII or recombinant FVIII products.

Patients with vWD have an inherited, non-sex linked bleeding disorder associated with abnormal platelet adhesion caused by deficiency in von Willebrand Factor (vWF) activity. FDA estimated that there are approximately 250 patients in the US with severe vWD who use plasma-derived products. Mucosal bleeding is common in patients with vWD due to the platelet adhesion disorder. In some cases there may be a deficiency in FVIII as well. Patients with severe vWD can experience persistent bleeding into joints resulting in pain, degeneration of joints, swelling and loss of range of motion similar to patients with HA. Mild forms of vWD are often treated successfully with desmopressin but more severe forms of the disease usually necessitate treatment with coagulation factor concentrates that contain both vWF and FVIII. Patients who need vWF must use plasma-derived sources of FVIII which contain vWF. No recombinant vWF is currently available.

FVIII from human plasma is manufactured in a number of different ways. FVIII manufactured from human plasma is purified by fractionation of the protein from large plasma pools containing thousands of donations of plasma. Because thousands of donations are used to assemble the plasma pools used in the manufacturing of pdFVIII, there is a possibility that a donation from a vCJD infected individual may be present in a large plasma pool used to manufacture pdFVIII. In turn, that may lead to exposure of product recipients to the vCJD agent and a risk of infection. Relatively recent advances in pdFVIII production technology, such as [redacted] have likely reduced potential exposure to the vCJD agent. However, further evaluation is necessary to more precisely determine the levels of vCJD clearance afforded by the manufacturing processes for each human pdFVIII product.

There are two approaches for the clinical treatment and control of HA using pdFVIII: (1) episodic treatment and (2) prophylaxis. Episodic treatment involves the administration of FVIII in response to bleeding episodes resulting from trauma or during and after surgery. Prophylaxis treatment requires administration of clotting factor concentrates on a regularly scheduled basis necessary to maintain a minimal level of FVIII (common acceptable trough level is 2-5% of base line level) to prevent bleeding episodes. In view of the demonstrated benefits of prophylaxis, the Medical and Scientific Advisory Council (MASAC) recommends that prophylaxis starting at an early age be considered as an optimal therapy for individuals with severe HA (MASAC 2001). Prophylaxis treatment requires

higher doses of FVIII than episodic treatment (Linden, Kolakoski *et al* 2003; Globe, Curtis *et al* 2004) and thus presents a potentially higher risk of vCJD to the patients than episodic treatment when human pdFVIII is used. Also, some HA patients develop antibodies to FVIII, called inhibitors, that limit the effectiveness of FVIII used in treatment. Inhibitors can develop with the use of either recombinant FVIII or pdFVIII products. In some cases the development of inhibitors is treated with immune tolerance therapy in which large doses of one million or more units of pdFVIII may be administered. Because of the large doses of pdFVIII used, immune tolerance therapy can pose a potential risk for vCJD exposure if vCJD agent were present in the pdFVIII product. As a simplifying assumption in the model we assumed that in a given year a patient received either exclusively prophylaxis treatment or episodic treatment, but not both.

Risk Assessment Framework

This risk assessment generally follows the four step paradigm described by the National Research Council (NRC, 1983) and consists of: (1) hazard identification, (2) hazard characterization, (3) exposure assessment, and (4) risk characterization. The hazard identification portion of the risk assessment provides an in-depth overview and analysis of all data and information sources to establish a causal relationship between the hazard and adverse effects on humans. The hazard characterization component (also known as dose-response) relates the information in the exposure assessment, which determines the dose, to the probability of adverse consequence(s) such as infection, illness, etc., expected at a given dose at the individual, subpopulation, or population level. Exposure assessment evaluates the routes of exposure to a hazard, the probability that exposure occurs and the amount (dose) of a hazardous agent to which a person or population may be exposed. Risk Characterization integrates the information from the hazard identification, hazard characterization and exposure assessment sections to characterize the probability and consequences of risk for individuals and populations.

II. HAZARD IDENTIFICATION

The hazard identification portion of the risk assessment provides an in-depth overview and analysis of information from laboratory studies, epidemiological studies, the scientific literature, government reports and other credible or peer-reviewed sources of data that establish a causal relationship between the hazard and adverse effects on humans. In this risk assessment, the vCJD agent is the hazard, and potential exposure can occur in individuals who use plasma-derived products that may have been manufactured from plasma that may have contained a donation(s) from a vCJD-infected individual. To date, there is no epidemiological evidence suggesting that vCJD has been transmitted by use of plasma derivative products. However, the probable transmission of vCJD to three recipients of red blood cell products donated by donors later diagnosed with vCJD in the UK raises the possibility of vCJD transmission via plasma-derived products.

Human vCJD was first reported in the United Kingdom in 1996 (Will *et al* 1996). As of August 2006 over 195 cases, 162 of them in the UK, have been reported worldwide. Both vCJD and BSE belong to a class of fatal neurodegenerative diseases known as transmissible spongiform encephalopathies (TSEs). There is strong evidence and general agreement that vCJD results from infection of humans

most probably via dietary exposure to bovine spongiform encephalopathy (BSE)-contaminated beef (Knight 2004). The leading theory is that the transmissible infectious agent is a prion, or proteinaceous infectious agent, that is an altered but pathogenic form of the PrP protein that is normally present in cells. The altered PrP, herein referred to as PrP^{TSE}, consistent with terminology recommended by the World Health Organization, is highly stable and resistant to degradation by high heat and chemical treatments commonly used to denature infectious agents in the manufacture of plasma derivatives. The incubation period for TSEs is long. The mean incubation period of BSE in cattle is approximately 4.5 years. In humans, vCJD acquired through dietary exposure is thought to incubate approximately 10 –12 years or longer, and individuals become symptomatic only in the last few months of the disease, making early detection very difficult. Confirmation of vCJD requires postmortem examination of brain tissue to confirm diagnosis, but prion protein has been detected in tonsil and appendix tissue of asymptomatic individuals as long as two years prior to the onset of symptoms. There are currently no validated tests available to detect the disease in its early stages of infection or to detect the presence of TSE agents in blood.

Transmission of TSEs through transfusion of blood products in animal models

Transmission of different TSE agents through the transfusion of blood or blood products has been demonstrated in animal models on multiple occasions. At least four studies reported transmission via blood transfusion in the same animal species: sheep experimentally infected with BSE (Houston *et al* 2000), sheep naturally infected with scrapie (Hunter *et al* 2002), hamsters with scrapie (Rohwer 2004), and mice with a human TSE (Brown *et al* 1999).

Brown, Rohwer, Taylor (Taylor *et al* 2000) and others have attempted to estimate the amounts of intracerebral (i.c.) infectivity present in blood, which generally fell between 2 and 20 i.c. ID_{50}/ml. A recent study of scrapie-infected hamsters concluded that approximately 58% of the infectivity present in whole blood was associated with plasma (Gregori *et al* 2004). The model uses this more conservative estimate in the published literature and assumes that 58% of infectivity is associated with plasma.

Transfusion transmission of vCJD in the United Kingdom

In December 2003 the UK government announced that vCJD had likely been transmitted to a 69 year-old patient via blood transfusion. The patient had received non-leukoreduced red blood cells in 1996 from a donor who died three years later of vCJD. This first report was followed by the announcement in July 2004 of another probable case of transfusion-transmitted vCJD. The patient died of a ruptured aortic aneurysm without clinical evidence of vCJD, but postmortem testing detected PrP^{TSE} in spleen tissue and cervical lymph node. In February 2006 a third case of probable transfusion transmitted vCJD was reported in the UK in a 31 year-old male; the patient had received a transfusion eight years earlier from a donor who died of vCJD 20 months after donation. None of the donors were known to have had vCJD at the time of donation.

It is possible that dietary exposure may have been responsible for some or all of the three cases that were reported after red blood cell transfusions; however, the probabilities for occurrence of either a single, or, particularly, two or three such events are small. As Llewelyn *et al* (2004) pointed out in their publication discussing the first presumed transfusion-transmitted case "the age of the patient

was well beyond that of most vCJD cases, and the chance of observing a case of vCJD in a recipient in the absence of transfusion transmitted infection is about 1 in 15,000 to 1 in 30,000." The combined probability that the first two transfusion cases, identified in two elderly patients in a small cohort of transfusion recipients—in an age group underrepresented among vCJD cases—both acquired infection from food is remote.

The presumptive transmission of vCJD via red blood cell transfusion in the UK raises the possibility that plasma derivatives may pose a risk. The UK authorities have notified physicians in the UK and their patients who received plasma derivatives made from plasma from UK donors about the potential for risk of vCJD from these products. These plasma derivative products included coagulation factors, as well as antithrombin III, and intravenous immune globulins. The derivatives of concern were manufactured from plasma of UK donors between 1980 and late in 1999, when--consistent with a decision announced in 1998—UK manufacturers stopped using UK plasma. The last expiry date for any of the UK products was in 2001. To date, no cases of vCJD have been reported in any recipients of plasma derivatives, either in the UK, where the risk is considered greatest, or elsewhere, including in patients who have received human plasma-derived coagulation products from implicated lots (e.g., lots manufactured from a pool containing plasma from a donor subsequently diagnosed with vCJD) made in the UK.

The vCJD risk for travelers with history of extended travel or residence in the UK, France, and other countries in Europe and reduction of risk via donor deferral

Public health control measures, such as surveillance, culling of sick animals, or banning specified risk materials, and others have been instituted relatively recently in many European countries, particularly in those with indigenous cases of confirmed BSE, in order to prevent potentially BSE-infected tissues from entering the human food supply. Since 1996, the UK has instituted some of the most stringent of these control measures, including a program that excludes all animals >30 months of age and prevents high risk tissue from slaughtered animals from entering the human food and animal feed supplies. In June 2000, the European Union Commission on Food Safety and Animal Welfare strengthened the European Union's BSE control measures by requiring all member states to remove specified risk materials from animal feed and human food chains; as of October 1, 2000 such bans had already been instituted in most member states.

Travelers to and residents of the UK, France and other countries in Europe during the period of BSE pandemic concern are possibly at increased risk of vCJD. However, the risk can not be determined precisely due to factors such as the great uncertainty about incubation period of the disease, the sensitivities of each country's surveillance for BSE and vCJD, the compliance with and effectiveness of public health measures instituted in each country to prevent BSE contamination of human food, and the cattle products from one country that are distributed and consumed elsewhere.

In the UK, the current risk of acquiring vCJD from eating beef and beef products appears to be extremely small, perhaps about 1 case per 10 billion servings (CDC, 2005). In the other countries of the world, this current risk, if it exists at all, would not likely be any higher than that in the UK if BSE-related. The implementation of animal and public health control measures has caused the prevalence of BSE to decline. The US blood donor deferral criteria currently in effect focus on the

time (cumulatively 3 months or more) that a person lived in the UK from 1980 through 1996, whereas for the rest of Europe the criteria focus on the time (cumulatively 5 years or more) that a person lived in these countries from 1980 through the present. This deferral policy is expected to reduce the risk of vCJD transmission via blood and plasma donations from potential infected donors.

Two cases of vCJD in US residents with history of residence in the UK

In 2002, the first case of vCJD was reported in the United States in a 22-year-old woman living in Florida. She is believed to have become infected with vCJD during her residence in the UK. The patient was born in Great Britain in 1979 and immigrated to the United States in 1992. In early November 2001, the patient was evaluated for depression and memory loss. In late January 2002, the patient was transported to the United Kingdom where her condition worsened. The diagnosis of vCJD was confirmed by western blot and immunohistochemical analysis. The patient died in June 2004, approximately 32 months after illness onset (Belay *et al* 2005).

A second case of vCJD was diagnosed by the UK National Creutzfeldt-Jakob Disease Surveillance Unit in November 2005 in a 30-year old man who resided in Texas during the period 2001-2005 (CDC 2006). The onset of symptoms occurred in early 2005 while the man was in Texas. He returned to the UK and died of the disease in early 2006. A postmortem examination confirmed the diagnosis of vCJD.

Surveillance studies to detect CJD and vCJD in patients with hemophilia

Studies in the United States

Because of the large number of blood products used, persons with hemophilia might be expected to be at risk of developing transfusion-related vCJD or classical Creutzfeldt-Jakob disease (CJD). However, a study conducted by the US Centers for Disease Control (CDC) (Evatt *et al* 1998) examined the brains of 24 decedents with a history of bleeding disorders and dementia and found no evidence of CJD in any of the cases.

Another study conducted by the CDC and the Hemophilia Treatment Center identified no cases of clinical diagnosis of CJD among over 12,000 HA patients who have been assessed since 1996. (Evatt *et al* 1998)

Studies in the United Kingdom

A study in the UK (reference: Lee *et al* 1998) conducted post mortem histological examination of the brains of 33 hemophilia patients who were treated with coagulant factor concentrates spanning the years from 1962 – 1995 and observed no evidence of vCJD.

In summary, the experimental and epidemiological evidence indicates the risk of blood transmission of vCJD is no longer theoretical but a real possibility. To date, there is no evidence suggesting that either human CJD or vCJD have been transmitted by use of plasma derivative products. However, transmission of vCJD via red blood cell tranfusions has likely occurred (Llewelyn *et al* 2004). Because the vCJD agent may be associated with plasma, it is plausible that plasma derivatives potentially pose a risk of transmitting the disease.

III. HAZARD CHARACTERIZATION

The hazard characterization component (also known as dose-response) relates the information in the exposure assessment, which determines the dose, to the adverse consequence(s) such as infection, illness, etc., at the individual, subpopulation, or population level. Determining dose-response relationships can be difficult to accomplish because data are limited, especially exposure and outcome data for humans. Other factors such as characteristics of the hazard (e.g. strain, chemical make-up, etc.), route of introduction, genetics of exposed individuals, influence the dose-response relationship but are often difficult to characterize. Often in lieu of human data, animal data are used and appropriately extrapolated as best as is possible to estimate the dose-response relationship for humans.

Another challenge is estimating the probability of infection when the exposure to TSEs is small and/or occurs repeatedly over a period of time. It is unknown whether for TSE diseases there is a minimal amount of the agent (presumably the prion protein PrP^{TSE}) or threshold that is needed to initiate infection in an individual. This phenomenon is seen with many other pathogens such as viruses or bacteria, for which infection requires exposure to at least one, and often more, units of the infectious agent. Furthermore, it is not known whether the effects of small multiple exposures over a period of time are cumulative and may result in the possibility of infection and disease equivalent to a single, larger exposure (e.g., via intracerebral injection in laboratory animals). Some risk assessments have made assumptions concerning the exposure and dose for TSE agent that leads to infection. For instance, the Det Norske Veritas (Feb 2003) blood products risk assessment assumes that exposure to infectivity, quantified in ID_{50} units, is cumulative over the period of one year. Based on advice from the TSEAC (2005), and consistent with suggestive data from studies of TSE agents in animal models (Diringer *et al* 1998, Jacquemot, *et al* 2005), FDA also assumes that exposure to vCJD ID_{50} is cumulative over a one year period. The ID_{50} is the common metric used to quantify the infectivity of TSEs. One ID_{50} is defined as the amount of infectious material or tissue that is necessary to initiate infection in 50% of the treated population. The route of exposure to TSE infectious material influences the efficiency of transmission of the disease. Based on advice provided to FDA by the TSEAC (October 31, 2005) the model assumes that transmission via the intravenous (i.v.) route is between 1 and 10 times less efficient than the transmission via the intracranial (i.c.) route.

In estimating the dose-response relationship for TSEs one could use a strict interpretation of the ID_{50} and assume a linear relationship between exposure and infection. In the pdFVIII model FDA assumed there was a linear relationship between the exposure dose of vCJD agent and the probability of infection. The ID_{50} relationship used in the model was based on infectious TSE units estimated from rodent model studies (Brown 1998, 1999; Rohwer 2004). We further assumed there was no threshold or minimum dose necessary to initiate infection, that is, exposure to even low quantities of vCJD agent has a probability of initiating infection in an individual, albeit the probability of infection would likely be low at low levels of exposure. The model further assumes that in such a case exposure to 1 ID_{50} would suggest a 50% probability of infection, exposure to 0.1 ID_{50} would suggest a 5% probability of infection, and so on. However, given the lack of information and high degree of uncertainty on the dose-response relationship because of the limited data available for TSE agents, it is plausible that low level exposures, even on a chronic basis, may not attain a threshold or minimum quantity of agent necessary to initiate infection in humans. Again, FDA makes a conservative

assumption that low-level exposure(s) over the period of one year to any quantity of vCJD agent could potentially lead to infection and that there is not a minimum dose necessary to initiate infection.

There are considerable uncertainties in determining the correct form for the vCJD-human dose-response model. For instance, the nature of the dose-response line, its slope, or whether it is more accurately described using a dose-response curve is uncertain because animal data are so limited and human data are not available. The FDA risk assessment estimates the potential individual risk of infection and assumes that a linear interpretation of the rodent model accurately reflects the pathology and progression of vCJD infection and disease in humans, but it may not. Furthermore, exposure to the vCJD agent may not necessarily lead to infection, and vCJD infection may not necessarily produce symptomatic vCJD disease or illness in an individual or population.

IV. EXPOSURE ASSESSMENT

Exposure assessment evaluates the routes of exposure to a hazard, the probability that exposure occurs and the amount (dose) of a hazardous agent to which a person or population may be exposed. This exposure assessment specifically addresses the probability of exposure and, if present, the quantity of vCJD agent that may potentially be present in plasma-derived FVIII products manufactured in the United States. The administration of pdFVIII and, thus, the route of exposure, is intravenous.

Plasma pools consisting of 6,000 or more donations collected from US plasma donors are used as the starting material from which a number of plasma-derived products are purified, including pdFVIII, which is addressed in this assessment. Because of the relatively large number of donations per plasma pool, there is a small probability that even in the United States some of the pools may contain a donation from a donor who may unknowingly be infected with vCJD, but who does not meet criteria for donor deferral, or who meets those criteria but fails to be deferred due to the limitations of the screening process.

Overview of Model for pdFVIII

Module 1 – Estimation of the prevalence of vCJD in the UK. Variant CJD prevalence in the UK was used in our model as the basis for estimating vCJD prevalence in US plasma donors. The model assumes that the major source of potential vCJD in the US would likely be associated with plasma donors with a history of travel and residency in the UK, France or other countries in Europe since 1980 and may have had dietary exposure to the BSE agent during their stay.

Two different data sources were used to estimate UK vCJD prevalence.

- An epidemiological modeling-based approach estimates a UK vCJD case prevalence of approximately ~1.8 cases per million population (Clarke and Ghani 2005).
- A tissue surveillance-based estimate for UK vCJD infection prevalence was generated using data from Hilton *et al* (2004) and yielded a mean estimate of 1 case per 4,225 – but was further adjusted to account for age of patients surveyed.

Module 2 –vCJD Prevalence in US Plasma Donors and Pools. This module estimates the number of US plasma donors that may potentially be infected with vCJD and the percentage/number of pools containing donations with vCJD agent. This module uses survey data to determine US plasma donors potentially at risk for vCJD, including those with a history of:

- Dietary exposure to BSE-contaminated beef during long term travel or residence in the UK (1980-1996), France and other countries in Europe (since 1980),
- Military service - posted on or residing near military facilities in Europe; and
- Transfusion with blood collected in Europe, or Euroblood.

US plasma donors potentially at risk for vCJD were further characterized by:

- Country of travel or residence,
- Specific duration of travel or residence, year of travel or residence,
- Age of donor, rate and frequency of plasma donation,
- Number of donations per pool, and type of plasma pool (source or recovered), and
- Effectiveness of donor deferral policies.

Module 3 - pdFVIII Manufacturing and Processing. This portion of the model calculated the likelihood and number of plasma pools potentially containing vCJD agent and the quantity of agent per plasma pool and pdFVIII vial based on:

- The probability of and predicted quantity of infectivity (i.v. ID_{50}) present per donation and pool
- Reduction in the quantity of potential vCJD agent during manufacture, and
- Total yield or quantity of pdFVIII produced from the plasma pool.

Module 4 - Utilization of pdFVIII by Hemophilia A patients. The potential exposure of an individual HA patient to the vCJD agent through use of pdFVIII was estimated in the model based on:

- the total quantity of pdFVIII used per year, and
- the estimated potential quantity of vCJD agent predicted in the pdFVIII product.

The quantity of pdFVIII utilized by an individual patient is dependent on the severity of the disease and the treatment regimen and was estimated using data from a Centers for Disease Control (CDC) sponsored study by 6 states by HA patients from 1993-1998

This risk assessment provides outputs that estimate annual exposure for several patient subpopulations with

Severe HA disease for persons in the following clinical treatment groups:

- Prophylaxis
- Prophylaxis plus inhibitor
- Prophylaxis plus inhibitor and immune tolerance
- Episodic
- Episodic plus inhibitor

vWD for adult (≥15 yrs of age) and young (≤15 yrs of age) persons, including those in either clinical treatment group: Prophylaxis or Episodic.

Figure 1 Exposure assessment diagram

Model of Exposure Assessment

INPUT	MODULE	OUTPUT
• Age distribution of reported vCJD cases • Tissue surveillance-based vCJD prevalence (most tissue samples were from UK 20-29 yr-old group) • Epidemiological modeling-based vCJD prevalence	**Module 1** Prevalence vCJD in UK	• Prevalence of vCJD infected individual (including asymptomatic) among UK age groups
• Travel history of US plasma donors to UK, France, Europe • Relative risk of UK, France, Europe • Age distribution of donors • Frequency of donation • Screening questionnaire • Size of plasma pool	**Module 2** vCJD Prevalence and Levels in US Plasma Donors	• Percentage of plasma pools containing vCJD agent • Number of infected donations in a vCJD plasma pool • Initial quantity of vCJD
• Initial quantity of vCJD agent in infected blood • Amount of plasma per donation • Size of plasma pool • Reduction of infectivity during manufacture • Yield of FVIII • Vial size	**Module 3** FVIII Manufacturing and Processing	• Percentage FVIII vials containing vCJD agent • Quantity vCJD agent in contaminated FVIII
• Severity of disease • Treatment regimen • Annual dosage per patient • FVIII IU per dosage	**Module 4** Utilization of FVIII	• Annual exposure to vCJD agent

IV. A. Estimation of vCJD Prevalence in the United Kingdom (Module 1)

The potential prevalence of vCJD in the UK was and continues to be dynamic and changes throughout time as people are exposed to the BSE agent, infected with vCJD, develop the disease and eventually die. Variant CJD exposure and infections in the UK population likely occurred in proportion to the UK BSE epidemic which peaked in 1992. The first human vCJD cases were referred to UK public health authorities in 1994. To date, the number of cases per year in the UK reached a maximum of 28 in the year 2000, and since then has been declining annually with a total of 5 deaths in year 2005.

The FDA model assumes that the major source of potential vCJD in the US would likely be associated with plasma donors with a history of travel and residency in the UK, France or other countries in Europe since 1980 and who may have had dietary exposure to the BSE agent during their stay. The potential vCJD prevalence in US plasma donors with a history of travel to BSE countries since 1980 was estimated based on the UK vCJD prevalence. For US donors the UK vCJD prevalence was adjusted based on the proportion of time spent in the UK, the year of travel and age of the donor. Calculation of the potential vCJD risk for donors who traveled to France was estimated relative to the UK risk (or the relative risk), based on the amount of UK beef imports, the number of domestically acquired vCJD cases, and other factors. The relative risk for vCJD for France was assumed to be 0.05 times that of the UK risk (or 0.05 times the UK vCJD prevalence). Applying similar criteria for other countries in Europe their relative risk was assumed to be 0.015 times that of the UK. Risk was calculated in the model for donors by multiplying the UK vCJD prevalence by either 0.05 for travel to France or 0.015 for travel to other European countries and further adjusting the prevalence to account for factors such as the proportion of time spent, the year of travel and age of the donor.

The prevalence of vCJD in the UK is difficult to estimate because of the long incubation period of the disease and a lack of a validated test that can detect infection in its asymptomatic stages. The prevalence of asymptomatic vCJD infections in the UK was estimated in the FDA model using two different approaches based on two different data sources:

- **An epidemiological modeling-based approach that combined information from a study by Clarke and Ghani (2005) and diagnosed vCJD cases for 2002 and 2003 was used to estimate a UK vCJD case prevalence of approximately ~ 1.8 cases per million population.** There are some limitations associated with estimates of future vCJD cases and vCJD incidence in the UK generated by epidemiological modeling based on the current reported vCJD cases. Several factors used in epidemiologic modeling approaches are difficult to quantify and add uncertainty to the final estimated number of future vCJD cases. These factors include: the intensity of human exposure to the BSE agent, incubation period, time of infection, and whether illness will develop in individuals who are not homozygous for methionine at codon 129 of PrP. All cases of vCJD to date have occurred in individuals who are homozygous for methionine at this location. A more detailed description of the derivation of the epidemiological modeling-based estimate and further discussion of the limitations of the approach can be found in section IV. A. 1. below.

- **A tissue surveillance-based estimate for UK vCJD prevalence was generated using the results of a UK study that tested stored tonsil and appendix tissues collected from patients in the 1990s for the accumulation of prion agent (Hilton *et al* 2004).** The study yielded a much higher estimate of 1 in 4,225 (237 infections per million). However, while unconfirmed, the findings from this study provide a higher prevalence estimate and therefore should also be

considered. A total of 3 positive appendix tissues were identified among 12,676 tissue samples tested, yielding a mean UK vCJD prevalence estimate of 1 case per 4,225. This prevalence estimate was further adjusted to account for the age of the patients surveyed (mostly 20 – 29 year olds) to arrive at a total population-based estimate of UK vCJD prevalence.
This study was not controlled using tissues from a non-BSE exposed population, and false positive interpretations of the findings cannot be ruled out. It is also not known whether this staining of appendiceal tissues is a reliable marker for vCJD pre-clinical infection or for an individual's capability to transmit the infection through blood donation. However, while unconfirmed, the findings from this study provide a higher prevalence estimate and therefore should also be considered. A more detailed description of the derivation of the tissue surveillance-based estimate and further discussion of the limitations of the tissue surveillance study can be found in section IV. A. 2. below.

Two spreadsheet models were developed for the FDA risk assessment – one for each of the two prevalence estimates – but otherwise the models were identical in all other ways. We describe the surveillance variables and assumptions in the sections immediately below.

IV. A. 1. UK vCJD prevalence estimated using epidemiological modeling results (Clarke and Ghani 2005) and diagnosed vCJD cases for 2002 and 2003

The first approach used to estimate UK vCJD prevalence in the FDA model relied largely on epidemiological modeling results (Clarke and Ghani 2005) that estimated future 70 vCJD cases in the UK for the years 2004 – 2080. Since the FDA model estimates the baseline vCJD infection risk for pdFVIII product used in the year 2002, we assumed the potential risk for US donors should be calculated based on a UK vCJD prevalence that included all vCJD cases and potentially incubating vCJD infections in the year 2002. Therefore to estimate the number of cases and future vCJD infections in the UK for the years 2002 – 2080 we added the 32 known diagnosed cases in years 2002 and 2003 and the estimated future 70 vCJD cases (Clarke and Ghani 2005). We assumed that the 70 future cases predicted by Clarke and Ghani (2005) would be incubating vCJD infection in 2002. Therefore, the FDA model estimated an average of 102 cases and incubating vCJD infections for the year 2002 and assumed a 95% confidence interval of 42 – 222 cases. The results of the input information and calculations for the number of vCJD cases in the UK in 2002 are summarized in **Table 4.1**. Assuming the population of the UK in 1997 is approximately 58 million, the prevalence of vCJD (United Kingdom Office for National Statistics, 1997) would be a mean of approximately 1.8 vCJD infections per million population (102 potential vCJD cases / 58 million).

Table 4.1. FDA model estimation of UK vCJD cases for years 2002 – 2080.

	Diagnosed vCJD cases in the UK (Health Protection Agency, 2006)			Estimation of future UK vCJD cases (Clark and Ghani 2005)	FDA model: Estimation of UK vCJD cases for years 2002 - 2080
Year(s)	2002	2003	Total	2004 - 2080	2002 - 2080
Number of vCJD	16	16	32	70 (10 – 190)	102 (42 – 222)

cases					

There are some limitations associated with estimates of future vCJD cases and vCJD incidence in the UK generated by epidemiological modeling based on the current reported vCJD cases. Many of the published models of future vCJD cases or vCJD incidence in the UK, including Clarke and Ghani (2005) and Cooper and Bird (2003), use simplifying assumptions in generating their predictions. Although these simplifying assumptions are a necessary part of vCJD case estimation efforts, they contribute considerable uncertainty to the final case estimates. Generally, the types of assumptions used to estimate vCJD cases fall into four general areas. First, the models must estimate the number of clinical and pre-clinical BSE-infected cattle slaughtered in the UK to estimate the intensity of human exposure to the BSE agent. Second, they assume a level of effectiveness of the 1989 Specified Ban on Offals which was assumed to reduce the quantity of infectious BSE agent in the food supply, thereby reducing human exposure in the UK. Third, the models generate an appropriate mathematical representation (or statistical distribution) for the incubation period, which is represented by many usi a unimodal statistical distribution. There may be constraints on the incubation period used in the model (e.g., the vCJD incubation period of all individuals in the population would not exceed 40 years, etc.). Fourth, many of the modeling approaches incorporate age-specific dependencies that influence exposure, susceptibility to the disease, and incubation period. Depending on the assumptions used, estimates of future cases of vCJD have varied considerably. Past estimates of vCJD cases from epidemiological models predicted from 250 to 440 future cases under certain assumptions (d'Aignaux et al 2001). As actual reported vCJD cases peaked in 2000 and have since been declining, predicted estimates of future cases have decreased (Boelle et al 2003, Clarke and Ghani 2005, Cooper and Bird, 2003).

There are additional uncertainties in predicting future vCJD cases that might arise from individuals with different genetic backgrounds and susceptibilities in the UK population. To date, all known cases of vCJD have occurred in individuals that were methionine homozygous (MM genotype) at codon 129 of the prion protein gene (PNRP). Recent research has identified two individuals who were valine homozygous (VV genotype, also called non-MM genotype) at PRNP codon 129 (Ironside *et al* 2006) among the three prion protein positive samples identified by Hilton *et al* (2004). Clarke and Ghani (2005) did incorporate the possibility of wider genetic susceptibilities in some of their estimates of future vCJD cases. However, because no cases of clinical vCJD have been identified in individuals with non-MM genotype, it is uncertain whether these individuals will in fact develop or transmit clinical disease. Therefore, any estimation of the incubation period for potential cases with the non-MM genotype would rely heavily on assumptions, which adds considerable uncertainty to any estimate of the size or number of cases in a possible secondary wave of vCJD cases that might occur in non-MM individuals.

IV. A. 2. UK vCJD Prevalence derived from a Tissue Surveillance study

We used a second approach for estimating UK vCJD prevalence drawing on results from a tissue surveillance study that tested lymphoreticular tissue samples (tonsils and appendices) for prion protein accumulation. The study was a retrospective survey of stored tonsil and appendix tissues surgically removed from UK patients in 1995 and subsequent years. The authors identified appendix samples from 3 patients as positive for lymphoreticular accumulation of prion protein out of a total of 12,674 patient samples tested (Hilton *et al* 2004). No tonsil biopsies showed such findings. The significance of the detection of prion protein in the appendix is not certain, and it is not known whether this test is a

reliable marker for either vCJD pre-clinical infection or the ultimate development of disease. Nor is it known whether or not such detection is a marker for an individual's potential capability to transmit infection through blood donation. Results from the tissue surveillance study are summarized in **Table 4.2.** Assuming the sensitivity and specificity of the testing method is 100%, this translates roughly to a vCJD prevalence of of 237 cases per million (95% CI: 49 – 692 cases per million) for all age groups. The authors (Hilton et al 2005) indicated that approximately 60% of the samples tested (from 7,600 patients) came from patients 20-29 years of age. Among the 20-29 year old group we calculated a vCJD prevalence of approximately 400 cases per million for which we assumed a 95% CI of 100-1200 cases per million.

Table 4.2. Summary of surveillance testing of tonsil and appendix tissues in the UK.

Reference	Ages of population examined	Years tissue taken	Number of positives	Total samples examined	Rate per million (95% CI)
Hilton DA, et al. 2004	10 – 60+ yrs (60% of patients were 20-29 yrs)	1995 - 1999	3 Appendices	14,964 Appendices 1,739 Tonsils 4,029 excluded	237/million (49–692 per million)

There are some possible limitations of using the Hilton *et al* tissue surveillance study in estimating vCJD prevalence. In their tissue survey, Hilton *et al* stressed that there were uncertainties and suggested caution in attempting a prevalence estimate for infection or a prediction of future vCJD cases in the UK based on detection by immunohistochemical staining of lymphoreticular accumulation of prion protein in three of 12,674 adequate tissue samples studied. First, because the stage of vCJD infection during which the appendix first accumulates detectable amounts of abnormal prion protein is not known and because the accumulations might not be uniformly distributed throughout the tissue, the prevalence of infection might have been underestimated. Second, because the study design (lacking examination of a large number of similarly obtained appendices from a non-BSE-epidemic country) did not permit an estimate of specificity of the method or an independent confirmation of results, it is possible that the results might have been false positives leading to an overestimation of prevalence. In their paper the authors stated: "Although immunohistochemical accumulation of PrP in lymphoreticular tissues has not been demonstrated in any disease other than vCJD, the significance of the positive samples in this study is not certain. In one case, the immunohistochemical pattern of immunoreactivity resembled that seen in appendix tissue from pre-clinical and autopsied cases of vCJD, but in the other two cases, a more finely granular pattern of staining was present in relation to follicular dendritic cells, raising the possibility that these may be false positives. However, we have been unable to demonstrate PrP immunoreactivity in a range of other disorders including other human prion diseases, neoplastic disease, or a range of inflammatory conditions."

Assumption used in the model: All vCJD cases that occur after 2002 are incubating in year 2002.

Prevalence of vCJD among the UK population and the vCJD risk from using plasma-derived factor products are expected to be different from year to year since 1980. In this risk assessment, the potential vCJD risk for pdFVIII products was estimated for the baseline year of 2002, but the results and conclusions also are likely to reflect the current vCJD risk for recipients of pdFVIII. Prevalence of vCJD in 2002 for a specific age population in the UK was extrapolated from two estimates of prevalence discussed above based on age information of reported vCJD cases. The prevalence derived from above two different approaches varied by approximately 130 fold. The discrepancy reflects the limitation on the current knowledge of the disease. In order to evaluate the impact of uncertainty in estimation of vCJD prevalence, the FDA risk assessment provides estimated risk outcomes stratified by two estimates of prevalence.

Assumption used in the model: Our model assumed that distribution of asymptomatic cases across age groups would be the same as the distribution of observed symptomatic cases.

Additional technical information and details of analyses and modeling approaches are provided in Appendix A under section **A - IV.A.**

IV. B. Estimation of vCJD Prevalence in US Plasma Donors and Plasma Pools (Module 2)

The largest source of potential vCJD risk in US plasma donors is presumably associated with donors who traveled to or resided for extended periods of time in the UK, France and other countries of Europe since 1980. These donors might be exposed to the BSE agent in contaminated beef products and infected with vCJD during travel and residence abroad. Other populations in the US at potential risk for vCJD include US military deployed for extended periods of time in the UK or other countries of Europe and individuals in the US who received blood collected in Europe ("Euroblood"). The prevalence of BSE in the US cattle population is very low and therefore there is a very low probability that domestic dietary exposure to the BSE agent would give rise to human vCJD cases. Because of this very low prevalence, risk via US domestic dietary exposure was assumed to be negligible in the model.

This module estimates the annual number of plasma pools that are used to manufacture pdFVIII from plasma collected in the United States, the number of pools that potentially contain a donation from an infected plasma donor, and the potential quantity of vCJD agent that may be present in a positive pool. The potential vCJD risk for US plasma donors is likely associated with dietary exposure to BSE agent during periods of travel or residence in the at-risk geographic areas where BSE occurred. The percentages of blood donors with a history of travel or residency in BSE countries, who are military members who resided in bases in UK and elsewhere in Europe during 1980-1996, and who are recipients of "Euroblood" were obtained from 1980-1996 Blood Donor Travel Survey conducted by American Red Cross (TSEAC 2000). The percentage was calculated by destination (e.g., the UK, France or other European countries) and duration of travel.

Two different types of plasma are used in manufacture of pdFVIII. Source Plasma is collected through plasmapheresis, a process that separates red blood cells from plasma and returns red blood cells to the donor. Recovered plasma is prepared from whole blood units collected from blood donors. Source

Plasma accounts for approximately 80% of the total plasma collected annually in the United States, and recovered plasma accounts for the remaining 20%. Source Plasma donors are usually younger than blood (recovered plasma) donors, and are thought to travel less so presumably their vCJD risk may be somewhat lower than that of blood donors. However, because of their younger age demographic, Source Plasma donors are likely to be more susceptible to vCJD infection. Additionally, Source Plasma pools are usually smaller and contain larger volume donations (an average of 700 milliliters) from fewer donors than recovered plasma pools (average volume of a donation is ~200 milliliters). Plasma from fewer donors reduces the chance that a plasma pool may contain a donation from an infected donor. However, because Source Plasma donors are allowed to donate more frequently, and give more plasma per donation, there is a greater chance that if a vCJD infected donor were in the Source Plasma donor pool that they may contribute multiple donations to a single plasma pool or donate to multiple pools. However, blood deferral policies instituted beginning in 1999 are believed to have reduced the risk of vCJD donations by more than 90%. The effectiveness of the deferral policy in removing potential vCJD risk from the donor and donation pool is included in the FDA model. Because of the unique characteristics and potential differences in risk for Source and recovered plasma donations and plasma pools, the FDA risk assessment modeled Source and recovered plasma pools separately, and considered factors that may result in different risk for pdFVIII product made from each of the two types of plasma.

IV. B. 1. a. Annual US plasma donors and characterization by age

Age is an important factor in estimating potential vCJD risk for US plasma donors. The FDA model is organized by age groups 18 and 19 yr olds, 10-14, 15-29, etc. (by five yr age groups to age 69) and calculates all risk information and makes all adjustments based on age groups. Each of these age groups forms a "bin" and in each of these bins donors are categorized by country of travel, vCJD prevalence (or relative risk) for country of travel, duration of travel, year of travel, type of donation (Source or recovered), donation rate, etc. The output at the end of this portion of the model is an estimation of the number of US donors in each age group that are potentially infected with vCJD. The model further incorporates the effect of FDA donor deferral policies, implemented beginning in 1999, that are believed likely to reduce the possible risk from blood donors potentially infected with vCJD by ~ 90%.

This specific portion of the model estimates potential age specific vCJD risk for both Source and recovered plasma donors. As mentioned above, donor age is an important factor associated with frequency of travel and susceptibility to the disease and influences the vCJD risk for a particular type of donor. For instance, Source Plasma donors as a group are generally younger than recovered plasma donors (see percentages of donors for Source and recovered plasma donors by age group in **Table 4.3**). Also, the younger Source Plasma donor population likely travels less, and thus, likely has a lower potential vCJD risk. However, this lower risk may be offset by the possibility that younger persons may be more susceptible to infection by the vCJD agent. The purpose of this portion of the model is to characterize plasma donors and their donations according to donor age to more accurately estimate the number of potential vCJD infected donors and donations containing vCJD agent. In turn this information will be used to estimate the probability that a plasma pool used in the manufacture of pdFVIII may contain a donation with vCJD agent.

Additional technical information and details of analyses and modeling approaches are provided in Appendix A under section **A - IV.B.**

Table 4.3. Reported vCJD cases in the UK and percent of US Source Plasma and blood (recovered plasma) donors by age groups

Age group	<10	10-14	15-19	18-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	>70
Reported vCJD cases in UK (through 2003)[a] (%)	0	5 (3.4%)	27 (18.4%)		32 (21.8%)	30 (20.4%)	22 (14.9%)	13 (8.8%)	5 (3.4%)	3 (2%)	5 (3.4%)	0 (0%)	5 (3.4%)		
Age distribution of US Source Plasma donors (%)[b]	0	0	0	12%	29.3%	14.1%	14.1%	9.6%	9.6%	5.8%	5.8%	0%	0%	0%	0%
Age distribution of US Blood (Recovered plasma) donors[c]	0	0	0	5%	13%	8%	10%	12%	13%	12%	11%	7%	4%	5%	0%

[a]Hilton *et al.* 2004

[b]Plasma Protein Therapeutics Association (Jan 07, 2005). Where data were organized in broader age group we allocated donor equally among smaller 5 year. age groups

[c] Data provided to FDA by Westat in 2002

IV. C. Estimation of the probability that a plasma pool may contain a donation from an infected donor that contains vCJD agent

The purpose of this section of the model is to estimate the prevalence of vCJD in US donors who may have been exposed to the BSE agent and potentially infected with vCJD during travel, residence, military service in the UK, France or other countries in Europe since 1980. The vCJD prevalence in U donors is then used to estimate the probability that a plasma pool may contain a donation from a vCJDinfected donor with infectious agent in their blood at the time of donation.

The starting material for manufacturing pdFVIII is a plasma pool containing donations from thousands of donors. The probability that a plasma pool contains a donation with vCJD agent is a function of the prevalence of vCJD in the US donor population and the total number of donors and donations present in a pool used to manufacture pdFVIII. For US donors with a history of travel, a key factor in estimating the vCJD risk is the region or country of travel, i.e., the UK, France or other countries in Europe, since 1980. From there we make several adjustments to the vCJD prevalence for US donors. The model incorporates the age of donors into the estimate of vCJD prevalence – donation rate for various age groups is important since the majority of donors are less than 40 years of age. Furthermore, vCJD prevalence for each age group is determined. Since vCJD primarily affects younger persons (median age 28 yrs) and donors are younger – they are at particular risk for vCJD and may unknowingly transmit the agent via donations. The model further adjusts vCJD prevalence based on the year of travel – for instance, a traveler in 1992 that visited the UK at the height of the BSE epidemic faces a higher BSE exposure risk and risk of vCJD infection than someone who traveled to the UK in 1997 after more

stringent food controls were implemented in the UK. Also, the model incorporates information on the duration of the travel based on survey information of travel history for whole blood users. Also considered in the model is the type of donation – whether Source Plasma or for recovered plasma, since the number of donations by an individual per year varies dramatically for these two types of plasma. Finally, the model assumes that *a plasma donation from a vCJD infected individual contains the infectious vCJD agent*, and thus poses a potential risk, if the individual is in the last half of the incubation period for the disease (and likely prionemic). However, current deferral policies prevent potentially infected donors with a history of extended travel or residence to BSE countries since 1980 from donating blood. *This geographic deferral policy effectively lowers the prevalence of vCJD in the US donor population by removing donors with a history of extended travel or residence in the UK and other countries in Europe since 1980.* The FDA risk assessment incorporates the effectiveness of current geographic deferral policy in reducing the risk of vCJD transmission through plasma derivatives. The final outputs or results from the model offer estimates of the potential number of Recovered and Source Plasma donors who may be infected with vCJD, and the model further derives an estimate of the number of infected donors who may actually have agent in their blood at the time of donation.

FDA evaluated a number of possible sources of exposure to the BSE agent that could potentially result in infection with vCJD in US plasma donors. The model and risk assessment assumes that the greatest potential vCJD risk for US plasma donors was likely associated with exposure to the BSE agent during extended travel or residence in the United Kingdom (for 3 months or more from 1980 – 1996), or France and other countries in Europe (5 or more years since 1980).

The following sections in the document describe in detail our mathematical approach for modeling and estimating the risk for US plasma donors who lived or resided in:

- United Kingdom from 1980 – 1996 for ≥ 3 months (Described in Appendix A - section A-IV.C.1.a.)
- France - since 1980 for ≥ 5 years (Described in section IV.C.1.b. and in Appendix A – sections in A-IV.C.1.b.)
- Other countries in Europe – since 1980 for ≥ 5 years (does not include plasma donors) (Described in section IV.C.1.c. and in Appendix A – sections in A-IV.C.1.c.)
- US Military personnel or their dependents – deployed in UK or other countries in Europe since 1980 (Described in section IV.C.1.d. and in Appendix A – sections in A-IV.C.1.d.)
- Euroblood recipients in US – that received blood collected from donors in Europe (Described in section IV.C.1.e. and in Appendix A – sections in A-IV.C.1.e.)

Dietary exposure in the US through consumption of domestic beef potentially contaminated with BSE agent was considered negligible based on our calculations, and was not included in the final model of this risk assessment.

Assumption used in the model: The BSE exposure risk for an individual on extended travel or during residence to the UK, France, or other countries in Europe since 1980 is proportional to the duration of the stay or time spent. For instance a person who lived in the UK for one year has one-fifth the risk of a donor who spent five years.

IV.C. 1. US plasma donors with history of travel to the UK, France or other Countries in Europe: Annual number potentially infected and vCJD agent is present in the blood

The model considered all major potential sources of vCJD infection for US plasma donors. The most likely cause of vCJD is dietary exposure of donors to the BSE agent through the consumption of BSE-contaminated beef during travel to a country where BSE was present in the cattle population. Accordingly, the greatest risk of BSE exposure in the UK likely occurred during the period from 1980 to 1996. The BSE exposure risk for France was likely lower than that of the UK and likely present since 1980. Also, other countries in Europe likely posed an even lower risk than France of human exposure to the BSE agent since 1980. Generally, because of the higher prevalence of BSE in the UK in the late 1980s and early-to-mid-1990s and the higher occurrence of vCJD in the UK human population (currently 162 cases as of August 2006), US donors who traveled to the UK from 1980 through 1996 are likely at higher risk for vCJD infection than donors who traveled to other European countries in the same time period. This model uses the concept of relative risk to estimate the vCJD risk (and prevalence) for a donor population – a value of 1 is used for the UK and this is equal to the vCJD prevalence. Relative risk is used to compare the risk of other regions to that of the UK and is estimated based on factors such as amount of contaminated feed, percentage of meat from the UK, number of cases of BSE, vCJD, etc. In subsequent sections on estimating risk for donors that traveled to France, France is assumed to have a relative risk of 0.05, since they received about 5% of their beef and feed supply from the UK and also have reported domestically-acquired vCJD cases.

The potential vCJD risk faced by US plasma donors exposed to vCJD during travel or residence in the UK (since 1980) is assumed in the model to be proportional to the time a donor spent in the UK (or France or other countries in Europe), and also a function of the age of the donor, and year of travel. Duration of travel is an indicator of possible exposure and we assumed that the probability of exposure was proportional to the time spent in the UK from 1980 - 1996. The longer the duration of travel, the higher the risk of human exposure to the BSE agent. The magnitude of possible exposure to the BSE agent is also influenced by the specific year of travel. The risk is the highest when travel took place during the peak of BSE epidemic in 1992. The FDA risk assessment grouped plasma donors based on age, destination, duration and year of travel, estimated the number of donors, probability of an individual being infected, and potential number of infected donors for each group. Then, numbers of infected donors from all groups were summed to arrive at an estimate of the total number of potential vCJD infected donors in the US that may contribute to FVIII plasma pools. The vCJD agent may only be present in the blood of an infected person during the last half of the disease. Accordingly, the FDA risk assessment considered only those vCJD-infected donors who were in the last half incubation period of the disease as being capable of possibly transmitting the disease to others through their plasma donations.

The FDA risk assessment evaluates the effectiveness of current geographic deferral policy in reducing the risk of vCJD transmission through plasma derivatives. Current policy defers individuals with history of long term travel in BSE epidemic areas since 1980, providing a barrier for donors potentially infected, thus effectively lowering the vCJD prevalence in the US donor population by an estimated 90% or more. However, there may be residual risk associated with donors who do not meet criteria for donor deferral, or who meet those criteria, but fail to be deferred due to limitations of the donor screening process. Although current policy defers US donors that received transfusions while in the UK

or France since 1980, the FDA risk assessment did not estimate the potential vCJD risk for these donors.

Assumption used in the model: vCJD risk for the US plasma donor population is a sum of the risk from all exposure sources.

Assumption used in the model: The FDA risk assessment assumed vCJD agent is present in the plasma of infected person only in the last half of the incubation period of the disease, based on animal studies on vCJD infectivity of blood.

Assumption used in the model: The mean incubation period for vCJD is 14 years, and the median incubation period is 13 years.

The United Kingdom has the highest number of reported BSE and vCJD cases in the world. US plasma donors that traveled to the UK during 1980-1996 are considered at risk of exposure to the BSE agent and possibly infected with vCJD. Donors that traveled to France and other countries in Europe are assumed to be at significantly lower risk since the BSE epidemic in those regions was many times smaller than in the UK. This part of the model further characterizes the plasma donors of each age group who have history of travel or residence to the UK (for ≥ 3 months from 1980 – 1996), and France or other countries in Europe (for ≥ 5 yrs since 1980), by duration and calendar year of travel, estimated the number of potential donors who may be infected, and number of donor who may be in the last half incubation period (prionemic) at year 2002.

IV. C. 1. a. US plasma donors with history of travel to the UK: Number of donors potentially infected and vCJD agent is present in the blood

This portion of the model calculates the potential vCJD risk for US plasma donors who traveled to the UK since 1980 and estimates the potential number of donors with vCJD agent present in their blood and donated to plasma pools used to manufacture pdFVIII. For blood and plasma donors with a history of travel to the UK FDA guidance (2002) currently recommends that blood and plasma collection centers "....defer blood and plasma donors who have traveled or resided in the U.K. for a cumulative period of 3 or more months between 1980 and the end of 1996." The deferral policy likely eliminates much approximately 90% of the potential vCJD risk associated with donor travel to BSE countries when the disease was present. The model incorporates the effectiveness of the deferral policy in reducing risk. However, residual vCJD risk remains from two sources. One source includes potential risk associated with deferrable donors that continue to donate because of limitations in the donor screening process. The second potential source is associated with donors with a history of travel that is less than the deferrable period (blood or plasma donors with a history of less than 3 months of travel to the UK).

In addition to the effectiveness or deferral policies, the residual risk of vCJD infection in US donors is calculated based on the proportion of time spent in the UK by US donors compared to a UK resident whose risk is equivalent to the UK vCJD prevalence. Additionally, the model considers factors such as calendar year of travel, age of donor, type of donation (Source or recovered plasma), possible incubation period of the disease, and whether vCJD agent is present in the blood of a vCJD infected donor. The outcome of this portion of the model predicts the number of US plasma donors who were

potentially infected with vCJD during travel to the UK (see Table 1). The model also predicts the number of donors that potentially have agent present in their plasma that may possibly donate to plasma pools used to manuafacture pdFVIII in the US.

Additional technical information and details on the model calculations of potential vCJD risk and modeling approaches are provided in Appendix A and described in sections in **A - IV.C.**

IV. C. 1. b. Estimation of the number of US plasma donors with a history of extended travel to France potentially infected and vCJD agent is present in the blood

The FDA risk assessment model assumes that the likely source for vCJD risk in US plasma donors is associated with those donors who have a history of travel to the UK from 1980 – 1996, or travel to France or other countries in Europe since 1980. Presumably the greatest vCJD risk resides with travel to the UK since the BSE epidemic was several orders of magnitude larger and the number of vCJD cases greater than that of any other country or region. However, donors who traveled to France are potentially at risk but that risk is likely significantly lower than that of the UK. France likely imported BSE-contaminated feed materials in the 1980s and 1990s and approximately 5% of its beef was supplied by the UK at the time of its BSE epidemic. To date, France has reported 20 cases of vCJD supporting the notion that there may be vCJD infection risk for US donors that may have traveled to or resided in France since 1980.

The FDA risk assessment model incorporates information from current guidance for geographic donor deferrals for vCJD (FDA 2002) to estimate potential vCJD risk for donors with a history of travel to countries where BSE has occurred. FDA guidance (2002) indicates that for donors with a history of travel to France "we now recommend deferral of blood and plasma donors with a history of 5 or more years of cumulative residence or travel in France since 1980." This portion of the model calculates the potential residual US vCJD risk based on the estimated vCJD prevalence among US plasma donors who traveled to France since 1980 and donated to plasma pools used to manufacture pdFVIII. The residual vCJD risk includes risk associated with donors who do not meet criteria for donor deferral (e.g., donors with a history of less than 5 years of travel to France), or who meet those criteria, but fail to be deferred due to limitations of the donor screening process. The model considers factors such as duration of travel, calendar year of travel, age of donor, type of donation (Source or recovered plasma), possible incubation period of the disease, and whether vCJD agent is present in the blood of a vCJD infected donor. The outcome of this portion of the model predicts the number of US plasma donors potentially infected with vCJD and results are shown in Table 4.4. The model goes on to predict the number of donors with a history of travel to France infected with vCJD that may potentially have agent present in their blood at the time of donation.

Additional technical details on the model calculations of potential vCJD risk for donors with a history of travel to France can be found in Appendix A – in sections under A-IV. C.1.b.

IV.C. 1. c. Number of US plasma donors with a history of travel to countries in Europe (other than the UK and France) potentially infected and vCJD agent is present in the blood

The FDA risk assessment model incorporates information from current guidance for geographic donor deferrals for vCJD (FDA 2002) in estimating potential vCJD risk for donors with a history of travel to countries where BSE has occurred. The model quantifies potential residual vCJD risk for US plasma donors. The model assumes that the residual vCJD risk likely originates from two sources, one source of potential risk is associated with donors with deferrable risk that continue to donate due to limitations in the donor screening process. The second source of vCJD risk is associated with donors with a history of travel that was less than the deferrable period (blood donors with a history of less than 5 years of travel to Europe). FDA guidance (2002) indicates that for donors with a history of travel to countries in Europe (other than the UK) "the current recommendation is to exclude from transfusion use, blood and blood components from donors with a history of 5 or more years of residence or travel in Europe outside of the UK". Furthermore, for donors with a history of travel to countries in Europe (other than the UK and France) the FDA guidance (FDA 2002) states "...we do not recommend that you defer Source plasma donors who have lived or traveled in Europe for 5 or more years".

The FDA risk assessment model reflects FDA guidance for vCJD deferral of Source Plasma and recovered plasma donors. Because the guidance recommendations for each type of plasma were different the model estimated the potential vCJD risk as follows:

- Recovered plasma donors – the FDA risk assessment **calculated** the potential vCJD risk because deferral was **recommended** for donors with a history of 5 or more years of residence or travel to countries in Europe (other than the UK)
- Source Plasma donors - the FDA risk assessment did **not calculate** the potential vCJD risk because deferral was **not recommended** for donors with a history of 5 or more years of residence or travel to countries in Europe (other than the UK and France).

The term "countries in Europe" as used in this portion of the risk assessment is defined as all countries in Europe (other than the UK and France). The UK and France BSE risk is assumed to be higher than that of other countries in Europe, therefore the potential donor vCJD risk for donors with a history of residence or travel to the UK and France described in sections IV.C. 1. a. and IV.C. 1. b.(and sections in Appendix A – under sections A-IV.C. 1. a. and A-IV.C. 1. b.), respectively, of this document. Also, US donors with a history of residence on US military bases in Europe may have a higher potential vCJD risk so their risk was calculated separately and is described in section IV.C.1.d.

This portion of the model calculates the vCJD prevalence, or number of US blood donors who traveled to other countries in Europe (other than the UK and France) since 1980 and were potentially infected with vCJD and donated to recovered plasma pools used to manufacture pdFVIII. Recovered plasma is plasma that is separated or "recovered" from a unit of whole blood soon after the blood is collected. The model considers factors such as duration of travel, calendar year of travel, age of donor, type of donation, possible incubation period of the disease, and whether vCJD agent is present in the blood of a vCJD infected donor. The outcome of this portion of the model predicts the number of US blood (recovered plasma) donors who are potentially infected with vCJD and have agent present in their plasma.

The model assumes that one of the most likely sources for vCJD risk in US plasma donors is associated with those donors who have a history of travel to the UK from 1980 – 1996, and France and other countries in Europe since 1980. Text in subsequent sections of this document will specifically discuss the potential vCJD infection risk for US plasma donors with a history of travel to countries in Europe (other than the UK and France) since 1980. Presumably the greatest vCJD risk resides with travel to the UK since 1980 since the BSE epidemic was several orders of magnitude larger and the number of vCJD cases greater than that of any other country or region. France is likely at significantly lower risk than the UK but the risk is still likely higher than the vCJD risk of other countries in Europe. There have been 20 cases of vCJD reported in France as of August 2006.

Donors who traveled to other countries in Europe (other than the UK or France) are potentially at risk but that risk is likely significantly lower than that of the UK, and France. Many European countries (other than the UK and France) likely imported BSE-contaminated feed materials in the 1980s and 1990s and approximately 1.5% of their beef may have been imported from the UK at the time of its BSE epidemic. The potential for BSE exposure to donors who traveled to or resided in other countries in Europe is possible. Hence, there may be a vCJD infection risk for blood donors who may have traveled to or resided in a European country (other than the UK and France) for periods greater than 5 years since 1980. The current US vCJD geographic deferral policy defers blood donors with a history of travel or residence in a country in Europe (other than the UK and France) for 5 years or more since 1980. Source Plasma donors who resided in a country in Europe (other than the UK and France) are not deferred from donation. Because Source Plasma donors are not deferred from donation, their risk is not estimated by the model. Therefore, this portion of the model only estimates potential vCJD risk for US recovered plasma donors who traveled to countries in Europe (other than the UK) since 1980.

Additional technical details on the model calculations of potential vCJD risk for donors with a history of travel to countries in Europe (other than the UK and France) can be found in Appendix A – in sections under A-IV. C.1.c.

IV. C. 1. d. Number of US plasma donors deployed by the military in the UK or other countries in Europe and potentially infected with vCJD

The FDA risk assessment model incorporates information from current guidance for geographic donor deferrals for vCJD (FDA 2002) in estimating potential vCJD risk for donors with a history of travel to countries where BSE has occurred. The FDA guidance (2002) indicates that for donors with a history of service on US military bases in Europe "we recommend that you should indefinitely defer current and former US military personnel, civilian military personnel, and their dependents who were stationed at European bases for 6 months or more during the time periods outlined (in the document)".

The model quantifies potential residual vCJD risk for deferrable donor populations. The residual vCJD risk likely includes two possible sources of risk. One source of risk is associated with donors with deferrable risk that continue to donate because of limitations in the donor screening process. A second possible source of risk is associated with donors who have a history of travel that is less than the deferrable period (blood donors with a history of less than 5 years of travel to Europe). For the purposes of this risk assessment we assumed that exposure to the BSE agent and potential vCJD infection of military personnel or dependents may have occurred during their deployment to US military bases in the UK, France and other European countries during the period from 1980 through 1996, through consumption of BSE contaminated beef procured for use on US military bases from the UK.

Exposure via UK beef likely varied but the model assumes that up to 35% of beef consumed on military bases in Europe came from the UK. The model assumes that approximately 2% of US blood and plasma donors may have been military, military family or their dependents posted to US military bases in the UK or elsewhere in Europe from 1980 through 1996 (TSEAC, 2002). It was further assumed that the average deployment period was 2 years. Because data on military service of plasma donors was not available, the risk assessment used data available on military deployment by whole blood donors.

Additional technical details on the model calculations of potential vCJD risk for donors with a history of military service in countries in Europe can be found in Appendix A – in sections under A-IV. C.1.d.

IV. C. 1. e. Annual number of US plasma donors who have been Euroblood recipients

Euroblood is whole blood that was collected at several different collection centers in Europe and shipped to and used by transfusion centers in the United States. The practice was stopped in 2002 with the implementation of geographic vCJD deferrals. The blood was used largely on in the New York City metropolitan area and possibly in other areas on the east coast of the US

The model assumed that a total of 1.2% of US blood donors may have received Euroblood (TSEAC, 2002). To our knowledge there are no specific data available for plasma donors, therefore, data for blood donors was used in this risk assessment.

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

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

This portion of the model sums the total number of all potential US donors that may have been infected with vCJD from different sources. The model estimates the total number of all plasma donors who may be infected with vCJD during extended residence, travel or military service in the UK, France, or other countries of Europe. Potential vCJD risk is also estimated for donors that may have received Europblood. Furthermore, the model estimates the number of total US donors potentially infected with vCJD and have agent present in their plasma.

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

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

Additional technical information and details of analyses and modeling approaches for estimating potential vCJD in the model are provided in Appendix A under section **A - IV.C.1.**

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

No validated test is currently available to detect the presence of vCJD agent in blood or plasma. The donor questionnaire, administered to all blood donors, can be used to potentially screen donors for potential vCJD risk based on travel history, specifically involving extended travel to the UK, France or other countries in Europe where BSE was known to occur. In 1999 the FDA implemented a donor deferral policy aimed at reducing the potential risk of donations from those potentially exposed to the BSE agent during extended travel to the UK, France and other countries of Europe. Current policies (FDA 2002) defer blood and plasma donors:

- diagnosed with vCJD or other forms of CJD
- at increased risk for CJD, e.g. the donors have received a dura mater transplant, or human pituitary-derived growth hormone; the donors have blood relatives diagnosed with CJD
- with a history of a 3-month or longer travel/residency period in the UK between 1980-96
- with a history of a 5-year or longer travel/residency period in France since 1980
- current or former US military personnel, civilian military personnel, and their dependents resided in Northern Europe for 6 months or more between 1980-90, or resided in military bases elsewhere in Europe for 6 months or more from 1980 to 1996
- received a transfusion of blood or blood components in the UK since 1980
- injected bovine insulin since 1980 unless it is confirmed that injected bovine insulin was not made after 1980 from UK cattle, and
- whole blood donors with a 5-year or longer travel/residency period in Europe (other than the UK) since 1980

Deferral of donors with a history of travel to BSE countries is an effective tool for eliminating a significant portion of potential vCJD risk in US donors. The model incorporates information on the effectiveness of US deferral policies in reducing potential vCJD risk and potential vCJD prevalence in the US donor population.

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.

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.

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.

Specific technical information and details of analyses and modeling approaches in estimating the effectiveness of donor deferral policies in reducing potential vCJD risk in US donors are provided in Appendix A under section **A - IV.C.2.**

Model Results:
The largest source of potential vCJD risk in US plasma donors is presumably associated with donors who traveled to or resided for extended periods of time in the UK, France and other countries of Europe since 1980. These donors might be exposed to the BSE agent in contaminated beef products and infected with vCJD during travel and residence abroad. Other populations in the US at potential risk for vCJD include US military deployed for extended periods of time in the UK or other countries of Europe and individuals in the US who received blood collected in Europe ("Euroblood"). The prevalence of BSE in the US cattle population is very low and therefore there is a very low probability that domestic dietary exposure to the BSE agent would give rise to human vCJD cases. Because of this very low prevalence, risk via US domestic dietary exposure was assumed to be negligible in the model.

The FDA FVIII risk assessment model uses the concept of relative risk to semi-quantitatively estimate the vCJD risk for US plasma donors with a history of travel to the UK, France and other countries of Europe since 1980. Relative risk is the vCJD risk in a population relative to the UK vCJD relative risk of 1 (or 100%), which is equal to the prevalence of vCJD in the UK. Elements used in the model to calculate vCJD risk for travelers include travel destination (UK, France or other countries of Europe), duration of travel, specific year of travel, and age of donor. The estimated vCJD risk for all potential routes was summed to generate the total mean predicted number of potential vCJD-infected plasma donors in the US. Because of current policies, a blood or plasma donor potentially infected with vCJD has a high probability (85% - 99% chance) of being deferred from donation. Since 2002 FDA has recommended that individuals who resided in the UK for a period of 3 months or more from 1980 to 1996, or resided in France or other countries of Europe for a period of 5 years or more since 1980 be deferred from donating blood or plasma. The model assumes the deferral policy in the US is approximately 85% to 99% effective in reducing the vCJD risk for blood and plasma-derived products. **Table 4.4** (below) shows results from the model predicting the mean number per year of potential vCJD-infected donors and the number of potential vCJD donors who are likely not deferred from donation and donate to plasma pools used to manufacture pdFVIII.

Although it is likely that most would be deferred by the current policy, some plasma donors potentially infected with vCJD may not be deferred and may donate to plasma pools used in the manufacture of pdFVIII. Totaling the estimated number of US donors potentially infected with vCJD yields a mean of approximately 0.01 donors per year based on calculations using a vCJD case-based epidemiological model estimated prevalence of ~1.8 in 1,000,000 (Clarke and Ghani 2005), or a mean of approximately 1.160 donors per year using calculations based on a tissue sample surveillance study yielding a prevalence estimate of 1 in 4,225 (Hilton *et al* 2004) (**Table 4.4**).

Table 4.4 Model Results: Annual Number of US plasma donors predicted by model to be potentially infected with vCJD and donate to plasma pools used to manufacture pdFVIII. Results from model provided for two different UK vCJD prevalence estimates. In the table the mean value is shown above with the 5th and 95th percentiles in parentheses below. The total number of vCJD donors for each prevalence estimate has been rounded to nearest decimal place.

	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)*	
	Mean number (5th - 95th perc)[a] US plasma donors with history of travel to:		Mean number (5th - 95th perc)[a] US plasma donors with history of travel to:	
	United Kingdom	*France, Europe, or* Military Service	United Kingdom	*France, Europe, or* Military Service
Total number vCJD donors for all US pdFVIII pools Prior to screening	*0.0493* (0–0)[b]	*0.0108* (0–0)[b]	*5.32* (0–13)	*0.77* (0–3)
Number vCJD donors NOT DEFERRED (ineffective screening)	*0.0035* (0–0)[b]	*0.0007* (0–0)[b]	*0.39* (0-2)	*0.056* (0–0)[b]
Number vCJD donors NOT DEFERRED (short-term travel <3 mos, UK; <5 yrs, FR and EU)	*0.0049* (0–0)[b]	0.0017 (0–0)[b]	*0.483* (0–2)	0.0343 (0–0)[b]
Total number vCJD infected donors NOT DEFERRED Donate to pdFVIII Plasma Pools	***0.013*** *(0–0)*[b]		***1.160*** *(0–4)*	

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

[b] For a 5th and 95th 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.

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

Model Results:
The percentages of source or recovered plasma pools, potentially containing vCJD agent, used to manufacture pdFVIII in the US were estimated by the model. The majority of pdFVIII is manufactured from Source Plasma and the minority from recovered plasma. Manufacturers provided information to FDA on the approximate range and average number of donations per plasma pool which was combined with information on market share to develop two aggregate statistical distributions, one each representing donations for source and for recovered plasma pools. The distributions were used to predict the number of donations per source or recovered plasma pool in the model. The model used information on the number of donations per pool by type (either source or recovered), combined with estimated yield of pdFVIII per pool, and estimated the total number of plasma pools used to manufacture pdFVIII products distributed in the US in 2002.

As a general comment, the number of donations per plasma pool influences the potential exposure risk for infrequent recipients of plasma derivatives. The use of fewer donations and smaller plasma pools during manufacturing would result in a lower percentage of plasma pools potentially containing vCJD agent and potentially expose a lower percentage of infrequent recipients to vCJD (if present). Frequent recipients of plasma-derived products would likely face a similar level of risk of potential vCJD exposure whether large or small numbers of donations per plasma pool are used in manufacturing.

Lower UK vCJD prevalence estimate of ~1.8 in 1,000,000 (based on Clarke and Ghani; 2005). The lower prevalence estimate used in the FDA model suggested that an average of 0.027% of all US plasma pools used to manufacture pdFVIII in the year 2002 potentially contained the vCJD agent (bottom, **Table 4.5**). The lower disease prevalence is associated with model results predicting a much lower percentage of plasma pools potentially containing vCJD agent. In fact, on average >99.9% of the time plasma pools would be predicted not to contain a donation from a vCJD infected donor. Only an average 0.10% recovered plasma pools would be predicted by the model to contain a vCJD donation from a US donor in any given year. Of interest at the lower prevalence, the model predicts that the occurrence of a recovered plasma pool with a vCJD donation would be infrequent (as indicated by 5th and 95th percentile values of 0); occurring (as estimated by the model), at a rate of 1 in 100 years. Also at the lower prevalence, a vCJD donation in a Source Plasma pool would be predicted to be even more infrequent and predicted by the model to occur at a rate of 1 in 200 years.

Higher UK vCJD prevalence estimate of 1 in 4,225 (Hilton et al 2004). The higher prevalence estimate used in the FDA model suggested that an average of 2.41% of all US plasma pools used to manufacture pdFVIII in 2002 were predicted by the model to contain vCJD agent (**Table 4.5**). It should be noted that fewer recovered plasma pools than Source Plasma pools are used in the US annually to produce pdFVIII. Also, recovered plasma pools contain the largest number of plasma donations. Since recovered plasma pools

contain many more donations than Source Plasma pools the likelihood that a recovered plasma pool may contain a donation from an individual potentially infected with vCJD is considerably higher than for a Source Plasma pool. Using the higher UK vCJD prevalence estimate, the model predicts that on average, 9.12% of recovered pools and 0.96% of Source Plasma pools potentially contain vCJD agent.

Table 4.5 Annual Percentage of US Plasma Pools Potentially containing a vCJD Donation. Results from model include only those US plasma pools used annually to manufacture pdFVIII.

- Results provided for two different UK vCJD prevalence estimates.

	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)	
	Source Mean (5th - 95th perc)[a]	Recovered Mean (5th - 95th perc)[a]	Source Mean (5th - 95th) perc)[a]	Recovered Mean (5th - 95th perc)[a]
Percent pools potentially containing vCJD agent	0.01% (0 – 0%)[b]	0.10% (0 – 0%)[b]	0.96% (0 – 5.88%)	9.12% (0 – 40.17%)
Average percent pools potentially containing vCJD agent	**0.027 %** (0 – 0 %)[b]		**2.41 %** (0 – 10 %)	

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

[b] For a 5th and 95th 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.

Additional technical details on the calculation of the annual total percentage of all plasma pools potentially containing a vCJD donation that are used to make pdFVIII in the US are provided in Appendix A in sections under A-IV. D.

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

Based on limited available data (see below), FDA believes that the quantity of infectivity present in blood from a vCJD infected individual in i.v. ID_{50} is likely represented by a distribution with the following characteristics: Minimum value = 0.1, 5th percentile = 2,

Most likely value = 10, 95th percentile = 30, and Maximum value= 1,000 i.v. ID_{50}. Given the possible parameters, statistical distributions were fitted to the selected parameters using Best Fit part of the @Risk Professional software package (Palisade Corporation, New York). Using the software we determined that a log normal statistical distribution of (2, 12, 30) i.c. ID_{50}/ml (5th percentile, most likely, and 95th percentile) with minimum and maximum of 0.1 and 1,000, respectively, provided the best fit.

Conclusions from several research groups arrive at somewhat similar estimates for the quantity of infectivity that might be present in the whole blood of mice and hamsters. Using a mouse model and human CJD Brown *et al* (1999) found a range from 0.5 to 15 mouse i.c. IU per ml which we assumed to be roughly equivalent to 1 to 30 i.c. ID_{50} (assuming a linear dose-response for infectivity). An infectious unit is the quantity of infectivity associated with a 100% probability of infection in recipients and roughly equates to two ID_{50} units (1 IU = 2 ID_{50}). Brown *et al* (1998, 1999) conducted experiments to determine the infectivity of buffy coat material and plasma but not red blood cells. Assuming that red blood cells retain approximately 25% of the infectivity of whole blood, then the infectivity present in whole blood could be estimated to be in the range of approximately 10 i.c. ID_{50} and 20 i.c. ID_{50} per ml. Cervenakova *et al* (2003) found levels as high as 20 – 30 infectious doses per ml (40-60 i.c. ID_{50} per ml) associated with buffy coat and plasma during incubating and symptomatic stages of the disease. Red blood cells were not found to be infectious. Transfusion of blood products using the hamster scrapie model by Rohwer suggests that addition of infectivity levels derived for individual blood components would generate a titer for whole blood of approximately 2 to 20 i.c. ID_{50}/ml. Summarizing the above literature it seems that the range of reported values for infectivity ranged from 0.5 to as high as 30 i.c. ID_{50} with the possibility that at times the infectivity present in blood may exceed this range.

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 medium 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).

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

This section of risk assessment estimated quantity of vCJD agent in each vCJD plasma pool that may be used to make pdFVIII. Quantity of infectious agent present in plasma

pools may vary depending on number of infected donations in the pool and the volume of each infected donation.

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.

Studies with mouse-adapted scrapie agent suggest that the i.v. route of administration is approximately 10 times less efficient in causing infection than the intracerebral route (Kimberlin *et al* 1996). Brown *et al* (1999) used a mouse-adapted human TSE agent to show that i.v. injection of plasma was about seven times less efficient and i.v. injection of buffy coat approximately 5 times less efficient than were i.c. inoculations of the same materials in transmitting infection. Based on discussion and advice from the FDA Transmissible Spongiform Encephalopathies Advisory Committee (TSEAC, 2005) the range of efficiency of the i.v. route (versus the i.c. route) was assumed in the model to range between the values of 1 and 10.

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.

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

The quantity of vCJD agent potentially present in a donation from a US donor infected with vCJD will be diluted out in a plasma pool among plasma from thousands of other donations. This section calculates the quantity of agent potentially present in a plasma pool potentially containing a donation that contained vCJD agent.

Assumption used in the model: We assumed only one infected donor per plasma pool, because based on the calculation in section IV. C. 5. the prevalence of vCJD in the US is very low and the chance a pool involves multiple donations from vCJD infected donors is small.

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

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

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

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

Module 3: Reduction in the quantity of vCJD agent during manufacture of pdFVIII

The plasma separated from whole blood is a protein rich, straw-colored liquid that contains FVIII, a number of other clotting factors, immune globulins, serum albumin and a number of other proteins. Individual proteins, such as FVIII, can be purified by dividing or fractionating the plasma into its various protein components. Fractionation steps may include alcohol precipitation, size exclusion, affinity chromatography, etc. The quantity of vCJD agent present in plasma-derived products may be reduced through removal of the agent during the fractionation process. Although the quantity of agent may be significantly reduced, it may not be entirely eliminated.

Common viral inactivation procedures such as heating, solvent-detergent treatment, and UV irradiation have little effect on the quantity of TSE infectivity present in plasma and plasma derivatives. However, several research studies suggest that TSE infectivity in plasma may be partially removed during the fractionation process. The plasma fractionation procedures, which may remove vCJD infectivity, are summarized in **Table 4.6.** (Lee et al. 2000; Stenland *et al.* 2002; Foster 2004; Foster, *et al.* 2004).

For a specific pdFVIII product, usually only one or two processing steps have been studied for potential reduction of infectivity. Experimental designs of these studies are not standardized; therefore, study results are not directly comparable. In order to achieve a high concentration of vCJD infectivity in initial materials, many studies used vCJD infected brain homogenate as spiking material, which may not mimic the physical form of infectious agent in the blood. Considering the uncertainty in the degree of reduction that can be achieved during various pdFVIII manufacturing processes, this risk assessment models three levels of potential reduction in infectivity, 2-3 $\log_{10}$, 4-6 $\log_{10}$ and 7-9 $\log_{10}$.

Table 4.6 Reduction factor (RF) of fractionation procedures

Fractionation Procedures	RF ($\log_{10}$ ID_{50})	References
Cryoseparation	0-1	(Foster *et al* 2000; Farrugia 2002; Lee *et al* 2002)
General fractionation		
3% PEG	1-3	(Farrugia 2002; Lee *et al* 2002)
11.5% PEG	2-4	(Farrugia 2002)
$Zn+Al(OH)_3$	1.7	(Foster *et al* 2000)
Ion exchange	2.7-3.5	(Foster *et al* 2000; Cervenakova *et al* 2002)
		(Foster *et al* 2000)
Membrane filtration	1	
Immunopurification	4.4-6.3	(Foster, Welch *et al* 2000; Cervenakova *et al* 2002)

IV.E. 3. Model results: Estimates of the per vial vCJD infection risk for US manufactured pdFVIII (Module 3)

The mean potential risk of vCJD infection per 1,000 IU vial of US manufactured pdFVIII is shown in **Table 4.7**. The mean potential per vial vCJD risk per year is a function of two factors:

1) Percentage of pdFVIII vials containing vCJD agent and,
2) Quantity of agent (i.v. ID_{50}) present in each vial.

If vCJD agent were present in US plasma pools, the risk assessment model assumed that the quantity of agent was likely reduced by manufacturing processes used to produce purified pdFVIII. Based on currently available experimental studies, it is estimated that pdFVIII products potentially have 4 $\log_{10}$ (or 10,000 fold) or greater manufacturing process reduction of the vCJD agent. **Table 4.7** shows potential risks associated with products attaining a 4-6 $\log_{10}$ level of reduction during manufacture. Results are shown only for 1,000 IU vials but the model assumed that the final purified pdFVIII product was packaged with equal likelihood into vial sizes of 250, 500, 1,000 and 1,500 international units (IU).

Per vial vCJD risk: Results based on lower epidemiological model estimated prevalence of ~1.8 in 1,000,000 (Clarke and Ghani, 2005). The per vial risk provides an estimate of the potential vCJD infection risk for a 1,000 IU vial of pdFVIII product manufactured from plasma collected from US donors. The model generated estimates of per vial risk using the lower prevalence estimate *(based on Clarke and Ghani 2005)* and results are shown in **Table 4.7.** Based on the lower prevalence estimate the average percent of plasma pools containing the vCJD agent is estimated to be 0.027%. Assuming a clearance of 4-6 $\log_{10}$ the model estimates that the average quantity of i.v. ID_{50} per vial is 3.59×10^{-5} for vials produced from a contaminated pool. This result can be interpreted to mean that only 1 in 55,710 vials made from a contaminated pool would contain an infectious dose of vCJD. Combining these estimates yields an average risk per vial of 1 in 210 million. Alternatively, this could be taken to mean that a patient would need to infuse 210 million vials of product before accumulating one full infectious dose of vCJD.

At this lower prevalence estimate, there is a lower probability that plasma pools contain a donation from a donor potentially infected with vCJD, and a pdFVIII vial would be much less likely to contain vCJD agent. Although the probability (0.027%) is lower, the mean quantity of vCJD agent (iv ID_{50}) and risk of exposure to vCJD agent (1 in 55,710) per vial derived from a pool containing a single vCJD donation would likely be unaffected by prevalence. Readers may notice that the 5th and 95th percentile intervals for all of the model outputs using the lower prevalence estimate (~1.8 per million) are from 0 to 0, meaning that the chance of an infected donor donating to a plasma pool would be an infrequent event. Greater than 99% of the time (on average) the model estimates the risk to be zero because vCJD agent was not present in pdFVIII product used during treatment. Again, the model predicts that, on average, 0.027% of the time the exposure to vCJD may be greater than zero.

Per vial vCJD risk: Results based on higher surveillance prevalence estimate of 1 in 4,225 (Hilton, et al 2004). The per vial risk provides an estimate of the potential vCJD infection risk for a 1,000 IU vial of pdFVIII product manufactured from plasma collected from US donors. The model generated estimates of per vial risk using the higher prevalence estimate (Hilton, et al 2004) and results are shown in **Table 4.7.** Using the higher prevalence estimate the average percent of plasma pools containing the vCJD agent is estimated to be 2.41%. Assuming a clearance of 4-6 $\log_{10}$ the model estimates that the average quantity of i.v. ID_{50} per vial is 3.59×10^{-5} for vials produced from a contaminated pool. This result can be interpreted to mean that only 1 in 55,710 vials made from a contaminated pool would contain an infectious dose of vCJD. Combining these estimates yields an average risk per vial of 1 in 2.3 million. Alternatively, this could be taken to mean that a patient would need to infuse 2.3 million vials of product before accumulating one full infectious dose of vCJD. Again, although the probability (2.41%) is higher at the higher prevalence, the mean quantity of vCJD agent (iv ID_{50}) and risk of exposure to vCJD agent (1 in 55,710) per vial derived from a pool containing a single vCJD donation would likely be unaffected by prevalence.

Table 4.7 Annual Predicted per Vial vCJD Infection Risk for US Manufactured pdFVIII from Model:

- Results for 1,000 IU vial
- Assumed manufacturing process reduction of 4-6 $\log_{10}$, and
- Two different UK vCJD prevalence estimates.

	4 - 6 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)		
Type of Plasma Pool	Percentage FVIII vials with vCJD agent (5th, 95th perc)[c]	Quantity iv ID_{50}[a] per vial* (5th- 95th perc)[c]	Mean potential per vial vCJDrisk[b] (5th- 95th perc)[c]	Percentage FVIII vials with vCJD agent (5th, 95th perc)[c]	Quantity iv ID_{50}[a] per vial* (5th- 95th perc)[c]	Mean** potential per vial vCJDrisk[b] (5th- 95th perc)[c]
Source	0.01% (0 – 0%)[d]	4.36×10^{-5} (4.51×10^{-6} – 1.43×10^{-4})	1 in 459 million (0, 0)[d]	0.96% (0 – 5.88%)	4.36×10^{-5} (4.51×10^{-6} – 1.43×10^{-4})	1 in 4.8 million (0, 1 in 238,000)
Recovered	0.10% (0 – 0%)[d]	2.56×10^{-6} (3.13×10^{-7} – 8.12×10^{-6})	1 in 800 million (0, 0)[d]	9.12% (0 – 40.17%)	2.56×10^{-6} (3.13×10^{-7} – 8.12×10^{-6})	1 in 8.6 million (0,1 in 613,000)
Average of all vials	0.027 % (0 – 0%)[d]	3.59×10^{-5} (8.18×10^{-7} – 1.29×10^{-4})	1 in 210 million (0, 0)[d]	2.41 % (0 – 10 %)	3.59×10^{-5} (8.18×10^{-7} – 1.29×10^{-4})	1 in 2.3 million (0, 1 in 155,000)

*Mean i.v. ID_{50} in vials containing vCJD agent

[a] iv ID_{50} represents the probability that 50% of those exposed to 1 ID_{50} intravenously may become infected with vCJD.

[b] Mean potential annual per vial vCJD risk – the risk of potential vCJD infection based on animal model dose-response information. Mean potential annual vCJD risk = Percentage vials with vCJD agent x mean quantity iv ID_{50} per year x 0.5 (50 % chance infection from ID_{50})

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

[d] For a 5th and 95th 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.

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

This section of the risk assessment models each infected plasma pool to estimate the potential reduction in infectivity for each pool during manufacturing processing, and to estimate the quantity of any remaining infectivity (I,v, ID_{50}s) in the pdFVIII product made from each pool.

The levels of reduction of vCJD agent achieved during manufacturing and processing varies among the pdF VIII products on the market. To our knowledge, the total level of reduction in vCJD agent achieved during manufacturing for any pdFVIII product on the market is not known. However, the levels of TSE clearance and reduction for some of the individual fractionation steps (or similar steps) used in the manufacture of some pdFVIII products is known. Based on TSE clearance studies in the published literature and manufacturers' data available to the FDA, FDA staff believe that the plasma-derived products currently on the market employ manufacturing processes that achieve a clearance of vCJD agent of 4 $\log_{10}$ or greater in the final pdFVIII product. 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.

Module 4: FVIII utilization and annual exposure

Background

Patients with hemophilia A (HA) have an inherited – recessive, sex-linked bleeding disorder that affects approximately 14,000 individuals in the United States (Soucie *et al* 1998). FDA estimated that there are approximately 1,800 patients in the US with severe disease who use plasma-derived products. The blood of affected individuals contains functionally abnormal or abnormally low concentrations of FVIII. FVIII is a protein in blood plasma that is part of the blood coagulation pathway and is critical for the normal clotting of blood. In the case of severe disease, FVIII is <1% of normal. Among severely affected persons, spontaneous bleeding or bleeding at the site of an injury or a joint is common and can lead to severe disability or death without treatment. The complications of HA can be prevented by appropriate clinical management and treatment with pdFVIII or recombinant FVIII products.

Traditionally, HA patients were treated with factor concentrates only when bleeding occurred, which is called episodic treatment. Currently, the adoption of a preventative form of treatment or prophylaxis therapy is increasing. Prophylactic therapy refers to treatment regimens that seek to prevent bleeding events with regular infusions of clotting factor concentration. Prophylactic treatment greatly decreases the likelihood of adverse events such as joint hemorrhage, and effectively prevented the development of chronic joint arthropathy and disability, but requires higher use of FVIII product than episodic treatment.

Patients with vWD have an inherited, non-sex linked bleeding disorder associated with abnormal platelet adhesion caused by deficiency in von Willebrand Factor (vWF) activity. FDA estimated that there are approximately 250 patients in the US with severe vWD who use plasma-derived products. Mucosal bleeding is common in patients with vWD due to the platelet adhesion disorder. In some cases there may be a deficiency in FVIII as well. Patients with severe vWD can experience persistent bleeding into joints resulting in pain, degeneration of joints, swelling and loss of range of motion similar to patients with HA. Mild forms of vWD are often treated successfully with desmopressin but more severe forms of the disease usually necessitate treatment with coagulation factor concentrates that contain both vWF and FVIII. Patients who need vWF must use plasma-derived sources of FVIII which contain vWF. No recombinant vWF is currently available.

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

The potential exposure of an individual HA or vWD patient or patient population with severe disease to the vCJD agent through use of pdFVIII was estimated in the model based on the:

- total quantity of pdFVIII used per year, and
- potential quantity of vCJD agent predicted in the pdFVIII product.

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

The quantity of pdFVIII utilized by an individual patient is dependent on the severity of the disease and the treatment regimen. Plasma-derived FVIII utilization and the size of each of the severe HA clinical treatment subpopulations were estimated using data from a Centers for Disease Control (CDC) sponsored study by 6 states by Hemophilia A patients from 1993-1998. This risk assessment provides outputs that estimate the annual exposure for several patient subpopulations with Severe HA disease for patients in the following clinical treatment groups:

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

- Episodic – No inhibitor
- Episodic - With inhibitor

Because patients with severe HA are likely to use higher quantities of pdFVIII product we reasoned that they would be at potentially greater risk, than those with moderate or mild hemophilia, if the vCJD agent were present in US manufactured product.

A summary of the utilization data used for the model are provided in the table below. Additional technical details of the analysis of FVIII utilization for this population are described in section A-IV.G. of Appendix A.

Table 4.8. Annual usage of pdFVIII by individual HA patients with severe disease-data and input distribution

		Input distribution			
Treatment Regimen	Inhibitor Status	n	(min, max)	Mean	95% CI
Prophylaxis	No Inhibitor	578	(300, 1200000)	157949	(21242, 282316)
	With Inhibitor – No Immune Tolerance	63	(2000, 800000)	190523	(26956, 447639)
	With Inhibitor – With Immune Tolerance	62	(100000, 2000000)	558700	(33235, 1592943)
Episodic	No Inhibitor	946	(0, 1000000)	85270	(4633, 244656)
	With Inhibitor	151	(2200, 1000000)	160458	(5314, 488906)

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 4.9. 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. The FVIII utilization data were used to calculate the potential vCJD risk for vWD patients; these results are shown in Tables 5.2A and 5.2B.

Table 4.9. Annual usage of pdFVIII by individual severe vWD patient -data and input distribution

Treatment Regimen	n	(min, max)	Mean	95% CI
Young (<15 yrs of age)				
Prophylaxis	9	(9200, 504625)	165713	(9346, 479457)
Episodic	14	(1010, 41850)	11045	(1013, 37543)
Adult (>15 yrs of age)				
Prophylaxis	17	(15000, 772800)	186880	(15570, 606670)
Episodic	18	(1000, 293800)	86923	(1362, 260660)

V. RISK CHARACTERIZATION

The risk characterization section of the risk assessment integrates information from the hazard identification, hazard characterization and the exposure assessment components to arrive at estimates of the risks posed by a hazard.

In this risk assessment data for hazard characterization are lacking, so we could not develop a human vCJD dose-response. The dose-response relationship provides information needed to use the exposure (dose) assessment results to estimate the probability of adverse responses including infection, illness or mortality – based on assessment of exposure (dose) to the hazard. Many TSE models and risk assessments, including our model, use the ID_{50}, or amount of material that leads to infection in 50% of the population, as a semi-quantitative estimate of the amount of TSE agent. The ID_{50} has been derived from rodent animal models and may or may not approximate infection and occurrence of vCJD in humans. This lack of knowledge about the animal data and how they relate to actual human clinical vCJD outcomes adds considerable uncertainty to the risk estimates generated by the model. The FDA risk assessment interprets the ID_{50} as representing a linear dose-response relationship or linear relationship between exposure and the probability of infection. In such a case exposure to 1 ID_{50} would suggest a 50% probability of infection, exposure to 0.1 ID_{50} would suggest a 5% probability of infection, and so on.

The final results of this risk assessment provide estimates of potential annual exposure and annual vCJD infection risk for patients with severe HA and for patients with severe vWD for pdFVIII manufactured from plasma collected in the US. The risk was estimated by applying the linear ID_{50} dose-response relationship, which provides a probability of vCJD infection in the two populations and various subpopulations within the two groups. Given the limited data available FDA believes that any extrapolation or interpretation has limited utility in actually estimating outcomes such as infection and illness. Therefore, any estimate of the risk based on estimates of exposure to the vCJD agent through use of pdFVIII will be imprecise and extremely uncertain.

V.A. THE MODEL

This risk assessment and simulation model links the available scientific and epidemiological data together to mathematically approximate the processes (predicted presence of vCJD in UK population, manufacturing, reduction of vCJD agent, and patient utilization) leading to potential exposure of US patients to vCJD agent present in US-manufactured pdFVIII. A summary of the variables, parameters and equations used in the model were described in Section III. Exposure Assessment and a summary of the variables and equations, data, and assumptions used in the model are provided in Appendix A. The model was run using @Risk software package (Palisades Corp, NY) to conduct the Monte Carlo analysis. Simulations of 10,000 iterations were run.

The risk assessment uses Monte Carlo simulation to randomly draw values from probability input distributions (which are statistical representations of input data) once per iteration; thousands of iterations are used to generate the model outputs as risk estimates. This simulation method is often used in situations when a model is complex, non-linear, or involves several uncertain parameters. The output generated is usually an aggregate distribution whose shape can be summarized using measures of central tendency (mean, median, mode) or with boundaries such as the 95% confidence interval (CI), the 5th and 95th percentiles (representing the 90% CI) or the range, bounded by the minimum and maximum values generated as part of the output. The strength of Monte Carlo analysis is that it generates resulting risk estimates as statistical distributions, which reflect the underlying uncertainty and variability of the original input data and parameters.

V. B. Model results: Estimated annual potential exposure to vCJD i.v. ID_{50} and potential vCJD risk through human pdFVIII used to treat severe HA

Individuals with HA vary in their degree of FVIII deficiency. Although the clinical spectrum generally can range from severe, to moderate, and to mild disease, this assessment specifically addresses potential vCJD exposure and risk for persons with severe HA. Among an estimated 14,000 HA population in the United States, approximately 50% have severe disease and 25% of all HA patients use human pdFVIII products. FDA

estimated that there are a total of approximately 1,800 HA patients (**Tables 5.1A. and 5.1B.**) with severe disease in the US that use human pdFVIII products. Although the estimated risk is very low, it is possible that some patients using human pdFVIII may potentially be exposed to vCJD agent if present in US manufactured product.

Estimation of PdFVIII product utilization by patients with severe HA. FDA obtained data on human plasma-derived FVIII utilization from the Centers for Disease Control (CDC). Data in the study were collected as part of a collaborative effort between CDC and six states during the time period 1993 – 1998. A summary of study results for New York State are described in Linden, et al. (2003). The comprehensive study collected standardized patient demographic, 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 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.

The data on quantity of pdFVIII product utilized annually were used to develop statistical distributions of product usage for patients by treatment group. The mean quantities of products utilized by HA patients on different treatment regimens are shown in **Table 5.1A. and 5.1B**. Approximately 1,100 records for patients utilizing pdFVIII were analyzed in this study. The percentage of each patient subpopulation in proportion to the total HA population in the CDC-Six State study was used to extrapolate the estimated number of total individuals in each patient subpopulation. From the study results, we estimated that there are a total of approximately 1,800 persons with severe HA in the US who use pdFVIII.

Results from the risk assessment model for patients with severe HA who are treated with pdFVIII product with a 4-6 $\log_{10}$ manufacturing process reduction of vCJD agent are shown in **Tables 5.1A. and 5.1B.** Generally results are expressed for patients in several different HA clinical treatment groups including:

- Prophylaxis
- Prophylaxis plus inhibitor
- Prophylaxis plus inhibitor and immune tolerance
- Episodic
- Episodic plus inhibitor

Potential exposure of severe HA patients to vCJD agent: Results based on lower epidemiological model estimated prevalence of ~1.8 in 1,000,000 (based on Clarke and Ghani, 2005). The model estimates that severe HA patients treated using a prophylaxis regimen, with inhibitor, with immune tolerance and treated with a pdFVIII product (with 4-6 $\log_{10}$ reduction of vCJD agent) has the highest pdFVIII usage of the groups we examined and potentially face the highest risk among HA patients. **Table 5.1A.** indicates that approximately 62 severe HA patients in a prophylaxis treatment regimen with inhibitor and immune tolerance use an average of 558,700 IU per person per year and are potentially

exposed to an average of 1.57×10^{-6} i.v. ID_{50} per person per year; representing an average potential vCJD risk of 1 in 1.3 million per person per year. If all of the assumptions in the model are correct at this lower estimated prevalence, this risk may yield 1 vCJD infection in an average of approximately 21,000 years of treatment among severe HA patients who are in a prophylaxis treatment regimen with inhibitor and immune tolerance. As mentioned earlier the 5th and 95th percentile intervals for all of the model outputs using the lower prevalence estimate (~1.8 per million) in **Table 5.1A.** are from 0 to 0 meaning that the chance of an infected donor donating to a plasma pool would be an infrequent event. Greater than 99% of the time (on average) the model estimates the risk to be zero because vCJD agent was not present in pdFVIII product used during treatment. However, the model predicts that 0.027% of the time the exposure to vCJD agent may be greater than zero, and there is a possible but low risk of vCJD infection.

The risk for the entire population is calculated by summing the cumulative risk potential of vCJD exposure and risk **(Table 5.1B.)**. Using the lower prevalence estimate, the model predicts that the approximately 1,800 severe HA patient population in the US uses a total of approximately 243 million IU pdFVIII and is exposed to an average of 6.50×10^{-4} i.v. ID_{50}. This total annual exposure for the entire severe HA population in the US is equivalent to a mean potential population-based vCJD risk of 1 in 3,077. At this expected level of risk, 1 vCJD infection would be predicted to occur in 3,077 years of treatment for the entire population of 1800 severe HA patients that use pdFVIII.

Potential exposure of severe HA patients to vCJD agent: Results based on higher surveillance prevalence estimate of 1 in 4,225 (Hilton, et al 2004). The model estimates that severe HA patients in a prophylaxis regimen, with inhibitor, with immune tolerance and treated with a pdFVIII product (with 4-6 $\log_{10}$ reduction of vCJD agent) potentially face the highest expected risk among HA patients. **Table 5.1A.** indicates that approximately 62 severe HA patients in a prophylaxis treatment regimen with inhibitor and immune tolerance use an average of 558,700 IU per person per year, and are potentially exposed to an average of 1.30×10^{-4} i.v. ID_{50} per person per year, using the higher prevalence estimate. This represents an average potential vCJD risk of 1 in 15,000 per person per year for the treatment group. If all of the assumptions used in the model are correct and considering the total number of 62 patients in this category (or population-based risk), this expected risk would yield 1 vCJD infection in 240 years of treatment among the patients under this category.

The risk for the entire severe HA population is calculated by summing the cumulative risk potential of vCJD exposure and risk from all individual patients under five categories (prophylaxis with no inhibitor, prophylaxis with inhibitor, prophylaxis with inhibitor and immune tolerance, episodic with no inhibitor and episodic with inhibitor) **(Table 5.1B.)**. Using the higher surveillance estimate, the model predicts that the approximate total of 1,800 severe HA patient population in the US uses a total of approximately 243 million IU pdFVIII, and is exposed to an average of 5.67×10^{-2} i.v. ID_{50} per year. This total annual exposure for the entire severe HA population in the US is equivalent to a mean potential

population-based vCJD risk of 1 in 35, i.e., 1 vCJD infection would be predicted to occur in 35 years of treatment in this 1800 severe HA patient population.

Table 5.1A. Model Results for All HA Patients who use a Hypothetical Factor VIII Product with 4-6 log_{10} Manufacture Process Reduction of vCJD Agent: ***Predicted Annual per Person Exposure to vCJD i.v. ID_{50} and Mean Potential per Person Annual vCJD Risk:***

- For patients with SEVERE disease, and
- Two different UK vCJD prevalence estimates.

				4 - 6 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)	
Treatment Regimen	**Inhibitor Status**	**Est. Total Number patients in US**	**Mean quantity FVIII used per person per year (5th - 95th perc)**	**Mean exposure to vCJD iv ID_{50}[a] per person per year (5th - 95th perc)[c]**	**Mean potential vCJD risk per person per year[b] (5th - 95th perc)[c]**	**Mean exposure to vCJD iv ID_{50}[a] per person per year (5th - 95th perc)[c]**	**Mean potential vCJD risk per person per year[b] (5th - 95th perc)[c]**
Prophylaxis	No Inhibitor	**578**	**157949 IU[d]** (21242 , 382316)	**4.99×10^{-7}** (0-0)[e]	1 in 4.0 million (0-0)[e]	**3.67×10^{-5}** (0 - 1.72×10^{-4})	1 in 54,000 (0 - 1 in 12,000)
	With Inhibitor – No Immune Tolerance	**63**	**190523 IU[d]** (26956, 447639)	**4.21×10^{-7}** (0-0)[e]	1 in 4.8 million (0-0)[e]	**4.86×10^{-5}** (0 - 2.17×10^{-4})	1 in 41,000 (0 - 1 in 9,000)
	With Inhibitor – With Immune Tolerance	**62**	**558700 IU[d]** (33235, 1592943)	**1.57×10^{-6}** (0-0)[e]	1 in 1.3 million (0-0)[e]	**1.30×10^{-4}** (0 - 5.39×10^{-4})	1 in 15,000 (0 - 1 in 3,700)
Episodic	No Inhibitor	**946**	**85270 IU[d]** (4633, 244656)	**2.12×10^{-7}** (0-0)	1 in 9.4 million (0-0)[e]	**1.91×10^{-5}** (0 - 8.50×10^{-5})	1 in 105,000 (0 - 1 in 24,000)
	With Inhibitor	**151**	**160458 IU[d]** (5314, 488906)	**2.49×10^{-7}** (0-0)[e]	1 in 8.0 million (0-0)[e]	**4.19×10^{-5}** (0 - 1.67×10^{-4})	1 in 48,000 (0 - 1 in 12,000)

[a] iv ID_{50} represents the probability that 50% of those exposed to 1 ID_{50} intravenously may become infected with vCJD.

[b] Mean potential annual vCJD risk – the risk of potential vCJD infection based on animal model dose-response information. Mean potential annual vCJD risk = Total mean quantity iv ID_{50} per year x 0.5 (50 % chance infection from ID_{50})

[c] The 5th - 95th perc (percentiles) are the minimum and maximum numbers that define the range of values constituting the 90% confidence interval. Accordingly, the mean risk estimates generated by the model should fall within this defined interval at least 90% of the time.
[d] IU - represents international units of Factor VIII and may be expressed using the term "unit" or "units" in this document.
[e] For a 5th and 95th 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.

Table 5.1B. Model Results for Total Population-based Exposure and Potential vCJD Risk for All Hemophilia A patients who use a Hypothetical pdFVIII Product with 4-6 $\log_{10}$ Manufacture Process Reduction of vCJD Agent:

Predicted annual per person exposure to vCJD i.v. ID_{50} and mean potential per person annual vCJD risk:

- For patients with SEVERE disease, and
- Two different UK vCJD prevalence estimates.

			4 - 6 $\log_{10}$ 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)	
	Est. Total Number severe HA patients in US	Mean Total quantity FVIII used by all patients per year (5th - 95th perc)[c]	Mean exposure to vCJD iv ID_{50}[a] of all patients per year (5th - 95th perc)[c]	Mean population – based potential vCJD risk[b] (5th - 95th perc)[c]	Mean exposure to vCJD iv ID_{50}[a] of all patients per year (5th - 95th perc)[c]	Mean population – based potential vCJD risk[b] (5th - 95th perc)[c]
Mean total annual exposure and population risk	1,800	243 million IU[d]	6.50×10^{-4} (0-0)[e]	1 in 3,077 years (0-0)[e]	5.67×10^{-2} (0 - 2.52×10^{-1})	1 in 35 years (0 - 1 in 8)

[a] iv ID_{50} represents the probability that 50% of those exposed to 1 ID_{50} intravenously may become infected with vCJD.
[b] Mean potential annual vCJD risk – the risk of potential vCJD infection based on animal model dose-response information. Mean potential annual vCJD risk = Total mean quantity iv ID_{50} per year x 0.5 (50 % chance infection from ID_{50})
[c] The 5th - 95th perc (percentiles) are the minimum and maximum numbers that define the range of values constituting the 90% confidence interval. Accordingly, the mean risk estimates generated by the model should fall within this defined interval at least 90% of the time.
[d] IU - represents international units of Factor VIII and may be expressed using the term "unit" or "units" in this document.
[e] For a 5th and 95th 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.

V. C. Model results: Estimated annual potential exposure to i.v. ID_{50} vCJD agent and potential vCJD risk through human pdFVIII used to treat severe von Willebrand disease (vWD)

Individuals with von Willebrand disease (vWD) vary in severity of disease, those with Type 3 disease have severe disease; this assessment specifically addresses potential vCJD exposure and risk for persons with severe vWD. FDA estimates that approximately 250 vWD patients have severe vWD disease in the United States and use human plasma-derived FVIII products to control their disease (Tables 5.2A. and 5.2 B.) The FDA model suggests that it is possible that some of these vWD patients using human pdFVIII may potentially be exposed to vCJD agent if present in US manufactured product. Results from the risk assessment model for patients with vWD and treated with pdFVIII product with a 4-6 $\log_{10}$ manufacturing process reduction of vCJD agent are shown in Tables 5.2A. and 5.2 B. Generally results are expressed for patients with von Willebrand disease (vWD) clinical treatment groups of either Prophylaxis or Episodic treatment.

Table 5.2A. Results von Willebrand Disease (vWD) patients[1] with Severe Disease: Predicted Potential Annual Exposure to vCJD i.v. ID_{50} and vCJD Risk:

- Assuming a processing reduction of 4-6 $\log_{10}$, and
- Two different UK vCJD prevalence estimates.

YOUNG vWD (≤ 15 yrs of age)						
			4 - 6 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)	
	Est. Total Number patients in US	Mean quantity product used per person per year (5th - 95th perc)[c]	Mean exposure to vCJD iv ID_{50}[a] per person per year (5th - 95th perc)[c]	Mean potential vCJD risk per person per year[b] (5th - 95th perc)[c]	Mean exposure to vCJD iv ID_{50}[a] per person per year (5th - 95th perc)[c]	Mean potential vCJD risk per person per year[b] (5th - 95th perc)[c]
Prophylaxis	39	165,713 IU[d] (9876, 454306)	4.30×10^{-7} (0 - 0)[e]	1 in 4.7 million (0 - 0)[e]	3.81×10^{-5} (0 - 1.54×10^{-4})	1 in 52,000 (0 - 1 in 13,000)
Episodic	60	11,045 IU[d] (1025, 34352)	4.14×10^{-8} (0 - 0)[e]	1 in 48 million (0 - 0)[e]	2.06×10^{-6} (0 - 6.83×10^{-6})	1 in 971,000 (0 - 1 in 293,000)
ADULT vWD (> 15 yrs of age)						
Prophylaxis	73	186,880 IU[d] (16910, 539877)	4.89×10^{-7} (0 - 0)[e]	1 in 4.1 million (0 - 0)[e]	4.32×10^{-5} (0 - 1.82×10^{-4})	1 in 46,300 (0 - 1 in 11,000)

Episodic	78	86,923 IU[d] (2182, 240338)	1.99×10^{-7} (0 - 0)[e]	1 in 10 million (0 - 0)[e]	1.90×10^{-5} (0 - 8.43×10^{-5})	1 in 1 million (0 - 1 in 24,000)

[1]Number (percent) patients in a CDC sponsored study with 6 states to survey treatment of Hemophilia A and B conducted 1993 - 1998. Our analysis included 14 patients (<15yrs) and 28 patients (≥15yrs) (total = 42) on prophylaxis or episodic treatment with Humate P only and no record of inhibitor.

[a]iv ID_{50} represents the probability that 50% of those exposed to 1 ID_{50} intravenously may become infected with vCJD.

[b]Mean potential annual vCJD risk – the risk of potential vCJD infection based on animal model dose-response information. Mean potential annual vCJD risk = Total mean quantity i.v. ID_{50} per year x 0.5 (50 % chance infection from ID_{50})

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

[d]IU - represents international units of Factor VIII and may be expressed using the term "unit" or "units" in this document.

[e]For a 5th and 95th 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.

Estimation of Factor VIII product utilization by patients with severe von Willebrand disease. FDA obtained data on pdFVIII utilization, presumably used in the treatment of severe von Willebrand disease, from the Centers for Disease Control (CDC). Details of the CDC – Six state collaborative study are described in the section above (section IV.G.2) on FVIII utilization. Annual usage of product by vWD patients was estimated based on an assumption that this patient class largely uses Humate P. Therefore, only records for patients utilizing Humate P were extracted from the CDC - Six state study conducted from 1993 – 1998 and used to develop statistical distributions of product usage for young vWD (≤15 yrs old) patients and adult vWD (> 15 yrs old) patients. The mean quantity of product utilized per year per patient group is shown in **Table 5.2A.** and **Table 5.2B.**

Table 5.2B. Von Willebrand Disease (vWD) Patients[1] with Severe Disease: Predicted Total Population-based Exposure to vCJD i.v. ID_{50} and Potential vCJD Risk:

- Assuming a processing reduction of 4-6 $\log_{10}$, and
- Two different UK vCJD prevalence estimates.

			4 - 6 $\log_{10}$ 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)	
	Est. Total Number severe vWD patients in US	Mean Total quantity FVIII used by all patients per year (5th - 95th perc)[c]	Mean exposure to vCJD iv ID_{50}[a] of all patients per year (5th - 95th perc)[c]	Mean population – based potential vCJD risk[b] (5th - 95th perc)[c]	Mean exposure to vCJD iv ID_{50}[a] of all patients per year (5th - 95th perc)[c]	Mean population – based potential vCJD risk[b] (5th - 95th perc)[c]
Mean total annual exposure and population	250	29.9 million IU[d]	7.05×10^{-5} (0 - 0)[e]	1 in 28,450 years (0 - 0)[e]	4.91×10^{-3} (0 - 2.59×10^{-2})	1 in 405 years (0 - 1 in 76)

risk		(3013, 311745)				

[1]Number (percent) patients in a CDC sponsored study with 6 states to survey treatment of Hemophilia A and B conducted 1993 - 1998. Our analysis included 14 patients (<15yrs) and 28 patients (≥15yrs) (total = 42) on prophylaxis or episodic treatment with Humate P only and no record of inhibitor.

[a]Iv ID_{50} represents the probability that 50% of those exposed to 1 ID_{50} intravenously may become infected with vCJD.

[b]Mean potential annual vCJD risk – the risk of potential vCJD infection based on animal model dose-response information. Mean potential annual vCJD risk = Total mean quantity i.v. ID_{50} per year x 0.5 (50 % chance infection from ID_{50})

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

[d]IU - represents international units of Factor VIII and may be expressed using the term "unit" or "units" in this document.

[e]For a 5th and 95th 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.

Potential exposure of severe von Willebrand disease patients to vCJD agent: Results based on lower epidemiological model estimated prevalence of ~1.8 in 1,000,000 (Clarke and Ghani, 2005). Adult vWD (>15yrs of age) patients with severe disease on prophylaxis consumed the largest quantities of pdFVIII product annually and may potentially be at greater vCJD risk. Using the lower epidemiological model prevalence estimate, analysis of pdFVIII utilization data indicated that 73 Adult vWD patients on prophylaxis treatment regimen used an average of 186,880 IU and are potentially exposed to an average of 4.89 x 10^{-7} i.v. ID_{50} per person per year, and representing an average potential vCJD risk of 1 in 4.1 million per person per year **(Table 5.2A.)**. At this level of risk, only 1 vCJD infection would be predicted to occur in an average of approximately 56,000 years. As mentioned earlier the 5th and 95th percentile intervals for all of the model outputs using the lower prevalence estimate (~1.8 per million) in **Table 5.2A.** are from 0 to 0 meaning that the chance of an infected donor donating to a plasma pool would be an infrequent event. Greater than 99% of the time (on average) the model estimates the risk to be zero because vCJD agent was not present in pdFVIII product used during treatment. However, the model predicts that 0.027% of the time the exposure to vCJD agent may be greater than zero, and there is a possible but low risk of vCJD infection.

Totaling the model results reveals that the approximately 250 severe vWD patients in the US used a total of 29.9 million IU, and are potentially exposed to an average total of 7.05 x 10^{-5} i.v. ID_{50} per year. This represents an average potential vCJD risk of 1 in 28,450 **(Table 5.2B.)** or (as predicted by the model) roughly equal to one vCJD infection observed over a time span of approximately 28,450 years in the population of 250 severe vWD patients.

Potential exposure of severe von Willebrand disease patients to vCJD agent: Results based on higher prevalence estimate of 1 in 4,225 (Hilton et al 2004). At the higher surveillance prevalence estimate, among the vWD patient populations examined by the model, results **(Table 5.2A.)** indicated that adult vWD (>15yrs of age) patients with severe disease on prophylaxis used the largest quantities of pdFVIII product annually and may potentially be at greater vCJD risk. Analysis of pdFVIII utilization data indicated that 73 Adult vWD patients on prophylaxis treatment regimen used an average of 186,880 IU per person per year and are potentially exposed to an average of 4.32 x 10^{-5} i.v. ID_{50} per person per year, representing an average potential vCJD risk of 1 in 46,300 per person per year **(Table 5.2A.)**. At this level of risk, only 1 vCJD infection would be predicted to occur in an

average of approximately 630 years for the population of 73 Adult vWD patients on prophylaxis treatment regimen.

The potential risk of vCJD infection for the entire population was calculated using the higher surveillance prevalence estimate. The model results shows that the approximately 250 severe vWD patients in the US used a total of 29.9 million IU (**Table 5.2B.**), and are potentially exposed to an average total of 4.91×10^{-3} i.v. ID_{50} per year. This represents an average potential vCJD risk of 1 in 405, i.e., of one vCJD infection observed over a time span of 405 years for the population of 250 severe vWD patients in the U.S.

Range of Predicted annual mean potential per HA patient vCJD risk for pdFVIII (Table 6)
The FDA risk assessment for potential vCJD infection risk for US manufactured pdFVIII generates results for several scenarios that reflect two key factors that greatly influence the final risk estimates including: (1) Reduction in vCJD agent in pdFVIII product during manufacture, and (2) UK vCJD prevalence estimate. As indicated earlier, the model used two widely different prevalence estimates, one lower prevalence estimate based on epidemiological modeling of predicted vCJD cases in the UK (Clarke and Ghani, 2005) of approximately 1.8 in 1 million and one higher prevalence estimate based on surveillance data of UK patient tissue samples (Hilton et al 2004) of 1 in 4,225. The use of these two estimates gives rise to a difference in results generated by the model that vary by an average of approximately 130 fold.

The model evaluated three separate categories of reduction in infectivity including 2-3 $\log_{10}$, 4-6 $\log_{10}$, and 7-9 $\log_{10}$. These three hypothetical categories were chosen to span the possible range of reduction of vCJD agent for pdFVIII products. **Table 5.3A. and 5.3B.** displays model results for a lower prevalence estimate and a higher prevalence estimate at all three levels of reduction. It should be noted that the mean difference between the lowest range of 2-3 $\log_{10}$ and the highest range of 7-9 $\log_{10}$ is nearly 1 million fold (6 $\log_{10}$). These two largest contributors to the final risk estimate also contribute to the greatest uncertainty in the model. Results from the model shown in **Tables 5.3A. and 5.3B.** indicate that there is a difference of approximately 20 to 55 million fold between the lowest and highest risk estimates of each patient group.

Table 5.3A. Range of *Predicted Annual Mean Potential per HA Patient vCJD risk for pdFVIII* – at *three levels of clearance: 7-9 log_{10}, 4-6 log_{10}, and 2-3 log_{10} and at a higher Prevalence and Lower Prevalence estimates and at .*

				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 product used per person per year (5th - 95th)[b]	Mean potential vCJD risk per person per year[a] (5th - 95th perc)[b]	Mean potential vCJD risk per person per year[a] (5th - 95th perc)[b]	Mean potential vCJD risk per person per year[a] (5th - 95th perc)[b]	Mean potential vCJD risk per person per year[a] (5th - 95th perc)[b]	Mean potential vCJD risk per person per year[a] (5th - 95th perc)[b]	Mean potential vCJD risk per person per year[a] (5th - 95th 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 5th- 95th 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 5th and 95th 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.

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This range or difference in the estimates of about 20 -55 million fold is reflected in the higher and lower prevalence results generated by the model shown in **Table 5.3A.** for each HA patient treatment group with severe disease. On closer inspection of the results in **Table 5.3A.** for patients with the most intensive pdFVIII product use, that is, the 62 patients on prophylaxis-with inhibitor and with immune tolerance, the effect of clearance on mean potential vCJD risk across the three ranges of clearance can be seen. At the low end of risk, the mean potential vCJD risk per patient per year risk (at 7-9 $\log_{10}$ and the lower prevalence estimate) is 1 in 551 million. Conversely, the highest risk for this patient group is seen at the 2-3 $\log_{10}$ clearance level and the higher prevalence estimate and is estimated by the model to be an average of 1 in 24. For patients on episodic treatment with no inhibitor who have a less intensive annual use of product, the model predicts the lowest risk (at 7-9 $\log_{10}$ and the lower prevalence estimate) to be 1 in 3.2 billion. The model predicts the highest risk for this group of patients, if they used pdFVIII product with a 2-3 $\log_{10}$ clearance level and the higher prevalence estimate, would be a mean potential per patient risk of 1 in 159.

Table 5.3B. Range of Total Population-based Exposure and Potential vCJD Risk from Model Predicted HA population with severe disease annual vCJD Exposure and Risk associated with use of plasma-derived Factor VIII:

- Lower Prevalence assumptions of Prevalence of 1.8 in 1,000,000 and 7-9 $\log_{10}$ reduction, and
- Higher Prevalence assumptions of Prevalence of 1 in 4,225 and 2-3 $\log_{10}$ reduction.

			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 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 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)
	Est. Total Number severe vWD patients in US	Mean Total quantity FVIII used by all patients per year (5th - 95th perc)[b]	Mean population – based potential vCJD risk[a] (5th - 95th perc)[c]	Mean population – based potential vCJD risk[a] (5th - 95th perc)[c]	Mean population – based potential vCJD risk[a] (5th - 95th perc)[c]	Mean population – based potential vCJD risk[a] (5th - 95th perc)[c]	Mean population – based potential vCJD risk[a] (5th - 95th perc)[c]	Mean population – based potential vCJD risk[a] (5th - 95th perc)[c]
Mean total annual exposure and population risk	1,800	243 million IU	1 vCJD Infection in 1.8 million years (0-0)[c]	1 vCJD Infection in 35,000 years (0 -1 in 9,000)	1 vCJD Infection in 3,100 years (0 -0)[c]	1 vCJD Infection in 40 years (0 -1 in 10)	1 vCJD Infection in 8 years (0 -1 in 2)	~13 vCJD Infections per year (0- 54 vCJD Infections)

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

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

[c] For a 5th and 95th 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.

The results from the risk assessment model shown in **Table 5.3A.** show a wide range of difference in the predicted risk and displays the range in our uncertainty and knowledge in

predicting the potential vCJD infection risk for HA patients who use US manufactured human pdFVIII. However, as further scientific information and data become available in the future, the uncertainty in the model may decrease and the estimates of vCJD risk for recipients of pdFVIII may become more precise.

Evaluating the total vCJD infection risk for the severe HA population of 1,800 by summing the total annual exposure (at the higher vCJD Infection prevalence estimated), the model predicts that the population would use a total average of approximately 243 million IU FVIII. If the patient population used product that attained a clearance of 7-9 $\log_{10}$ and assuming the lower prevalence the model predicts that for the total patient population the mean total annual risk would be 1 case in 1.6 million years representing a negligible vCJD risk that would likely not give rise to new cases of the disease. At the other end of the spectrum at the 2-3 $\log_{10}$ clearance level and the higher prevalence the model predicts a mean of approximately 13 vCJD infections per year **(Table 5.3.B.)** for the patient population.

V. D. Sensitivity analysis

Sensitivity analysis is used to identify the input parameter or parameters that have the greatest impact on the risk estimates generated by the model and are done by varying the values of key input parameters and evaluating the effect on the final risk estimate. Our goal in doing these analyses was to identify the key input parameters that have the greatest influence on annual exposure to the vCJD agent. The model was examined and candidate variables for the sensitivity analysis were chosen from the model that exhibited the largest potential for variability and/or uncertainty and those values are listed in Table 5-7. Importance analysis is a type of sensitivity analysis. Our importance analysis used two values, one at the minimum or 5th percentile value and one at the maximum or 95th percentile value to provide a reasonable estimate of impact across the range tested. The results from the importance analysis are displayed as tornado plots (**Figures 2.A., 2.B. and 2.C.**), which graphically shows the relative influence of each input parameter evaluated on the final model estimates. The most influential factors are displayed at the top of the plot and those that are least influential or those with negative influence on the risk are at the bottom of the plot.

For the FVIII risk assessment the output being monitored in the sensitivity and importance analyses was annual exposure (I_{yr}) to vCJD agent quantified in i.v.ID_{50} units. The sensitivity and importance analysis were conducted using the HA patient population on prophylaxis treatment regimens with inhibitor and being treated for immune tolerance as the example population used to do the analyses. This population displayed the largest mean usage and the widest range in product utilization. We assumed that the sensitivity and importance analysis results are representative of all the HA and vWD patient populations included in our study since all of the populations were assumed to differ only by the total average quantity of pdFVIII utilized per year.

The importance analysis was performed for each variable by doing two sets of simulations, each with 5,000 iterations. For each set of simulations the value of one testing variable was set at the minimum or 5th percentile value for the input distribution and the simulation run; for the second run the variable was set at the maximum or 95th percentile value and the simulation run. The importance analysis was run separately each time using one of the three surveillance estimate

ranges. The first analysis used a range of 0.7 to 700 per million, which encompasses the entire range for both the HIGH and LOW prevalence estimates. The second analyses used the higher vCJD Infection prevalence estimate of 1 in 4,225 (or 237 per million) derived from a tissue surveillance study (Hilton et al 2004). This prevalence was based on the variable ($P_{vCJD\text{-}Surv}$) in the model that used data from a tissue surveillance study. To do the sensitivity analysis we used a 5th percentile value of 49 per million and a 95th percentile value of 692 per million. The third set of analyses used the lower vCJD Case prevalence estimate of ~1.8 per million based on epidemiological modeling from actual vCJD occurrence conducted by Clarke and Ghani (2005). This prevalence was ($P_{vCJD\text{-}Epi}$) based on epidemiologic modeling and to do the sensitivity analysis we used a 5th percentile value of 0.7 per million and a 95th percentile value of 4 per million. The results of all simulations and the ranking of input parameters by their importance is represented graphically using a tornado plot shown in **Figures 2.A. , 2.B. and 2.C.** The tornado plot displays the correlations between key inputs in the model and the model output of exposure. A tornado plot prioritizes the various input factors with the most influential factors at the top and those that are least influential or those with negative influence on the risk are at the bottom of the plot.

Table 5.4: Input Variables included in Importance Analysis

Description of variables	Name of input variable	Importance analysis values
Entire range of estimated vCJD prevalence in UK (cases/million)	$Prev_{vCJD\text{-}UK}$	Minimum: 0.7 Maximum: 700
High prevalence estimate of vCJD in UK (cases/million)	$Prev_{vCJD\text{-}UK(Surveillance)}$	5th perc: 49 95th perc: 692
Low vCJD prevalence in UK (cases/million)	$Prev_{vCJD\text{-}UK\ (Epi\ model)}$	5th perc: 0.7 95th perc: 4.0
Efficiency of donor deferral policy	Eff_{Def}	Minimum: 85% Maximum: 99%
Efficiency of i.c. versus i.v. route	$A_{ic\text{-}iv}$	Minimum: 0.1 Maximum: 1
Number of donors per plasma pool	DR_{Pool}	Minimum: 6500 Maximum: 360000
Quantity of i.c. infectivity in infected human blood	I_{bl}	5th perc: 2 95th perc: 30
Manufacturing yield of FVIII (IU/L plasma)	Y_{VIII}	Minimum: 120 Maximum: 250
Log Manufacture Reduction of vCJD agent	R_{Log}	Minimum: 2 Maximum: 9
FVIII used per year (IU/year)	IU_{yr}	5th perc: 10000 95th perc: 4000000

Sensitivity analysis is used to study the quantitative relationship between the input variables and risk output. Same as in importance analysis, output to be monitored in sensitivity analysis is annual exposure (I_{yr}) to vCJD of young HA patients under prophylaxis treatment with inhibitor and immune tolerance treatment. Sensitivity analysis for an input variable consists of multiple simulations. In each simulation the testing input variable is fixed at one value within the input range. Results of sensitivity analysis are presented only for the most important input variables, which were identified by the ranking provided by the importance analysis.

Fig 2. A. Importance Analysis ranking influential factors for predicted annual vCJD exposure (I_{yr}) using prevalence estimate encompassing the range of values for both high and low prevalence from 0.7 to 700 vCJD cases per million UK population. Tornado chart showing impact of input variables on estimated annual exposure of severe HA patient with prophylaxis, inhibitor and immune tolerance treatment

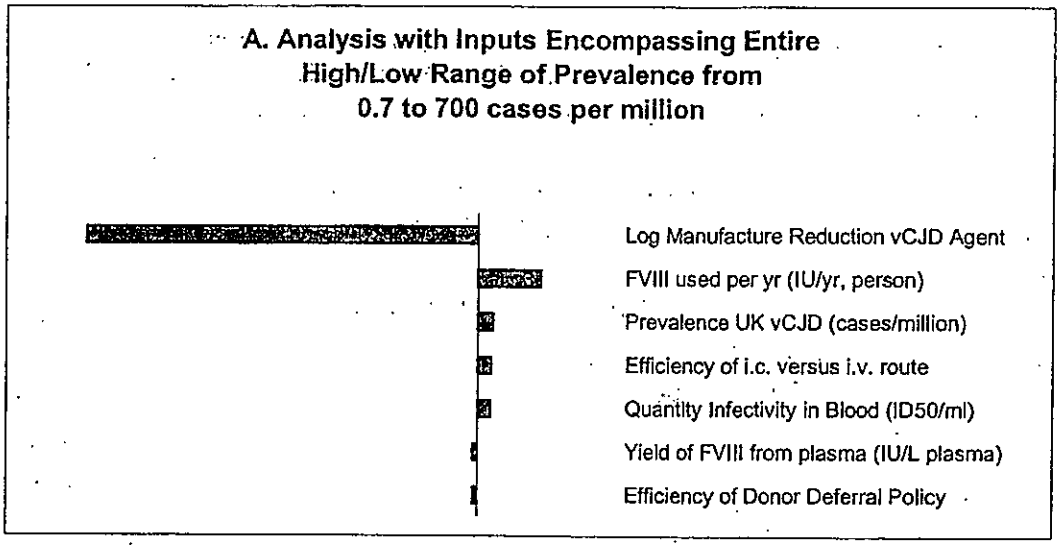


Fig 2. B. FVIII Importance Analysis ranking influential factors for predicted annual vCJD exposure (I_{yr}) using Tissue Surveillance-based (HIGH) prevalence estimate. Tornado plot showing impact of input variables on estimated per treatment course exposure of pdFVIII recipients.

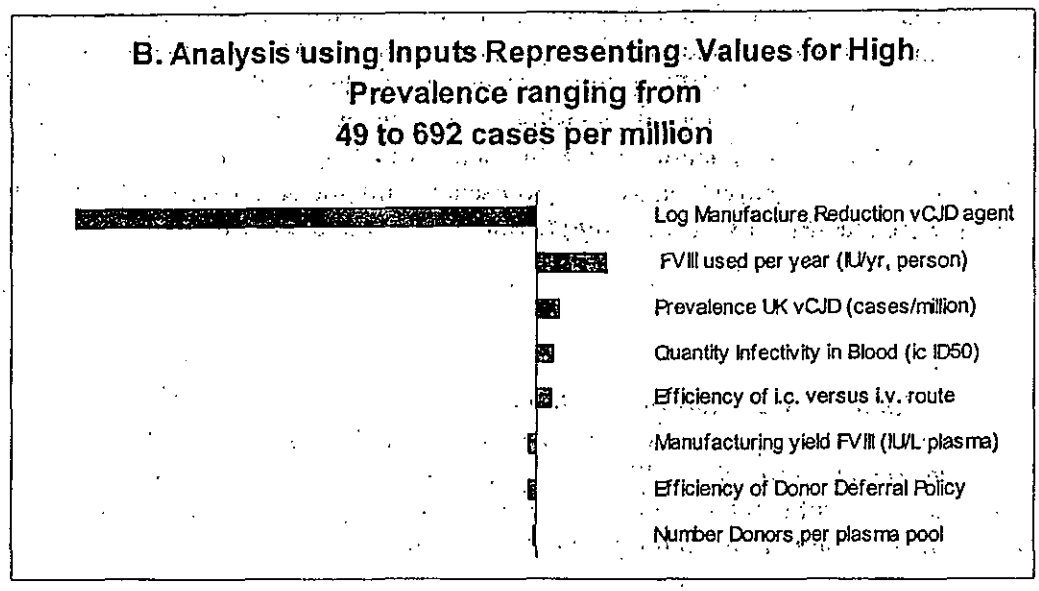
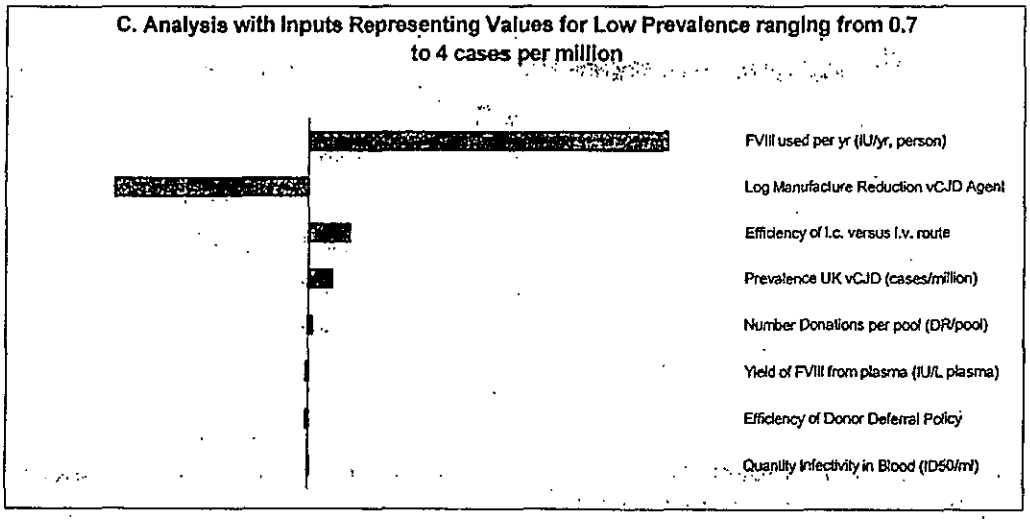


Fig 2. C. FVIII Importance Analysis ranking influential factors for predicted annual vCJD exposure (I_{yr}) using Epi Modeling-based (LOW) prevalence estimate. Tornado plot showing impact of input variables on estimated per treatment course exposure of pdFVIII recipients.



Some input variables are used multiple times in the original model, for instance each type of plasma pool (Source or recovered) was modeled on an individual basis. Other examples are pool size ($DR_{pool\text{-}S}$ and $DR_{pool\text{-}R}$), yield (Y_{FVIII}), quantity of i.c. infectivity in the infected human blood (I_{bl}) and the reduction of infectivity during manufacturing (R_{Log}). In importance analysis and sensitivity analysis, when these input variables are tested, we assumed that there was no difference among the pools. When evaluating the impact of a specific variable all other values are held constant during the simulation. When simulating parameters with multiple values (e.g., size of recovered plasma pools) all values are the same for the simulation. The magnitude of changes in risk output associated with changes of input variables are graphed in the tornado chart, which

represents the relative ranking of the input variables by their impacts on the risk outcome. The importance analysis was conducted for three possible ranges of UK vCJD prevalence: one set of analysis for tonsil survey based estimate, one set for epidemiology model-based estimate and another set for the two prevalence estimates combined.

The order of the influence of the specific input factors varies slightly when the importance analysis is conducted using the three difference prevalence estimates. When a higher prevalence estimate was used (either the combined prevalence (0.7 to 700 per million) the tornado plots in **Figures 2.A. and 2.B.** both show that clearance or Log reduction of the vCJD agent (R_{Log}) during the manufacturing process is the dominant factor that influences the annual exposure or risk for a pdFVIII recipient. The importance analysis suggests that changes in the input values for prevalence used in the analysis can cause some visible changes in the rank order of the influence of the various input factors. A change in the rank order of model factors is seen when the lower prevalence estimate of 0.7 to 4 per million is used (**Figure 2. C.**). The dominant factor potentially driving risk then becomes the quantity of pdFVIII used by a patient.

In our importance analysis the five variables that had significant influence on the output of the model were clearance of i.v. ID_{50} from pdFVIII products, pdFVIII use (IU/yr), UK vCJD prevalence, adjustment for the efficiency of transmission via the i.c. route vs. the i.v. route, and the quantity of i.v. ID_{50} in blood. Changes in prevalence did cause the variable parameters to reassort and change rank when the different prevalence estimates were used. Overall, however, they were somewhat similar in asserting their influence on the estimated risk outcome(s), but had significantly less influence when compared to that of reduction of infectivity during processing and manufacture. Although these types of sensitivity analysis and tornado plots are often used to identify influential factors of risk, their use has some limitations. Factors are examined singly or in isolation so interaction among various factors that may influence the risk estimate are not addressed.

General comments on model outputs

The risk estimations in this section of the risk assessment are predicated on the assumption that there is homogeneous mixing and dispersion of vials from all pools among all donors. In reality, vials may not be dispensed homogeneously and it is likely that patients draw from only one or a few manufactured lots of pdFVIII product in a given year. FDA did not have data to model this non-homogeneous dispensing of pdFVIII but the model can be used to estimate the average maximal level of i.v. ID_{50} exposure if on a very rare chance all vials used by a patient in a given year happened to contain vCJD agent.

V. E. Uncertainty and Data Gaps

Uncertainty arises from the absence of information or availability of limited information. In our probabilistic model statistical distributions are used, where possible, to represent the uncertainty of much of the information used in the model. There are uncertainties in the information and the model that we were unable to quantify and that are not represented in the final risk estimates. Some of the difficult to quantify uncertainties are associated with the extrapolation of a human dose-response relationship based on animal data, an assumed linear dose response with no

uncertainty or variability bounds, and assumption of infectivity in the last 50% of the incubation period. We express the uncertainty of the final risk estimates generated from the model using a mathematical mean (average) of exposure in ID_{50} units and the 5th and 95th percentiles, which represent the 90% confidence interval for each estimate. The uncertainty for the risk estimates generated by this FVIII risk assessment model is significant and decision makers should use the results with caution. Similarly, patients and physicians should understand that the uncertainties are too great at this time to determine the presence, absence or degree of actual risk. In the future, additional research and information may be substituted for assumptions or used to improve estimates for the individual parameters and ultimately improve the precision of the final risk estimates generated by the model.

Even considering the associated uncertainty of estimated risks, risk assessment provides an estimate of risk based on the current and known information. It is still a useful tool that can inform the science-based decision making process. It can identify data gaps and research priorities where additional research and information would have the greatest impact on enhancin the final risk estimates. The sensitivity analysis results in Section IV.C. indicated that the risk assessment results are highly dependent upon log reduction of vCJD agent (R_{Log}) during the manufacturing process. The modeled estimates were based upon levels of reduction seen for manufacturing steps of several different types of plasma-derived products that were similar in some but not all respects to those used in the manufacture of FVIII products. More high quality data on the levels of vCJD agent clearance achieved during the pdFVIII manufacturing would likely improve the final risk estimate generated by the FDA model. Given the lack of data on vCJD agent clearance for pdFVIII uncertainty is considerable.

Better information on when infectivity is present in human blood during the incubation period is a critical factor in the model, especially if the higher vCJD infection prevalence estimate (of 1 in 4,225) is in the range of the actual vCJD prevalence, and would improve predictions generated by the model. There are no data available on the level of infectious units or ID_{50} units present in the bloodstream of vCJD infected individuals at the time of blood donation. The model extrapolates an estimate of the level of vCJD agent that might be present in human blood based on data from several animal models. However, the presence and level of agent present in an infected individual at the time of blood donation could differ from our assumption and this adds to the uncertainty of the risk assessment outcomes.

The model estimates exposure to the vCJD agent in the form of intravenous ID_{50} units. Data are not available to estimate the probability of various clinical outcomes, such as infection or illness that might be predicted to arise from exposure to a particular level of agent. Although we did estimate a probability of infection in our model, the uncertainty associated with the estimate is considerable. However, a meaningful dose-response model would need to be generated for vCJD exposure in humans to improve estimates of the probability of adverse clinical outcomes for humans. The type of data needed to generate a dose-response model that would improve the quality of TSE risk assessment predictions would necessitate injection of groups of animals at several different concentrations of ID_{50}, including low doses below 1 ID_{50} using a protocol that mimics transfusion transmission of vCJD in humans. Both infection and duration of the incubation periods at several different i.v. ID_{50} concentrations would be useful endpoints for developing informative dose-response relationships. Given the state of the current TSE science, estimates of the probability of vCJD infection or illness arising from exposure to the vCJD agent are still extremely uncertain. Nevertheless risk assessment is a tool that provides insight into

important factors where additional research is needed into production processes, tools, or strategies that may further reduce vCJD risks and advance product safety for patients.

The manufacturing processes for pdFVIII are highly varied – therefore, any potential clearance of the vCJD agent during production is likely variable and dependent upon the specific steps used to produce the final product. For example, the techniques applied in fractionation process vary from manufacture to manufacture including the sizes of plasma pools used for producing pdFVIII, the yield of products, and the reduction of infectivity during processing varies within a limited range from batch to batch. In addition the utilization of pdFVIII varies from individual to individual. This risk assessment considers the typical production and utilization. Uncertainty from the model should be appreciated. Human plasma-derived FVIII is typically prepared through successive steps of large scale fractionation during the manufacturing process. Cryoprecipitation is the first and a common step in preparation of pdFVIII. Afterward, cryoprecipitate undergoes further fractionation procedures such as precipitation, absorption/desorption, ion exchange and filtration to yield intermediate purity FVIII, [redacted] In certain cases some hospitals may prepare small amount of cryoprecipitate FVIII from small plasma pools (1-8 donations/pool) for special treatment purposes. Preliminary risk assessment results indicated that the risk that vCJD would be transmitted through cryoprecipitated AHF is relatively low due to the small size of plasma pool and small numbers of donors involved. This risk assessment uses 3 ranges of possible clearance of vCJD agent from pdFVIII of 2-3 $\log_{10}$, 4-6 $\log_{10}$, and 7-9 $\log_{10}$ to cover the possible ranges for all pdFVIII products presently in the marketplace.

General comments on model outputs

The risk estimations in this section of the risk assessment are predicated on the assumption that there is homogeneous mixing and dispersion of vials from all pools among all donors. In reality, vials may not be dispensed homogeneously and it is likely that patients draw from only one or a few manufactured lots of pdFVIII product in a given year. FDA did not have data to model this non-homogeneous dispensing of pdFVIII but the model can be used to estimate the average maximal level of i.v. ID_{50} exposure if on a very rare chance all vials used by a patient in a given year happened to contain vCJD agent.

V. F. Conclusions

Results from the FDA pdFVIII risk assessment model suggest that the risk of vCJD infection from US manufactured pdFVIII generally appears likely to be very low, but may not be zero. For US plasma donors, the major source of vCJD risk is dietary exposure during travel and/or residency in the UK, France, or other countries in Europe since 1980. Although donor deferral criteria in place since 1999 have reduced the risk of donation by exposed persons some are not deferred and potentially may donate plasma that contains the vCJD agent. However, the model suggests that the likelihood of a vCJD contaminated plasma pool is low.

Manufacturing processes for human pdFVIII products likely reduce the quantity of vCJD agent, if present, but the level of reduction through manufacturing steps is not precisely known. Clearance of TSE agents in manufacturing appears to vary among products, but has not been measured in standardized studies which might allow more meaningful direct comparisons. Based on currently available experimental studies, it is estimated that pdFVIII products potentially have

4 $\log_{10}$ (or 10,000 fold) or greater manufacturing process reduction of the vCJD agent. Assuming a 4-6 $\log_{10}$ manufacturing process reduction, the modeling predicts that the potential risk per person per year for patients with severe HA using pdFVIII ranges from1 in 15,000 for the higher vCJD prevalence estimate and high product usage to 1 in 9.4 million for the lower vCJD prevalence estimate and low product usage. Due to the wide range of methods used for clearance studies currently available, gaps in information, and the results of the model, it is not possible at this time to determine with any certainty if a specific product may be less or more safe than another.

Although results of the model suggest exposure to vCJD agent is possible, and there is a potential risk of infection that is likely to be very low, it is not possible for the model to provide a *precise* estimate of the vCJD risk in general, or of the actual risk to individual patients. Although the actual risk is highly uncertain, the risk assessment model indicates that the most important factors affecting risk are the clearance of the vCJD agent though manufacturing steps, how much product individuals used, and the vCJD prevalence in the UK donor population.

In considering the results of the risk assessment it is important to note that to date we are not aware of any cases of vCJD having been reported worldwide in patients receiving plasma-derived products, including pdFVIII.. This includes patients receiving large amounts of other products manufactured from UK plasma donations over a long period of time. This observation suggests that the actual risk of vCJD infection from pdFVIII is likely to be very low. The absence of cases does not rule out the possibility of exposure that could potentially result in illness in some recipients at some future point in time.

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APPENDIX A

Supplemental technical information for the FDA Risk Assessment

The sections in this appendix provide additional technical information and details of data and modeling approaches used in specific sections (but not all sections) of Section IV. The heading and numbering of each section in this appendix mirrors the sections in "Section IV. Exposure Assessment" portion of the risk assessment.

A- IV. A. Estimation of vCJD Prevalence in the United Kingdom (Module 1)

A-IV. A. 3. Estimation of age-specific vCJD prevalence based on the age distribution of diagnosed vCJD cases in the UK

Cases of vCJD occur in relatively young individuals (median age of 28 years) compared to classic CJD. Blood and plasma donors are usually at the age 18-40, among whom the vCJD prevalence would be expected to be higher than the prevalence among general population. Because age specific rates of donation and vCJD infection would likely have a large effect on the final risk estimate the FDA model carefully characterizes the age specific prevalence of vCJD and donation rate. Throughout the FDA model, age specific vCJD prevalence rates are calculated for each five year age group beginning at age group of 10 – 14 yrs, 15-19 yrs and so on – and applied in estimating vCJD risk and prevalence for the residents of different geographic regions and the US blood and plasma donors who traveled to those regions. The percentage of reported vCJD cases by age is shown in **Table A-4.3.** The model assumes that the age-specific percentage and prevalence of incubating asymptomatic cases reflects the same age-specific trend as for reported cases of symptomatic vCJD and deaths from vCJD.

Table A-4.3. Reported vCJD cases in the UK and percent of US Source Plasma and blood (recovered plasma) donors by age groups

Age group	<10	10-14	15-19	18-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	>70
Reported vCJD cases in UK (through 2003)[a] (%)	0	5 (3.4%)	27 (18.4%)		32 (21.8%)	30 (20.4%)	22 (14.9%)	13 (8.8%)	5 (3.4%)	3 (2%)	5 (3.4%)	0 (0%)	5 (3.4%)		
Age distribution of US Source Plasma donors (%)[b]	0	0	0	12%	29.3%	14.1%	14.1%	9.6%	9.6%	5.8%	5.8%	0%	0%	0%	0%
Age distribution of US Blood (Recovered plasma) donors[c]	0	0	0	5%	13%	8%	10%	12%	13%	12%	11%	7%	4%	5%	0%

[a]Hilton *et al.* 2004

[b]Plasma Protein Therapeutics Association (Jan 07, 2005). Where data were organized in broader age group we allocated donor equally among smaller 5 year age groups

[c] Data provided to FDA by Westat in 2002

Some of the general variables for generating age specific estimates from the model are described below.

Variable: *age* - Age of vCJD cases in 5-year increments

Variable: $vCJD_{UK(age)}$ - Reported vCJD cases in the UK by 5-year age groups (through 2003) beginning at 10 – 14 yrs, 15-19 yrs and so on.

Data used in the model: Data on the vCJD cases in the UK was derived from Hilton et al. (2004). The data includes cases through the end of 2003.

Variable: $Perc_{vCJD(age)}$- Percentage vCJD cases attributed by each age group from 10 – 14 yrs, 15-19 yrs and so on.

Assumption used in the model: We assume each of four age groups, 55-59 yrs, 60-64 yrs, 65-69 yrs and 70-74 yrs, contributes same percentage in vCJD cases.

For the four (five-year) age groups from 55-74yrs we assumed an equal percentage of cases were present in each of the four groups since there were very few vCJD cases in this age range. To estimate the percentages for each group we identified five reported cases (specifically, three reported cases in the age-specific prevalence grouping shown in Hilton et al. (2004) for persons aged 55-74 yrs and two cases of blood transfusion vCJD (each > 64 yrs of age) (Llewelyn 2004, Peden 2005)) in the 55-74 yr age range. The five cases in the 55-74 yr old age group are shown in **Table A-4.3**. We assumed an average of 1.25 cases for each of the four age groups from the ages of 55-74 yrs and divided by the total number of vCJD cases for all age groups to get the percentage of cases for each of the four sub age groups, 55-59 yrs, 60-64 yrs, 65-69 yrs and 70-74 yrs.

The percentage of vCJD cases in the UK from each age group is represented by the equation:

$$Perc_{vCJD(age)} = (vCJD_{UK(age)} / \sum_{age=0-4}^{>85} vCJD_{UK(age)}) \times 100\% \qquad \text{(IV. A. 1-1)}$$

A-IV. A. 3. a. Estimating the UK vCJD prevalence predicted by epidemiological modeling (Clarke and Ghani 2005) for each age group

Variable: $vCJD_{since2002}$-Predicted clinical vCJD cases in the UK from 2002 afterward (cases). Predicted clinical cases from 2002 afterward include 32 vCJD cases diagnosed in 2002 and 2003 and 70 (95% CI of 10-190) future cases between 2004 and 2080 predicted by Clarke and Ghani (2005), which give a total of 102 cases (95% CI: 42-222 cases) after 2002.

Variable: $Asym\text{-}vCJD_{(age)}$ - Number of asymptomatic vCJD infected individuals from a specific age group in year 2002.

$$Asym\text{-}vCJD_{(age)} = vCJD_{since2002} \times Perc_{vCJD(age)} \qquad \text{(IV.A.2-4)}$$

Variable: $Prev_{Asym\text{-}vCJD(age)}$- Prevalence of asymptomatic vCJD infected individuals in the UK by age groups (cases/million).

The prevalence of asymptomatic vCJD cases in the UK by age group is estimated using the equation:

$$Prev_{Asym\text{-}vCJD(age)} = Asym\text{-}_{vCJD(age)}/Pop_{UK(age)} \qquad \text{(IV.A.2-5)}$$

A-IV. A. 3. b. Estimating the UK vCJD prevalence derived from tissue surveillance for each age group

For the risk assessment model we converted the 3 in 12,674 presumptive positive rate to an average rate of vCJD in the UK population of 1 in 4,225 (and used the 1 / 20,300 to 1 / 1,450 at 95% CI; proportions were converted from the 95% CI reported by Hilton et al (2004)). Demographic information of reported vCJD cases (**Table A-4.3**) indicated that the younger population (20 -29 yrs of age) that was deliberately oversampled in this study may have been more susceptible to the disease. The vCJD prevalence among UK donors might, therefore, be over-represented by the prevalence of 20-29 years age group derived from the surveillance study. Assuming the sensitivity and specificity of the testing method is 100%, the estimated rate of 1 in 4,225 translates roughly to a vCJD prevalence of 237 cases per million (95% CI: 49 – 692 cases per million) for all age groups. The authors (Hilton et al 2005) indicated that approximately 60% of the samples tested (from 7,600 patients) came from patients 20-29 years of age. Among the 20-29 year old group we calculated a vCJD prevalence of approximately 400 cases per million for which we assumed a 95% CI of 100-1200 cases per million.

We then derived the prevalences for the remainder of the UK donor population by determining the proportional difference between the vCJD prevalence from the tissue study group and the number of actual reported vCJD cases for donors in the 20-29 years age group. This proportion was then applied to the remaining age groups in the distribution of reported vCJD cases to determine the prevalence for each age group. By multiplying our extrapolated vCJD prevalence for incubating cases by the total donor population we were able to estimate the number of possible incubating vCJD cases in each US donor age group. We assumed that a plasma pool used to manufacture pdFVIII product in the US in the year 2002 consisted 6,000 to 360,000 donations, and several donations in the pool likely came from the same donor. The estimated prevalence was then used to generate variables and parameters representing the potential number of vCJD donors or donations that might be present in a plasma pool.

Variable: $Prev_{Asym\text{-}vCJD(20\text{-}30)}$ Prevalence of asymptomatic vCJD infected individuals in the UK 20-30 year old age group (cases/million)

Assumptions used in the model: The vCJD infectious agent is present in the blood of the individual when the the accumulation of prion protein can be detected in lymphoreticular tissue. Prevalence of vCJD asymptomatic individuals in the UK 20-30 year old age group is likely to be 400 cases/million, 95% CI=100-1200 cases/million. The values for this variable were estimated from the Hilton *et al* studies (2000, 2002, 2004).

Variable: $Pop_{UK(age)}$- Population in the UK by age groups (Thousands).

Data used in the model: The data for UK population were sourced from UK government statistics (UK National Statistics, 2005). Where UK data were organized in broader categories of 10 to 15 years we allocated population equally among smaller 5 year age groups.

Variable: $Asym\text{-}vCJD_{(20\text{-}30)}$ - The number of asymptomatic vCJD infected individuals in the 20-30 yr-old UK age group. This variable is represented by the equation:

$$Asym\text{-}vCJD_{(20\text{-}30)} = Prev_{vCJD(20\text{-}30)} \times Pop_{UK(20\text{-}30)} \qquad \text{(IV.A.2-1)}$$

Variable: $Asym\text{-}vCJD_{(age)}$ - Number of asymptomatic vCJD infected individuals in the UK by age groups

Assumptions used in the model: Number of asymptomatic vCJD infected individuals from an age group is proportional to the percentage of reported vCJD cases from that age group. The age distribution of asymptomatic vCJD cases was assumed to be the same as that of symptomatic cases.

The number of asymptomatic vCJD individuals in the UK per age group was estimated using the following equation:

$$Asym\text{-}vCJD_{(age)} = Asym\text{-}vCJD_{(20\text{-}30)} \times (Perc_{vCJD(age)} / Perc_{vCJD(20\text{-}30)}) \qquad \text{(IV.A.2-2)}$$

Variable: $Prev_{Asym\text{-}vCJD(age)}$- Prevalence of asymptomatic vCJD infected individuals in the UK by age groups (cases/million).

The prevalence of asymptomatic vCJD cases in the UK by age group is estimated by the equation:

$$Prev_{Asym\text{-}vCJD(age)} = Asym\text{-}_{vCJD(age)} / Pop_{UK(age)} \qquad \text{(IV.A.2-3)}$$

A-IV. B. Estimation of vCJD Prevalence in US Plasma Donors and Plasma Pools (Module 2)

A-IV. B. 1. a. Annual US plasma donors and characterization by age

A-IV. B. 1. b. Source Plasma collection in the United States: characterized by donor age

Variable: DN_S – Annual number of Source Plasma units used to make pdFVIII.

Assumption used in the model: It was assumed that, on average, 3.3 million units of Source Plasma were used in each year to make pdVIII. It was further assumed that there is a 10% standard deviation in the number of Source Plasma units used to make pdFVIII for any given year.

Data used in the model: The annual number of Source Plasma units was back calculated based on annual units of pdVIII product made from Source Plasma, the average yield of pdFVIII (187 units per liter

plasma) and average volume of single unit of Source Plasma (700 ml per unit). The information on annual units of pdFVIII made from plasma collected in the US, yield of factor VIII and unit volume of plasma were collected from pdFVIII manufacturers.

Variable: DR_S–Annual number of donors who contribute Source Plasma for manufacture of pdFVIII.

Assumption used in the model: It was assumed that there are approximately 1 million Source Plasma donors in the US each year. It was further assumed that Source Plasma from any individual donor may be used to make pdFVIII. Therefore, we calculated that there were approximately 1 million donors who contributed Source Plasma for the manufacture of pdFVIII. It was further assumed that there could be a 10% standard deviation in the number of donors in any given year.

Variable: *Age* – Age information for US plasma donors was grouped in a two year increment for 18-19 years old because the model assumed that 18 was the minimum age of donation. The remaining population was grouped by 5-year increments – including 20- 24yrs old, 25-29yrs old, and so on

Variable: $DR_{S\text{-}perc(age)}$ - The percentage of Source Plasma donors from a given age group.

Data used in the model: Distribution of US Source Plasma donors by age was obtained from the Plasma Protein Therapeutics Association (2005). Where data (PPTA, 2005) were organized in broader age groups of 10 years or 15 years, we generated 5-year age subgroups by allocating the percentage equally among each subgroup.

Variable: $DR_{S(age)}$ – The annual Source Plasma donors by age groups who contribute plasma for pdFVIII manufacturing is represented by the equation:

$$DR_{S(age)} = DR_S \times DR_{S-perc(age)} \qquad \text{(IV.B.1-1)}$$

A-IV. B. 1. c. Recovered plasma collection in the United States: Characterized by donor age

Variable: DN_R - Annual units of recovered plasma used to make pdFVIII.

Assumption used in the model: It was assumed that approximately 1,800,000 units of recovered plasma are used to make pdFVIII annually. This estimation was generated by backcalculation beginning with the total quantity of pdFVIII manufactured in the US. It was further assumed that there was a 10% standard deviation in the number of units for any given year.

Data used in the model: The annual number of total units of pdFVIII manufactured from recovered plasma collected in the US was estimated by back calculation. The calculation was based on the total quantity of annual units of pdVIII product made from recovered plasma collected in the US. We can further estimate the number of donations used to make the pdFVIII from recovered plasma using estimates in the literature for the average yield of pdFVIII 187 units per liter of plasma (WFH, 2004) and average volume of single unit of recovered plasma (200 ml per unit). The information on annual units of pdFVIII made from plasma collected in the US was collected from pdVIII manufacturers.

Variable: $DN_{Bl\text{-}perc(age)}$ – The percentage of blood units donated by a given age group.

Data used in the model: Distribution of blood units by donor age group was obtained from Westat data provided to FDA in 2002 (Data shown in A-4.3).

Variable: $DN_{R(age)}$ – Annual units of recovered plasma used to make pdFVIII by donor age group

$$DN_{R(age)} = DN_R \times DN_{Bl-perc(age)} \quad \text{(IV.B.2-1)}$$

Variable: $DR_{R(age)}$ – Annual number of donors by age group who contribute recovered plasma that is used for manufacture of pdFVIII

Assumption used in the model: Each unit of recovered plasma used to make pdFVIII comes from different donors. Therefore, number of donors from an age group equals the number of donations from that age group.

The annual number of recovered plasma donors by age group was calculated using the equation:

$$DR_{R(age)} = DN_{R(age)} \quad \text{(IV.B.2-2)}$$

Variable: DR_R - The annual total of potential recovered plasma donors who contribute the plasma that is used for manufacture of pdFVIII, which was estimated in the model using the summation function:

$$DR_R = \sum_{age=18-19}^{70-74} DR_{R(age)} \quad \text{(IV.B.2-3)}$$

A-IV. B. 2. Total plasma donors and donations- for manufacture of pdFVIII in the US

Variable: DR_{Tot} - The annual total of potential plasma donors who contribute plasma for pdFVIII manufacturing is estimated by summing the number of Source Plasma donors and recovered plasma donors and is represented by the equation:

$$DR_{Tot} = DR_S + DR_R \quad \text{(IV.B.3-1)}$$

Variable: DN_{Tot} - The annual total of potential plasma units used to make pdFVIII is estimated by summing the number of Source Plasma donations and recovered plasma donations and is represented by the equation:

$$DN_{Tot} = DN_S + DN_R \quad \text{(IV.B.3-2)}$$

A-IV. C. Estimation of the probability that a plasma pool may contain a donation from an infected donor that contains vCJD agent

IV.C. 1. US plasma donors with history of travel to the UK, France or other Countries in Europe: Annual number potentially infected and vCJD agent is present in the blood

A-IV. C. 1. a. US plasma donors with history of travel to the UK: Number of donors potentially infected and vCJD agent is present in the blood

A-IV. C. 1. a. i. US plasma donors with history of travel to the UK: Percentage of donors and duration of travel

The risk of vCJD infection in US plasma donors is a function of the intensity of exposure to the BSE agent. The intensity of exposure is assumed to be proportional to the amount of time spent, or duration of travel, in the UK and the prevalence of BSE in UK cattle during the period from 1980 – 1996. The FDA model used data from the National Blood Donor Travel Survey 1980-1996 (TSEAC 2000) to derive estimates of the percentages of US donors with a history of extended travel or residence (≥ 3 months) in the UK during 1980-1996, and to derive the frequencies for various durations of travel for 3 months or more. The period of 3 months or more corresponds to the length of time in the current policy that defers donors that traveled to or resided in the UK. The travel survey data on blood donors pose a limitation because the survey was conducted on whole blood donors and may not exactly reflect the travel histories of plasma donors. Unfortunately, to our knowledge there is not travel data available on plasma donors. Therefore, we assumed that plasma donor travel characteristics to the UK and other countries in Europe since 1980 are similar to those of whole blood donors and used this information in the FDA risk assessment. Some may argue that plasma donors travel less frequently than their blood donor counterparts so use of data on blood donors may overestimate the risk.

Data used in the model: National Blood Donor Travel Survey 1980-1996 was conducted by the American Red Cross and presented at the Transmissible Spongiform Encephalopathies Advisory Committee (TSEAC 2000).

Variable: i - The duration interval used to group donors who traveled to the UK from 1980-1996 based on the quantity of time spent in the UK during the period from 1980 – 1996.

Variable: D_i - The average duration of time (in months) for interval i representing the duration of travel or residence by US donors in the UK during the period from 1980 – 1996.

Variable: $CumPerc_{BIDR\text{-}UKi}$ – The cumulative percentage of blood donors who traveled to the UK within duration interval i or longer.

Variable: $Perc_{BIDR\text{-}UKi}$ - Percentage of blood donors who traveled to the UK within duration interval i. This variable was converted from $CumPerc_{BIDR\text{-}UKi}$

Variable: $Perc_{BIDR-UKi/UK}$ - The percentage of blood donors who traveled for a specific duration interval *i* among all donors who have ever traveled to the UK is represented by the equation:

$$Perc_{BIDR-UKi/UK} = (Perc_{BIDR-UKi} / CumPerc_{BIDR-UK,i>1day-1month}) \times 100\% \qquad \text{(IV.C.1.a-1)}$$

A-IV.C.1.a.ii. All US plasma donors with a history of travel to the UK: Percentage and number of donors in each age group by year and duration of travel

For the purposes of our analyses we grouped all donors and donors who traveled to the UK between 1980 and 1996 into age groups of five year increments (20 – 24yrs, 25 – 29 yrs, etc). Because the minimum age of donation is 18, the model also included the donor group 18 & 19 years of age. The percentage of donors in each age group who traveled to the UK between 1980 and 1996 was calculated based on the total annual number donors who traveled to the UK between 1980 and 1996 compared to (or divided by) the total number of donors, and the age specific odds ratio for travel.

As mentioned earlier, data are lacking on the travel characteristics of plasma donors, so the FDA used travel survey data collected from blood donors to estimate past travel history. Because plasma donors are less likely to travel use of these data may yield an overestimate of the actual risk. Characteristics of blood donors on travel including the percentage of donors from each age group who traveled to the UK during period between 1980 and 1996, and distribution of donor travel by duration were applied to plasma donors for estimation of the number of plasma donors from each age group who have traveled or resided in the UK from 1980 to 1996 for specific periods of time ranging from less than 3 months to greater than 5 years duration. Furthermore, the model used data that detailed the number of annual visits of US travelers to the UK to allocate donor travel specifically to an individual calendar year.

- **Calculation of the annual number of blood donors who traveled to the UK from 1980 through 1996**

Blood donors donate whole blood and soon after the liquid plasma portion of whole blood is separated and plasma is called recovered plasma. The model assumes that approximately 200 mls of recovered plasma are produced from a unit of whole blood.

Variable: DR_{BI} - The annual total number of potential blood donors in the US per year

Data used in the model: There are approximately 8 million individuals who donate blood each year in the United States (Westat, 2002).

Variable: $Perc_{BIDR-UK}$ - Percentage of US blood donors who traveled to the UK during the period from 1980 through 1996.

Data used in the model: Approximately, 22.5% of US blood donors have a history of travel to the UK any time during the period from 1980 through 1996, according to data contained in the National Blood Donor Travel Survey (TSEAC 2000).

Variable: $DR_{Bl\text{-}UK}$ -Total number of blood donors estimated to have traveled to the UK from 1980 through 1996

$$DR_{Bl-UK} = DR_{Bl} \times Perc_{BlDR-UK} \qquad \text{(IV.C.1.a-2)}$$

- **Calculation of the percentage of blood donors for each specific age group**

Variable: *Age*- Age of donors grouped in 5 year increments (e.g., 20 – 24 yrs, 25 – 29yrs, etc.) per year and 18-19 yr old age cohort.

Variable: $Perc_{BlDR(age)}$-Percentage blood donors in a specific age group.

Variable: ***BLDR(age)***- Annual number of blood donors in a specific age group

$$Perc_{BLDR(age)} = BLDR(age) / \sum_{age=18-19}^{65-69} BLDR(age) \qquad \text{(IV.C.1.a-3)}$$

Variable: ***BLDN***-Annual total number of blood donations in the US.

Variable: $Perc_{BlDN(age)}$- Percentage of blood donations in each specific age group of US donors.

Data used in the model: Percentage of blood donations by age group was obtained from Westat (2002).

Variable: $Freq_{BlDN(age)}$-Average annual number of blood donations from a donor in a specific age group

Data used in the model: Information on the average annual number of donations bydonors in each specific age group was obtained from Westat (2002).

$$BLDR(age) = BLDN \times Perc_{BLDN(age)} / Freq_{DN(age)} \qquad \text{(IV.C.1.a-4)}$$

Replace *BLDR(age)* in equation IV.C.1.a-3 with equation IV.C.1.a.-4, resulting in the expression:

$$Perc_{BlDR(age)} = (Perc_{BlDN(age)} / Freq_{BlDN(age)}) / \sum_{age=18-19}^{65-69} (Perc_{BlDN(age)} / Freq_{BlDN(age)}) \qquad \text{(IV.C.1.a-5)}$$

Variable : DR_{Bl}-The annual total number of blood donors in the US, which is assumed to be 8 million.

Variable: $DR_{Bl(age)}$- The annual number of blood donors in each five-year age group and the18-19 yr old age cohort.

$$DR_{Bl(age)} = DR_{Bl} \times Perc_{BlDR(age)} \qquad \text{(IV.C.1.a-6)}$$

Variable: $DR_{BI\text{-}UK}$ -Total number of US blood donors who have traveled to the UK during the period 1980 - 1996

Variable: $Perc_{BIDR\text{-}UK(age)}$ - The percentage of US blood donors in an age group who traveled to the UK during the period 1980 - 1996.

$$DR_{BI-UK} = \sum_{age=18-19}^{65-69} (Perc_{BIDR-UK(age)} \times DR_{BI(age)}) \qquad \text{(IV.C.1.a-7)}$$

Variable: $Odd_{T(age)}$- Age specific odd ratios for travel compared to the age group 18-19 years.

Data used in the model: The odds ratios for likelihood of travel for each age group were derived from the travel data obtained from 1980-1996 blood donor travel survey. An odds ratio of 1 was assigned to the donor group aged 18-19 years. The odds ratios for other age groups is a function of the travel frequency of those age groups compared to the travel frequency of the age group of 18-19 years

$$Perc_{BIDR-UK(age)} = Odd_{T(age)} \times Perc_{BIDR-UK(18-19)} \qquad \text{(IV.C.1.a-8)}$$

Replacing the variable, $Perc_{BIDR\text{-}UK(age)}$, in equation IV.C.1.a-7 with equation IV.C.1.a-8 the percentage of blood donors in the age group of 18-19 years of age who traveled to the UK was calculated using the following equation:

$$Perc_{BIDR-UK(18-19)} = DR_{BI-UK} \,/\, \sum_{age=18-19}^{65-69} (Odd_{T(age)} \times DR_{BI(age)}) \qquad \text{(IV.C.1.a-9)}$$

A-IV. C. 1. a. ii. a. Number of US Source Plasma donors who traveled to the UK in a specific year from 1980 to 1996 and by age group

Variable: *age* - Age of US plasma donors in groups by 5-year increments and 18-19 yr old age cohort.

Variable: $DR_{S(age)}$ (calculated in section A-IV.B. 1.) - The annual number of donors by age group who contribute Source Plasma to make pdFVIII.

Variable: $Perc_{BIDR\text{-}UK(age)}$ (calculated in section A-IV.C.1.a.i.b.) - the percentage of blood donors in each age group who traveled to the UK between 1980-1996.

Variable: $DR_{S\text{-}UK(age)}$ - Number of Source Plasma donors who traveled to the UK from 1980 through 1996 by age groups.

Assumptions used in the model: The percentage of Source Plasma donors who traveled to the UK is the same as the percentage of blood donors of the same age group.

The number of Source Plasma donors who traveled to the UK from 1980 to 1996 by age group is represented by:

$$DR_{S-UK(age)} = DR_{S(age)} \times Perc_{BIDR-UK} \quad \text{(IV.C.1.a-8)}$$

The risk of vCJD infection in US donors who traveled to the UK was assumed proportional to the relative level of exposure to the BSE agent in each year through the UK food supply. The proportional risk was derived based on the number of BSE-reported cattle in a given year from 1980 through 1996 divided by the total number of BSE cases to date. The model generates categories (or bins) for Source Plasma donors by year of travel and estimates the risk more accurately by incorporating the information about proportional risk due to the BSE epidemic in the UK

In 1996 after the emergence of human vCJD cases the UK government implemented stringent food chain controls that decreased the number of high risk animals and high risk tissues containing BSE agent from entering the human food supply. In the early 1980s human exposure may have begun at a low level as BSE spread among the UK cattle population. The BSE epidemic expanded throughout the 1980s and peaked in 1992, then risk started to decrease as animal feed measures were implemented and more stringent human food chain controls were implemented in 1996. Today, a few hundred cases of BSE are identified in the UK annually – but it is unlikely that the animals or products from BSE-infected animals in the UK enter the human food supply. The model incorporates the changing dynamics of the BSE epidemic since 1980 and accounts for relative changes in the levels of human, specifically US plasma donors, exposure to the BSE agent and possible vCJD infection.

Variable: y - Calendar year of travel.

Variable: V_y - Number of visits by year to the UK by US travelers (in thousands)

Data used in the model: Number of visits by year to the UK by US travelers (UK Government Statistics, 2005).

The yearly distribution of travel visits by each age group was adjusted to account for the minimum age of 18 when a donor can donate plasma or blood. Therefore, in calculating the US donor risk for vCJD the yearly distribution of travel visits by each age group was adjusted to account for this requirement. The model adjusted the potential vCJD exposure for younger donors who were born during the period from 1980 to 1986 and would have essentially a zero chance of being exposed to the BSE agent in the years prior to their birth. Therefore, donors 18 years of age in 2002 were assumed to have zero exposure to the BSE agent prior to 1985, those 19 years of age in 2002 were assumed to have zero exposure prior to 1984, those 20 years of age in 2002 were assumed to have zero exposure prior to 1983, those 21 years of age in 2002 were assumed to have zero exposure prior to 1982, those 22 years of age in 2002 were assumed to have zero exposure prior to 1981. The model assumed that there was zero exposure of all donors prior to 1980.

Assumption used in the model: US Source Plasma donors have similar travel patterns to the US blood donor population, which is assumed to be similar for the larger US population.

Assumption used in the model: It was assumed that no US traveler visited the UK more than once per year. This may potentially overestimate the vCJD risk for US plasma donors (because repeat travel by the

same donor is not addressed) and underestimate it in certain other cases (travelers who visit multiple times per year). FDA found no data that quantified the numbers of multiple visits or repeat visits by the same traveler that likely occurred for US donors with a history of UK travel.

Variable: $V_{y/1996}$ - The number of visits to the UK by US travelers in year y compared to the number of visits in 1996 is represented by the equation:

$$V_{y/1996} = V_y / V_{1996} \qquad \text{(IV.C.1.a-9)}$$

Variable: *age* - Age of US plasma donors in groups of 5-year increments (e.g., 20-24 yrs, etc.) and 18-19 yr old age cohort..

Variable: $DR_{S(age)}$ (calculated in section A-IV.B. 1.) - the annual Source Plasma donations by age groups.

Variable: $DR_{S\text{-}UK(age)}$ - Number of Source Plasma donors who traveled to the UK from 1980 through 1996 by age group in five-year increments and 18-19 yr old age cohort.

Assumptions used in the model:

- The same percentage of Source Plasma donors traveled to UK as blood donors
- Frequencies of travels are similar among the donors of different age groups.
- Travel rates for the general US population are the same as the travel rate for blood and plasma donors.

The number of Source Plasma donors who traveled to the UK from 1980 to 1996 by age group is represented by:

$$DR_{S\text{-}UK(age)} = DR_{S(age)} \times Perc_{DR\text{-}UK} \qquad \text{(IV.C.1.a-5)}$$

Variable: $DR_{S\text{-}UK(age),y}$ - the number of Source Plasma donors who traveled to the UK in year y by age group

Source Plasma donors with a history of travel to the UK among each age group ($DR_{S\text{-}UK(age)}$) was allocated to individual travel years based on the yearly distribution of visits to the UK by US travelers (UK National Statistics, 2005). The yearly distribution of travel visits by each age group was adjusted to account for the minimum age of 18 when a donor can donate plasma or blood. Therefore, in calculating the US donor risk for vCJD the yearly distribution of travel visits by each age group was adjusted to account for this requirement. The model adjusted the potential vCJD exposure for younger donors who were born during the period from 1980 to 1986 and would have essentially a zero chance of being exposed to the BSE agent in the years prior to their birth. Therefore, donors 18 years of age in 2002 were assumed to have zero exposure to the BSE agent prior to 1985, those 19 years of age in 2002 were assumed to have zero exposure prior to 1984, those 20 years of age in 2002 were assumed to have zero exposure prior to 1983, those 21 years of age in 2002 were assumed to have zero exposure prior to 1982, those 22 years of age in 2002 were assumed to have zero exposure prior to 1981. The model assumed that there was zero exposure of all donors prior to 1980.

<u>Assumption used in the model</u>: US Source Plasma donors have similar travel patterns as the general US population and US blood donors.

The number of US Source Plasma donors who have traveled to the UK in year y between 1980-1996 is represented by the equation:

$$DR_{S-UK(age)y} = DR_{S-UK(age)} \times V_{y/1996} / \sum_{y=1980}^{1996} V_{y/1996} \quad \text{(IV.C.1.a-10)}$$

A-IV. C. 1. a. ii. b. US Source Plasma donors with history of travel to the UK: Duration of travel by age group

There were no data that we are aware of that details the travel histories of Source Plasma donors in the US. Travel data for US blood donors was used to estimate travel patterns for Source Plasma donors after an adjustment for the frequency of travel based on the age of Source Plasma donors and the age-specific odds ratios for travel, which was obtained from 1980-1996 Blood Donor Travel Survey (TSEAC, 2000). The model used the data on the number of Source Plasma donors who have traveled to the UK in a specific year and subdivided those individuals into additional categories based on estimated duration of stay. The categories of duration of stay was estimated based on the Blood Donor Travel Survey (TSEAC, 2000). Use of blood donor travel data in the model implicitly assumes that travel rates are similar for both blood and plasma donors. However, it is thought that plasma donors likely travel less and are therefore at lower risk for vCJD, therefore the model results may overestimate the potential vCJD risk for plasma donors.

Variable: i - The duration interval used to group blood donors who had traveled to UK from 1980-1996 based on the time they spent in the UK (same variable used above in section A-IV. C. 1. a. i.).

Variable: D_i - The average duration of time for interval i (months) (same variable used above in section A-IV. C. 1. i.).

Variable: $DR_{S-UK(age),y}$ - the number of Source Plasma donors who traveled to the UK in year y by age group (calculated in A-IV. C. 1. a. ii. (a))

Variable: $Perc_{B/DR-UKi/UK}$ - The percentage of blood donors who traveled for a specific duration interval i among all donors who have ever traveled to the UK (calculated in A-IV. C. 1. a. i. a)

Variable: $DR_{S-UK(age)y,i}$ - Number of Source Plasma donors within a specific age group that traveled to the UK in year y for a duration of i and is represented by the equation:

$$DR_{S-UK(age)y,i} = DR_{S-UK(age)y} \times Perc_{DR-UKi/UK} \quad \text{(IV.C.1.a-11)}$$

A-IV. C. 1. a. ii. c. Number of US recovered plasma donors with a history of travel to the UK in a specific year from 1980 – 1996 by age group

Recovered plasma is plasma that is separated or "recovered" from a unit of whole blood soon after the blood is collected. As expected, recovered plasma donor donation characteristics mirror those of whole blood donors. A recovered plasma donor can donate plasma a maximum of six times per year (or once every 54 days)– and on average we assumed a recovered donation is approximately 200 milliliters (versus an average of 700 milliliters for a Source Plasma donation).

Variable: y – **year of travel** (same variable used above in section A-IV. C. 1. a. ii. a) to the UK during the period 1980 - 1996 by US plasma donors.

Variable: age – age groups of the population in five-year increments (same variable used above in section A-IV. B. 1.).

Variable: $DR_{R(age)}$ - number of potential recovered plasma donors per year by age group (described in section A-IV. B. 2).

Variable: $Perc_{BIDR\text{-}UK(age)}$ (calculated in section A-IV.C.1.a.i.b.) - the percentage blood donors in each specific age group who have traveled to the UK between 1980-1996.

Variable: $DR_{R\text{-}UK(age)}$ – The number of recovered plasma donors who have traveled to the UK from 1980 through 1996 by age group and is represented by the equation:

$$DR_{R-UK(age)} = DR_{R(age)} \times Perc_{BIDR-UK(age)} \qquad \text{(IV.C.1.a-12)}$$

The model categorizes US recovered plasma donors by year of travel in order to estimate the potential vCJD risk more accurately by incorporating the information about BSE epidemic in the UK. The number of beef cattle affected each year by the BSE epidemic in the UK changed throughout the epidemic. Donors who visited the UK at the height of the BSE epidemic in 1992, we assumed, were more likely to be exposed to BSE agent (and vCJD risk) than a donor who visited in 1996 after food chain controls were implemented. The model accounts for this changing exposure potential by analyzing US donors who may have traveled to the UK for each year from 1980 through 1996. The number of recovered plasma donors who traveled to the UK was allocated to individual travel year based on the yearly distribution of visits to the UK by US travelers determined from UK travel data.

Variable: $DR_{R\text{-}UK(age)}$ - Number of recovered plasma donors traveled to the UK from 1980 through 1996 by age groups (calculated above).

Variable: $V_{y/1996}$ – The number of visits to the UK by US travelers in year y compared to the number of visits in 1996 (calculated in A-IV.C.1.a. ii. a.).

Data used in the model: Number of visits by year to the UK by US travelers was determined using UK Government Statistics (2005).

Assumption about variable: US recovered plasma donors have a similar travel pattern as the US total population. The yearly distribution of travel visits by each age group was adjusted to account for the minimum age of 18 when a donor can donate plasma or blood. Therefore, in calculating the US donor risk for vCJD the yearly distribution of travel visits by each age group was adjusted to account for this requirement. The model adjusted the potential vCJD exposure for younger donors who were born during

the period from 1980 to 1986 and would have essentially a zero chance of being exposed to the BSE agent in the years prior to their birth. Therefore, donors 18 years of age in 2002 were assumed to have zero exposure to the BSE agent prior to 1985, those 19 years of age in 2002 were assumed to have zero exposure prior to 1984, those 20 years of age in 2002 were assumed to have zero exposure prior to 1983, those 21 years of age in 2002 were assumed to have zero exposure prior to 1982, those 22 years of age in 2002 were assumed to have zero exposure prior to 1981. The model assumed that there was zero exposure of all donors prior to 1980.

The number of recovered plasma donors who traveled to the UK in year y by age groups during the period from 1980-1996 is represented by the equation:

$$DR_{R-UK(age)y} = DR_{R-UK(age)} \times V_{y/1996} / \sum_{y=1980}^{1996} V_{y/1996} \qquad \text{(IV.C.1.a-13)}$$

A-IV. C. 1. a. ii. d. US recovered plasma donors with history of travel to the UK: Duration of travel by age group

Recovered plasma donors who traveled to the UK in a specific year ($DR_{R-UK(age)y}$) in the years 1980-1996 were further partitioned in the model into subgroups or "bins" based on travel duration and by 5-year age groups and 18-19 yr old age cohort. Data on the percentage of blood donors who traveled to the UK since 1980 for a certain duration(s) (TSEAC 2000) was used in this risk assessment.

Variable: i - The duration interval used to group blood donors who had traveled to the UK from 1980-1996 based on the time they spent in the UK (same variable used above in section A-IV. C. 1.)

Variable: D_i - The average duration of time for interval i (months) (same variable used above in section A-IV. C. 1.)

Variable: $DR_{R-UK(age),y}$ - The number of recovered plasma donors who traveled to the UK in year y by age group (calculated in A-IV. C. 1. a. ii. c)

Variable: $Perc_{BIDR-UKi/UK}$ - The percentage of blood donors who traveled for a specific duration interval i among all donors who have ever traveled to the UK (calculated in A-IV. C. 1. a. i. a)

Variable: $DR_{R-UK(age)y,i}$ - The number of recovered plasma donors among an age group who have traveled to the UK in year, y ,for duration of i and represented by the expression:

$$DR_{R-UK(age)y,i} = DR_{R-UK(age)y} \times Perc_{DR-UKi/UK} \qquad \text{(IV.C.1.a-14)}$$

A-IV. C. 1. a. iii. US plasma donors with a history of travel to the UK: Adjustment of relative risk to account for variations in BSE risk by specific year and travel duration

As indicated in previous sections the FDA model assumed that the relative vCJD risk for UK residents residing for any five-year period or longer from 1980 through 1996 is assumed to have a value of 1, because the BSE epidemic in UK cattle and exposure of the human population to the BSE agent in the UK was greater than any other country. The relative risk value of 1 equates to 100% of the UK asymptomatic and symptomatic vCJD prevalence, which is difficult to estimate. The relative risk value is assigned based on factors such as domestic UK beef consumption, and the rate and number of vCJD cases, and indigenous BSE cases that may have occurred (TSEAC 2004). BSE was first diagnosed in the United Kingdom in 1986 and the epidemic peaked in 1992, a year when the risk of exposure to the BSE agent would have likely been highest for residents and visitors to the UK. Human exposure risk to the BSE agent would likely have decreased dramatically in 1996 with the culling of animals over 30 months of age from the food production system and the institution of food chain controls to prevent high risk tissues that might contain BSE agent from entering the food and animal food supplies. Presumably there were dramatic variations in the BSE exposure risk, and hence, the human vCJD infection risk that occurred from year to year. Therefore, the model adjusted the vCJD risk for US plasma donors with a history of extended travel or residence in the UK by multiplying by the proportional BSE risk per year (e.g., the BSE exposure risk in a given year compared to the total BSE risk since 1980). Additionally, the model included calculations on the estimated duration of UK travel or residence by US plasma donors based on US donor survey data (TSEAC 2000) to generate a more accurate vCJD risk estimate.

A-IV. C. 1. a. iii. a. Variant CJD risk for individual UK residents from 1980 through 1996

Variable: R_{UK}- The accumulated vCJD risk per UK resident from 1980 through 1996.

Assumption used in the model: The UK population has the highest risk of exposure to BSE or vCJD, we assumed the average accumulated risk per UK individual is 1. Also, the relative risk for UK residents is 1, which is equivalent to the UK vCJD prevalence.

A-IV. C. 1. a. iii. b. US plasma donors with a history of travel to the UK: Adjustment for the proportional individual BSE exposure risk for the UK population per year between 1980 to 1996.

The model calculates the risk and potential magnitude of BSE exposure for donors, in any given year in the UK since 1980, as a function of the number of BSE cases in a specific year divided by the total of all BSE cases since 1980.

Variable: y – year of travel (same as variable used above in section A-IV. C. 1. a. ii. A.) by US plasma donor to the UK from 1980 to 1996.

Variable: BSE_{UKy}- The annual number of reported BSE cases in the UK since 1986 (OIE, 2005).

Variable: R_{UKy}- Proportional BSE exposure risk in the UK by specific year from 1980 to 1996.

Assumptions used in the model:

- The BSE exposure risk, and hence, most of the vCJD risk in the UK occurred largely between 1980 and 1996.
- The vCJD risk in the UK was assumed to be negligible after 1996, when stringent food chain controls were put in place to prevent contamination of beef with high risk tissue.
- The yearly rate of the human exposure risk to the BSE agent in the UK is proportional to the number of reported BSE annual cases in the UK
- The vCJD risk is additive for each year of residency during the specific time period.
- A person residing for five or more years during the time period between 1980 and 1996 in the UK is assumed to have a relative risk of 1 (or 100%), i.e., a probability of vCJD infection that is the same as that of the entire UK population.

The proportional BSE risk in the UK per specific year prior to 1997 is represented by the equation:

$$R_{UKy} = R_{UK} \times BSE_{UKy} / \sum_{y=1980}^{1996} BSE_{UKy} \qquad \text{(IV.C.1.a-15)}$$

A-IV. C. 1. a. iii. c. US plasma donors with a history of travel to the UK: BSE exposure risk and vCJD risk in year *y* for a period of *i*, during the period from 1980 to 1996.

Variable: $R_{DR\text{-}UKy,i}$- The potential vCJD risk of an individual US donor who traveled to the UK in specific year during the period 1980-1996 for a specific duration.

The potential vCJD risk for the US plasma donor subpopulation that traveled to the UK in a specific year for a specific duration was calculated using a pro-rated monthly rate, which was calculated based on the proportional BSE exposure risk in the UK in the specific year. The blood donor travel survey conducted by the American Red Cross (TSEAC 2000) collected data on the accumulated stay of donors in the UK from 1980 through 1996, which, for simplicity, was assumed to be the duration of a single, consecutive stay, when calculating the risk.

Assumptions used in the model:

- Risk of vCJD infection is proportional to the duration of the stay in the UK during the period 1980-1996
- All travelers evaluated completed a single, consecutive stay

As mentioned earlier, any US plasma donor with 5 years or more of accumulated stay in the UK is assumed to have average risk of 1, a risk equal to the average risk of an UK resident and equal to the UK vCJD prevalence.

The BSE exposure risk for US plasma donors with a stay less than or equal to one year – is represented by the equation:

$$R_{DR-UKy,i} = (R_{UKy} / 12) \times D_i \qquad \text{(IV.C.1.a-16)}$$

for $i_{upper} \leq 1$ years;

The BSE exposure risk for US plasma donors with a stay less than five years but greater than or equal to one year is represented by the equation:

$$R_{DR-UKy,i} = (Average(R_{UKy} : R_{UK(y+Roundup(i_{upper,0})})/12) \times D_i \quad \text{(IV.C.1.a-17)}$$

for 5 years $< i_{upper} \geq 1$ year;

The BSE exposure risk for US plasma donors with a stay greater than or equal to five – is represented by the equation:

$$R_{DR-UKy,i} = 1 \quad \text{(IV.C.1.a-18)}$$

for $i_{upper} \geq 5$ years

A-IV. C. 1. a. iv. US plasma donors with a history of travel to the UK: Probability of potential infection with vCJD based on duration of travel to the UK and age

This section describes the portion of the model that estimates the probability that a US plasma donor in a specific age group, who traveled to the UK for a specific duration during the time-span of 1980 through 1996, was infected with vCJD.

Variable: $Pr_{vCJD-UK(age)}$ – the probability of vCJD infection per individual UK resident of a specific age group

Variable: $Prev_{Asym-vCJD(age)}$- Prevalence of asymptomatic vCJD infection in the UK for each age groups in five-year increments (e.g., 20-24 yrs, etc.) and the 18-19yr old group (calculated in A-IV.A.3.b.).

$$Pr_{vCJD-UK(age)} = Prev_{Asym-vCJD(age)} / 1000000 \quad \text{(IV.C.1.a-19)}$$

Variable: $Pr_{vCJD-DR-UK(age)y,i}$ – The probability of infection for individual US plasma donor of a specific age group who had traveled to the UK in a specific year for a specific duration

Assumption used in the model: Probability of infection is proportional to the risk of exposure

$$Pr_{vCJD-DR-UK(age)y,i} = Pr_{vCJD-UK(age)} \times R_{DR-UKy,i} \quad \text{(IV.C.1.a-20)}$$

A-IV. C. 1. a. v. Number of all US pdFVIII plasma donors with history of travel to the UK and potentially infected with vCJD

This section of the model estimates the total number of all US plasma donors potentially infected with vCJD during travel to the UK from 1980 through 1996. To derive the total number of donors the model separately estimates the number of potentially infected Source Plasma donors and potentially infected recovered plasma donors (described in the subsequent sections below) and sums the two.

A-IV. C. 1. a. v. a. Number US Source Plasma donors with history of travel to the UK and potentially infected with vCJD during travel to the UK

Plasma is collected from Source Plasma donors in a process called plasmapheresis in which an average of approximately 700 milliliters of plasma are collected. Source Plasma donors donate an average of 14 times per year, but can donate up to 48 times per year.

This component of the model estimates the number of US Source Plasma donors potentially infected with vCJD during travel to the UK from 1980 through 1996.

Variable: $DR_{vCJD\text{-}S\text{-}UK(age)y,i}$- Number of Source Plasma donors potentially infected with vCJD during travel to the UK during 1980-1996 by age, year and duration of travel.

$$DR_{vCJD-S-UK(age)y,i} = Bionomial(DR_{S-UK(age)y,i}, \Pr_{vCJD-DR-UK(age)y,i}) \quad \text{(IV.C.1.a-21)}$$

Variable: $DR_{vCJD\text{-}S\text{-}UKy}$ - Number of Source Plasma donors potentially infected with vCJD in year y during travel/residency in the UK.

$$DR_{vCJD-S-UK} = \sum_{Age=18-19yrs}^{50-54yrs} \sum_{i=1day-3months}^{>=5years} DR_{vCJD-S-UK(age)y,i} \quad \text{(IV.C.1.a-22)}$$

Variable: $DR_{vCJD\text{-}S\text{-}UK\text{-}Defy}$- Number of Source Plasma donors potentially infected with vCJD in year y and not deferred by current policy.

$$DR_{vCJD-S-UK-defy} = \sum_{Age=18-19yrs}^{50-45yrs} \sum_{i=3-5months}^{>=5years} DR_{vCJD-S-UK(age)y,i} \quad \text{(IV.C.1.a-23)}$$

Current deferral policy (FDA 2002) defers individuals who have history of travel to the UK from 1980 through 1996 for an accumulated residence of 3 months or more from donating blood and plasma. The number of potentially infected donors who meet deferral criteria was calculated by equation:

Variable: $DR_{vCJD\text{-}S\text{-}UK\text{-}Res}$- Residual risk due to the number of Source Plasma donors potentially infected with vCJD not deferred by current policy

$$DR_{vCJD-S-UK-Resy} = \sum_{Age=18-19}^{50-54yrs} DR_{vCJD-S-UK(age)y,i=1day-3months} \quad \text{(IV.C.1.a-24)}$$

A-IV. C. 1. a. v. b. Number of US Source Plasma donors with a history of travel to the UK and potentially infected and with vCJD agent present in their blood

Perhaps the most critical component of the model is the estimation of whether a plasma donation was collected from a vCJD-infected donor that contained infectious vCJD agent in their blood at the time of

donation. Based on data from animal studies, the model assumes that vCJD infectious individuals have infectious vCJD agent present in the blood during the last half of the incubation period. This portion of the model calculates the number of Source Plasma donors who may potentially contain infectious vCJD agent in their blood at the time of donation.

Variable: y - The calendar year in which a plasma donor traveled and infected with vCJD.

Assumption used in the model: This risk assessment assesses the risk for pdFVIII product made in 2002.

Variable: $T_{Inf\text{-}2002y}$ - Time Period between infection/travel and year of 2002 when the plasma was collected

Variable: $Pr\text{-}LH_y$ - Probability the disease is in the last half incubation period of the disease (and donor is prionemic), if infected in year y

Variable: $T_{Inf\text{-}2002y}$ - Time period between infection/travel and 2002 when the plasma was collected.

$$T_{Inf-2002y} = 2002 - y \qquad \text{(IV.C.1.a-25)}$$

For an individual to have vCJD agent present in their blood and plasma (prionemic) in 2002, the elapsed period of time since infection up to 2002 ($I_{Inf\text{-}2002y}$) should be equal to or greater than the half of incubation period of the disease.

Assumption used in the model: The variability and uncertainty of the incubation period of vCJD is represented mathematically by a gamma distribution, specifically Gamma (4.7, 3.6). A gamma distribution is usually used to represent the time between events, in this case the time from infection to the occurrence of symptomatic disease. The distribution is defined by two parameters, one that produces the shape of the curve and a second that generates the scale between events, which in this case is the mean incubation period of 14 years.

Variable: $Pr_{LH\text{-}y}$ -The probability an individual has vCJD agent present in their blood and plasma in year 2002 (the baseline year of the model) was calculated by the expression:

Cumulative frequency of Gamma (4.7, 3.6), at x = 2×(1997-y)

Variable: $DR_{vCJD\text{-}S\text{-}UKy}$ - Total number of Source Plasma donors potentially infected with vCJD in year y during travel/residency in the UK.

Variable: $DR_{vCJD\text{-}S\text{-}UK\text{-}LHy}$ - Total number of Source Plasma donors potentially infected with vCJD in year y during travel/residency in the UK and were in the last half incubation period of the disease in 2002 at the time of donation.

$$DR_{vCJD-S-UK-LHy} = Binomial(DR_{vCJD-S-UKy}, \Pr_{LH-y}) \qquad \text{(IV.C.1.a-26)}$$

Variable: $DR_{vCJD\text{-}S\text{-}UK\text{-}def_y}$ - Total number of Source Plasma donors potentially infected with vCJD in year y during travel/residency in the UK and met deferral criteria

Variable: $DR_{vCJD\text{-}S\text{-}UK\text{-}def\text{-}LH_y}$ - Total number of Source Plasma donors in the last half incubation period of the disease (prionemic) and met current deferral criteria (FDA 2002).

$$DR_{vCJD-S-UK-Def-LH_y} = Binomial(DR_{vCJD-S-UK-Def_y}, \Pr_{LH-y}) \quad \text{(IV.C.1.a-27)}$$

Variable: $DR_{vCJD\text{-}S\text{-}UK\text{-}Res_y}$ - Total number of Source Plasma donors potentially infected with vCJD in year y during travel/residency in the UK and did not meet deferral criteria

Variable: $DR_{vCJD\text{-}S\text{-}UK\text{-}Res\text{-}LH_y}$ - Total number of Source Plasma donors in the last half of the incubation period of the disease who did not meet current deferral criteria (FDA 2002).

$$DR_{vCJD-S-UK-Res-LH_y} = Binomial(DR_{vCJD-S-UK-Res_y}, \Pr_{LH-y}) \quad \text{(IV.C.1.a-28)}$$

A-IV. C. 1. a. v. c. Number of US recovered plasma donors with history of travel to the UK and potentially infected with vCJD

Recovered plasma donors donate whole blood from which the plasma is separated out (or recovered). Like blood donors recovered plasma donors donate an average of 1.7 times per year but can donate up to 6 times per year. The model assumes the average amount of plasma in a recovered plasma unit is approximately 200 milliliters.

This component of the model estimates the number of US recovered plasma donors potentially infected with vCJD during travel to the UK from 1980 through 1996.

Variable: $DR_{vCJD\text{-}R\text{-}UK(age)y,i}$ - Number of recovered plasma donors potentially infected with vCJD during travel to the UK during 1980-1996 by age, year and duration of travel

$$DR_{vCJD-R-UK(age)y,i} = Bionomial(DR_{R-UK(age)y,i}, \Pr_{vCJD-DR-UK(age)y,i}) \quad \text{(IV.C.1.a-29)}$$

Variable: $DR_{vCJD\text{-}R\text{-}UK\,y}$ - Total number of recovered plasma donors potentially infected with vCJD in year y

$$DR_{vCJD-R-UK_y} = \sum_{Age=18-19}^{50-54} \sum_{i=1day-3months}^{>=5years} DR_{vCJD-R-UK(age)y,i} \quad \text{(IV.C.1.a-30)}$$

Variable: $DR_{vCJD\text{-}R\text{-}UK\text{-}Def_y}$ - Number of recovered plasma donors potentially infected with vCJD in year y and deferred by current policy

$$DR_{vCJD-R-UK-Def_y} = \sum_{Age=18-19}^{50-54} \sum_{i=3-5months}^{>=5years} DR_{vCJD-R-UK(age)y,i} \quad \text{(IV.C.1.a-31)}$$

Variable: $DR_{vCJDS\text{-}UK\text{-}Resy}$ - Residual risk due to the number of recovered plasma donors potentially infected with vCJD not deferred by current policy and represented by the equation:

$$DR_{vCJD-R-UK-resy} = \sum_{Age=18-19}^{50-54} DR_{vCJD-R-UK(age)y,i=1day-3months} \qquad \text{(IV.C.1.a-32)}$$

A-IV. C. 1. a. v. d. Number of US recovered plasma donors with a history of travel to the UK and potentially infected and with vCJD agent present in their blood

As discussed in the sections above the most critical determinant in the model of whether exposure occurs is the estimation of whether a plasma donation was collected from a vCJD infected donor who had infectious vCJD agent in their blood (e.g., was prionemic) at the time of donation. Based on data from animal studies, the model assumes that vCJD infectious individuals have infectious vCJD agent present in the blood during the last half of the incubation period. This portion of the model calculates the number of recovered plasma donors who may potentially have infectious vCJD agent in their blood at the time of donation.

Variable: $Pr_{LH\text{-}y}$ -The probability an individual will have vCJD agent in blood and plasma (prionemic) in year 2002

Variable: $DR_{vCJD\text{-}R\text{-}UKy}$- Total number of recovered plasma donors potentially infected with vCJD in year y during travel/residency in the UK (calculated in A-IV. C. 1. a. v. b)

Variable: $DR_{vCJD\text{-}R\text{-}UK\text{-}LHy}$ - Total number of recovered plasma donors potentially infected with vCJD in year y during travel/residency in the UK and in the last half incubation period of the disease.

$$DR_{vCJD-R-UK-LHy} = Binomial(DR_{vCJD-R-UKy}, \Pr_{LH-y}) \qquad \text{(IV.C.1.a-33)}$$

Variable: $DR_{vCJD\text{-}R\text{-}UK\text{-}defy}$- Total number of recovered plasma donors potentially infected with vCJD in year y during travel/residency in the UK and met deferral criteria (calculated in A-IV. C. 1. a. v. c)

Variable: $DR_{vCJD\text{-}R\text{-}UK\text{-}def\text{-}LHy}$ - Total number of recovered plasma donors in the last half incubation period of the disease who met deferral criteria.

$$DR_{vCJD-R-UK-Def-LHy} = Binomial(DR_{vCJD-R-UK-Defy}, \Pr_{LH-y}) \qquad \text{(IV.C.1.a-34)}$$

Variable: $DR_{vCJD\text{-}R\text{-}UK\text{-}Res y}$- Total number of recovered plasma donors potentially infected with vCJD in year y during travel/residency in the UK and did not meet deferral criteria (calculated in A-IV. C. 1. a. v. c).

Variable: $DR_{vCJD\text{-}R\text{-}UK\text{-}Res\text{-}LHy}$ - Total number of recovered plasma donors in the last half incubation period of the disease who did not meet deferral criteria

$$DR_{vCJD-R-UK-Res-LHy} = Binomial(DR_{vCJD-R-UK-Res y}, \Pr_{LH-y}) \quad \text{(IV.C.1.a-35)}$$

A-IV. C. 1. a. v. e. Number of <u>all</u> US plasma donors with a history of travel to the UK and potentially infected with vCJD

This section sums the total number of <u>all</u> US plasma donors, predicted by the model to donate to plasma pools used in manufacturing pdFVIII made from plasma collected in the US. This includes <u>Source Plasma</u> donors and recovered plasma donors predicted by the model to be infected with vCJD and arrives at an estimate of the total number of US donors potentially infected with vCJD.

Variable: $DR_{vCJD\text{-}UK}$ - Total number of plasma donors potentially infected with vCJD during travel/residence in the UK

$$DR_{vCJD-UK} = \sum_{y=1980}^{1996} DR_{vCJD-S-UKy} + \sum_{y=1980}^{1996} DR_{vCJD-R-UKy} \quad \text{(IV.C.1.a-36)}$$

Variable: $DR_{vCJD\text{-}UK\text{-}Def}$ - Total number of plasma donors potentially infected with vCJD during travel/residence in the UK and met deferral criteria

$$DR_{vCJD-UK-Def} = \sum_{y=1980}^{1996} DR_{vCJD-S-UK-Defy} + \sum_{y=1980}^{1996} DR_{vCJD-R-UK-Defy} \quad \text{(IV.C.1.a-37)}$$

Variable: $DR_{vCJD\text{-}UK\text{-}Res}$- Total number of plasma donors potentially infected with vCJD during travel/residence in the UK and did not meet deferral criteria

$$DR_{vCJD-UK-Res} = \sum_{y=1980}^{1996} DR_{vCJD-S-UK-Res y} + \sum_{y=1980}^{1996} DR_{vCJD-R-UK-Res y} \quad \text{(IV.C.1.a-38)}$$

A-IV. C. 1. a. v. f. Total of all US plasma donors with a history of travel to the UK and potentially infected and with vCJD agent present in their blood

Again, whether a donor contains vCJD agent in their blood is a pivotal calculation for the model since a donation from such an individual would contain vCJD agent that may find its way into a large plasma pool of thousands of donations that are used to manufacture pdFVIII. This section sums the number of US Source Plasma donors and recovered plasma donors predicted by the model to be infected with vCJD

and contain vCJD agent in their blood and arrives at an estimate of the total number of US donors potentially infected with vCJD and prionemic.

Variable: $DR_{vCJD\text{-}UK\text{-}LH}$ - Total number of plasma donors in the last half incubation period of the disease

$$DR_{vCJD-UK-LH} = \sum_{y=1980}^{1996} DR_{vCJD-S-UK-LHy} + \sum_{y=1980}^{1996} DR_{vCJD-R-UK-LHy} \qquad \text{(IV.C.1.a-39)}$$

Variable: $DR_{vCJD\text{-}UK\text{-}Def\text{-}LH}$ - Total number of plasma donors in the last half incubation period of the disease and met deferral criteria

$$DR_{vCJD-UK-Def-LH} = \sum_{y=1980}^{1996} DR_{vCJD-S-UK-Def-LHy} + \sum_{y=1980}^{1996} DR_{vCJD-R-UK-Def-LHy} \qquad \text{(IV.C.1.a-40)}$$

Variable: $DR_{vCJD\text{-}UK\text{-}Res\text{-}LH}$- Total number of plasma donors in the last half incubation period of the disease and did not meet deferral criteria

$$DR_{vCJD-UK-Res-LH} = \sum_{y=1980}^{1996} DR_{vCJD-S-UK-Res-LHy} + \sum_{y=1980}^{1996} DR_{vCJD-R-UK-Res-LHy}$$

A-IV. C. 1. b. Estimation of the number of US plasma donors with a history of extended travel to France potentially infected and vCJD agent is present in the blood

A-IV.C.1.b.i. US plasma donors with a history of travel to France: Percentage of donors and travel duration

In this portion, blood donors are characterized by frequency and duration of travel to France since 1980. The risk of vCJD infection is a function of exposure to the BSE agent and is assumed to be proportional to the amount of time spent, or duration of travel, in France since 1980. The FDA model used data from the National Blood Donor Travel Survey 1980-1996 (TSEAC 2000) to derive estimates of the percentages of US donors with a history of extended travel or residence (≥ 5 years) in France since 1980, and to derive the frequencies for various durations of travel for 5 years or more. Since the baseline year to estimate potential vCJD risk for US donors in our model was 2002 trends in the National Blood Donor Travel Survey 1980-1996 (TSEAC 2000) were extrapolated from the year 1997 to 2002 when necessary to estimate potential travel characteristics and risk beyond 1996. The period of 5 years or more corresponds to the length of time in the current policy that defers donors who traveled to or resided in France. The travel survey data on blood donors pose a limitation because the survey was conducted on whole blood donors and may not exactly reflect the travel histories of plasma donors. Unfortunately, to our knowledge there is not travel data available on plasma donors. Therefore, we assumed that plasma donor travel characteristics to the France since 1980 are similar to those of whole blood donors and used this information in the FDA risk assessment. Some may argue that plasma donors travel less frequently than their blood donor counterparts so use of data on blood donors may overestimate the risk.

Data used in the model: National Blood Donor Travel Survey 1980-1996 was conducted by the American Red Cross and presented at the Transmissible Spongiform Encephalopathies Advisory Committee (TSEAC 2000).

Variable: i - The duration interval used to group donors who had traveled to France from 1980-1996 based on the quantity of time spent in France during the period from 1980 – 1996.

Variable: D_i - The average duration of time (months) for interval i representing the duration of travel or residence by US donors in France during the period from 1980 – 1996.

Variable: $CumPerc_{BIDR\text{-}FRi}$ – The cumulative percentage of blood donors who traveled to France within duration interval i or longer.

Data used in the model: Travel data for US blood donors was obtained from a blood donor survey conducted by the American Red Cross and presented at the Transmissible Spongiform Encephalopathies Advisory Committee (TSEAC, 2000).

Variable: $Perc_{BIDR\text{-}FRi}$ - Percentage of blood donors who have traveled to France within duration interval i. This variable was converted from $CumPerc_{BIDR\text{-}FRi}$

Variable: $Perc_{BIDR\text{-}FRi/FR}$- The percentage of blood donors who traveled for a specific duration interval i among all donors who have ever traveled to France is represented by the equation:

$$Perc_{BIDR-FRi/FR} = (Perc_{BIDR-FRi} / CumPerc_{BIDR-FR,i>1day-1month}) \times 100\% \qquad \text{(IV.C.1.b-1)}$$

IV. C. 1. b. Estimation of the number of US plasma donors with a history of extended travel to France potentially infected and vCJD agent is present in the blood

A-IV.C.1.b.ii. Number of US plasma donors with a history of travel to France by age group, year of travel and duration of travel

This part of risk assessment calculates the annual number of US source and recovered plasma donors that traveled to France by specific year(s) and for a specific duration of time since 1980 by age. For the purposes of our analyses we grouped all donors and donors who traveled to France since 1980 into age groups of five year increments (20 = 24yrs, 25 = 29 yrs, etc) and the two year cohort for 18 and 19 years of age.

We estimated the frequency of donor travel by age group based on travel data for the US population and donor survey data. First, the total number of blood donors who traveled to France between 1980 and 1996 was estimated by multiplying the total number of US blood donors in a specific year by the percentage of donors (from survey data) who traveled to France. The percentage of donors in each age group that traveled to France since 1980 was calculated based on the total annual number donors who traveled to France since 1980 compared to (or divided by) the total number of donors, and the age specific odds ratio for travel. Finally, the information on the number of donors from each age group who traveled was

calculated by year and duration of travel. The risk of a US donor acquiring vCJD is a function of duration of the stay, as well, the year(s) (since 1980) they resided in France.

- **Calculation of the annual number of blood donors who traveled to France from 1980 through 1996**

Variable : DR_{BI}-The annual total number of potential blood donors in the US

Data used in the model: There are approximately 8 million individuals who donate blood each year in the United States (Westat, 2002).

Variable: $Perc_{BIDR\text{-}FR}$ - The total percentage of US blood donors who traveled to France during the period from 1980 through 1996.

Data used in the model: Approximately, 15.6% of US blood donors reported a history of travel to France during the period from 1980 through 1996, based on the travel data of US blood donors (TSEAC, 2000).

Variable: $DR_{BI\text{-}FR}$ -Total number of blood donors who have traveled to France during 1980 and 1996

$$DR_{BI-FR} = DR_{BI} \times Perc_{BIDR-FR} \qquad \text{(IV.C.1.b-2)}$$

Then, the percentage donors in each age group that traveled to France between 1980 and 1996 was calculated based on the total number donors who traveled to France, the number of donors from each age group and the odds ratio of travel for each age group.

Variable: $DR_{BI(age)}$- Annual number of blood donors from each age group (calculated A-IV.C.1.a)

Variable: $Perc_{BIDR\text{-}FR(age)}$ - The percentage of US blood donors of an age group who traveled to France during the period from 1980 through 1996.

Total number of blood donor who traveled to France equals to the sum of donors from all age groups who have ever traveled to France:

$$DR_{BI-FR} = \sum_{age=18-19}^{65-69} (Perc_{BIDR-FR(age)} \times DR_{BI(age)}) \qquad \text{(IV.C.1.b-3)}$$

Variable: $Odd_{T(age)}$- Odds ratios of each age group for the likelihood of travel compared to the group of age 18-19 year-olds.

Data used in the model: The odds ratio of travel for each age group was derived from the travel data obtained from 1980-1996 blood donor travel survey (TSEAC 2000). An odds ratio of 1 was assigned to donor group of age 18-19. Odds ratio of other age group represents the frequency of travel of those age groups compared to the group of age 18-19

$$Perc_{BlDR-FR(age)} = Odd_{T(age)} \times Perc_{BlDR-FR(18-19)} \quad \text{(IV.C.1.b-4)}$$

Replacing equation IV.C.1.b-4 for $Perc_{BlDR-FR(age)}$ in equation IV.C.1.b-3, percentage blood donors from age group of 18-19 who have traveled to France can be calculated by following equation:

$$Perc_{BlDR-FR(18-19)} = DR_{Bl-FR} \Big/ \sum_{age=18-19}^{65-69} (Odd_{T(age)} \times DR_{Bl(age)}) \quad \text{(IV.C.1.b-5)}$$

Then, the percentage of blood donors from other age groups who have traveled to France can be calculated using equation IV.C.1.b-4 (above).

A-IV. C. 1. b. ii. a. Number of US Source Plasma donors with a history of travel to France by age group and specific year of travel

This section of the model computes the number of US Source Plasma donors who traveled to France based on annual total of Source Plasma donors and the estimated percentage of Source Plasma donors who have traveled to France between 1980 and 1996. Travel after 1996 was extrapolated from the percentage donors who travel between 1980 and 1996 and yearly travel data. To factor in travel frequency associated with donor age, the number of donors who have traveled was calculated by age groups.

Variable: ***age*** - Age of US plasma donors in groups of 5-year increments (20 – 24 yrs, 25 – 29yrs, etc) and the 18-19 year old cohort.

Variable: $DR_{S(age)}$ (calculated in section A-IV.B.1.b.) - the annual Source Plasma donations by age groups.

Variable: $Perc_{BlDR-FR(age)}$ (calculated in section A-IV.C.1.b.i..b.) - the percentage blood donors from an age group who have traveled to France between 1980-1996

Variable: $DR_{S-FR(age)}$ - Number of Source Plasma donors who traveled to France from 1980 through 1996 by age group.

Assumptions used in the model: The percentage of Source Plasma donors who traveled to France is the same as blood donors of the same age group.

The number of Source Plasma donors who traveled to France from 1980 to 1996 by age group is represented by:

$$DR_{S-FR(age)} = DR_{S(age)} \times Perc_{BlDR-FR} \quad \text{(IV.C.1.b-6)}$$

The model assumes that the risk that a traveler was exposed to the BSE agent in France is associated with the magnitude of the BSE epidemic in the UK in the year of travel. Major exposure risk in France was presumably from consumption of beef imported from the UK that was produced from cattle infected with BSE. The model breaks down Source Plasma donors by year of travel, in order to estimate the potential

US donor vCJD risk more accurately by incorporating the information about the magnitude of the BSE epidemic in the UK in a given year.

Variable: $V_{y/1996}$ - The number of visits to the UK by US travelers in year y compared to the number of visits in 1996 (calculated in A-IV. C. 1. a. ii. a.).

Variable: $DR_{S\text{-}FR(age),y}$ - Number of Source Plasma donors with history of travel to France in year y by age groups

The number of Source Plasma donors who have traveled to France was allocated to individual travel year based on the yearly distribution of visits to France.

$$DR_{S-FR(age)y} = DR_{S-FR(age)} \times V_{y/1996} / \sum_{y=1980}^{1996} V_{y/1996} \qquad \text{(IV.C.1.b-7)}$$

for travel during 1980-1996;

$$DR_{S-FR(age)y} = DR_{S-FR(age)1996} \times V_{y/1996} \qquad \text{(IV.C.1.b-8)}$$

for travel after 1996

Assumption used in the model: The yearly frequency and distribution of travel to France by US donors was ascertained from UK travel data and the blood donor survey data (TSEAC 2000). Therefore, in calculating the US donor risk for vCJD, donors the yearly distribution of travel visits by age groups was adjusted to account for the requirement that donors be 18 years of age or older. The model also accounted for the fact that some younger donors born during the period 1980 to 1986 may not have been born and would have essentially a zero chance of being exposed to BSE agent. Therefore, donors 18 years of age in 2002 were assumed to have zero exposure to the BSE agent prior to 1985, those 19 years of age in 2002 were assumed to have zero exposure prior to 1984, those 20 years of age in 2002 were assumed to have zero exposure prior to 1983, those 21 years of age in 2002 were assumed to have zero exposure prior to 1982, those 22 years of age in 2002 were assumed to have zero exposure prior to 1981. The model assumed that there was zero exposure of all donors prior to 1980.

A-IV. C. 1. b. ii. b. Number of US Source Plasma donors and duration of travel to France by age group

There are no data detailing the travel histories of Source Plasma donors available. Travel data for blood donors was used for Source Plasma donors after an adjustment for the frequency of travel based on the age of Source Plasma donors and the age-specific odds ratios for travel, which were obtained from 1980-1996 Blood Donor Travel Survey (TSEAC, 2000).

The model further subdivides the number of Source Plasma donors who traveled to France in a specific year by duration of stay. While there were no specific travel data detailing travel patterns to France since 1980 available for US Source Plasma donors, data on travel patterns for whole blood donors was used as a proxy. Donor travel in the model was subdivided into categories based on the percentage of blood donors

who traveled to France for certain durations (Watanabe, 2000) (>5yrs, ≤5yrs, etc) was used in this risk assessment.

Variable: i - The duration interval used to group blood donors who had traveled to France from 1980-1996 based on the time they spent in France (same variable used above in section A-IV. C. 1. a. i.).

Variable: D_i - The average duration of time for interval i (months) (same variable used above in section A-IV. C. 1. i.).

Variable: $DR_{S\text{-}FR(age),y}$ - the number of Source Plasma donors who traveled to France in year y by age group (calculated in A-IV. C. 1. b. ii.)

Variable: $Perc_{BIDR\text{-}FRi/FR}$- The percentage of blood donors who traveled for a specific duration interval i among all donors who have ever traveled to France (calculated in A-IV. C. 1. b. i.)

Variable: $DR_{S\text{-}FR(age)y,i}$ - Number of Source Plasma donors among an age group who have traveled to France in year y for a duration of i and is represented by the equation:

$$DR_{S-FR(age)y,i} = DR_{S-FR(age)y} \times Perc_{DR-FRi/FR} \qquad \text{(IV.C.1.b-9)}$$

A-IV. C. 1. b. ii. c. Number of US recovered plasma donors with history of travel to France in a specific year between 1980 and 1996 – and by age group

Recovered plasma is plasma that is separated or "recovered" from a unit of whole blood soon after the blood is collected. As expected, recovered plasma donor donation characteristics mirror those of whole blood donors. A recovered plasma donor can donate plasma a maximum of six times per year – and on average a recovered donation is approximately 200 milliliters (versus an average of 700 milliliters for a Source Plasma donation).

Variable: y – **Year of travel** (same variable used above in section A-IV. C. 1. b. ii. a) to France since 1980 by US plasma donors.

Variable: **age** – Age of the population by five-year increments (same variable used above in section A-IV. B. 1.).

Variable: $DR_{R(age)}$ - Number of potential recovered plasma donors per year by age group (described in section A-IV. B. 2).

Variable: $Perc_{BIDR\text{-}FR(age)}$ (calculated in section A-IV.C.1.b.i.)- The percentage blood donors from an age group who have traveled to France between 1980-1996

Variable: $DR_{R\text{-}FR(age)}$ - Number of recovered plasma donors who traveled to France from 1980 through 1996 by age groups and is represented by the equation:

$$DR_{R-FR(age)} = DR_{R(age)} \times Perc_{B|DR-FR(age)} \quad \text{(IV.C.1.b-10)}$$

The risk a traveler was exposed to BSE in France is proportional to the magnitude of the BSE epidemic in the UK in the year of travel. Because the major exposure risk in France is assumed to be from consumption of BSE contaminated beef imported from the UK, the model subdivides recovered plasma donors and groups them by year of travel. This provides a more precise estimate of the risk by incorporating the specific information on donor and donation characteristics and details that better capture the dynamics of the BSE epidemic in the UK on a year by year basis.

Variable: $V_{y/1996}$ - The number of visits to the UK by US travelers in year y compared to the number of visits in 1996 (calculated in A-IV.C.1.a)

Variable: $DR_{R-FR(age),y}$ - Number of recovered plasma donors with a history of travel to France in year by age groups

Number of recovered plasma donors who have traveled to France was allocated to individual travel year based on the yearly distribution of visits to the UK by US travelers.

$$DR_{R-FR(age)y} = DR_{R-FR(age)} \times V_{y/1996} / \sum_{y=1980}^{1996} V_{y/1996} \quad \text{(IV.C.1.b-11)}$$

for travel during 1980-1996;

$$DR_{R-FR(age)y} = DR_{R-FR(age)1996} \times V_{y/1996} \quad \text{(IV.C.1.b-12)}$$

for travel after 1996

Assumptions used in the model: The yearly distribution of travel to France by US donors is similar to the yearly distribution of travel to the UK by US donors- this is based on travel data and the blood donor survey (TSEAC 2000). The yearly distribution of travel visits by each age group was adjusted to account for the minimum age of 18 when a donor can donate plasma or blood. Therefore, in calculating the US donor risk for vCJD the yearly distribution of travel visits by each age group was adjusted to account for this requirement. The model adjusted the potential vCJD exposure for younger donors who were born during the period from 1980 to 1986 and would have essentially a zero chance of being exposed to the BSE agent in the years prior to their birth. Therefore, donors 18 years of age in 2002 were assumed to have zero exposure to the BSE agent prior to 1985, those 19 years of age in 2002 were assumed to have zero exposure prior to 1984, those 20 years of age in 2002 were assumed to have zero exposure prior to 1983, those 21 years of age in 2002 were assumed to have zero exposure prior to 1982, those 22 years of age in 2002 were assumed to have zero exposure prior to 1981. The model assumed that there was zero exposure of all donors prior to 1980.

A-IV. C. 1. b. ii. d. US recovered plasma donors with a history of travel to France and specific year of travel and duration of travel by age group

Recovered plasma donors who traveled to France in a specific year ($DR_{R-FR(age)y}$) since 1980 were further partitioned into the subgroups based on travel duration and by 5-year age groups. Data on the percentage

of blood donors who traveled to France since 1980 for certain duration(s) (TSEAC, 2000) was used in this risk assessment.

Variable: i - The duration interval used to group blood donors who had traveled to France from 1980-1996 based on the time they spent in France (same variable used above in section A-IV. C. 1.)

Variable: D_i - The average duration of time for interval i (months) (same variable used above in section A-IV. C. 1.)

Variable: $DR_{R\text{-}FR(age),y}$ - The number of recovered plasma donors who traveled to France in year y by age group (calculated in A-IV. C. 1. b. iv. c.)

Variable: $Perc_{B|DR\text{-}FR/FR}$- The percentage of blood donors who traveled for a specific duration interval i among all donors who have ever traveled to France (calculated in A-IV. C. 1. b. ii. a.)

Variable: $DR_{R\text{-}FR(age)y,i}$- Number of recovered plasma donors among an age group who have traveled to France in year, y ,for duration of i.

$$DR_{R-FR(age)y,i} = DR_{R-FR(age)y} \times Perc_{DR-FR|FR} \qquad \text{(IV.C.1.b-13)}$$

A-IV.C. 1. b. iii. US plasma donors with history of travel to France: Adjustment of the relative risk for France based on the magnitude of the UK BSE risk and by travel duration in a specific year

As indicated in previous sections the FDA model assumed that the relative vCJD risk for UK residents residing for any five-year period or longer from 1980 through 1996 is assumed to have a value of 1, because exposure to BSE in the UK was greater than any other country. The relative risk value of 1 equates to 100% of the UK asymptomatic and symptomatic vCJD prevalence which is difficult to estimate. The relative risk value for France is 0.05 (or 5% of the UK risk). The relative risk value is assigned based on factors such as domestic UK beef consumption, and the rate and number of vCJD cases, and indigenous BSE cases that may have occurred (TSEAC 2004). France received meat and bone meal from the UK during the BSE epidemic and approximately 5% of its beef was imported from the UK as of August 2006, France reported 20 cases of vCJD in its human population. Additionally, the model included calculations on the estimated duration of travel in France or residence by US plasma donors to generate a more accurate vCJD risk estimate. Current US vCJD geographic deferral policy defers donors with a history of residence in France for a period of 5 years or more since 1980.

A-IV. C. 1. b. iii. a. US plasma donors with a history of travel to France: Average accumulated risk of residence since 1980

Variable: R_{FR} – The cumulative risk of individual residents of France from 1980 till present; assuming that the cumulative risk of a UK individual from 1980 through 1996 is 1.

Assumption used in the model: The average cumulative risk of a resident of France since 1980 is 0.05 relative to 1, the average accumulated risk of UK individual since 1980, based on UK beef imports, vCJD cases and indigenous BSE in France

A-IV. C. 1. b. iii. b. US plasma donors with history of travel to France: Proportional risk of individual resident per year since 1980

Variable: y – **year** (same variable used in A-IV. C. 1. a. iv.)

Variable: BSE_{UKy} (same variable used in A-IV. C. 1. a. iii.)

Variable: BSE_{FRy} - Annual numbers of reported BSE cases in France including indigenous and imported cases

Data used in the model: Data on the annual number of reported BSE cases in France was obtained from the World organization for animal health (OIE) (2005).

Variable: R_{FRy} - Proportional risk in France in a specific year

Assumptions used in the model:

- Variant CJD Risk in France occurred starting in 1980 to the present. Evidence indicates that vCJD and BSE cases are still emerging.
- Risk is additive, and can be pro-rated in a yearly and further monthly basis.
- Yearly rate of the risk in France is proportional to the reported BSE annual cases (including indigenous and imported cases) in France.

A-IV. C. 1. b. iii. c. US plasma donors with a history of travel to France: Potential vCJD risk for donors who traveled in year y for a period of i

Variable: $R_{DR\text{-}FR,i}$ - The risk of an individual US donor who traveled to France in a specific year with a specific duration of travel, assuming a cumulative risk for a UK individual from 1980 through 1996 is 1 (or equivalent to the UK vCJD prevalence for the entire UK population).

The vCJD risk for the US plasma donor subpopulation that traveled to France in a specific year for a specific duration was calculated by applying a prorated monthly rate of risk, which was calculated based on the yearly rate of the risk in France during the year of travel. The blood donor travel survey (TSEAC, 2000) collected information on the accumulated stay of the donors in France from 1980 through 1996, which, for simplicity, was used to calculate the duration of consecutive stay, when calculated the risk.

Assumptions used in the model:

- Risk is proportional to the duration of the stay
- All travelers have consecutive stays
- US plasma donor subpopulation having more than 5 years accumulated stay in France have average risk of 0.05, which is the same as the average risk of individual resident of France (equivalent to 5% of the UK vCJD prevalence).

$$R_{DR-FRy,i} = (R_{FRy} / 12) \times D_i$$ (IV.C. 1. b•-14)

for i< 1 years;

$$R_{DR-FRy,i} = (Average(R_{FRy} : R_{FR(y+I)}) / 12) \times D_i$$ (IV.C.1.b-15)

for 5 years <i>=1 year;

$$R_{DR-FRy,i} = 0.05$$ (IV.C.1.b-16)

for i>= 5 years

A-IV.C. 1. b. iv. US plasma donors with history of travel to France: Probability of vCJD infection for donor of a specific age group, in a specific year, for a specific duration, i

This section describes the portion of the model that estimates the potential probability that a US plasma donor in a specific age group who traveled to France for a specific duration since 1980 was infected with vCJD.

Variable: $Pr_{vCJD-FR(age)}$ Probability of vCJD infection in an individual resident of France in a specific age.

Variable: $Pr_{vCJD-DR-FR(age)y,i}$ - Probability of infection for individual US plasma donor of a specific age group who have traveled to France in a specific year for a specific duration.

Assumption about variable: Probability of vCJD infection being proportional to the risk of exposure to the BSE agent and represented by the equation:

$$\Pr_{vCJD-DR-FR(age)y,i} = \Pr_{vCJD-UK(age)} \times R_{DR-FRy,i}$$ (IV.C.1.b-17)

A-IV.C. 1. b. v. Total number of all US plasma donors with a history of travel to France: Number potentially infected with vCJD

A-IV.C. 1. b. v. a. Number of US Source Plasma donors with a history of travel to France and potentially infected with vCJD

Plasma is collected from Source Plasma donors in a process called plasmapheresis in which approximately 700 milliliters of plasma are collected. Source Plasma donors donate an average of 14 units per year, but can donate up to 48 times per year.

This component of the model estimates the number of US Source Plasma donors potentially infected with vCJD during travel to the UK from 1980 through 1996.

Variable: $DR_{vCJD\text{-}S\text{-}FR(age)y,i}$ - Number of Source Plasma donors potentially infected with vCJD during travel to France since 1980 by age, year and duration of travel.

$$DR_{vCJD-S-FR(age)y,i} = Bionomial(DR_{S-FR(age)y,i}, \Pr_{vCJD-DR-FR(age)y,i}) \quad \text{(IV.C.1.b-18)}$$

Variable: $DR_{vCJD\text{-}S\text{-}FRy}$ - Number of Source Plasma donors potentially infected with vCJD in year y during travel/residence in France.

$$DR_{vCJD-S-FRy} = \sum_{Age=18-19yrs}^{50-54yrs} \sum_{i=1day-3months}^{>=5years} DR_{vCJD-S-FR(age)y,i} \quad \text{(IV.C.1.a-19)}$$

Variable: $DR_{vCJD\text{-}S\text{-}FR\text{-}Defy}$ - Number of Source Plasma donors potentially infected with vCJD in year y and meet deferral criteria.

Current deferral policy defers individuals who have a history of travel to France since 1980 for an accumulated time of over 5 years from donating blood and plasma. The number of potentially infected donors who meet deferral criteria was calculated by equation:

$$DR_{vCJD-S-FR-Defy} = \sum_{Age=18-19}^{50-54yrs} DR_{vCJD-S-FR(age)y,i>=5years} \quad \text{(IV.C.1.a-20)}$$

Variable: $DR_{vCJD\text{-}S\text{-}FR\text{-}Resy}$ - Residual risk due to the number of Source Plasma donors potentially infected with vCJD in year y and not deferred by current policy

$$DR_{vCJD-S-FR-Resy} = \sum_{Age=18-19yrs}^{50-54yrs} \sum_{i=1-30days}^{>3-5years} DR_{vCJD-S-FR(age)y,i} \quad \text{(IV.C.1.a-21)}$$

A-IV. C. 1. b. v. b. Number of US Source Plasma donors with history of travel to France and potentially infected and vCJD agent is present in the blood

Perhaps the most critical component of the model is the estimation of whether a plasma donation was collected from a vCJD infected donor who had infectious vCJD agent in their blood (i.e., was prionemic at the time of donation). Based on data from animal studies, the model assumes that vCJD infectious individuals have infectious vCJD agent present in the blood during the last half of the incubation period. This portion of the model calculates the number of Source Plasma donors who may potentially contain infectious vCJD agent in their blood at the time of donation.

Variable: y-The calendar year in which a plasma donor traveled and infected with vCJD

Assumption used in the model: This risk assessment assesses the risk for pdFVIII product made in 2002 (but risk is assumed to be similar up to the year 2006).

Variable: $T_{Inf\text{-}2002y}$-Time Period between infection/travel and year of 2002 when the plasma was collected

Variable: $Pr\text{-}LH_y$-Probability the individual is in the last half incubation period of the disease, if infected in year y

Variable: $T_{Inf\text{-}2002y}$-Time period between infection and travel and 2002 when the plasma was collected

$$T_{Inf-2002y} = 2002 - y \qquad \text{(IV.C.1.b-22)}$$

For an individual to have vCJD agent present in their blood and plasma (prionemic) in 2002, the elapsed period of time since infection up to 2002 ($I_{Inf\text{-}2002y}$) should be equal to or less than the remaining half of incubation period of the disease; in another words, the incubation period of the disease should be equal to or less than twice as much as $I_{Inf\text{-}2002y}$.

Assumption used in the model The variability and uncertainty of the incubation period of vCJD is represented mathematically by a gamma distribution, specifically Gamma (4.7, 3.6). A gamma distribution is usually used to represent processes that occur sequentially, in this case infection, incubation period of the disease, etc. The distribution is defined by two parameters (or arguments) that produce the shape of the curve and generates a mean incubation period of 14 years and a median incubation period of 13 years.

Variable: $Pr_{LH\text{-}y}$-The probability an individual will be prionemic in the year 2002, was determined using the distribution:

Cumulative frequency of Gamma (4.7, 3.6), at x=2×(1997-y)

Variable: $DR_{vCJD\text{-}S\text{-}FRy}$- Total number of Source Plasma donors potentially infected with vCJD in year y during travel/residency in France (calculated in A-IV. C. 1. b. v. a.)

Variable: $DR_{vCJD\text{-}S\text{-}FR\text{-}LHy}$ - Total number of Source Plasma donors potentially infected with vCJD in year y during travel/residency in France and in the last half incubation period of the disease.

$$DR_{vCJD-S-FR-LHy} = Binomial(DR_{vCJD-S-FRy}, \Pr_{LH-y}) \quad \text{(IV.C.1.b-23)}$$

Variable: $DR_{vCJD\text{-}S\text{-}FR\text{-}defy}$ - Total number of Source Plasma donors potentially infected with vCJD in year y during travel/residency in France and met deferral criteria (calculated in A-IV. C. 1. b. v. a)

Variable: $DR_{vCJD\text{-}S\text{-}FR\text{-}def\text{-}LHy}$ - Total number of Source Plasma donors in the last-half of the incubation period of the disease who met deferral criteria.

$$DR_{vCJD-S-FR-Def-LHy} = Binomial(DR_{vCJD-S-FR-Defy}, \Pr_{LH-y}) \quad \text{(IV.C.1.b-24)}$$

Variable: $DR_{vCJD\text{-}S\text{-}FR\text{-}Resy}$ - Total number of Source Plasma donors potentially infected with vCJD in year y during travel/residency in France and did not met deferral criteria (calculated in A-IV. C. 1. b. v. a)

Variable: $DR_{vCJD\text{-}S\text{-}FR\text{-}Res\text{-}LHy}$ - Total number of Source Plasma donors in the last half incubation period of the disease who did not met deferral criteria or were not deferred is represented by the equation:

$$DR_{vCJD-S-FR-Res-LHy} = Binomial(DR_{vCJD-S-FR-Resy}, \Pr_{LH-y}) \quad \text{(IV.C.1.b-25)}$$

A-IV.C. 1. b. v. c. Number of US recovered plasma donors with a history of travel to France and potentially infected with vCJD

Variable: $DR_{vCJD\text{-}R\text{-}FR(age)y,i}$ - Number of recovered plasma donors potentially infected with vCJD during travel to France since 1980 by age, year and duration of travel.

$$DR_{vCJD-R-FR(age)y,i} = Bionomial(DR_{R-FR(age)y,i}, \Pr_{vCJD-DR-FR(age)y,i}) \quad \text{(IV.C.1.b-26)}$$

Variable: $DR_{vCJD\text{-}R\text{-}FRy}$ - Total number of recovered plasma donors potentially infected with vCJD in year y:

$$DR_{vCJD-R-FRy} = \sum_{Age=18-19}^{50-54} \sum_{i=1day-3months}^{>=5years} DR_{vCJD-R-FR(age)y,i} \quad \text{(IV.C.1.b-27)}$$

Current deferral policy defers individuals who have history of travel to France since 1980 for an accumulated residence of 5 years or more from donating blood and plasma. The number of potentially infected donors who meet the deferral criteria was calculated by equation:

$$DR_{vCJD-R-FR-Defy} = \sum_{Age=18-19}^{50-54\,yrs} DR_{vCJD-R-FR(age)y,i>=5\,years} \qquad \text{(IV.C.1.b-28)}$$

Variable: $DR_{vCJD-S-FR-Resy}$- The residual risk due to the number of recovered plasma donors potentially infected with vCJD in year y and not deferred by current policy

$$DR_{vCJD-R-FR-Resy} = \sum_{Age=18-19\,yrs}^{50-54\,yrs} \sum_{i=1-30\,days}^{>3-5\,years} DR_{vCJD-R-FR(age)y,i} \qquad \text{(IV.C.1.b-29)}$$

A-IV. C. 1. b. v. d. Number of US recovered plasma donors with history of travel to France and potentially infected and vCJD agent is present in the blood

As discussed in the sections on Source Plasma (above) the most critical component of the model is the estimation of whether a plasma donation was collected from a vCJD infected donor who had infectious vCJD agent in their blood (i.e., was prionemic at the time of donation). Based on data from animal studies, the model assumes that vCJD infectious individuals have infectious vCJD agent present in the blood during the last half of the incubation period. This portion of the model calculates the number of recovered plasma donors who may potentially contain infectious vCJD agent in their blood at the time of donation.

Variable: Pr_{LH-y} -The probability an individual will have vCJD agent present in their blood or present (prionemic) at the time of donation in the year 2002 (calculated in A-IV.C.1.a.v. b.)

Variable: $DR_{vCJD-R-FRy}$- Total number of recovered plasma donors potentially infected with vCJD in year y during travel/residence in France (calculated in A-IV. C. 1. b. v. c.)

Variable: $DR_{vCJD-R-FR-LHy}$ - Total number of recovered plasma donors potentially infected with vCJD in year y during travel/residence in France and in the last half incubation period of the disease.

$$DR_{vCJD-R-FR-LHy} = Binomial(DR_{vCJD-R-FRy}, \Pr_{LH-y}) \qquad \text{(IV.C.1.b-30)}$$

Variable: $DR_{vCJD-R-FR-defy}$- Total number of recovered plasma donors potentially infected with vCJD in year y during travel/residency in France and met deferral criteria (calculated in A-IV. C. 1. b. v. c)

Variable: $DR_{vCJD-R-FR-def-LHy}$ - Total number of recovered plasma donors in the last half incubation period of the disease who met deferral criteria and presumably were deferred from donation.

$$DR_{vCJD-R-FR-Def-LHy} = Binomial(DR_{vCJD-R-FR-Defy}, \Pr_{LH-y}) \qquad \text{(IV.C.1.b-31)}$$

Variable: $DR_{vCJD\text{-}R\text{-}FR\text{-}Resy}$- Total number of recovered plasma donors potentially infected with vCJD in year y during travel/residency in France and did not met deferral criteria and were likely not deferred from donation (calculated in A-IV. C. 1. b. v. c.)

Variable: $DR_{vCJD\text{-}R\text{-}FR\text{-}Res\text{-}LHy}$ - Total number of recovered plasma donors in the last half incubation period of the disease who did not meet deferral criteria and were likely not deferred from donation.

$$DR_{vCJD-R-FR-Res-LHy} = Binomial(DR_{vCJD-R-FR-Resy}, \Pr_{LH-y}) \quad \text{(IV.C.1.b-32)}$$

A-IV. C. 1. b. v. e. Number of all US plasma donors with history of travel to France and potentially infected with vCJD

This section sums the number of all US plasma donors, predicted by the model to donate to plasma pools used in manufacturing pdFVIII made from plasma collected in the US. This includes recovered plasma donors and Source Plasma donors, and generates an estimate for the total number of donors potentially infected with vCJD during extended travel to France since 1980.

Variable: $DR_{vCJD\text{-}FR}$ - Total number of plasma donors potentially infected with vCJD during travel/residence in France

$$DR_{vCJD-FR} = \sum_{y=1980}^{1996} DR_{vCJD-S-FRy} + \sum_{y=1980}^{1996} DR_{vCJD-R-FRy} \quad \text{(IV.C.1.b-33)}$$

Variable: $DR_{vCJD\text{-}FR\text{-}Def}$ - Total number of plasma donors potentially infected with vCJD during travel/residence in France and meet deferral criteria

$$DR_{vCJD-FR-Def} = \sum_{y=1980}^{2002} DR_{vCJD-S-FR-Defy} + \sum_{y=1980}^{2002} DR_{vCJD-R-FR-Defy} \quad \text{(IV.C.1.b-34)}$$

Variable: $DR_{vCJD\text{-}FR\text{-}Res}$- Total number of plasma donors potentially infected with vCJD during travel/residence in the UK and did not meet deferral criteria

$$DR_{vCJD-FR-Res} = \sum_{y=1980}^{2002} DR_{vCJD-S-FR-Resy} + \sum_{y=1980}^{2002} DR_{vCJD-R-FR-Resy} \quad \text{(IV.C.1.b-35)}$$

A-IV. C. 1. b. v. f. Total number of US plasma donors with history of travel to France and are potentially infected and vCJD agent is present in the blood

Again, whether a donor contains vCJD agent in their blood is a pivotal calculation in the model since a donation from such an individual would contain vCJD agent that may find its way into a large plasma pool of thousands of donations that are used to manufacture pdFVIII. This section sums the number of

US Source Plasma donors and recovered plasma donors predicted by the model to be infected with vCJD and contain vCJD agent in their blood and arrives at an estimate of the total number of US donors potentially infected with vCJD and who are prionemic.

Variable: $DR_{vCJD\text{-}FR\text{-}LH}$ - Total number of plasma donors in the last half incubation period of the disease

$$DR_{vCJD-FR-LH} = \sum_{y=1980}^{2002} DR_{vCJD-S-FR-LHy} + \sum_{y=1980}^{2002} DR_{vCJD-S-FR-LHy} \qquad \text{(IV.C.1.b-36)}$$

Variable: $DR_{vCJD\text{-}FR\text{-}Def\text{-}LH}$ - Total number of plasma donors in the last half incubation period of the disease and met deferral criteria

$$DR_{vCJD-FR-Def-LH} = \sum_{y=1980}^{2002} DR_{vCJD-S-FR-Def-LHy} + \sum_{y=1980}^{2002} DR_{vCJD-R-FR-Def-LHy} \qquad \text{(IV.C.1.b-37)}$$

Variable: $DR_{vCJD\text{-}FR\text{-}Res\text{-}LH}$ - Total number of plasma donors in the last half incubation period of the disease and did not met deferral criteria

$$DR_{vCJD-FR-Res-LH} = \sum_{y=1980}^{2002} DR_{vCJD-S-FR-Res-LHy} + \sum_{y=1980}^{2002} DR_{vCJD-R-FR-Res-LHy} \qquad \text{(IV.C.1.b-38)}$$

A-IV.C. 1. c. Number of US plasma donors with a history of travel to countries in Europe (other than the UK and France) potentially infected and vCJD agent is present in the blood

A-IV.C.1.c.i. US recovered plasma donors with a history of travel to countries in Europe: Percentage of US donors and travel duration

In this portion of the FDA risk assessment, US blood (recovered plasma) donors are characterized by frequency and duration of travel to countries in Europe (other than the UK) during the period 1980-1996. The risk of vCJD infection is a function of exposure to the BSE agent and is assumed to be proportional to the amount of time spent, or duration of travel, in countries in Europe (other than the UK) since 1980. The FDA model used data from the National Blood Donor Travel Survey 1980-1996 (TSEAC 2000) to derive estimates of the percentages of US donors with a history of extended travel or residence (≥ 5 years) in other countries in Europe (other than the UK and France) since 1980, and to derive the frequencies for various durations of travel for 5 years or more. The period of 5 years or more corresponds to the length of time in the current policy that defers blood (recovered plasma) donors who traveled to or resided in European countries (other than the UK).

Data used in the model: National Blood Donor Travel Survey 1980-1996 was conducted by the American Red Cross and presented at the TSEAC in 2000.

Variable: i - The duration interval used to group donors who had traveled to countries in Europe from 1980-1996 based on the quantity of time spent in Europe (other than the UK and France) during the period from 1980 – 1996.

Variable: D_i - The average duration of time (in months) for interval i representing the duration of travel or residence by US donors in countries in Europe (other than the UK and France) during the period from 1980 – 1996.

Variable: $CumPerc_{BIDR\text{-}EUi}$ – The cumulative percentage of blood donors who traveled to countries in Europe (other than the UK and France) within duration interval i or longer.

Data used in the model: Travel data for US blood donors was obtained from a blood donor survey conducted by the American Red Cross and presented at the TSEAC in 2000.

Variable: $Perc_{BIDR\text{-}EUi}$ - Percentage of blood donors who traveled to countries in Europe (other than the UK and France) within duration interval i. This variable was converted from $CumPerc_{BIDR\text{-}EUi}$

Variable: $Perc_{BIDR\text{-}EUi/EU}$ - The percentage of blood donors who traveled for a specific duration interval i among all donors who have ever traveled to countries in Europe (other than the UK and France) is represented by the equation:

$$Perc_{BIDR-EUi/EU} = (Perc_{BIDR-EUi} / CumPerc_{BIDR-EU,i>1day-1month}) \times 100\% \qquad \text{(IV.C.1.c-1)}$$

The following portion of the risk assessment estimated the frequency of travel for each recovered plasma donor by age group based on travel data of blood donors. First, estimates for blood donors who traveled to countries in Europe (other than the UK and France) between 1980 and 1996 was calculated to generate the total number of US blood donors and percentages of donors who traveled. For the purposes of our analyses we grouped all donors and donors who traveled to countries in Europe since 1980 into age groups of five-year increments (20 – 24yrs, 25 – 29 yrs, etc) and for the 18 – 19 year old cohort. The percentage of donors in each age group that traveled to countries in Europe since 1980 was calculated based on the total annual number donors who traveled to Europe since 1980 compared to (or divided by) the total number of donors, and the age specific odds ratio for travel.

- **Calculation of the annual number of blood donors who traveled to countries in Europe (other than the UK and France) from 1980 through 1996**

Variable : DR_{BI} - The annual total number of potential blood donors in the US.

Data used in the model: There are approximately 8 million individuals who donate blood each year in the United States (Westat, 2002).

Variable: $Perc_{BIDR\text{-}EU}$ - The total percentage of US blood donors who traveled to countries in Europe (other than the UK and France) during the period from 1980 through 1996.

Data used in the model: Approximately, 15.6% of US blood donors have histories of travel to countries in Europe (other than the UK and France) during the period from 1980 through 1996, based on the travel data of US blood donors (TSEAC, 2000).

Variable: $DR_{BI\text{-}EU}$ -Total number of blood donors who have traveled to countries in Europe (other than the UK and France) during the period 1980 - 1996.

$$DR_{BI-EU} = DR_{BI} \times Perc_{BIDR-EU} \qquad \text{(IV.C.1.c-2)}$$

Then, the percentage of donors in each age group who traveled to countries in Europe (other than the UK and France) between 1980 and 1996 was calculated based on the total number donors who traveled to countries in Europe, the number of donors from each age group, and the odds ratio of travel for each age group.

Variable: $DR_{BI(age)}$- Annual number of blood donors from each age group (calculated IV.C.1.a)

Variable: $Perc_{BIDR\text{-}EU(age)}$ - Annual percentage of US blood donors of an age group who traveled to countries in Europe during the period from 1980 through 1996.

Total number of blood donor who traveled to countries in Europe (other than the UK and France) equals to the sum of donors from all age groups who have ever traveled to Europe:

$$DR_{BI-EU} = \sum_{age=18-19}^{65-69} (Perc_{BIDR-EU(age)} \times DR_{BI(age)}) \qquad \text{(IV.C.1.c-3)}$$

Variable: $Odd_{T(age)}$- The odds ratio for each five-year age group (e.g. 20-24 yrs, etc.) of travelers was compared to the group of age 18-19 yr olds.

Data used in the model: The odds ratios of travel to countries in Europe (other than the UK and France) for each age group was derived from the travel data obtained from 1980-1996 blood donor travel survey. An odds ratio of 1 was assigned to the donor group of age 18-19 yr olds. The odds ratios for the other age groups were generated by comparing the frequency of travel for those age groups to the group of age 18-19 yr-olds.

$$Perc_{BIDR-EU(age)} = Odd_{T(age)} \times Perc_{BIDR-EU(18-19)} \qquad \text{(IV.C.1.c-4)}$$

The percentage of blood donors from the age group of 18-19 yr olds who have traveled to countries in Europe (other than the UK and France) can be calculated by the following equation:

$$Perc_{BIDR-EU(18-19)} = DR_{BI-EU} \Big/ \sum_{age=18-19}^{65-69} (Odd_{T(age)} \times DR_{BI(age)}) \qquad \text{(IV.C.1.c-5)}$$

Then, the percentage blood donors from other age groups who traveled to Europe (other than the UK and France) can be calculated using the equation (A-IV.C.1.c-4).

A-IV. C. 1. c. ii. US recovered plasma donors who traveled to countries in Europe: Total number by year of travel, duration of travel and by age group

This part of the risk assessment calculates the annual number of US recovered plasma donors who traveled to countries in Europe (other than the UK and France) since 1980. The number of donors from an age group who traveled was calculated by year and duration of travel. The risk of a US donor acquiring vCJD is a function of duration of the stay, as well as the year(s) (since 1980) they resided in Europe.

A-IV. C. 1. c. ii.a. Number of US recovered plasma donors who traveled to Europe in a specific year between 1980 and 1996 by age group

This portion of the model estimates the potential vCJD risk for US recovered plasma donors with a history of travel to countries in Europe (other than the UK and France). Recovered plasma is derived from single units of Whole Blood as a by-product in the preparation of blood components from whole blood collection and is intended for further manufacturing. As expected, recovered plasma donor donation characteristics mirror those of whole blood donors. A recovered plasma donor can donate plasma a maximum of six times per year – and on average a recovered donation is approximately 200 milliliters (versus an average of 700 milliliters for a Source Plasma donation).

Variable: y – year of travel (same variable used above in section A-IV. C. 1. b. ii. a.) to a country in Europe (other than the UK or France) since 1980 by US plasma donors.

Variable: age – Age groups of the population by five-year increments (same variable used above in section A-IV. B. 1.) and the two year cohort for 18 and 19 year olds for US recovered plasma donors who traveled to countries in Europe (other than the UK and France).

Variable: $DR_{R(age)}$ - Number of potential US recovered plasma donors per year by age group (described in section A-IV. B. 2.).

Variable: $Perc_{BIDR\text{-}EU(age)}$ (calculated in section A-IV.C.1.b.ii.b.)- The percentage US blood donors by age group who have traveled to countries in Europe (other than the UK and France) between 1980-1996.

Variable: $DR_{R\text{-}EU(age)}$ - Number of recovered plasma donors who traveled to countries in Europe (other than the UK and France). from 1980 through 1996 by age group and is represented by the equation:

$$DR_{R-EU(age)} = DR_{R(age)} \times Perc_{BIDR-EU(age)} \qquad \text{(IV.C.1.c-10)}$$

The risk a traveler was exposed to BSE in Europe is proportional to the magnitude of the BSE epidemic in the UK in the year of travel. Because the major exposure risk in Europe was assumed to be from consumption of beef contaminated with BSE agent imported from the UK. The model groups recovered plasma donors by year of travel. This provides a more precise estimate of the risk by incorporating the (age and year) specific information and details that better capture the dynamics of the BSE epidemic in the UK on a year by year basis. Travel for the years not covered by the UK National Survey 1997 to 2002 relied on extrapolation of trends from 1996 and before to estimate travel characteristics up to the baseline year of 2002 in the model (see equation A-IV.C.1.c-12 (below)).

Variable: $V_{y/1996}$ - The number of visits to the UK by US travelers in year y compared to the number of visits in 1996 (calculated in A-IV.C.1.a.)

Variable: $DR_{R\text{-}EU(age)y}$ - Number of recovered plasma donors who traveled to Europe in year y by age groups.

The number of recovered plasma donors who have traveled to countries in Europe (other than the UK and France) was allocated to individual travel year based on the yearly distribution of visits to the UK by US travelers.

$$DR_{R-EU(age)y} = DR_{R-EU(age)} \times V_{y/1996} / \sum_{y=1980}^{1996} V_{y/1996} \qquad \text{(IV.C.1.c-11)}$$

for travel during 1980-1996;

$$DR_{R-EU(age)y} = DR_R \times V_{y/1996} \qquad \text{(IV.C.1.c-12)}$$

for travel after 1996.

Assumption used in the model: The yearly distribution of travel to countries in Europe (other than the UK and France) by US recovered plasma donors is similar to the yearly distribution of travel to the UK by US travelers. The yearly distribution of travel visits by each age group was adjusted to account for the minimum age of 18 when a donor can donate plasma or blood. Therefore, in calculating the US donor risk for vCJD the yearly distribution of travel visits by each age group was adjusted to account for this requirement. The model adjusted the potential vCJD exposure for younger donors who were born during the period from 1980 to 1986 and would have essentially a zero chance of being exposed to the BSE agent in the years prior to their birth. Therefore, donors 18 years of age in 2002 were assumed to have zero exposure to the BSE agent prior to 1985, those 19 years of age in 2002 were assumed to have zero exposure prior to 1984, those 20 years of age in 2002 were assumed to have zero exposure prior to 1983, those 21 years of age in 2002 were assumed to have zero exposure prior to 1982, those 22 years of age in 2002 were assumed to have zero exposure prior to 1981. The model assumed that there was zero exposure of all donors prior to 1980.

A-IV. C. 1. c. ii. b. Number of US recovered plasma donors who traveled to countries in Europe by specific year of travel and duration of travel by age group

Recovered plasma donors who traveled to countries in Europe (other than the UK and France) in a specific year ($DR_{R\text{-}EU(age)y}$) since 1980 were further partitioned into the subgroups in the model based on travel duration and by 5-year age groups and also the two year cohort of donors 18 and 19 years of age. Data on the percentage of blood donors who traveled to countries in Europe (other than the UK and France) since 1980 for a certain duration(s) (TSEAC, 2000) were used in this risk assessment.

Variable: i - The duration interval used to group blood donors who had traveled to countries in Europe (other than the UK and France) from 1980-1996 based on the time spent (same variable used above in section A-IV. C. 1.).

Variable: D_i - The average duration of time for interval i (months) (same variable used above in section A-IV. C. 1.)

Variable: $DR_{R\text{-}EU(age),y}$ - The number of recovered plasma donors who traveled to countries in Europe (other than the UK and France) in year y by age group

Variable: $Perc_{BIDR\text{-}EU/FEU}$- The percentage of blood donors who traveled for a specific duration interval i among all donors who have ever traveled to countries in Europe (other than the UK and France) (calculated in A-IV. C. 1. c. i).

Variable: $DR_{R\text{-}EU(age)y,i}$- Number of recovered plasma donors within a specific age group who have traveled to countries in Europe (other than the UK and France) in year, y ,for duration of i.

$$DR_{R-EU(age)y,i} = DR_{R-EU(age)y} \times Perc_{DR-EU/EU} \qquad \text{(IV.C.1.c-13)}$$

A-IV.C. 1. c. iii. US recovered plasma donors who traveled to countries in Europe: Adjustment of relative risk for the proportion of exposure to the BSE agent per year and by duration of travel and by age group

As indicated in previous sections the FDA model assumed that the relative vCJD risk for UK residents residing for any five-year period or longer from 1980 through 1996 is assumed to have a value of 1, because exposure to BSE in the UK was greater than that of any other country. The relative risk value of 1 equates to 100% of the UK asymptomatic and symptomatic vCJD prevalence, which is difficult to estimate. Again, based on information in FDA guidance (2002), the relative risk value for France was assumed to be 0.05 (or 5% of the UK risk). The relative risk value is assigned based on factors such as domestic UK beef consumption, and the rate and number of vCJD cases, and indigenous BSE cases that may have occurred (FDA 2002). Countries in Europe (other than the UK and France) received meat and bone meal from the UK during the BSE epidemic and approximately 1.5% of their beef was imported from the UK. Additionally, the model included calculations on the estimated duration of travel or residence in Europe by US plasma donors to generate a more accurate vCJD risk estimate. Current US vCJD geographic deferral policy defers blood donors with a history of residence in countries in Europe (other than the UK and France) for a period of 5 years or more since 1980; this policy does not include Source Plasma donors.

A-IV. C. 1. c. iii. a. Number of US recovered plasma donors with a history of travel to countries in Europe: Average accumulated vCJD risk for donors since 1980, assuming that the average accumulated risk for a UK individual since 1980 is 1

This section calculates the number of US plasma donors with a history of travel to countries in Europe (other than the UK and France) and their average accumulated vCJD risk since 1980, assuming that the average accumulated risk for a UK individual since 1980 is 1.

Variable: R_{EU} - Ac– The cumulative vCJD risk of an individual resident of countries in Europe (other than the UK and France) from 1980 till now; assuming the accumulated risk of a UK individual from 1980 through 1996 is 1.

Assumption used in the model: The average accumulated vCJD risk for travel to countries in Europe (other than the UK and France) by an individual resident since 1980 was assumed to be 0.015 relative to 1, the average accumulated risk of UK individual since 1980, based on UK. It was assumed that approximately 1.5% or less of the beef imports, imported into many countries since 1980 was imported from the UK. The 0.015 relative risk value also considers the number of human vCJD cases present and the presence of indigenous BSE in European countries (other than the UK and France) since 1980.

A-IV. C. 1. c. iii. b. US plasma donors with a history of travel to countries in Europe: Proportional risk per individual resident per year since 1980

Variable: Y_{epi} –y Years of BSE epidemic in countries in Europe (other than the UK and France).

Variable: BSE_{UKy} Annual numbers of reported BSE cases in the UK.

Variable: BSE_{EUy} - Annual numbers of reported BSE cases in European countries other than the UK and France.

Data used in the model: Data on the annual number of reported cases of BSE in cattle in European countries was obtained from the Orgainization Internationale de Epizootics (OIE) (2005).

Variable: R_{EUy} - Proportional vCJD risk for European countries (other than the UK and France) in a specific year

Assumptions used in the model:

- The risk of vCJD and BSE in European countries (other than the UK and France) has been present since 1980 and continues to present day. As of August 2006, very few cases of BSE continue to be reported in European countries (other than the UK and France)..
- The vCJD risk is assumed to be additive, and can be prorated on a yearly or monthly basis.
- The yearly rate of the vCJD risk in European countries (other than the UK and France) is proportional to the reported BSE annual cases in Europe (including indigenous and imported cases)

A-IV. C. 1. c. iii. b. US recovered plasma donors with a history of travel to countries in Europe: Potential vCJD risk for an individual in year y for a period of i since 1980

Variable: $R_{DR\text{-}EUy_{y,i}}$ - Risk for individual US donors who traveled to countries in Europe other than the UK and France in a specific year for a specific duration, assuming the accumulative risk of a UK person resident in the years 1980 through 1996 is 1.

The vCJD risk for the US plasma donors with less than 5 years accumulated stay in Europe was calculated based on travel to European countries other than the UK and France in a specific year for a specific duration of travel. Potential exposure risk was calculated using a prorated monthly rate, which was calculated based on the yearly rate of the risk (1 month = 1/12 x yearly risk) in Europe during the year of travel. US plasma donors with a total accumulated stay in countries in Europe (other than the UK or France) of 5 years or more is assumed to have average risk of 0.015, which is the same as the risk of an individual citizen or long-term resident of a country in Europe (other than the UK or France). Information on duration of accumulated stays was collected in the blood donor travel survey; however, for simplicity we assumed all travel was consecutive. The blood donor travel survey (TSEAC 2000) collected information on the accumulated stay of US donors who stayed in Europe (other than the UK or France) from 1980 through 1996. For simplicity, these data were used to estimate the duration of consecutive stay, which was used to calculate the potential vCJD risk for recovered plasma donors.

Assumptions used in the model:

- Risk is proportional to the duration of the stay
- All the travelers' stays were assumed to be single and consecutive stays.
- US plasma donor subpopulation having 5 or more years accumulated stay in countries in Europe (other than the UK or France) have an average risk of 0.015, which is the same as the average risk of individual European resident.

For < 1 year;

$$R_{DR-EUy,i} = (Average(R_{EUy} : R_{EU(y+i)})/12) \times D_i \qquad \text{(IV. C. 1. c-14)}$$

for 5 years <*i*>=1 year;

$$R_{DR-EUy,i} = 0.015 \qquad \text{(IV. C. 1. c-15)}$$

for *i*>= 5 years

A-IV. C. 1. c. iv. US recovered plasma donors with a history of travel to countries in Europe: Probability of vCJD infection for a donor of a specific age group, who traveled in a specific year for a specific duration, i

This section describes the portion of the model that estimates the potential probability that a US plasma donor in a specific age group, who traveled to countries in Europe (other than the UK or France) for a specific duration since 1980 was infected with vCJD.

Variable: $Pr_{vCJD\text{-}UK(age)}$ – the probability of infection for an individual UK resident of a specific age group (calculated in A-IV. C. 1. a. iv.).

Variable: $Pr_{vCJD\text{-}DR\text{-}EU(age)y,i}$ - Probability of infection for an individual US plasma donor of a specific age group who have traveled to countries in Europe other than the UK and France in a specific year with specific duration.

Assumption used in the model: The probability of vCJD infection is proportional to the risk of exposure

$$\Pr_{vCJD-DR-EU(age)y,i} = \Pr_{vCJD-UK(age)} \times R_{DR-EUy,i} \qquad \text{(IV.C.1.c-16)}$$

A-IV.C. 1. c. v. Number of US recovered plasma donors with a history of travel to countries in Europe: Number potentially infected with vCJD.

Variable: $DR_{vCJD\text{-}R\text{-}EU(age)y,i}$ - Number of recovered plasma donors potentially infected with vCJD during travel to countries in Europe (other than the UK and France) since 1980 by age, year and duration of travel

$$DR_{vCJD-R-EU(age)y,i} = Bionomial(DR_{R-EU(age)y,i}, \Pr_{vCJD-DR-EU(age)y,i}) \qquad \text{(IV.C.1.c-26)}$$

Variable: $DR_{vCJD\text{-}R\text{-}EUy}$ - Total number of recovered plasma donors potentially infected with vCJD in year y

$$DR_{vCJD-R-FRy} = \sum_{Age=18-19}^{50-54} \sum_{i=1day-3months}^{>=5years} DR_{vCJD-R-FR(age)y,i} \qquad \text{(IV.C.1.c-27)}$$

Variable: $DR_{vCJD\text{-}R\text{-}EU\text{-}Defy}$- Number of recovered plasma donors potentially infected with vCJD in year y and deferred by current policy

Current FDA guidance (FDA 2002) recommends deferral of individuals who have history of travel to countries in Europe (other than the UK or France) since 1980 for an accumulated stay of 5 years or more from donating blood. The number of potential vCJD-infected recovered plasma donors who meet current deferral criteria (FDA 2002) was calculated by the equation:

$$DR_{vCJD-R-EU-Defy} = \sum_{Age=18-19}^{50-54} DR_{vCJD-R-EU(age)y,i>=5years} \qquad \text{(IV.C.1.c-28)}$$

Variable: $DR_{vCJDS\text{-}EU\text{-}Resy}$ – The residual risk associated with recovered plasma donors potentially infected with vCJD that meet deferral criteria but because of limitations in the donor screening process and are not deferred by current policy; is represented by the equation:

$$DR_{vCJD-R-EU-Resy} = \sum_{Age=18-19}^{50-54} \sum_{i=1-30days}^{>=3-5years} DR_{vCJD-R-EU(age)y,i} \qquad \text{(IV.C.1.c-29)}$$

A-IV. C. 1. c. vi. Number of US recovered plasma donors who traveled to countries in Europe: Number potentially infected and vCJD agent is present in the blood

The most critical component of the model is the estimation of whether a plasma donation was collected from a vCJD infected donor that contained infectious vCJD agent in their blood (or was prionemic) at the time of donation. Based on data from animal studies, the model assumes that vCJD infectious individuals have infectious vCJD agent present in the blood during the last half of the incubation period. This portion of the model calculates the number of recovered plasma donors who may potentially contain infectious vCJD agent in their blood at the time of donation.

Variable: $Pr_{LH\text{-}y}$ -The probability an individual was prionemic in year 2002.

Variable: $DR_{vCJD\text{-}R\text{-}EUy}$- Total number of recovered plasma donors potentially infected with vCJD in year y during travel/residence in European countries (other than France).

Variable: $DR_{vCJD\text{-}R\text{-}EU\text{-}LHy}$ - Total number of recovered plasma donors potentially infected with vCJD in year y during travel/residence in a country in Europe (other than the UK or France) and are in the last half incubation period of the disease (and has vCJD agent present in their blood).

$$DR_{vCJD-R-EU-LHy} = Binomial(DR_{vCJD-R-EUy}, \Pr_{LH-y}) \qquad \text{(IV.C.1.c-30)}$$

Variable: $DR_{vCJD\text{-}R\text{-}EU\text{-}defy}$- Total number of recovered plasma donors potentially infected with vCJD in year y during travel/residency in European countries (other than the UK or France) and met deferral criteria and were presumably deferred from donation .

Variable: $DR_{vCJD\text{-}R\text{-}EU\text{-}def\text{-}LHy}$ - Total number of recovered plasma donors in the last half incubation period of the disease (and presumably has vCJD agent present in their blood) who met deferral criteria and were presumably deferred from donation.

$$DR_{vCJD-R-EU-Def-LHy} = Binomial(DR_{vCJD-R-EU-Defy}, \Pr_{LH=y}) \qquad \text{(IV.C.1.c-31)}$$

Variable: $DR_{vCJD\text{-}R\text{-}EU\text{-}Resy}$- Total number of recovered plasma donors potentially infected with vCJD in year y during travel/residency in countries in Europe (other than the UK or France) and did not meet the deferral criteria and were likely not deferred .

Variable: $DR_{vCJD\text{-}R\text{-}EU\text{-}Res\text{-}LHy}$ - Total number of recovered plasma donors in the last half of the incubation period of the disease who did not met the deferral criteria and were likely not deferred from donation:

$$DR_{vCJD-R-EU-Res-LHy} = Binomial(DR_{vCJD-R-EU-Resy}, Pr_{LH-y})$$ (IV.C.1.c-32)

A-IV. C. 1. d. Number of US plasma donors deployed by the military in the UK or other countries in Europe and potentially infected with vCJD

A-IV. C. 1. d. i. Percentage of US plasma donors deployed at US military bases in the UK or other countries in Europe during the years 1980 through 1996

Variable: $Perc_{DR-DOD}$ - Percentage of US blood donors who were military residents in countries in Europe for ≥ 6 months from 1980 through 1996.

Assumption used in the model: Approximately 2% of US blood donors have been military residents in European countries between 1980-1996 (TSEAC 2002). There were no data for plasma donors, therefore, data for US blood donors was used to estimate the number of US donors stationed in US military facilities during the period 1980-1996

- The FDA model assumed that the same percentage of plasma donors have been in the military and deployed in European countries as blood donors.

A-IV. C. 1. d. ii. Number of US plasma donors deployed by Military in the UK or other countries in Europe by year of deployment since 1980

A-IV. C. 1. d. ii. a. Number of US Source Plasma donors stationed at US military facilities in the UK or countries in Europe during the period from 1980 -1996 by year of deployment

Variable: y - Calendar year of deployment

Variable: $DODy$ - Number of US military residents, their family and dependents who resided on US military facilities in Europe by year from 1980 through 1996.

Assumption used in the model: The risk of BSE exposure and vCJD infection for donors previously deployed to US military facilities in the UK or countries in Europe after 1996 was assumed to be negligible, because it is assumed that most of the risk was associated with imported UK beef. Food chain controls put in place in the UK after 1996 were assumed to reduce the BSE exposure risk to negligible levels (TSEAC, 2002) and shipment of UK beef to US military facilities had stopped in 1996 or earlier.

Variable: age - age of donors in grouped by five-year increments (e.g., 20-24, etc.) and the 18-29 year old group (same variable used above in section A-IV.C.1.a.ii.)

$$Perc_{DR-DODy} = (DOD_y / \sum_{y=1980}^{1996} DOD_y) \times 100\%$$ (IV.C.1.d-1)

Variable: $DR_{S(age)}$ – Age of donors of Source Plasma (calculated in section A-IV.B. 1.)

Variable: $Perc_{DR\text{-}DOD}$ – Percentage of Source Plasma donors who have a history of military deployment in Europe since 1980 (calculated in section A-IV. C. 1. d. ii. a.)

Variable: $DR_{S\text{-}DOD(age)}$ - Estimated annual number of Source Plasma donors who have history of military deployment in the UK or Europe by age

Assumption about variable: We assumed 3% of Source Plasma donors have a history of military deployment and residence in the UK, France or other countries of Europe during any of the years from 1980-1996 and would have similar donation demographics and characteristics as whole blood donors.

The estimated annual number of Source Plasma donors who have a history of military deployment in Europe by age is represented by the equation:

$$DR_{S-DOD(age)} = DR_{S(age)} \times Perc_{DR-DOD} \qquad \text{(IV.C.1.d-2)}$$

Variable: $DR_{S\text{-}DOD(age)y}$ – Number estimated annual number of Source Plasma donors who have resided on military bases in Europe by age and deployment year

$$DR_{S-DOD(age)y} = DR_{S-DOD(age)} \times Perc_{DR-DODy} \qquad \text{(IV.C.1.d-3)}$$

A-IV. C. 1. d. ii. b. Number of recovered plasma donors with a history of military deployment at US military facilities in the UK or other countries in Europe during the period 1980-1996 by year of deployment

Variable: *age* - Age of donors grouped by five-year increments (e.g., 20-24, etc.) and the 18-29 year old group. No data for the yearly distribution of deployment of military plasma donors in the UK, France or other countries in Europe was available. The age distribution of donors in the military was estimated from Department of Defense (DOD) data (2005). The donation rate for military staff was estimated using the blood donor survey data (TSEAC, 2002).

Variable: $DR_{R\text{-}(age)}$ - Annual number of recovered plasma donors by age .

Assumption used in the model: We assumed 3% of recovered plasma donors were grouped by deployment year based on the yearly distribution of military deployment and residence in the UK or Europe during 1980-1996 .(DOD 2005).

$$DR_{R-DOD(age)y} = DR_{R-DOD(age)} \times Perc_{DR-DODy} \qquad \text{(IV.C.1.d-4)}$$

Variable: $DR_{R(age)}$ - Annual number of recovered plasma donors by age (calculated in section A-IV.B. 2.) grouped by five-year increments (e.g., 20-24, etc.) and the 18-29 year old group

Variable: $Perc_{DR\text{-}DOD}$ - Percentage of recovered plasma donors who have a history of military deployment in the UK and countries in Europe since 1980 (calculated in section A-IV. C. 1. d. ii. a.)

Variable: $DR_{R\text{-}DOD(age)}$ - Estimated annual number of recovered plasma donors who have a history of military deployment in the UK and countries in Europe by age.

Assumption used in the model: The same percentage of recovered plasma donors have a history of military deployment as blood donors.

The estimated annual number of recovered plasma donors who have history of military deployment in the UK and countries in Europe by age is represented by the equation:

$$DR_{R-DOD(age)} = DR_{R(age)} \times Perc_{DR-DOD} \qquad \text{(IV.C.1.d-5)}$$

Assumption used in the model: The annual distribution of US military service members and their dependents residing on US military bases in Europe represents the yearly distribution of deployment in the UK and countries in Europe of US military recovered plasma donors

$$DR_{R-DOD(age)y} = DR_{R-DOD(age)} \times Perc_{DR-DODy} \qquad \text{(IV.C.1.d-6)}$$

A-IV. C. 1. d. iii. Adjustment of the Relative Risk for the proportional variation in the BSE exposure risk in the UK and the military deployment duration per specific year during the period from 1980 - 1996

Variable: R_{Base} - The cumulative vCJD risk of individual military personnel who were deployed and resided in the UK or Europe for the entire period from 1980 through 1996: it is assumed that the accumulated risk is equal to that of a UK resident and is assumed to be 1 (or equal to the UK vCJD prevalence) for this period.

Assumption used in the model: The cumulative risk of US military residents in Europe from 1980 through 1996 is 0.35. This estimate is based on the assumption that approximately 35% of the beef consumed by military personnel in Europe between 1980-1996 was imported from the UK (FDA 2002).

Variable: y – Year of deployment (same variable used above in A-IV. C. 1. d. ii. a.)

Variable: y_{epi} – The specific year of BSE epidemic in the UK.

Assumption about variable: The BSE epidemic in the UK was assumed to have started in 1980 and at first was not detected. The first cases of BSE were reported in 1986.

Variable: BSE_{UKy} - Number of diagnosed BSE cases in the UK by year from 1980 through 1996

Data used in the model: Data are from the World organization for animal health (OIE 2005). Data were not collected for individual years prior to 1997. A total of 446 cases of BSE were reported by European countries (other than the UK) during the time period from 1980 through 1996 and were allocated to individual years by assuming the cases were increasing in a linear fashion by year.

Variable: R_{Basey} - Proportional vCJD risk for donors that resided on US military bases in Europe in a specific year

Assumptions used in the model:

- The vCJD risk for US military facilities in Europe was present from 1980 through 1996. There was negligible vCJD risk after 1996 – the model assumed the major source of vCJD risk for US military bases in Europe was associated with imported UK beef. When food chain controls were implemented in the UK in 1996 – the model assumed the risk to be negligible.
- It was assumed that the vCJD risk was additive and can be prorated on a yearly base.
- The vCJD risk in a specific year was assumed to be proportional to the reported BSE cases in the UK in that specific year.

Proportional vCJD risk in the US military bases in a specific year was calculated by the equation:

$$R_{Basey} = R_{Base} \times BSE_{UKy} / \sum_{y=1980}^{1996} BSE_{UKy} \qquad \text{(IV.C.1.d-7)}$$

Variable: $R_{DR\text{-}DODy}$ - Risk of individual military personnel who lived in Europe for a period of two years starting from deployment year y, and assumes the cumulative risk of a UK individual from 1980 through 1996 is 1.

Assumption used in the model: The model assumed an average of two consecutive years of deployment:

$$R_{DR-DODy} = R_{Basey} + R_{Base(y+1)} \qquad \text{(IV.C.1.d-8)}$$

Variable: $Pr_{vCJD\text{-}UK(age)}$ - Probability of infection for individual UK resident of a specific age group (calculated in A-IV. C. 1.).

Variable: $Pr_{vCJD\text{-}DR\text{-}DOD(age)y}$ - Probability of infection for individual US plasma donor of a specific age group that lived on or near a US military bases in Europe starting from year y with duration of two years

Assumption used in the model: Probability of infection is proportional to the risk of exposure

$$Pr_{vCJD-DR-DOD(age)y} = Pr_{vCJD-UK(age)} \times R_{DR-DODy} \qquad \text{(IV.C.1.d-9)}$$

A-IV. C. 1. d. iv. Number of all US plasma donors potentially infected with vCJD during residence at a US military base in the UK or other countries in Europe from 1980 to 1996

The section estimates the number of Source and recovered plasma donors with a history of deployment in the UK or countries in Europe during the period from 1980 through 1996 and sums the number of vCJD cases that may have vCJD agent in their blood (or be prionemic) at the time of donation from each pathway to derive the total number of all donors potentially infected with vCJD that may have vCJD agent in their blood (or be prionemic).

A-IV. C. 1. d. iv. a. Potential number of US Source Plasma donors with a history of military deployment in the UK or other countries in Europe from 1980 to 1996 potentially infected with vCJD

Variable: $\mathbf{DR_{vCJD\text{-}S\text{-}DOD(age)y}}$ - Potential number of Source Plasma donors infected during residency on US military facilities in the UK or Europe from 1980-1996 by age, and year of deployment

$$DR_{vCJD-S-DOD(age)y} = Binomial(DR_{S-DOD(age)y}, \Pr_{vCJD-DR-DOD(age)y}) \qquad \text{(IV.C.1.d-10)}$$

Variable: $\mathbf{DR_{vCJD\text{-}S\text{-}DOD}}$ - Potential number total of Source Plasma donors infected during residency on US military bases in Europe from 1980-1996 is represented by the expression:

$$DR_{vCJD-S-DOD} = \sum_{y=1980}^{1996} \sum_{age=18-19}^{70-74} DR_{vCJD-S-DOD(age)y} \qquad \text{(IV.C.1.d-11)}$$

A-IV. C. 1. d. iv. b. Potential number of Source Plasma donors with a history of deployment to a US military facility in the UK or other countries of Europe from 1980 to 1996 in the last half incubation period of the disease

This section estimates the number of Source Plasma donors that may potentially be infected with vCJD who may have vCJD agent in their blood (or be prionemic) at the time of donation.

Variable: y-The calendar year in which a plasma donor was deployed to a US military base in Europe.

Assumption used in the model: This risk assessment assesses the vCJD risk for pdFVIII product made in 2002 but it is assumed that the potential vCJD risk is similar to the present day risk in 2006.

Variable: $T_{Inf\text{-}2002y}$-Time period between infection/travel and the year 2002 when the plasma was collected.

Variable: $Pr\text{-}LH_y$- Probability that the vCJD disease is in the last half of the incubation period of the disease, if infected in year y and the individual has infectious vCJD agent present in their blood and plasma (or was prionemic).

Variable: $T_{Inf\text{-}2002y}$ - Time period between infection/travel and 2002 when the plasma was collected is represented by the expression:

$$T_{Inf-2002y} = 2002 - y \qquad \text{(IV.C.1.d-12)}$$

For an individual to be prionemic in 2002, the remaining period of time since infection up to 2002 ($I_{Inf-2002y}$) should be equal to or less than the half of incubation period of the disease.

Assumption used in the model: The variability and uncertainty of the incubation period of vCJD is represented mathematically by a gamma distribution, specifically Gamma (4.7, 3.6). A gamma distribution is usually used to represent processes that occur sequentially or the time between events. In this case it would be the time from infection to the time until the appearance of clinical disease (incubation period of the disease). The distribution is defined by two parameters: one that produces the shape of the curve; and a second generates the scale for the distribution, which in this case is represented by the mean incubation period of 14 years.

Variable: Pr_{LH-y} -The probability an individual was prionemic in year 2002-was calculated by using the cumulative frequency of Gamma (4.7, 3.6), at x=2×(1997-y)

Variable: $DR_{vCJD-S-DODy}$- Total number of Source Plasma donors potentially infected with vCJD in year y during military deployment on European bases (calculated in A-IV. C. 1. d. v. a.).

Variable: $DR_{vCJD-S-DOD-LHy}$ - Total number of Source Plasma donors potentially infected with vCJD in year y during military deployment to US military bases in European countries and in the last half incubation period of the disease.

$$DR_{vCJD-S-DOD-LHy} = Binomial(DR_{vCJD-S-DODy}, \Pr_{LH-y}) \qquad \text{(IV.C.1.d-13)}$$

A-IV. C. 1. d. iv. c. Number of US recovered plasma donors with a history of deployment to a US military base in the UK or other countries in Europe during the period 1980-1996 and potentially infected with vCJD

Variable: $DR_{vCJD-R-DOD(age)y}$ - Potential number of recovered plasma donors infected during deployment and residency on or near US military bases in Europe from 1980-1996 by age, and year of deployment

$$DR_{vCJD-R-DOD(age)y} = Binomial(DR_{R-DOD(age)y}, \Pr_{vCJD-DR-DOD(age)y}) \qquad \text{(IV.C.1.d-14)}$$

Variable: $DR_{vCJD-R-DOD}$ - Potential number of recovered plasma donors infected during residency on US military bases in Europe from 1980-1996 is represented by the equation:

$$DR_{vCJD-R-DOD} = \sum_{y=1980}^{1996} \sum_{age=18-19}^{70-74} DR_{vCJD-R-DOD(age)y} \qquad \text{(IV.C.1.d-15)}$$

A-IV. C. 1. d. iv. d. Recovered plasma donors with a history of deployment to a US military base in the UK or other countries in Europe: Potential number of donors in the last half of vCJD incubation period and vCJD agent is present in the blood

This portion of the model calculates the potential number of vCJD infected recovered plasma donors who are in the last half incubation period of the disease and presumably may contain vCJD agent in their blood (or are prionemic).

Variable: Pr_{LH-y} -The probability a vCJD-infected donor had vCJD agent present in their blood and plasma at the time of donation (was prionemic) in the year 2002 (calculated in A-IV.C.1.d.v.b).

Variable: $DR_{vCJD-R-DODy}$- Total number of recovered plasma donors potentially infected with vCJD in year y during military deployment on or near bases in Europe (calculated in A-IV. C. 1. d. v. c.)

Variable: $DR_{vCJD-R-DOD-LHy}$ - Total number of recovered plasma donors potentially infected with vCJD in year y during military deployment on or near bases in Europe and in the last half incubation period of the disease.

$$DR_{vCJD-R-DOD-LHy} = Binomial(DR_{vCJD-R-DODy}, \Pr_{LH-y}) \qquad \text{(IV.C.1.d-16)}$$

A-IV. C. 1. d. iv. e. Number of all vCJD infected plasma donors during deployment to a US military base in a country in Europe from 1980-1996

Variable: $DR_{vCJD-DOD}$ - Potential number of total plasma donors infected during residence on US military bases in Europe from 1980-1996

$$DR_{vCJD-DOD} = \sum_{y=1980}^{1996} DR_{vCJD-S-DOD} + \sum_{y=1980}^{1996} DR_{vCJD-R-DOD} \qquad \text{(IV.C.1.d-17)}$$

Variable: $DR_{vCJD-DOD-Def}$ - Potential number of total plasma donors infected during residence on US military bases in Europe from 1980-1996 and meet deferral criteria

Assumption used in the model: Current policy defers individuals who have been deployed or resided on a US military base in Europe from 1980 to 1996 for a cumulative stay of 6 months or more. We assumed all US Department of Defense (DOD) deployments are 6 months or longer, and therefore, all individuals have a history of deployment to a US military base in Europe are deferred.

$$DR_{vCJD-DOD-Def} = DR_{vCJD-DOD} \qquad \text{(IV.C.1.d-18)}$$

A-IV. C. 1. d. iv. f. Potential number of all plasma donors in the last half of vCJD incubation period

This portion of the model estimates the potential number of all vCJD infected plasma donors with a history of military service posted at a US military base in the UK or countries in Europe fron 1980-1996 who are in the last half incubation period of the disease and their blood and plasma presumably contain infectious vCJD agent (or are prionemic).

Variable: $DR_{vCJD\text{-}DOD\text{-}LH}$ - Potential number of total plasma donors infected during residence on US military bases in Europe from 1980-1996 and are in the last half incubation period of the disease

$$DR_{vCJD-DOD-LH} = \sum_{y=1980}^{1996} DR_{vCJD-S-DOD-LH} + \sum_{y=1980}^{1996} DR_{vCJD-R-DOD-LH} \qquad \text{(IV.C.1.d-19)}$$

Variable: $DR_{vCJD\text{-}DOD\text{-}Def}$ - Potential number of total plasma donors infected during residence on US military bases in Europe from 1980-1996 and meet deferral criteria

$$DR_{vCJD-DOD-Def} = DR_{vCJD-DOD} \qquad \text{(IV.C.1.d-20)}$$

A-IV. C. 1. d. i. Percentage of US plasma donors deployed at US military bases in the UK or other countries in Europe during the years 1980 through 1996

Variable: $Perc_{DR\text{-}DOD}$ - Percentage of US blood donors who were military residents in countries in Europe for ≥ 6 months from 1980 through 1996.

Assumption used in the model: Approximately 2% of US blood donors have been military residents in European countries between 1980-1996 (TSEAC 2002). There were no data for plasma donors, therefore, data for US blood donors was used to estimate the number of US donors stationed in US military facilities during the period 1980-1996

- The FDA model assumed that the same percentage of plasma donors have been in the military and deployed in European countries as blood donors.

A-IV. C. 1. d. ii. Number of US plasma donors deployed by Military in the UK or other countries in Europe by year of deployment since 1980

A-IV. C. 1. d. ii. a. Number of US Source Plasma donors stationed at US military facilities in the UK or countries in Europe during the period from 1980 -1996 by year of deployment

Variable: ***y*** - Calendar year of deployment

Variable: ***DODy*** - Number of US military residents, their family and dependents who resided on US military facilities in Europe by year from 1980 through 1996.

Assumption used in the model: The risk of BSE exposure and vCJD infection for donors previously deployed to US military facilities in the UK or countries in Europe after 1996 was assumed to be negligible, because it is assumed that most of the risk was associated with imported UK beef. Food chain controls put in place in the UK after 1996 were assumed to reduce the BSE exposure risk to negligible levels (TSEAC, 2002) and shipment of UK beef to US military facilities had stopped in 1996 or earlier.

Variable: ***age*** - age of donors in grouped by five-year increments (e.g., 20-24, etc.) and the 18-29 year old group (same variable used above in section A-IV.C.1.a.ii.)

$$Perc_{DR-DODy} = (DOD_y / \sum_{y=1980}^{1996} DOD_y) \times 100\% \qquad \text{(IV.C.1.d-1)}$$

Variable: $DR_{S(age)}$ – Age of donors of Source Plasma (calculated in section A-IV.B. 1.)

Variable: $Perc_{DR-DOD}$ – Percentage of Source Plasma donors who have a history of military deployment in Europe since 1980 (calculated in section A-IV. C. 1. d. ii. a.)

Variable: $DR_{S-DOD(age)}$ - Estimated annual number of Source Plasma donors who have history of military deployment in the UK or Europe by age

Assumption about variable: We assumed 3% of Source Plasma donors have a history of military deployment and residence in the UK, France or other countries of Europe during any of the years from 1980-1996 and would have similar donation demographics and characteristics as whole blood donors.

The estimated annual number of Source Plasma donors who have a history of military deployment in Europe by age is represented by the equation:

$$DR_{S-DOD(age)} = DR_{S(age)} \times Perc_{DR-DOD} \qquad \text{(IV.C.1.d-2)}$$

Variable: $DR_{S-DOD(age)y}$ – Number estimated annual number of Source Plasma donors who have resided on military bases in Europe by age and deployment year

$$DR_{S-DOD(age)y} = DR_{S-DOD(age)} \times Perc_{DR-DODy} \qquad \text{(IV.C.1.d-3)}$$

A-IV. C. 1. d. ii. b. Number of recovered plasma donors with a history of military deployment at US military facilities in the UK or other countries in Europe during the period 1980-1996 by year of deployment

Variable: *age* - Age of donors grouped by five-year increments (e.g., 20-24, etc.) and the 18-29 year old group. No data for the yearly distribution of deployment of military plasma donors in the UK, France or other countries in Europe was available. The age distribution of donors in the military was estimated from Department of Defense (DOD) data (2005). The donation rate for military staff was estimated using the blood donor survey data (TSEAC, 2002).

Variable: $DR_{R\text{-}(age)}$ - Annual number of recovered plasma donors by age

Assumption used in the model: We assumed 3% of recovered plasma donors were grouped by deployment year based on the yearly distribution of military deployment and residence in the UK or Europe during 1980-1996 .(DOD 2005).

$$DR_{R-DOD(age)y} = DR_{R-DOD(age)} \times Perc_{DR-DODy} \qquad \text{(IV.C.1.d-4)}$$

Variable: $DR_{R(age)}$ - Annual number of recovered plasma donors by age (calculated in section A-IV.B. 2.) grouped by five-year increments (e.g., 20-24, etc.) and the 18-29 year old group

Variable: $Perc_{DR\text{-}DOD}$ - Percentage of recovered plasma donors who have a history of military deployment in the UK and countries in Europe since 1980 (calculated in section A-IV. C. 1. d. ii. a.)

Variable: $DR_{R\text{-}DOD(age)}$ - Estimated annual number of recovered plasma donors who have a history of military deployment in the UK and countries in Europe by age.

Assumption used in the model: The same percentage of recovered plasma donors have a history of military deployment as blood donors.

The estimated annual number of recovered plasma donors who have history of military deployment in the UK and countries in Europe by age is represented by the equation:

$$DR_{R-DOD(age)} = DR_{R(age)} \times Perc_{DR-DOD} \qquad \text{(IV.C.1.d-5)}$$

Assumption used in the model: The annual distribution of US military service members and their dependents residing on US military bases in Europe represents the yearly distribution of deployment in the UK and countries in Europe of US military recovered plasma donors

$$DR_{R-DOD(age)y} = DR_{R-DOD(age)} \times Perc_{DR-DODy} \qquad \text{(IV.C.1.d-6)}$$

A-IV. C. 1. d. iii. Adjustment of the Relative Risk for the proportional variation in the BSE exposure risk in the UK and the military deployment duration per specific year during the period from 1980 - 1996

Variable: R_{Base} - The cumulative vCJD risk of individual military personnel who were deployed and resided in the UK or Europe for the entire period from 1980 through 1996: it is assumed that the accumulated risk is equal to that of a UK resident and is assumed to be 1 (or equal to the UK vCJD prevalence) for this period.

Assumption used in the model: The cumulative risk of US military residents in Europe from 1980 through 1996 is 0.35. This estimate is based on the assumption that approximately 35% of the beef consumed by military personnel in Europe between 1980-1996 was imported from the UK (FDA 2002).

Variable: y – Year of deployment (same variable used above in A-IV. C. 1. d. ii. a.)

Variable: y_{epi} – The specific year of BSE epidemic in the UK.

Assumption about variable: The BSE epidemic in the UK was assumed to have started in 1980 and at first was not detected. The first cases of BSE were reported in 1986.

Variable: BSE_{UKy} - Number of diagnosed BSE cases in the UK by year from 1980 through 1996

Data used in the model: Data are from the World organization for animal health (OIE 2005). Data were not collected for individual years prior to 1997. A total of 446 cases of BSE were reported by European countries (other than the UK) during the time period from 1980 through 1996 and were allocated to individual years by assuming the cases were increasing in a linear fashion by year.

Variable: R_{Basey} - Proportional vCJD risk for donors that resided on US military bases in Europe in a specific year

Assumptions used in the model:

- The vCJD risk for US military facilities in Europe was present from 1980 through 1996. There was negligible vCJD risk after 1996 – the model assumed the major source of vCJD risk for US military bases in Europe was associated with imported UK beef. When food chain controls were implemented in the UK in 1996 – the model assumed the risk to be negligible.
- It was assumed that the vCJD risk was additive and can be prorated on a yearly base.
- The vCJD risk in a specific year was assumed to be proportional to the reported BSE cases in the UK in that specific year.

Proportional vCJD risk in the US military bases in a specific year was calculated by the equation:

$$R_{Basey} = R_{Base} \times BSE_{UKy} / \sum_{y=1980}^{1996} BSE_{UKy} \qquad \text{(IV.C.1.d-7)}$$

Variable: $R_{DR\text{-}DOD_y}$ - Risk of individual military personnel who lived in Europe for a period of two years starting from deployment year y, and assumes the cumulative risk of a UK individual from 1980 through 1996 is 1.

Assumption used in the model: The model assumed an average of two consecutive years of deployment:

$$R_{DR-DOD_y} = R_{Base_y} + R_{Base(y+1)} \qquad \text{(IV.C.1.d-8)}$$

Variable: $Pr_{vCJD\text{-}UK(age)}$ - Probability of infection for individual UK resident of a specific age group (calculated in A-IV. C. 1.).

Variable: $Pr_{vCJD\text{-}DR\text{-}DOD(age)y}$ - Probability of infection for individual US plasma donor of a specific age group that lived on or near a US military bases in Europe starting from year y with duration of two years

Assumption used in the model: Probability of infection is proportional to the risk of exposure

$$\Pr_{vCJD-DR-DOD(age)y} = \Pr_{vCJD-UK(age)} \times R_{DR-DOD_y} \qquad \text{(IV.C.1.d-9)}$$

A-IV. C. 1. d. iv. Number of all US plasma donors potentially infected with vCJD during residence at a US military base in the UK or other countries in Europe from 1980 to 1996

The section estimates the number of Source and recovered plasma donors with a history of deployment in the UK or countries in Europe during the period from 1980 through 1996 and sums the number of vCJD cases that may have vCJD agent in their blood (or be prionemic) at the time of donation from each pathway to derive the total number of all donors potentially infected with vCJD that may have vCJD agent in their blood (or be prionemic).

A-IV. C. 1. d. iv. a. Potential number of US Source Plasma donors with a history of military deployment in the UK or other countries in Europe from 1980 to 1996 potentially infected with vCJD

Variable: $DR_{vCJD\text{-}S\text{-}DOD(age)y}$ - Potential number of Source Plasma donors infected during residency on US military facilities in the UK or Europe from 1980-1996 by age, and year of deployment

$$DR_{vCJD-S-DOD(age)y} = Binomial(DR_{S-DOD(age)y}, \Pr_{vCJD-DR-DOD(age)y}) \qquad \text{(IV.C.1.d-10)}$$

Variable: $DR_{vCJD\text{-}S\text{-}DOD}$ - Potential number total of Source Plasma donors infected during residency on US military bases in Europe from 1980-1996 is represented by the expression:

$$DR_{vCJD-S-DOD} = \sum_{y=1980}^{1996} \sum_{age=18-19}^{70-74} DR_{vCJD-S-DOD(age)y} \qquad \text{(IV.C.1.d-11)}$$

A-IV. C. 1. d. iv. b. Potential number of Source Plasma donors with a history of deployment to a US military facility in the UK or other countries of Europe from 1980 to 1996 in the last half incubation period of the disease

This section estimates the number of Source Plasma donors that may potentially be infected with vCJD who may have vCJD agent in their blood (or be prionemic) at the time of donation.

Variable: y-The calendar year in which a plasma donor was deployed to a US military base in Europe.

Assumption used in the model: This risk assessment assesses the vCJD risk for pdFVIII product made in 2002 but it is assumed that the potential vCJD risk is similar to the present day risk in 2006.

Variable: $T_{Inf\text{-}2002y}$-Time period between infection/travel and the year 2002 when the plasma was collected.

Variable: $Pr\text{-}LH_y$- Probability that the vCJD disease is in the last half of the incubation period of the disease, if infected in year y and the individual has infectious vCJD agent present in their blood and plasma (or was prionemic).

Variable: $T_{Inf\text{-}2002y}$ - Time period between infection/travel and 2002 when the plasma was collected is represented by the expression:

$$T_{Inf-2002y} = 2002 - y \qquad \text{(IV.C.1.d-12)}$$

For an individual to be prionemic in 2002, the remaining period of time since infection up to 2002 ($I_{Inf\text{-}2002y}$) should be equal to or less than the half of incubation period of the disease.

Assumption used in the model: The variability and uncertainty of the incubation period of vCJD is represented mathematically by a gamma distribution, specifically Gamma (4.7, 3.6). A gamma distribution is usually used to represent processes that occur sequentially or the time between events. In this case it would be the time from infection to the time until the appearance of clinical disease (incubation period of the disease). The distribution is defined by two parameters: one that produces the shape of the curve; and a second generates the scale for the distribution, which in this case is represented by the mean incubation period of 14 years.

Variable: $Pr_{LH\text{-}y}$ -The probability an individual was prionemic in year 2002-was calculated by using the cumulative frequency of Gamma (4.7, 3.6), at x=2×(1997-y)

Variable: $DR_{vCJD\text{-}S\text{-}DODy}$- Total number of Source Plasma donors potentially infected with vCJD in year y during military deployment on European bases (calculated in A-IV. C. 1. d. v. a.).

Variable: $DR_{vCJD\text{-}S\text{-}DOD\text{-}LHy}$ - Total number of Source Plasma donors potentially infected with vCJD in year y during military deployment to US military bases in European countries and in the last half incubation period of the disease.

$$DR_{vCJD-S-DOD-LHy} = Binomial(DR_{vCJD-S-DODy}, \Pr_{LH-y}) \quad \text{(IV.C.1.d-13)}$$

A-IV. C. 1. d. iv. c. Number of US recovered plasma donors with a history of deployment to a US military base in the UK or other countries in Europe during the period 1980-1996 and potentially infected with vCJD

Variable: $DR_{vCJD\text{-}R\text{-}DOD(age)y}$ - Potential number of recovered plasma donors infected during deployment and residency on or near US military bases in Europe from 1980-1996 by age, and year of deployment

$$DR_{vCJD-R-DOD(age)y} = Binomial(DR_{R-DOD(age)y}, \Pr_{vCJD-DR-DOD(age)y}) \quad \text{(IV.C.1.d-14)}$$

Variable: $DR_{vCJD\text{-}R\text{-}DOD}$ - Potential number of recovered plasma donors infected during residency on US military bases in Europe from 1980-1996 is represented by the equation:

$$DR_{vCJD-R-DOD} = \sum_{y=1980}^{1996} \sum_{age=18-19}^{70-74} DR_{vCJD-R-DOD(age)y} \quad \text{(IV.C.1.d-15)}$$

A-IV. C. 1. d. iv. d. Recovered plasma donors with a history of deployment to a US military base in the UK or other countries in Europe: Potential number of donors in the last half of vCJD incubation period and vCJD agent is present in the blood

This portion of the model calculates the potential number of vCJD infected recovered plasma donors who are in the last half incubation period of the disease and presumably may contain vCJD agent in their blood (or are prionemic).

Variable: $Pr_{LH\text{-}y}$ -The probability a vCJD-infected donor had vCJD agent present in their blood and plasma at the time of donation (was prionemic) in the year 2002 (calculated in A-IV.C.1.d.v.b).

Variable: $DR_{vCJD\text{-}R\text{-}DODy}$- Total number of recovered plasma donors potentially infected with vCJD in year y during military deployment on or near bases in Europe (calculated in A-IV. C. 1. d. v. c.)

Variable: $DR_{vCJD\text{-}R\text{-}DOD\text{-}LHy}$ - Total number of recovered plasma donors potentially infected with vCJD in year y during military deployment on or near bases in Europe and in the last half incubation period of the disease.

$$DR_{vCJD-R-DOD-LHy} = Binomial(DR_{vCJD-R-DODy}, \Pr_{LH-y}) \quad \text{(IV.C.1.d-16)}$$

A-IV. C. 1. d. iv. e. Number of all vCJD infected plasma donors during deployment to a US military base in a country in Europe from 1980-1996

Variable: $\mathbf{DR_{vCJD-DOD}}$ - Potential number of total plasma donors infected during residence on US military bases in Europe from 1980-1996

$$DR_{vCJD-DOD} = \sum_{y=1980}^{1996} DR_{vCJD-S-DOD} + \sum_{y=1980}^{1996} DR_{vCJD-R-DOD} \quad \text{(IV.C.1.d-17)}$$

Variable: $\mathbf{DR_{vCJD-DOD-Def}}$ - Potential number of total plasma donors infected during residence on US military bases in Europe from 1980-1996 and meet deferral criteria

Assumption used in the model: Current policy defers individuals who have been deployed or resided on a US military base in Europe from 1980 to 1996 for a cumulative stay of 6 months or more. We assumed all US Department of Defense (DOD) deployments are 6 months or longer, and therefore, all individuals have a history of deployment to a US military base in Europe are deferred.

$$DR_{vCJD-DOD-Def} = DR_{vCJD-DOD} \quad \text{(IV.C.1.d-18)}$$

A-IV. C. 1. d. iv. f. Potential number of all plasma donors in the last half of vCJD incubation period and have vCJD agent present in the blood

This portion of the model estimates the potential number of all vCJD infected plasma donors with a history of military service posted at a US military base in the UK or countries in Europe fron 1980-1996 who are in the last half incubation period of the disease and their blood and plasma presumably contain infectious vCJD agent (or are prionemic).

Variable: $\mathbf{DR_{vCJD-DOD-LH}}$ - Potential number of total plasma donors infected during residence on US military bases in Europe from 1980-1996 and are in the last half incubation period of the disease

$$DR_{vCJD-DOD-LH} = \sum_{y=1980}^{1996} DR_{vCJD-S-DOD-LH} + \sum_{y=1980}^{1996} DR_{vCJD-R-DOD-LH} \quad \text{(IV.C.1.d-19)}$$

Variable: $\mathbf{DR_{vCJD-DOD-Def}}$ - Potential number of total plasma donors infected during residence on US military bases in Europe from 1980-1996 and meet deferral criteria

$$DR_{vCJD-DOD-Def} = DR_{vCJD-DOD} \quad \text{(IV.C.1.d-20)}$$

Variable: DR_{Tot} - (calculated in section A-IV.B.3.) Annual number of plasma donors

Variable: DR_S - (calculated in section A-IV.B.1.) Annual number of Source Plasma donors

Variable: DR_R - (calculated in section A-IV.B.2.) Annual number of recovered plasma donors

Variable: $Perc_{DR\text{-}Eurob}$ - Percentage of blood donors who were Euroblood recipients

Assumption used in the model: 1.2% plasma donors were Euroblood recipients

Variable: DR_{Eurob} - Annual number of plasma donors who were Euroblood recipients

$$DR_{Eurob} = DR_{Tot} \times Perc_{DR-Eurob} \quad \text{(IV.C.1.e-1)}$$

Variable: $DR_{S\text{-}Eurob}$ - Annual number of Source Plasma donors who were Euroblood recipients

Assumption used in the model: We assumed 1.2% of US Source Plasma donors were Euroblood recipients

$$DR_{S-Eurob} = DR_S \times Perc_{DR-Eurob} \quad \text{(IV.C.1.e-2)}$$

Variable: $DR_{R\text{-}Eurob}$ - Annual number of recovered plasma donors who were Euroblood recipients – represented by the equation:

$$DR_{R-Eurob} = DR_R \times Perc_{DR-Eurob} \quad \text{(IV.C.1.e-3)}$$

A-IV. C. 1. e. Annual number of US plasma donors who have been Euroblood recipients

A-IV. C. 1. e. i. Annual number of US plasma donors who have been Euroblood recipients

A-IV. C. 1. e. ii. Annual number of potential vCJD-infected Euroblood donors and estimated annual units of Euroblood potentially containing vCJD agent

This section of the model estimates the quantity of Euroblood units predicted to have been transfused into US plasma donors in a one year period, the number of European donors involved, the number of possible vCJD infected European Euroblood donors, and the total quantity of vCJD infected units given by the Euroblood donors.

Variable: $DNBl_{UK(age)}$ - Blood donations in the UK by age of donors.

Data used in the model: Information about UK blood donors was provided by CDSC (2005).

Variable: $Perc_{DN\text{-}UK(age)}$ - Percentage distribution of the blood donations in the UK by donor age, and is represented by equation:

$$Perc_{DN-UK(age)} = DN_{BI-UK(age)} / \sum_{age=18}^{>65} DN_{BI-UK(age)} \quad \text{(IV.C.1.e-5)}$$

Variable: $EUBL_{(age)}$ - Units of Euroblood that were donated by a specific age group of European donors and transfused into US plasma donors

Total units of Euroblood received by US plasma donors of one year period is allocated by age of European donors based on the age distribution of UK blood donors

Assumption used in the model: We assumed the age distribution for Euroblood donors is the same as UK blood donors

$$EUBL_{(age)} = EUBL_{Tot} \times Perc_{DN-UK(age)} \quad \text{(IV.C.1.e-6)}$$

Variable: $DR_{EUBL(age)}$ – The number of European donors were grouped by age in five-year increments (e.g., 20-24 yrs, etc) and the 18-19 yr old group that have contributed Euroblood that may have been transfused into US plasma donors per one year period

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

Assumption used in the model: Each unit of Euroblood received by US plasma donors of one year-period came from different European donors and is expressed by the equation:

$$DR_{EUBL(age)} = EUBL_{(age)} \quad \text{(IV.C.1.e-7)}$$

The probability of infection of individual European blood donors is calculated below based on the probability of infection per individual UK resident and the relative risk of a resident in a country elsewhere in Europe (other than France) compared to the risk of a UK resident.

Variable: R_{EU} – The cumulative risk of an individual European resident from 1980 till the present; assumes that the cumulative risk of a UK individual from 1980 through 1996 is 1 (same variable as used in (A-IV.C.1.c.iii)

Variable: $Pr_{vCJD\text{-}UK(age)}$ - Probability of infection for individual UK resident of a specific age group (same variable as used in (A-IV.C.1. c. iv.).

Variable: $Pr_{vCJD\text{-}EU(age)}$-Probability of infection for an individual European resident of a specific age group.

Assumption used in the model: Probability of infection is proportional to the risk of exposure:

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

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.

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

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.

<u>Assumption about variable</u>: One infected European donor produces one unit of infected Euroblood.

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

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

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

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

<u>Assumption used in the model</u>: 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.

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

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 <u>Source Plasma</u> donors being infected due to transfusion with a Euroblood unit:

$$DR_{vCJD-S-EUBL} = Binomial(DR_{S-EUBL}, \mathrm{Pr}_{vCJD-EUBL-recip}) \qquad \text{(IV.C.1.e-12)}$$

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

$$DR_{vCJD-R-EUBL} = Binomial(DR_{R-EUBL}, \mathrm{Pr}_{vCJD-EUBL-recip}) \qquad \text{(IV.C.1.e-13)}$$

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

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

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:

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

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

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 wh 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 <u>all</u> 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 <u>not removed</u> 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 [redacted] and most likely to be [redacted] based on data from pdFVIII manufacturers.

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. 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.

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. 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) – 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 [redacted] of pdFVIII products were made from Source Plasma, and [redacted] 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 [redacted] for Source and [redacted] 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

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

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

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

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

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

Variable: $Perc_s$ – Represents the percentage of pdFVIII assumed in the model to be made from 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 [redacted] of the total pdFVIII supply distributed annually in the US is manufactured from Source Plasma and [redacted] from recovered plasma pools. Information on pool size (number of donors), average number of donations per donor, size of individual recovered plasma donations (200 mls) and Source Plasma donations (700 mls) were used to first determine the amount of plasma present in a pool. Then, data on the average yield of pdFVIII per liter of plasma (187 IU), was used to calculate the total number of Source and recovered plasma pools and the results were summed to determine the total number of plasma pools used to manufacture pdFVIII in the US each year. The total number (or percentage) of plasma pools potentially containing vCJD agent was determined in the model based on pool size and the probability that a pool contained a vCJD agent.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Variable: ***Pr(vCJD-pool$_s$)***- Probability of a Source Plasma pool containing vCJD agent

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

The FDA model employed three stratifications of clearance:

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

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

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

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

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

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

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

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

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

Data used in the model: Information for Source Plasma pool size was collected by the FDA from pdFVIII manufacturers. The size of Source Plasma pools ranged from 6,000 donors per pool to 60,000

donors per pool with mean of [redacted] donations per pool. The distribution was generated based on the pool size data provided by pdFVIII manufacturers and the market share of the products based on information supplied annually to the FDA by manufacturers. Manufacturers supplied FDA with information on the average number of donations from individuals in the pool.

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

Variable: $DN_{DR\text{-}Avg}$-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 [redacted] donations per donor, with a most likely of [redacted] donations per donor. For recovered plasma, it was assumed that the most likely number of donations per donor was only 1.

Variable: DN_V-Volume of one unit of plasma, depending on plasma type (for Source Plasma, same as $DN_{V\text{-}S}$ 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)

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

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

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

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

- Prophylaxis – No inhibitor

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

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

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

		Original Data			Input distribution (Generalized Beta distribution)				
Treatment Regimen	Inhibitor Status	n	Mean	95% CI	α	β	(min, max)	Mean	95% CI
Prophylaxis	No Inhibitor	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)

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

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

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

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

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

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

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

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

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

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

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

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

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

APPENDIX

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

1. September 18, 2006 TSEAC transcripts (Topic I, pages 69-177): http://www.fda.gov/ohrms/dockets/ac/06/transcripts/2006-4240t1.pdf, accessed 11/02/06.

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.

7. Brown, KE. Detection and quantitation of parvovirus B19. Journal of Clinical Virology 31: 1-4, 2004.

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 (5th - 95th)[b]	Mean potential vCJD risk per person per year[a] (5th - 95th perc)[b]	Mean potential vCJD risk per person per year[a] (5th - 95th perc)[b]	Mean potential vCJD risk per person per year[a] (5th - 95th perc)[b]	Mean potential vCJD risk per person per year[a] (5th - 95th perc)[b]	Mean potential vCJD risk per person per year[a] (5th - 95th perc)[b]	Mean potential vCJD risk per person per year[a] (5th - 95th 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 5th- 95th 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 5th and 95th 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.

BENE2006-025

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.

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

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**

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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.	

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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.

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 7 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	人ハプトグロビン		研究報告の公表状況	Plos Pathogens 2006; 2(10):956-963	公表国 フランス	
販売名（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	使用上の注意記載状況・その他参考事項等
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、同じマウス一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。	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。 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。

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Isolation from Cattle of a Prion Strain Distinct from That Causing Bovine Spongiform Encephalopathy

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To date, bovine spongiform encephalopathy (BSE) and its human counterpart, variant Creutzfeldt-Jakob disease, have been associated with a single prion strain. This strain is characterised by a unique and remarkably stable biochemical profile of abnormal protease-resistant prion protein (PrP^{res}) isolated from brains of affected animals or humans. However, alternate PrP^{res} signatures in cattle have recently been discovered through large-scale screening. To test whether these also represent separate prion strains, we inoculated French cattle isolates characterised by a PrP^{res} of higher apparent molecular mass—called H-type—into transgenic mice expressing bovine or ovine PrP. All mice developed neurological symptoms and succumbed to these isolates, showing that these represent a novel strain of infectious prions. Importantly, this agent exhibited strain-specific features clearly distinct from that of BSE agent inoculated to the same mice, which were retained on further passage. Moreover, it also differed from all sheep scrapie isolates passaged so far in ovine PrP-expressing mice. Our findings therefore raise the possibility that either various prion strains may exist in cattle, or that the BSE agent has undergone divergent evolution in some animals.

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Introduction

While transmissible spongiform encephalopathies (TSEs) in small ruminants and humans are believed to involve distinct prion strains [1,2], a single prion strain has been associated so far with bovine spongiform encephalopathy (BSE) and its human counterpart, variant Creutzfeldt-Jakob disease (vCJD) [3–6]. In particular, the abnormal, protease-resistant form of prion protein (PrP^{res}) that accumulates in the brains of infected individuals [7] shows a consistently unique electrophoretic profile in immunoblots [8]. However, the biochemical testing of the brains of slaughtered and fallen cattle, which was intensified since 2000 in European countries as a means to protect the consumers, has led to the discovery of positive samples that showed distinct PrP^{res} profiles. These atypical profiles have been sorted into two groups so far, provisionally termed H-type when the size of the protease resistant fragments is higher than for BSE, and bovine amyloidotic spongiform encephalopathy, or L-type, when it is lower [9,10]. These observations raise the possibility that as yet unrecognised prion strains may exist in cattle as in other species [11], and have potential implications in terms of public health. Unlike bovine amyloidotic spongiform encephalopathy isolates, which derive from animals with defined histopathological abnormalities [10], precise information corroborating a prion disease is lacking for H-type cases. It was therefore crucial to determine through experimental transmission whether such cases reflect some alteration in PrP metabolism, possibly in aging animals, or involve a truly infectious agent.

In this study, we report the transmission of a TSE-like disease by inoculation of French cattle isolates identified as H-type variants to two lines of PrP transgenic mice. Furthermore, we provide compelling evidence that this agent has unique features compared to epizootic BSE and other related agents. We also establish that there is no link with ovine TSE isolates transmitted so far to these models.

Results

H-Type Isolates Are Transmissible to Mice

Two transgenic mouse lines were used as recipient for transmission experiments. The tg540 line is a newly established line that expresses bovine PrP (Protocol S1), resulting in an enhanced susceptibility to BSE agent compared to conventional mice [6,12]. The tg338 line, expressing the VRQ ($Val^{136}Arg^{154}Gln^{171}$) allele of ovine PrP, has allowed an efficient transmission of natural scrapie isolates from sheep and goat [13,14]. The rationale for including tg338 mice in this study was the possibility that characterisation of a prion

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Abbreviations: BSE, bovine spongiform encephalopathy; PrP^{res}, protease-resistant prion protein; TgBov, bovine tg540; TgOv, ovine tg338; TSE, transmissible spongiform encephalopathies; vCJD, variant Creutzfeldt-Jakob disease

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Synopsis

Prions are unconventional agents of proteic nature that are formed of abnormal conformations of the host-encoded prion protein (PrP). They cause fatal neurodegenerative diseases in both animals and humans, and can be transmitted between species as exemplified in humans by the emergence of variant Creutzfeldt-Jakob disease following the epidemic of bovine spongiform encephalopathy (BSE) in the United Kingdom. Since diagnosis of prion infection is only possible once the central nervous system has been invaded, brains of slaughtered or fallen cattle are routinely screened in Europe to protect the consumers from BSE. This has unexpectedly led to the discovery of unprecedented PrP conformations that were distinct from the single one associated so far with BSE or BSE-related diseases. To precisely determine their etiology, the authors have studied the transmissibility of these new conformations, termed H-type, to transgenic mice expressing either bovine or ovine PrP. They show that these cases are highly pathogenic for these mice. The authors also demonstrate that they are not directly related to the agent involved in the BSE epidemic, supporting the view for isolation of a new prion strain from cattle, whose prevalence and associated zoonotic risk should be carefully monitored in the future.

accidentally passed from small ruminants to cattle might be facilitated on such mice, by comparison with the ovine isolates transmitted so far. Tg540 (tgBov) and tg338 (tgOv) mice overexpress PrP in the brain at similar levels (~8- to 10-fold). Both lines have a normal lifespan, the same as $PrP^{0/0}$ mice on which the transgenes were introduced. H-type isolates representative of a series of seven samples identified in France were inoculated intracerebrally to tgBov and tgOv mice (Table 1). Typical BSE agents from cattle and from other species was inoculated to the same mice for the sake of comparison. Remarkably, all H-type isolates induced a neurological disease on primary transmission, with a 100% attack rate in both mouse lines. The mean survival times observed with cases no. 1 and no. 2 in tgBov mice, ~400 d, appeared to be prolonged compared to those for cattle, sheep, goat BSE, and human vCJD inocula, which ranged from ~250 to 380 d. Such a discrepancy could reflect a lesser infectivity of H-type samples, consistent with their comparatively lower PrP^{res} content [9]. Moreover, the survival time was reduced by ~100 d on subpassage, approaching that for BSE from cattle or other sources on secondary passage, or on primary passage for inocula of presumably higher titre (i.e., producing no substantial reduction of survival time on subpassage: BSE no. 3 and ARQ [$Ala^{136}Arg^{154}Gln^{171}$] no. 1). Upon transmission to tgOv mice, the mean incubation period produced by the four H-type cases was strikingly homogeneous (586–612 d), consistent with a potentially unique agent (Table 1). This was comparable to or even shorter than the incubation periods of epizootic BSE or related inocula on the same mice (560–792 d). As illustrated in Figure 1, the relative incubation periods observed on tgOv and tgBov mice appeared to differ significantly among the H-type and BSE-type agents. In addition, the reduction in incubation period observed upon secondary transmission of H-type (case no. 2) on tgOv mice was significantly less dramatic than that observed for vCJD and sheep BSE inocula (Table 1). Overall, these suggested that H-type and BSE might be different TSE agents.

H-Type PrP^{res} Profile Is Preserved in Transgenic Mice

The brains of diseased mice were analysed by immunoblotting for the accumulation of abnormal PrP. PrP^{res} was readily detected in all mice tested since the first passage, consistent with the efficient transmission observed in both lines (10/10 and 33/33 positive brains for tgBov and tgOv mice, respectively). The PrP^{res} molecular profile was fairly uniform

Table 1. Transmission of Bovine Molecular Variant Cases (H-Type) to Transgenic Mice Expressing Bovine or Ovine PrP

Isolate	Case Number	Passage	Mean survival time, d ± SEM (n/n_0)[a]	
			tgBov Mice	tgOv Mice
H-type	1	First	414 ± 10 (5/5)	612 ± 26 (10/10)
		Second	317 ± 6 (8/8)	ND
	2	First	401 ± 9 (5/5)	595 ± 18 (8/8)
		Second	296 ± 3 (9/9)	319 ± 10 (6/6)
	3	First	ND	607 ± 12 (6/6)
	5	First	ND	586 ± 15 (9/9)
BSE	1	First	377 ± 22 (6/6)	ND
	3	First	298 ± 7 (9/9)	704 ± 36 (7/7)
		Second	283 ± 10 (5/5)	NA
Sheep BSE[b]	ARQ 1	First	278 ± 2 (6/6)	560 ± 60 (5/5)
		Second	263 ± 6 (6/6)	178 ± 2 (4/4)
	ARQ 3	First	339 ± 25 (5/5)	ND
	ARR 1	First	340 ± 8 (7/7)	ND
Goat BSE[c]	CH636	First	253 ± 9 (6/6)	590 ± 43 (4/4)
		Second	291 ± 27 (5/5)	NA
Variant CJD	NHBY0/0003	First	343 ± 8 (5/5)	792 ± 22 (6/6)
		Second	293 ± 11 (6/6)	195 ± 9 (6/6)
Control	Sheep brain	First	793 ± 26 (0/9)	835 ± 15 (0/6)

NA, not available; ND, not done.
[a]Intracerebral inoculation with 2 mg brain tissue equivalent; n/n_0: diseased/inoculated.
[b]Experimental cases.
[c]Field case.
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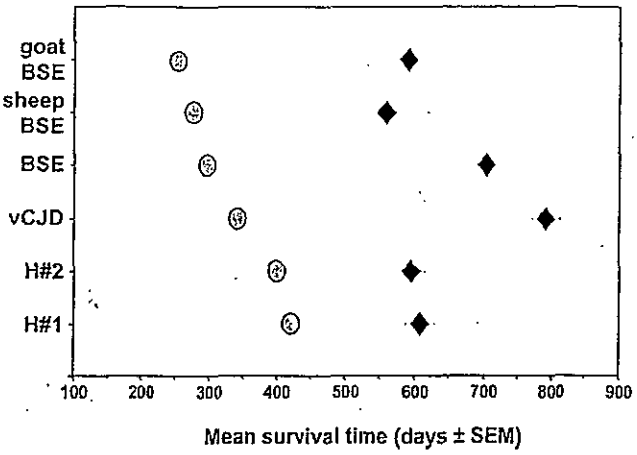

Figure 1. Survival Time in Transgenic Mice Infected with H-Type and BSE-Type Agents

Mean survival times (days ± SEM) upon primary transmission are shown for tgBov (grey circles) and tgOv (black diamonds) mice inoculated with H-type cases, BSE, and related isolates (see Table 1). The intervals between the incubation times on each line are significantly different for H-type and BSE agents ($p < 0.0002$, Fisher test).

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among the isolates. Remarkably, like the BSE agent for which the typical signature was conserved whatever the donor species (≥ 3 brains analysed per combination), the H-type agent essentially retained its biochemical phenotype upon serial transmission to tgBov as well as to tgOv mice expressing a heterologous PrP^C (Figure 2 and below). Compared to BSE PrP^{res}, it was characterised by a significantly higher apparent molecular mass (difference measured for unglycosylated species: 0.9 ± 0.05 kDa and 0.7 ± 0.06 kDa in tgBov and tgOv mice, respectively) and the relative proportions of glycoforms were essentially similar. A further difference was the lack of detectable PrP^{res} in the spleen of H-type diseased tgOv mice (three to five spleens tested per isolate), while this accumulated at substantial levels after BSE or vCJD infection (Figure 2B).

H-Type and Epizootic BSE Agents Exhibit Distinct Neuropathological Features

We next examined the PrP^{res} targeting and the vacuolation in the brain, which are known to exhibit a strain-dependent variation [6,15,16]. This was performed on tgBov mice since they express a PrP^C homologous to that of the donors, including the number of octarepeats [17], thus providing a relevant context for comparing H-type and epizootic BSE isolates. H-type isolates showed a similar distribution of PrP^{res} deposits on both primary and

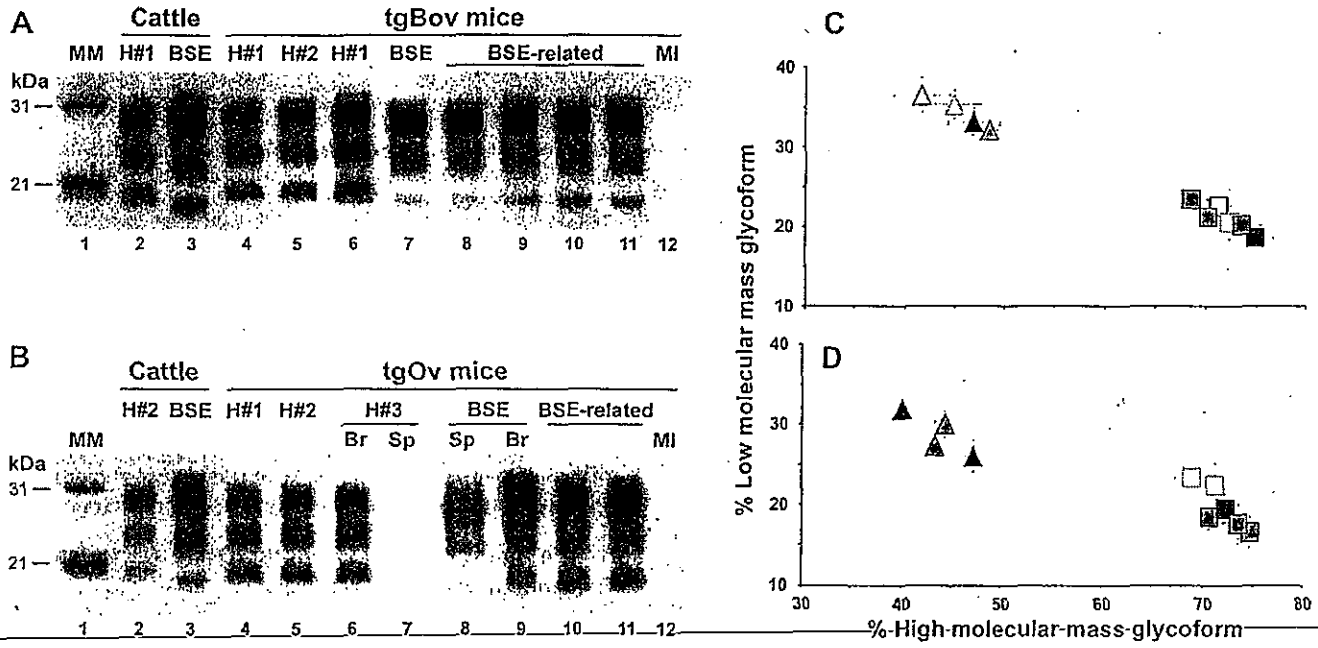

Figure 2. Western Blot Analysis of PrP^{res} in the Brains of Transgenic Mice Infected with H-Type or BSE-Type Agents

(A) Primary or secondary (lane 6) transmission to tgBov mice. BSE-type inocula include cattle BSE no. 3 (lanes 3 and 7), sheep BSE ARQ no. 1 and ARR no. 1 (lanes 8 and 9), goat BSE (lane 10), and vCJD (lane 11). The PrP^{res} profiles of both H-type and BSE agents in cattle (lanes 2 and 3) are essentially similar to those in tgBov mice (lanes 4–11). Brain tissue equivalent loaded: 2.5 mg in lane 2; 0.15 mg in lane 3; 0.5 mg in lanes 4–12. MI, mock-infected brain; MM, molecular markers.

(B) Primary transmission to tgOv mice. H-type agent shows a distinct PrP^{res} pattern in the brain (Br) compared to BSE agents (lane 9, BSE no. 3; lane 10, goat BSE; lane 11, vCJD). Note the lack of PrP^{res} signal in the spleen (Sp) of H-type–infected mice (lane 7), unlike that in BSE-infected mice (lane 8). Brain or spleen tissue equivalent loaded: 3 mg in lane 2; 0.15 mg in lane 3; 0.5 mg in lanes 4–6; 2 mg in lanes 7–12.

(C and D) Ratio of high- and low-molecular-mass PrP^{res} glycoforms in the brains of tgBov (C) and tgOv (D) mice following challenge with H-type or BSE agents (data plotted as means ± SEM). H-type isolates are represented as triangles (no. 1, blue; no. 2, orange; no. 3, pink; and no. 5, black) and BSE agents as squares (BSE no. 3, red; sheep BSE ARQ no. 1, grey; sheep BSE ARR no. 1, yellow; goat BSE, brown; and vCJD, light blue). Secondary transmissions are represented by unfilled symbols of the same colour. Note the strikingly distinct glycoform ratio between H-type and BSE groups in both mouse lines, as reported in cattle [9].

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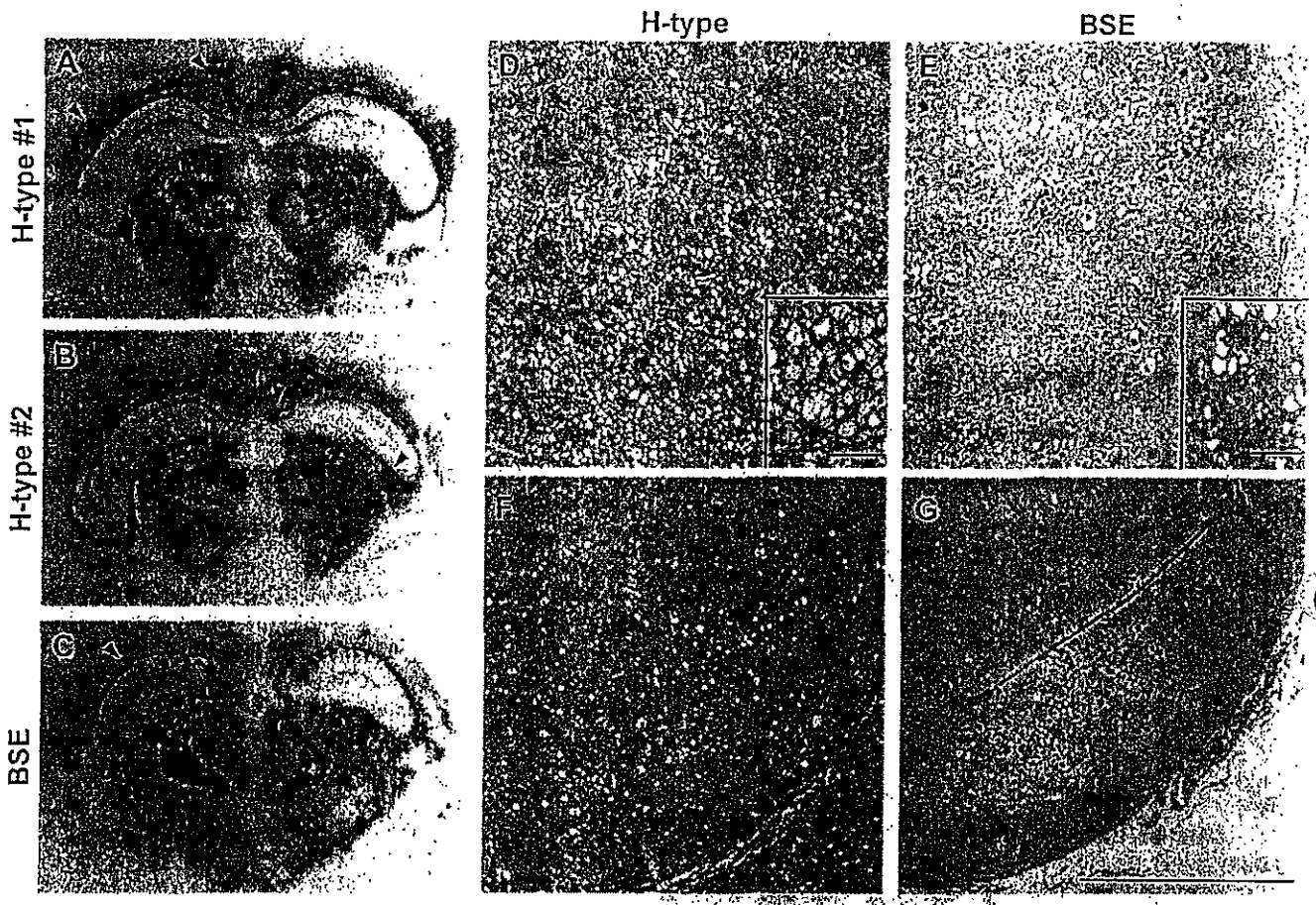

Figure 3. Regional Distribution of PrP^{res} and Vacuolar Changes in the Brains of Bovine Transgenic Mice Infected with H-Type or BSE Agents

Histoblots of representative coronal sections of tgBov mouse brains at the levels of the hippocampus are shown. The distribution of PrP^{res} deposits was similar among H-type isolates (A) (B), and different from that of cattle BSE (C) in several areas indicated by arrowheads, such as the cortex, the corpus callosum and dorsal commissure, alveus, fimbria, and stratum oriens of the hippocampus. Note that intensity of PrP deposition markedly differed between H-type and BSE agents. Illustration of how this appears by immunohistochemistry in the striatum (D) (E) and substantia nigra (F) (G), H-type–infected mice being less intensively labelled than those infected with BSE agent. By contrast, spongiosis was much more severe in H-type–infected brains. Bars: 30 μm; insert: 7 μm.

DOI: 10.1371/journal.ppat.0020112.g003

secondary transmission, as assessed by histoblotting on brain coronal sections (Figure 3A–3B). The staining did not differ from that seen with cattle BSE in several regions, such as the striatum and several nuclei of the thalamus, including the geniculate, ventral postero-lateral and -medial as well as the brain stem (Figure 3A–3C and data not shown). However, other areas such as the cerebral cortex, the corpus callosum including the cingulum, the dorsal commissure, the alveus, and fimbria of the hippocampus were predominantly stained with H-type, whereas BSE PrP^{res} was rather confined in the stratum oriens of the hippocampus (Figure 3A–3C). Moreover, the overall intensity and aspect of PrP deposition markedly differed between the two types of agents. While immunochemistry revealed various types of PrP deposits in both cases, thin diffuse PrP deposits were predominant in H-type–infected brains, whereas the most frequent type was granular in BSE-infected mouse brains. In several areas, including the striatum and the substantia nigra (Figure 3D–3G), there was a striking lack of correlation between the intensity of PrP deposition and the severity of the vacuolation. Overall, the vacuolation was much more intense in the case of H-type variant (Figures 3 and 4): areas such as the septum, hypothalamus, hippocampus, and cortex showed severe spongiosis, accompanied by a pronounced reactive glial astrocytosis based on GFAP staining (not shown), while BSE-induced vacuolation was moderate in the same areas.

H-Type Agent Is Distinct from the Ovine TSE Isolates Transmitted so Far to tgOv Mice

We finally examined whether H-type isolates may have an ovine TSE origin. The majority of typical and atypical sheep scrapie isolates we have studied so far transmits before a year to tgOv mice ([13,14] and our unpublished data). Only a group of sheep scrapie isolates from Italy (SSit) was found to infect tgOv mice after a prolonged survival time within the range of H-type cases. Indeed three of them, SSit cases no. 5, no. 7, and no. 8, induced a typical neurodegenerative disease with a mean survival time of 698 ± 20 d (5/5 animals affected), 659 ± 31 d (7/7), and 569 ± 37 d (4/4), respectively. Case no. 5 incubation time was still longer than H-type case no. 2 on subpassage (417 ± 20 d, 6/6 animals affected). The PrP^{res} molecular profile observed in the brain of SSit-diseased mice

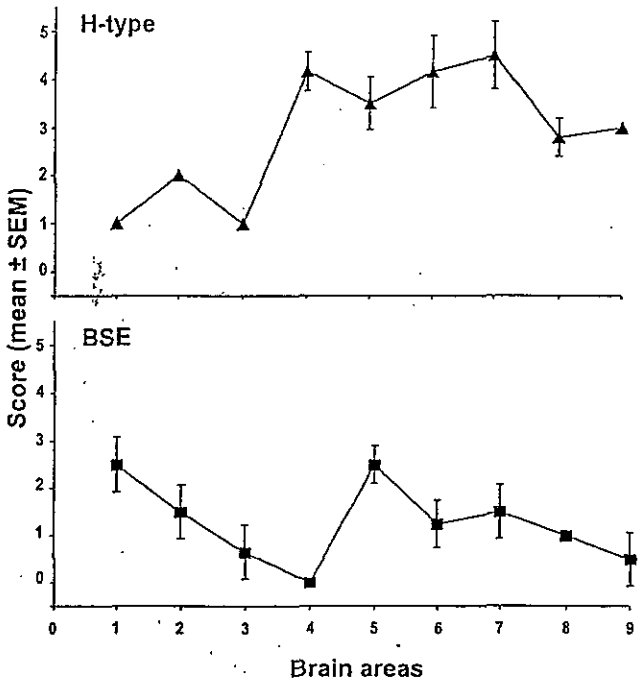

Figure 4. Lesion Profiles in tgBov Mice Infected with H-Type or BSE Agents

Mean scores (± SEM) reflecting the intensity of vacuolation are shown for H-type (no. 1 and no. 3, triangles) and BSE (no. 1 and no. 3, squares). The nine grey-matter areas used to construct the profile are as follows: dorsal medulla (1); cerebellar cortex (2); superior colliculus (3); hypothalamus (4); medial thalamus (5); hippocampus (6); septum (7); medial cerebral cortex at the level of the thalamus (8); and medial cerebral cortex at the level of the septum (9).

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(more than four brains analysed per isolate) was characterised by a significantly higher apparent molecular mass (difference of 0.7 ± 0.2 kDa) and a slightly higher proportion of diglycosylated PrP^{res} as compared with H-type-derived PrP^{res} (Figure 5A–5C). These features were conserved on secondary transmission (Figure 5A–5C). Another difference was again the pronounced accumulation of SSit-associated PrP^{res} in the spleen, while this was still impaired in H-type-infected mice, even after two passages (three to five spleens tested per combination; Figures 2B and 5A).

We then compared by histoblot distribution and nature of PrP^{res} deposits within the brains of tgOv mice infected with a second passage of H-type (no. 2) and SSit (no. 5) cases. Both markedly differed between the two agents as illustrated in Figure 5. Indeed, large plaques of SSit-associated PrP^{res} were present in the pretectal nuclei and in related structures of the limbic system such the fornix, the alveus, fimbria, and subiculum of the hippocampus. H-type-associated PrP^{res} was detected instead in the corpus callosum, cortex, and ventromedial thalamic nuclei (Figure 5D and unpublished data). The deposits seem rather thin or granular. SSit case no. 8, which gave the shortest incubation period in tgOv mice, was also inoculated by intracerebral route to tgBov mice. Of note, no disease has been observed yet in mice monitored up to 600 d after infection. In conclusion, these data suggest that the H-type agent is unrelated to the ovine TSE isolates transmitted so far to our transgenic lines.

Discussion

In this study we show that cattle brain samples positive for abnormal PrP with a distinct molecular pattern, called H-type, consistently produces a fatal, TSE-like disease upon inoculation to both bovine and ovine PrP transgenic mice. These results, corroborating the recent transmission to wild-type mice [18], formally establish that such cases involve an authentic TSE infectious agent. Importantly, we provide detailed evidence that this newly recognised agent differs from epizootic BSE agent derived from cattle or other species.

Both molecular and biological criteria support the conclusion that H-type and BSE agents are distinct prion strains. First, the incubation periods upon transmission to mice expressing either bovine or ovine PrP produced different patterns. Thus, while primary transmission to tgOv mice led to longer survival times for both agents, the increase relative to tgBov mice was significantly less for H-type than for BSE-type agents (Figure 1). Second, the molecular profiles of the PrP^{res} fragments detected in the brain of diseased mice were clearly distinguishable in either line. Strikingly, differences observed in terms of fragment size and glycoform ratio were essentially the same as in cattle brain. Third, unlike that for BSE agents, no PrP^{res} signal could be seen in the spleen of H-type-infected tgOv mice, indicative of a stronger neurotropism at least in this host. Fourth, histopathological examination of tgBov mice revealed a contrasting picture. Typically, severe spongiosis and diffuse PrP deposition were present in several areas of H-type-infected brains, while the same areas of BSE-infected brains showed limited spongiosis together with marked PrP deposition. Such discrepancies are unlikely to result from unequal survival times since they were also observed on secondary passage, where the two agents had comparable incubation duration (unpublished data).

The isolation from cattle of a prion strain distinct from the one implicated in the BSE epidemics raises several concerns. One is whether H-type isolates might result from an exposure to prions of small ruminants via alimentary or environmental sources, since cattle have been shown to be susceptible to experimental infection by sheep scrapie agent [19]. In this regards, the better compatibility between ovine PrP sequence and H-type as compared to BSE was intriguing (Figure 1). However, our investigations do not support this. Among the five groups of natural isolates we have identified so far in tgOv mice ([13,14] and our unpublished data), only one group, made up mostly of SSit isolates, proposed to be of iatrogenic origin [20], showed an incubation time as prolonged as for H-type cases. However, the PrP^{res} molecular profile, nature of deposits, and distribution within the brain as well as the differential accumulation in the spleen strongly distinguish H-type and SSit isolates. In addition, the latter failed so far to transmit to tgBov mice.

H-type and BSE agents might be related despite their distinguishable phenotypes. The isolation of an additional strain upon exposure of transgenic or wild-type mice to the epizootic BSE agent has been reported [21], thus questioning its strain homogeneity. Also, molecular typing studies have revealed the presence of a minor, non-BSE-type PrP^{res} component in BSE- and vCJD-infected brains [22]. Hence, H-type isolates could arise from the preferential amplification in certain individuals of a subcomponent present in BSE

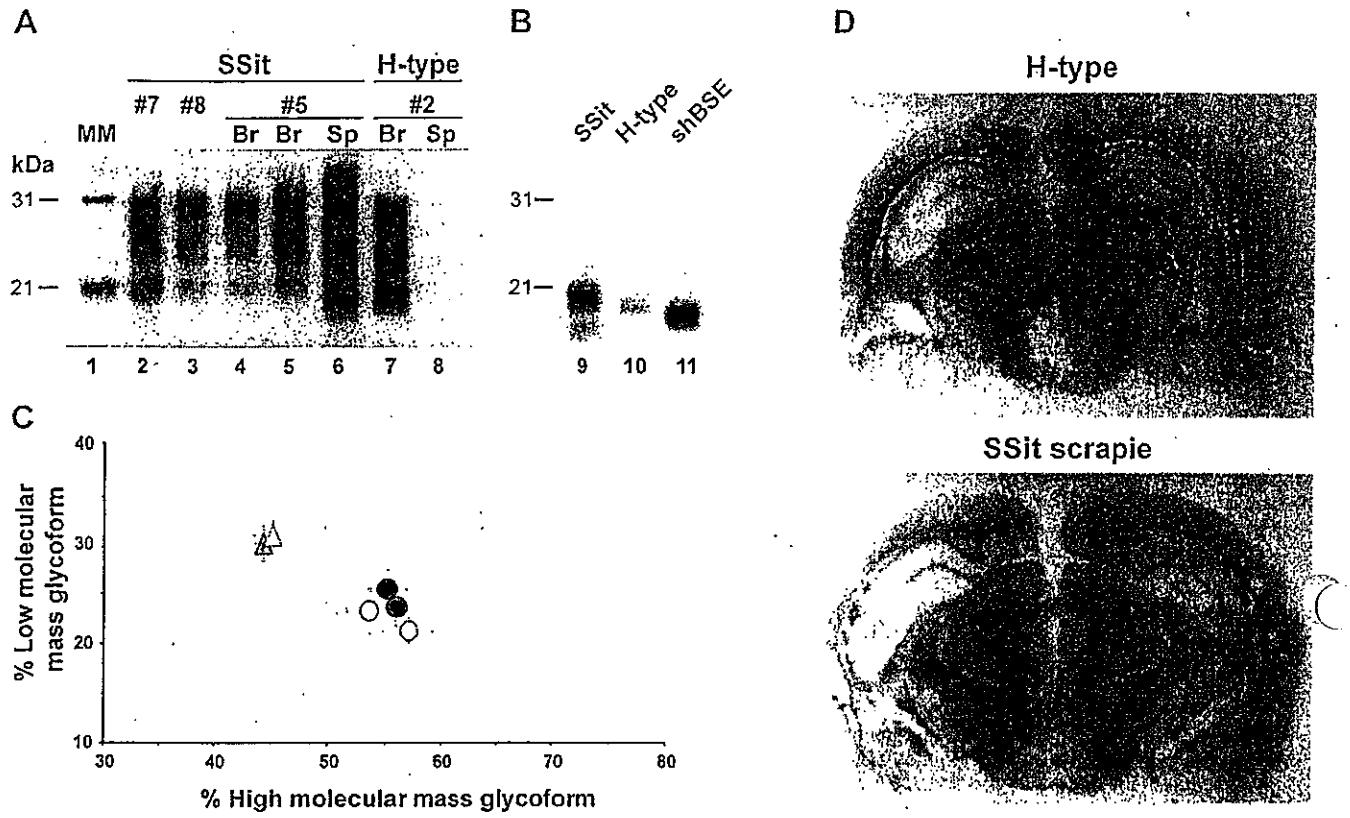

Figure 5. Comparison of H-Type and SSit Isolate Features upon Transmission to tgOv Mice

(A and B) Western blot analysis of PrP^{res} in the brains and spleens of tgOv mice infected with H-type or SSit isolates at first (lanes 2–4) and second passage (lanes 5–11). H-type PrP^{res} shows a distinct pattern in the brain (Br) compared to SSit. The apparent molecular mass of SSit PrP^{res} is higher than that of H-type or sheep BSE (shBSE), as shown after PNGase treatment (B). Note also that PrP^{res} is detected in the spleen (Sp) of SSit- but not of H-type-infected mice. Tissue equivalent loaded: 1.5 mg in lanes 2–4; 0.04 mg in lane 5; 0.5 mg in lanes 6–7; 2 mg in lane 8; 0.01 mg in lane 9; 0.1 mg in lanes 10–11. MM, molecular markers.

(C) Ratio of high- and low-molecular-mass PrP^{res} glycoforms in the brain of tgOv mice infected with H-type or SSit isolates (data plotted as mean ± SEM). One H-type isolate (no. 2) is represented as orange triangle. SSit isolates are represented as circles (SSit no. 5, red; no. 7, brown; no. 8, yellow). Secondary transmissions are represented by unfilled symbols of the same colour. Note the stably distinct glycoform ratios between H-type and SSit agents upon serial passage.

(D) Regional distribution of PrP^{res} in the brain of tgOv mice infected with H-type or SSit isolates. Histoblots of representative coronal sections of tgOv mouse brains at the levels of the hippocampus are shown. The distribution of H-type-associated PrP^{res} deposits was different from that of SSit in regions such as the alveus of the hippocampus, the corpus callosum, the pretectal nuclei, the cortex, and the ventromedial thalamus. Note that the size of PrP^{res} deposits markedly differed between the two types of isolates.

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infectious sources. Comparing H-type and BSE-derived variant prions identified in mice might be informative in that respect.

Alternatively, such unusual cases could reflect the existence of a natural, sporadic disease in cattle. Although it is unclear yet if such infections may lead to a clinical disease in the natural host, they seem to occur at a low frequency, which is reminiscent of the situation known for sporadic CJD in humans [23,24]. Of note, the disparities between intensity of PrP deposition and severity of vacuolation in the brains of H-type–inoculated tgBov mice have also been observed with sporadic CJD both in human or mouse infected brains [21,25]. These data, however, need to be consolidated through further investigations, including epidemiological analysis. Indeed, an implication of this latter scenario is that such bovine "atypical" cases could occur in countries free of BSE exposure. The acquisition of novel properties by an endogenous, sporadic cattle TSE agent, as occasioned on passage through an intermediary host or a physicochemical treatment such as that applied to carcass-derived products, has been invoked as one possible origin for the emergence of BSE epidemics [7]. With the isolation of such agents, we can now address this issue experimentally.

In conclusion, our findings support the view that at least two and potentially three [10] distinct prion strains may be present in cattle. The current uncertainties regarding the origin, prevalence, and potential risk for humans of a strain of TSE agent unrecognised until recently should support continued efforts to characterise it in vivo and uphold the surveillance exerted on cattle.

Materials and Methods

Isolates. The H-type [9], goat BSE (CH636 case [26]), and experimental sheep BSE samples [27] were provided by the French TSE Reference Laboratory (Agence Française de Sécurité Sanitaire des Aliments [AFSSA], Lyon, France). The samples from French BSE cases and from experimental sheep BSE (ARR [$Ala^{136}Arg^{154}Arg^{171}$] genotype [28]) were provided by the Institut National de la Recherche Agronomique (INRA; Toulouse, France) and the Institute for Animal

Health (IAH) Neuropathogenesis Unit (Edinburgh, United Kingdom), respectively. The vCJD isolate was a World Health Organization (WHO) reference sample from the National Institute for Biological Standards and Control (NIBSC; Potters Bar, United Kingdom). SSit isolates were provided by the Instituto Superiore di Sanita (ISS; Rome, Italy).

Transgenic mice and transmission assays. The tg540 line expresses the bovine PrP allele with 6 octarepeats under the control of the cytomegalovirus (CMV) promoter on a FVB mouse line with $PrP^{0/0}$ background (Protocol S1). The tg338 line expresses the $V_{136}R_{154}Q_{171}$ allele of ovine PrP at a homozygous state, on a mouse $PrP^{0/0}$ background [29]. The transgene construct (tg3) consists in a bacterial artificial chromosome (BAC) insert of 125 kb of sheep DNA [13]. All experiments were performed according to national guidelines. Each inoculum was prepared extemporaneously in a class II microbiological cabinet using disposable equipment. Individually identified 6- to 10-wk-old mice were inoculated intracerebrally with 20 µl of a 10% (wt/vol) brain homogenate in 5% glucose. Mice were monitored daily once ill and killed in extremis.

Analysis of PrP^{res} molecular pattern. All procedures regarding purification and detection of PrP^{res} from brains and spleens of infected mice were as described [14]. ICSM18 [30] or Sha31 [31] anti-PrP antibodies were used. Enzymatic deglycosylation was performed on denatured PrP^{res} with 1,000 U of recombinant PNGase (New England Biolabs, Beverly, Massachusetts, United States) for 2 h at 37 °C in 1% Nonidet P40 and the proprietary buffer as described [30]. Determination of glycoform ratio and apparent molecular mass was performed with the GeneTools software after acquisition of chemiluminescent signals with a GeneGnome digital imager (Syngene, Frederick, Maryland, United States).

Histopathology. For histoblot analysis [32], brains were rapidly removed from killed mice and frozen on dry ice. Thick 10-µm cryostat sections were cut, transferred onto Superfrost slides, and kept at −20 °C until use. The procedure was performed as described [14] using the 12F10 anti-PrP antibody [33]. All immunohistochemistry procedures regarding tissue processing have been described previously [34]. Samples were fixed in neutral-buffered 10% formalin (4% formaldehyde) before paraffin embedding. After deparaffinisation, 6-µm-thick tissue sections were stained with haematoxylin/eosin. Vacuolation profiles were established, following the standard method described by Fraser and Dickinson [15], by using two to three brains per isolate.

Supporting Information

Protocol S1. Description of the Bovine PrP Transgenic Mice (tg540 Line)

Found at DOI: 10.1371/journal.ppat.0020112.sd001 (92 KB DOC).

Accession Numbers

The GenBank (http://www.ncbi.nlm.nih.gov/Genbank) accession numbers for the genes and gene products discussed in this paper are bovine PrP (NM181015) and sheep PrP (M31313).

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Author contributions. JLV and HL conceived and designed the experiments. VB, AB, ALD, FR, TLL, NC, GT, and JLV performed the experiments. VB, AB, and HL analyzed the data. AGB and TB contributed reagents/materials/analysis tools. VB and HL wrote the paper.

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Competing interests. The authors have declared that no competing interests exist.

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No. 23

医薬品 研究報告 調査報告書

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研究報告の概要	使用上の注意記載状況・その他参考事項等
○慢性消耗病に感染したシカの唾液および血液中の感染性プリオン シカ科動物における慢性消耗病(CWD)やその他のプリオン疾患の伝播には、体液中のプリオン潜在が重大な懸念事項である。この問題を解決するため、CWD非感染シカのコホートをCWD陽性のシカの唾液、血液または尿・糞便に曝露させた。その結果、CWDを伝播しうる感染性プリオンが唾液(経口経路)および血液(輸血経路)中に認められた。この結果から、CWDはシカ科の動物に容易に伝播すると言える。プリオンに感染した体液との接触には注意が必要である。	赤血球M・A・P「日赤」 照射赤血球M・A・P「日赤」 赤血球濃厚液-LR「日赤」 照射赤血球濃厚液-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
CWD感染シカの唾液および血液からCWD陰性シカに感染性プリオンが伝播したとの報告である。	今後も引き続き、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。

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abnormal hyperphosphorylation of TDP-43 might play a role in FTLD-U pathogenesis. Because UBIs are defined by ubiquitin immunohistochemistry, we asked whether TDP-43 recovered from urea fractions of FTLD-U brains is ubiquitinated, and this was shown to be the case by immunoprecipitation studies using the rabbit polyclonal anti–TDP-43 followed by immunoblot analyses with both anti–TDP-43 and ubiquitin antibodies (Fig. 3D).

FTLD-U and ALS have been suggested to be part of a clinicopathological spectrum (*23*), sharing similar pathogenic mechanisms that affect different populations of CNS neurons. We examined classic ALS cases for the presence of TDP-43–positive UBIs (table S1, nos. 54 to 72). Although none of the inclusions typical of ALS were detected by mAbs 182 and 406, all UBIs (including skeinlike, round, and Lewy body–like inclusions) in motor neurons of ALS were robustly double-labeled by TDP-43 and ubiquitin antibodies (Fig. 4, A to F) and by single-label TDP-43 immunohistochemistry (Fig. 4, G to I). A significant number of ALS patients demonstrate UBIs in hippocampus and frontal and temporal cortex (*23*), which were also immunolabeled by TDP-43 (Fig. 4, J and K).

Immunoblots of urea fractions of spinal cord as well as frontal and temporal cortices of ALS cases demonstrated a disease-specific signature for TDP-43 similar to that described above for FTLD-U (Fig. 4L). Dephosphoryation of the urea fractions showed that the 45-kD band in ALS corresponds to pathologically hyperphosphorylated TDP-43 as in FTLD-U (Fig. 4M). However, because the presence of UBIs in ALS cases is more variable than their presence in FTLD-U, not all brain regions examined in all cases exhibited pathological TDP-43.

These studies identify TDP-43 as the major disease protein in the signature UBIs of FTLD-U and ALS. Although pathologically altered TDP-43 proteins were present in all sporadic and familial FTLD-U as well as ALS cases, there were subtle differences in these abnormal TDP-43 variants among the three FTLD-U subtypes, which may be the result of similar but not identical pathogenic mechanisms. The differential distribution of UBIs detected by ubiquitin antibodies in FTLD-U subtypes (*18*) supports this view.

TDP-43 is a ubiquitously expressed, highly conserved nuclear protein (*24*) that may be a transcription repressor and an activator of exon skipping (*21*, *25*, *26*) as well as a scaffold for nuclear bodies through interactions with survival motor neuron protein (*27*). TDP-43 is normally localized primarily to the nucleus, but our data indicate that, under pathological conditions in FTLD-U, TDP-43 is eliminated from nuclei of UBI-bearing neurons, a consequence of which may be a loss of TDP-43 nuclear functions. Moreover, nuclear UBIs are rare in sporadic FTLD-U because most pathological TDP-43 accumulates in neuronal cell bodies or their processes, and it is unclear whether physiological TDP-43 is present at significant quantities in the cytoplasm, axons, and dendrites of normal neurons. Lastly, both FTDP-17U pedigrees examined here contain *PGRN* gene mutations (*11*), but the relation between TDP-43 and *PGRN*, which encodes a secreted growth factor involved in the regulation of multiple processes in development, wound repair, and inflammation (*28*), remains unclear.

The identification of TDP-43 as the major component of UBIs specific to sporadic and familial FTLD-U as well as sporadic ALS resolves a long-standing enigma concerning the nature of the ubiquitinated disease protein in these disorders. Thus, these diseases may represent a spectrum of disorders that share similar pathological mechanisms, culminating in the progressive degeneration of different selectively vulnerable neurons. These insights into the molecular pathology of FTLD-U and ALS can accelerate efforts to develop better therapies for these disorders.

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Supporting Online Material
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Material and Methods
Figs. S1 to S3
Table S1
References

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Infectious Prions in the Saliva and Blood of Deer with Chronic Wasting Disease

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A critical concern in the transmission of prion diseases, including chronic wasting disease (CWD) of cervids, is the potential presence of prions in body fluids. To address this issue directly, we exposed cohorts of CWD-naïve deer to saliva, blood, or urine and feces from CWD-positive deer. We found infectious prions capable of transmitting CWD in saliva (by the oral route) and in blood (by transfusion). The results help to explain the facile transmission of CWD among cervids and prompt caution concerning contact with body fluids in prion infections.

The prion diseases, or transmissible spongiform encephalopathies (TSEs), are chronic, degenerative, neurological diseases with uniformly fatal outcomes. TSEs are characterized by the conversion of the normal cellular prion protein (PrP^c) to an aberrant insoluble partially protease-resistant isoform (PrP^{res}). CWD, a transmissible spongiform encephalopathy of cervids (deer, elk, and moose), was first observed in the 1960s in captive deer and free-ranging deer and elk in northeastern Colorado and southeastern

Wyoming (*1–4*). CWD has now been identified in 14 states in the United States and two Canadian provinces. Despite its facile transmission, the exact mode of CWD infection has not been determined. Indeed, surprisingly little is known about the transmission of naturally occurring TSEs. For example, scrapie in sheep has been recognized for centuries, yet the precise mode of natural transmission remains unclear (*5, 6*).

To determine whether infectious prions capable of transmitting CWD are present in body fluids and excreta of CWD-infected deer (CWD+), we exposed four cohorts (numbered 1 to 4, n = 3 to 4 per cohort) of 6-month-old CWD-naïve hand-raised white-tailed deer (*Odocoileus virginianus*) fawns from Georgia, United States (Table 1) to blood, saliva, a combination of urine and feces, or brain from free-ranging or captive CWD+ mule deer (*Odocoileus hemionus*) from Colorado, United States (tables S1 and S2). A control cohort (cohort 5, n = 2) received matching inocula collected from confirmed CWD-negative white-tailed deer (*O. virginianus*) from Georgia, United States. Because polymorphism in the normal prion protein gene (PRNP) may influence CWD susceptibility or incubation time in white-tailed deer, PRNP codon 96 genotype for each deer was determined (table S2) (*7*).

The deer fawns were housed in separate isolation suites under strict isolation conditions to exclude adventitious sources of prion exposure [supporting online material (SOM) text], thus permitting conclusions based on only the point-source exposure. After inoculation, the deer were monitored for CWD infection by serial tonsil biopsy performed at 0, 3, 6, and 12 months postinoculation (pi), and at termination (18 to 22 months pi). Equal portions of tissue were collected and stored (–70°C or fixed in 10% formalin) at each serial collection time point (tonsil) and at study termination (palantine tonsil, brain, and retropharyngeal lymph nodes) for the detection of the protease-resistant abnormal prion protein associated with CWD (PrP^{CWD}) (*8*).

Serial tonsil biopsy of each recipient deer revealed that infectious CWD prions were present in saliva and blood from CWD+ donor deer (Table 2). As expected, PrP^{CWD} was demonstrated between 3 and 12 months pi in tonsil biopsies of all four animals inoculated either orally or intercranially with CWD+ brain (cohort 4). More notably, PrP^{CWD} was detected in tonsil biopsies of two of three deer each in both the saliva and blood cohorts (numbers 1 and 2) at 12 months pi. By contrast, deer in the urine and feces inoculation cohort 3 remained tonsil biopsy negative for PrP^{CWD} throughout the 18-month study. Animals in the negative control inoculation cohort 5 also remained tonsil biopsy negative throughout the study.

Deer cohorts 1 (blood), 2 (saliva), and 3 (urine and feces) were electively euthanized at 18 months pi to permit whole-body examination for PrP^{CWD}. The greatest scrutiny was directed toward those tissues previously established to have highest frequency of PrP^{CWD} deposition in infected deer and generally regarded as the most sensitive indicators of infection—medulla oblongata and other brainstem regions, tonsil, and retropharyngeal lymph node. We found unequivocal evidence of PrP^{CWD} in brain and lymphoid tissue of all six tonsil biopsy–positive deer in cohorts 1 (blood) and 2 (saliva), whereas all deer in cohorts 3 and 5 were negative for PrP^{CWD} in all tissues (Table 2 and Figs. 1 and 2).

The transmission of CWD by a single blood transfusion from two symptomatic and one asymptomatic CWD+ donor is important in at least three contexts: (i) It reinforces that no tissue from CWD-infected cervids can be considered free of prion infectivity; (ii) it poses the possibility of hematogenous spread of CWD, such as through insects; and (iii) it provides a basis for seeking in vitro assays sufficiently sensitive to demonstrate PrP^{CWD} or alternate prion protein conformers in blood—one of the grails of prion biology and epidemiology.

The identification of blood-borne prion transmission has been sought before with mixed results (*9–11*). Bovine spongiform encephalopathy and scrapie have been transmitted to naïve sheep through the transfer of 500 ml of blood or buffy coat white blood cells from infected sheep (*12, 13*). In addition, limited but compelling evidence argues for the transmission of variant Creutzfeldt-Jakob disease (vCJD) through blood from asymptomatic donors (*14–16*). Even in sporadic CJD, PrP^{res} has been found in periph-

Table 1. CWD prion bioassay inoculation cohorts. Cohort 1 fawns received either a single intraperitoneal (IP) inoculation of 250 ml of frozen citrated blood (n = 2) or an intravenous (IV) transfusion with 250 ml fresh citrated whole blood (n = 1) each from a single CWD+ donor. Cohort 2 fawns received a total of 50 ml saliva, each from a different CWD+ donor, orally (PO) in three doses over a 3-day period. Cohort 3 fawns received a total of 50 ml urine and 50 g of feces PO, each from a different CWD+ donor, in divided doses over a 3- to 14-day period. As positive controls, cohort 4 fawns were inoculated with a 10% brain homogenate from a CWD+ donor deer through either a single intracranial (IC) injection of 1 g equivalent of brain (n = 2) or PO with a total of 10 g equivalents of brain (n = 2) divided over a 3-day period. Cohort 5 fawns (n = 2) were inoculated with equivalent amounts of each of the above materials from a single CWD-negative donor deer to serve as negative controls for the study.

Animal cohort	n	Inoculum	Route (n)	Amount	No. of inoculations
1	3	Blood	IV (1), IP (2)	250 ml	1
2	3	Saliva	PO (3)	50 ml	3
3	3	Urine and feces	PO (3)	50 ml + 50 g	3 to 14
4	4	Brain	IC (2), PO (2)	1 g (IC), 10 g (PO)	1 (IC), 3 (PO)
5	2	All of the above	PO (2)	All of the above	1 to 14

Table 2. PrP^{CWD} detection by longitudinal tonsil biopsy and necropsy of deer exposed to body fluids or excreta from CWD+ deer. PrP^{CWD} assay results for tonsil (T), brain (B) (medulla oblongata at obex), and retropharyngeal lymph node (RLN) are shown. The number of deer in which PrP^{CWD} was detected (*8*) is shown over the total number of deer in the cohort. One of the three original animals inoculated with urine and feces was euthanized prematurely 61 days pi due to a bacterial infection. The deer in cohorts 1, 2, and 3 were terminated at 18 months (mo.) pi. Two of the four cohort 4 deer were terminated at 20 and 21 months pi. The two cohort 5 deer were terminated at 22 months pi.

Animal cohort	Inoculum	Biopsy collection					
		3 mo. (T)	6 mo. (T)	12 mo. (T)	Termination		
					T	B	RLN
1	Blood	0/3	0/3	2/3	3/3	2/3	3/3
2	Saliva	0/3	0/3	2/3	3/3	2/3	3/3
3	Urine and feces	0/2	0/2	0/2	0/2	0/2	0/2
4	Brain	1/4	2/4	4/4	2/2	2/2	2/2
5	Negative samples	0/2	0/2	0/2	0/2	0/2	0/2

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eral organs of some patients (*17*). The present work helps establish that prion diseases can be transmitted through blood.

The presence of infectious CWD prions in saliva may explain the facile transmission of CWD. Cervid-to-cervid interactions (SOM text), especially in high density and captive situations, would be expected to facilitate salivary cross-contact (*11*, *18*, *19*). Salivary dissemination of prions may not be limited to CWD. Protease-resistant prion protein has been demonstrated in the oral mucosa, taste buds, lingual epithelium, vomeronasal organ, and olfactory mucosa of hamsters infected with transmissible mink encephalopathy (*19*) and ferrets infected with CWD (*20*). Although no instance of CWD transmission to humans has been detected, the present results emphasize the prudence of using impervious gloves during contact with saliva or blood of cervids that may be CWD-infected.

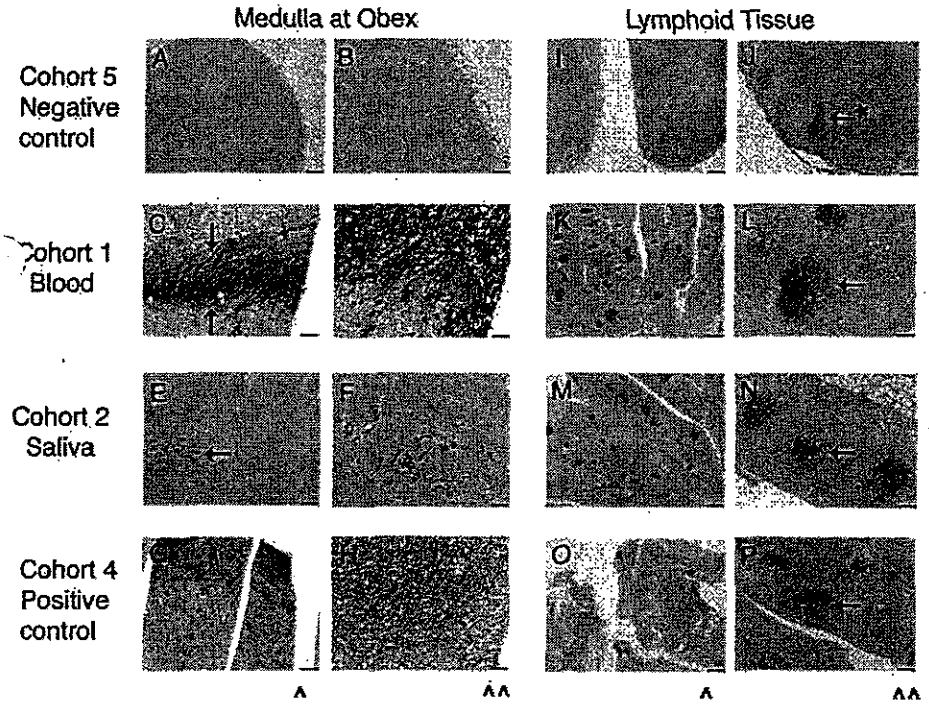

Fig. 1. PrP^{CWD} demonstrated by immunohistochemistry in tonsil, brain (medulla oblongata at obex), and retropharyngeal lymph node of deer receiving saliva or blood from CWD-infected donors. CWD immunohistochemistry is shown in the medulla at obex (**A** to **H**) and either tonsil or retropharyngeal lymph node (**I** to **P**) (*8*). Arrows indicate PrP^{CWD} staining (red) within brain and lymphoid follicles. Arrow with asterisk indicates lymphoid follicle negative for PrP^{CWD}. ^, scale bar = 50 μm; ^^, scale bar = 110 μm.

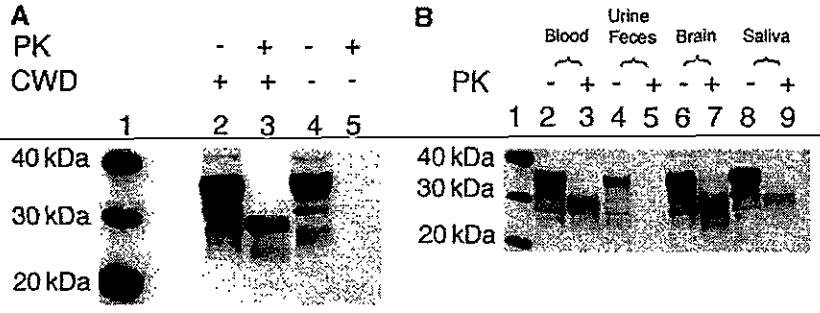

Fig. 2. Immunoblot demonstration of PrP^{CWD} in brain (medulla) of white-tailed deer. (**A**) PrP^{CWD} detection in positive and negative control deer (*8*). Lane 3 demonstrates the expected molecular weight shift upon partial proteinase K (PK) digestion of PrP^{CWD} in CWD+ deer, whereas lane 5 shows the complete digestion of PrP^{c} in CWD-negative deer. Molecular weight markers are indicated in lane 1. (**B**) Assay for PrP^{CWD} in medulla at obex homogenates for deer inoculated with blood, urine and feces, brain, and saliva, with and without PK digestion (*8*). Molecular weight markers are indicated in lane 1. Lanes 3, 7, and 9 demonstrate the detection of PrP^{CWD}, whereas lane 5 demonstrates the lack of PrP^{CWD}.

Environmental contamination by excreta from infected cervids has traditionally seemed the most plausible explanation for the dissemination of CWD (*21*). However, we could not detect PrP^{CWD} in cohort 3 deer inoculated repeatedly with urine and feces from CWD+ deer and examined up to 18 months pi (Table 2). There are several reasons to view this negative finding cautiously, including small sample size, elective preclinical termination, and potential variation in individual susceptibility that may be associated with the 96 G/S polymorphism in the PRNP gene (*7*, *22*). Although no genotype of white-tailed deer is resistant to CWD infection, PRNP genotypes S/S or G/S at codon 96 appear to have reduced susceptibility manifest by longer survival (*7*). Both deer in cohort 3 (urine and feces) were subsequently shown to be of the PRNP 96 G/S genotype. Thus, it is possible, although we think unlikely, that these deer had a prolonged incubation period (>18 months pi) before the amplification of PrP^{CWD} became detectable in tissues. Recent studies have shown that PrP^{res} is poorly preserved after incubation with intestinal or fecal content (*23*, *24*). Further research using cervid and surrogate cervid PrP transgenic mice (*25*) are indicated to continue to address the presence of infectious CWD prions in excreta of CWD+ deer and to provide a more substantial basis for reconsideration of the assumption that excreta are the chief vehicle for CWD dissemination and transmission.

The results reported here provide a plausible basis for the efficient transmission of CWD in nature. We demonstrate that blood and saliva in particular are able to transmit CWD to naïve deer and produce incubation periods consistent with those observed in naturally acquired infections (*3*, *26*). The time from exposure to first detection of PrP^{CWD} by tonsil biopsy was variable—as short as 3 months but as long as 18 months (likely underestimates due to sampling frequency). The results also reinforce a cautious view of the exposure risk presented by body fluids, excreta, and all tissues from CWD+ cervids.

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Supporting Online Material
www.sciencemag.org/cgi/content/full/314/5796/133/DC1
Material and Methods
SOM Text
Tables S1 and S2
References

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Modulation of Cell Adhesion and Motility in the Immune System by Myo1f

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Although class I myosins are known to play a wide range of roles, the physiological function of long-tailed class I myosins in vertebrates remains elusive. We demonstrated that one of these proteins, Myo1f, is expressed predominantly in the mammalian immune system. Cells from Myo1f-deficient mice exhibited abnormally increased adhesion and reduced motility, resulting from augmented exocytosis of β2 integrin–containing granules. Also, the cortical actin that co-localizes with Myo1f was reduced in Myo1f-deficient cells. In vivo, Myo1f-deficient mice showed increased susceptibility to infection by *Listeria monocytogenes* and an impaired neutrophil response. Thus, Myo1f directs immune cell motility and innate host defense against infection.

In both mouse and human genomes, 16 genes encode conventional class II muscle and nonmuscle myosins, with 25 "unconventional" myosin genes encoding 11 other classes (*1*). Natural mutations of various myosin genes result in an array of genetic disorders, including cardiomyopathies, deafness, blindness, glomerular nephritis, and neuropathies (*2, 3*). The class I myosins are the largest group of unconventional myosins and are evolutionarily ancient, existing in a wide range of species from yeast to vertebrates (*1, 4*). Mice and humans have a total of eight class I myosin heavy-chain genes, six of which encode short-tailed forms (Myo1a, b, c, d, g, and h) and two of which encode long-tailed (amoeboid) forms (Myo1e and f) (*1*). All class I myosins consist of an N-terminal motor domain, light-chain–binding IQ motifs, and a basic tail homology 1 (TH1) domain thought to affect interactions with membranes (*2*). The long-tailed class I myosins have an additional proline-rich TH2 domain and a TH3 domain containing a single Src homology 3 (SH3) domain (*2*).

The class I myosins in *Dictyostelium* and yeast are involved in migration, phagocytosis, endocytosis, and actin remodeling (*5, 6*). Short-tailed class I myosins in vertebrates are involved in more specialized functions, such as the adaptation of hair cells in the ear (*7*) and the transport of vesicles and organelles (*8, 9*), as well as the structural maintenance of the enterocyte microvilli (*10*). However, the function of long-tailed class I myosins in vertebrates is poorly characterized (*11–14*).

Myo1f was first identified in our screen for differentially expressed genes in subsets of murine lymphocytes. In contrast to previous data suggesting the widespread expression of Myo1f in tissues (*15*), our results, which we obtained using specific probes, showed that Myo1f is selectively expressed in the spleen, mesenteric lymph nodes, thymus, and lung (Fig. 1A). By comparison, specific detection of Myo1e showed a predominant expression pattern in the spleen and mesenteric lymph nodes and moderate expression in the lung, small intestine, and large intestine (Fig. 1B). Within the lymphoid tissues, natural killer (NK) cells, macrophages, and dendritic cells were found to express considerable levels of both Myo1f and Myo1e; neutrophils and B cells showed selective expression of Myo1f and Myo1e, respectively (Fig. 1, C and D).

To determine the function of Myo1f in the vertebrate immune system, we generated Myo1f gene–deficient mice. We focused on neutrophils because Myo1f was detected exclusively in neutrophils (Fig. 1, C and D). Immunoglobulin G (IgG)–mediated phagocytosis was similar between wild-type and knockout (KO) neutrophils (Fig. 1E). To evaluate the degree of pathogen killing that follows phagocytosis, we measured the production of reactive oxygen species. Again, no considerable difference was detected between wild-type and KO neutrophils (Fig. 1F). Thus, Myo1f is dispensable for both the phagocytosis of bacteria and their destruction.

Integrin-mediated adhesion to the vascular endothelium is crucial in the process of neutrophil migration to infected tissue, and the dominant integrins involved in this process belong to the β2 integrin (CD18) family (*16*). Myo1f-deficient neutrophils exhibited strong adhesion to integrin ligands, including the intercellular adhesion molecule–1 (ICAM-1) (CD54) and fibronectin (Fig. 2, A and B). Activation of neutrophils by the proinflammatory cytokine tumor necrosis factor–α did not compensate for this difference, suggesting that increased adhesion did not result from changes in the activation status of Myo1f-deficient cells. Experiments with a blocking antibody showed that most of the adhesion was mediated by β2 integrin (Fig. 2, A and B). In addition, Myo1f affected only integrin-mediated adhesion, not integrin-independent adhesion to polylysine-coated substrate (Fig. 2C) (*17*). Spreading of Myo1f-deficient neutrophils on ICAM-1 was also increased as compared to that of wild-type neutrophils (Fig. 2D). Increased spreading was not due to a loss of cortical tension (fig. S2), which acts to maintain the round shape of the cells (Fig. 2E). In contrast, myosin I double mutants in *Dictyostelium* exhibit abnormalities

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研究報告の概要

○PRDT TSE親和性リガンドを用いた血中の内在性TSE感染性の除去及びMacoPharma P-Capt™ Filterへのリガンドの組み込み
背景:供血後にvCJDで死亡した供血者の血液を輸血されたことが判明し、疾患が検知可能となるまで生存した受血者19名のうち、vCJD輸血感染症例は3例で感染率は15%以上である。外科的に除去した組織の調査では、英国のvCJD潜伏症例は最低でも4000例と見積もられ、うち平均7%が受血者である。
目的:プリオンタンパク質およびTSE感染性に高親和性のリガンドを開発し、血液製剤によるTSE感染症伝播リスクを軽減するため、RBCやその他血液成分からTSE感染性を除去する器具に当該リガンドを組み入れること。
方法:Pathogen Removal and Diagnostics Technologies(PRDT)は、全血、RBCまたは血漿存在下の脳由来プリオンタンパク質およびTSE感染性と高親和性のリガンドを得るため数百万の化合物のスクリーニングを行った。血中の内在性TSE感染性の除去をテストするため、スクレイピー感染ハムスターから4時間以内に血液~500 mlsを採取し、商用フィルターで白血球除去を行い被験樹脂を通過させた。全血、白血球除去血液および樹脂通過血液を分注し、限界希釈法で力価測定を行った。ハムスター100匹に各サンプルの分注50μg(合計5mL)を接種した。ハムスターの自然死が起り始めた540日で実験を終了し、プリオンアミロイドの証拠がないか各動物の脳を調べた。
結果:もっとも優れた樹脂は、脳由来プリオンタンパク質でスパイクしたRBC 10^7ID/mlの力価を、4 log(10)ID(50)以上減少させ、血液やRBCに関して非常に低濃度の感染性に対して求められる性能を大きく上回った。脳由来物スパイクの妥当性が不確実であることから、血中に内在する感染源の除去能についても評価した。樹脂処理した血液を接種したハムスター100匹のうち、感染したハムスターはいなかった。当該樹脂は、TSE血液感染性(> 1.2 log(10)ID)を除去した。この樹脂は広範囲の血液適合性検査にパスした。これは、MacoPharmaにより白血球除去赤血球からTSE感染性を除去する独立型のP-Capt™ filterに取り入れられている。
結論:PRDTの樹脂は、高濃度のTSE感染性を吸着し、RBC存在下でも効果が高く、白血球除去血液中の低濃度内在性感染性を検出限界まで除去する。P-Capt™ filterとして実現した当該樹脂は、血液および血液製剤によるvCJD伝播のリスクを有意に減少させるはずである。

使用上の注意記載状況・その他参考事項等

赤血球M・A・P「日赤」
照射赤血球M・A・P「日赤」
赤血球濃厚液-LR「日赤」
照射赤血球濃厚液-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
PRDT TSE親和性リガンドならびにリガンドを組み入れたMacoPharma P-Capt™ Filterを用いて血中に存在する内在性TSE感染性を除去できたとの報告である。	今後も引き続き、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。

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to the whole blood and RCC filtrations, including losses in tubes and bags by transfer, of about 20 g Hb. The CompoSafe Pr filtration causes an additional loss compared to whole blood filtration of about 7 g Hb. The filtration over the CompoSafe Pr filter induced a slight increase of hemolysis (about 0.03% increase), but this did not result in a more rapid increase during subsequent storage: after 42 days 0.26% hemolysis for group I and 0.16% for group II were detected. For group I at day 42 1.3 % of the red cells were positive for AnnexinV (representing PS-exposure), whereas for group II this was 0.9 % (comparable to standard leukodepleted RCC in SAGM). The amount of ATP was predicted to be above 2.7μmol/g Hb at day 35, with about 15 mM glucose remaining at day 42.

Conclusion: Despite the double filtration step in the total procedure (one to leukoreduce the whole blood and one to remove prions from RCC), the remaining RCC met the European requirements for Hb content. The amount of Hb in the final RCC is similar to that in leukodepleted RCC prepared from whole blood after buffy coat depletion. The in vitro quality after 42 days was similar to those of standard leukodepleted RCC, prepared from whole blood after buffy coat depletion.

P-091
DETECTION OF INFECTIOUS PRION IN BLOOD BY PROTEIN MISFOLDING CYCLIC AMPLIFICATION TECHNOLOGY (PMCA)

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Background: Since the publication of three cases of probable transmission to British patients of the variant of Creutzfeldt-Jacob Disease (vCJD) by blood transfusion, it is likely that infectious prion protein (PrPsc) is present in human blood. Studies on rodent indicate that the estimated sensitivity level of assays needs to reach a minimum of 1 femtomolar (0.1pg/ml or 10IU/ml) in order to detect PrPsc in the blood of patients in the pre-clinical phase of the disease. No test actually available does reach this level of detection and the development of highly sensitive assay for detection of PrPsc in blood is essential to evaluate secondary transmission of the disease by blood transfusion.

Aim: We have chosen to amplify the PrPsc by saPMCA (serial automated Protein Misfolding Cyclic Amplification) prior to the detection of very low levels of infectious prion present in the blood.

Objective: to develop a screening test for PrPsc in human blood components. The first phase consists in the manual reproduction and optimization of the PMCA technology described by C. Soto on hamster brain, in order to adapt the method on an automated sonicator (Misonix S-3000), allowing the detection of PrPsc in blood.

Methods: PMCA allows accelerated production of infectious prions by successive incubation and sonication steps. During incubation, aggregates of PrPsc proteins are produced from low quantity of PrPsc. This template initiates transconformation of the normal prion protein (PrPc) into PrPsc. Sonication of the aggregates leads to numerous small amplification units, each one allowing new conversions. Amplified PrPsc is then detected by Western Blot.

Results: After optimizations, manual PMCA prior to detection by Western blot permits to amplify by 3log10 folds the initial input of PrPsc present in hamster brain or in leukocytes. The saPMCA has then been optimized for high-efficiency amplification of PrPsc. The performances of the Misonix S-3000 have been evaluated on hamster brain which has confirmed the high throughput of the assay. The saPMCA method is reproducible and specific. Adaptation of this technology for PrPsc detection in blood is in progress.

Conclusion: The saPMCA prior to detection by Western blot appears to be a powerful approach for early diagnosis of prion diseases. The development of this technology as a non invasive screening test for PrPsc in human blood donation will allow to evaluate the potential spread of the prion by blood transfusion.

P-092
REMOVAL OF THE ENDOGENOUS TSE INFECTIVITY PRESENT IN BLOOD USING PRDT TSE AFFINITY LIGANDS AND INTEGRATION OF THE LIGANDS INTO THE MACOPHARMA P-CAPT(TM) FILTER

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Background: To date, there have been three transfusion transmitted cases of vCJD among 19 recipients that are known to have received blood from persons that later died of vCJD and lived long enough themselves to have developed detectable disease. This is a transmission rate of ~15%. If any of the other 16 recipients were infected it will be even higher (www.cjd.ed.ac.uk/TMER). A survey of surgically removed tissues concluded that the number of incubating cases of vCJD in the UK was at least 4000 (Hilton et al. 2004, J. Pathol. 203:733-9). 7% of this group would on average be blood donors.

Aim: To develop ligands with strong affinity for the prion protein and TSE infectivity and incorporate them into devices to remove TSE infectivity from RBCs and other blood components to reduce the risk of transmission of TSE infections from blood products.

Methods: Pathogen Removal and Diagnostics Technologies, PRDT, screened millions of compounds to obtain high affinity ligands that strongly bind brain-derived prion protein and TSE infectivity in the presence of whole blood, RBC or plasma. To test for removal of the endogenous TSE infectivity that is present in blood, ~500 mls of blood was collected in < 4 hours from scrapie infected hamsters, leukoreduced by a commercial filter, and passed through the test resin. Aliquots of whole blood, leukoreduced blood and resin flow-throughs were titered by the limiting dilution method. A total of 5 mls of each sample was inoculated in 50 □l aliquots into 100 hamsters. The experiment was terminated at 540 days when hamsters begin to die of natural causes and the brain of every animal was checked for evidence of prion amyloid.

Results: The best resins reduced the titer of a brain-derived spike into RBC of 10(7) ID/ml by over 4 log(10)ID(50), far exceeding the capacity needed for the very low concentrations of infectivity associated with blood or RBC. To address the uncertainty about the relevance of brain-derived spikes, the lead resin was also assessed for its ability to remove the infectivity endogenously present in blood. There were no infections among the 100 hamsters inoculated with the resin treated blood. The resin removed > 1.2 log(10)ID of relevant TSE blood infectivity. This resin has also passed a broad range of hemocompatibility tests. It has now been incorporated by MacoPharma into the P-Capt™ filter, a stand alone device for removing TSE infectivity from leukoreduced red blood cells.

Summary: PRDT's lead resin adsorbs high concentrations (10(7) ID50/ml) of brain derived TSE infectivity with high efficiency (4 log(10)ID50) even in the presence of RBC, and removes the low concentrations (10 ID/ml) of endogenous infectivity that is present in leukoreduced blood to the limit of detection (>1.2 log(10)ID). Implemented as the Macopharma P-Capt(TM) filter it should significantly reduce the risk of transmission of vCJD by blood and blood products.

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B　個別症例報告概要

○　総括一覧表
○　報告リスト

個別症例報告のまとめ方について

個別症例報告が添付されているもののうち、個別症例報告の重複を除いたものを一覧表の後に添付した（国内症例については、資料Eにおいて集積報告を行っているため、添付していない）。

感染症定期報告の報告状況(2006/12/1～2007/2/28)

血対ID	受理日	報告者名	一般名	生物由来成分名	原材料名	原産国	含有区分	文献	症例	適正使用措置
60184	2006/12/01	日本赤十字社	解凍人赤血球濃厚液	解凍人赤血球濃厚液	人血液	日本	有効成分	有	無	無
60185	2006/12/14	ベネシス	ポリエチレングリコール処理抗破傷風人免疫グロブリン 乾燥抗破傷風人免疫グロブリン	破傷風抗毒素	人血液	米国	有効成分	有	無	無
60186	2006/12/20	日本赤十字社	人赤血球濃厚液	人赤血球濃厚液	人血液	日本	有効成分	有	有	無
60187	2006/12/20	日本赤十字社	人全血液	人全血液	人血液	日本	有効成分	有	無	無
60188	2006/12/20	日本赤十字社	抗HBs人免疫グロブリン	抗HBs人免疫グロブリン	人血液	日本	有効成分	有	無	無
60189	2006/12/26	化学及血清療法研究所	乾燥スルホ化人免疫グロブリン	スルホ化人免疫グロブリンG	ヒト血液	①米国(ベニロン)②日本(献血ベニロンーⅠ)	有効成分	有	無	無
60190	2006/12/26	化学及血清療法研究所	乾燥濃縮人アンチトロンビンⅢ	アンチトロンビンⅢ	ヒト血液	日本	有効成分	有	無	無
60191	2006/12/28	バクスター	該当なし	トロンビン	人血漿	米国	有効成分	無	有	無
60192	2006/12/28	バクスター	該当なし	人血清アルブミン	人血漿	米国	添加物	無	有	無
60193	2006/12/28	バクスター	該当なし	ヒト凝固性たん白質(フィブリノゲン加第XⅢ因子)	人血漿	米国	有効成分	無	有	無
60194	2006/12/28	バクスター	該当なし	アプロチニン液	ウシ肺	ウルグアイ又はニュージーランド	有効成分・添加物	無	有	無
60195	2006/12/28	バクスター	該当なし	ヘパリンナトリウム	ブタ腸	中国	製造工程	無	有	無
60196	2006/12/28	バクスター	乾燥イオン交換樹脂処理人免疫グロブリン	人免疫グロブリンG	人血漿	米国	有効成分	無	有	無
60197	2006/12/28	バクスター	乾燥イオン交換樹脂処理人免疫グロブリン	人血清アルブミン	人血漿	米国	添加物	無	有	無
60198	2007/1/11	ベネシス	人ハプトグロビン	人ハプトグロビン	人血液	非献血:米国、献血:日	有効成分	有	無	無
60199	2007/01/12	第一ラジオアイソトープ研究所	テクネチウム大凝集人血清アルブミン(99mTc)	テクネチウム大凝集人血清アルブミン(99mTc)	ヒト血液	米国	有効成分	有	無	無
60200	2007/01/24	ZLBベーリング	ペプシン処理人免疫グロブリンG	ペプシン処理人免疫グロブリンG	ヒト血液	米国、ドイツ、オースト	有効成分	有	有	無
60201	2007/01/24	ZLBベーリング	ペプシン処理人免疫グロブリンG	ペプシン	ブタの胃	米国	製造工程	無	無	無
60202	2007/01/24	ZLBベーリング	乾燥濃縮人アンチトロンビンⅢ	乾燥濃縮人アンチトロンビンⅢ	ヒト血液	米国、ドイツ、オースト	有効成分	有	有	無
60203	2007/01/25	化学及血清療法研究所	乾燥濃縮人血液凝固第Ⅷ因子	血液凝固第Ⅷ因子	ヒト血液	日本	有効成分	有	無	無
60204	2007/01/26	日本製薬	乾燥人血液凝固第Ⅸ因子複合体	血液凝固第Ⅸ因子複合体	人血液	日本	有効成分	有	無	無
60205	2007/01/26	日本メジフィジックス	ガラクトシル人血清アルブミンジエチレントリアミン五酢酸テクネチウム(99mTc)	ガラクトシル人血清アルブミンジエチレントリアミン五酢酸テクネチウム(99mTc)	生物学的製剤基準人血清アルブミン	日本	有効成分	無	無	無
60210	2007/01/29	バクスター	加熱人血漿たん白	人血清アルブミン	人血漿	米国	有効成分	無	無	無
60211	2007/01/29	バクスター	人血清アルブミン	ヘパリンナトリウム	ブタ腸	中国	製造工程	無	無	無
60212	2007/01/29	バクスター	人血清アルブミン	人血清アルブミン	人血漿	米国	有効成分	無	無	無
60213	2007/01/29	バクスター	活性化プロトロンビン複合体濃縮製剤	乾燥人血液凝固第Ⅷ因子阻害物質補正活性複合体	人血漿	米国	有効成分	無	無	無

血対ID	受理日	報告者名	一般名	生物由来成分名	原材料名	原産国	含有区分	文献	症例	適正使用措置
60214	2007/01/29	バクスター	活性化プロトロンビン複合体濃縮製剤	ヘパリンナトリウム	ブタ腸	該当なし	添加物	無	無	無
60215	2007/01/29	バクスター	ルリオクトコグアルファ(遺伝子組換え)	培養補助剤(抗第Ⅷ因子モノクローナル抗体製造用-1)	ウシ血液	米国	製造工程	無	無	無
60216	2007/01/29	バクスター	ルリオクトコグアルファ(遺伝子組換え)	アプロチニン	ウシ肺	ニュージーランド	製造工程	無	無	無
60217	2007/01/29	バクスター	ルリオクトコグアルファ(遺伝子組換え)	培養補助剤(抗第Ⅷ因子モノクローナル抗体製造用-2)	ウシ肝臓	米国又はカナダ	製造工程	無	無	無
60218	2007/01/29	バクスター	ルリオクトコグアルファ(遺伝子組換え)	ウシ胎児血清(抗第Ⅷ因子モノクローナル抗体製造用)	ウシ血液	オーストラリア	製造工程	無	無	無
60219	2007/01/29	バクスター	ルリオクトコグアルファ(遺伝子組換え)	ルリオクトコグアルファ(遺伝子組換え)	遺伝子組換えチャイニーズハムスター卵巣細胞株	該当なし	有効成分	無	無	無
60220	2007/01/29	バクスター	ルリオクトコグアルファ(遺伝子組換え)	ウシ血清アルブミン	ウシ血液	米国	製造工程	無	無	無
60221	2007/01/29	バクスター	ルリオクトコグアルファ(遺伝子組換え)	人血清アルブミン	人血漿	米国	添加物	無	無	無
60222	2007/01/29	バクスター	ルリオクトコグアルファ(遺伝子組換え)	インスリン(抗第Ⅷ因子モノクローナル抗体製造用)	ウシ膵臓	米国	製造工程	無	無	無
60224	2007/02/14	第一ラジオアイソトープ研究所	ヨウ化人血清アルブミン(131I)	ヨウ化人血清アルブミン(131I)	ヒト血液	日本	有効成分	無	無	無
60225	2007/02/20	日本製薬	①加熱人血漿たん白 ②人血清アルブミン ③乾燥ポリエチレングリコール処理人免疫グロブリン ④トロンビン ⑤乾燥濃縮人アンチトロンビンⅢ ⑥人免疫グロブリン ⑦乾燥人血液凝固第Ⅸ因子複合体	ヘパリン	ブタ腸粘膜	ブラジル	①～⑥製造工程 ⑦添加物・製造工程	無	無	無
60226	2007/02/21	ベネシス	人血清アルブミン 乾燥濃縮人アンチトロンビンⅢ 人ハプトグロビン 乾燥濃縮人血液凝固第Ⅷ因子	ヘパリン	ブタ小腸粘膜	中国	製造工程	無	無	無
60227	2007/02/23	ZLBベーリング	人C1-インアクチベーター	人C1-インアクチベーター	ヒト血液	米国、ドイツ、オーストリア	有効成分	有	有	無
60228	2007/02/23	ZLBベーリング	人血清アルブミン 人免疫グロブリンG 破傷風抗毒素 フィブリノゲン加第XⅢ因子 ペプシン処理人免疫グロブリンG 乾燥濃縮人アンチトロンビンⅢ	ヘパリンナトリウム	ブタ腸粘膜	中国	製造工程	無	無	無
60229	2007/02/27	化学及血清療法研究所	乾燥抗破傷風人免疫グロブリン	抗破傷風人免疫グロブリン	ヒト血液	米国	有効成分	有	無	無
60230	2007/02/27	化学及血清療法研究所	乾燥人血液凝固第Ⅸ因子複合体 乾燥濃縮人血液凝固第Ⅸ因子	血液凝固第Ⅸ因子	ヒト血液	日本	有効成分	無	無	無
60231	2007/02/27	化学及血清療法研究所	乾燥人血液凝固第Ⅸ因子複合体 乾燥濃縮人血液凝固第Ⅸ因子 乾燥濃縮人アンチトロンビンⅢ	ヘパリンナトリウム	ブタ小腸粘膜	中国、フランス、米国、カナダ	製造工程	無	無	無

別紙様式第4

感染症発生症例一覧

番号	感染症の種類		発現国	性別	年齢	発現時期	転帰	出典	区分	備考
	器官別大分類	基本語								
1	感染症および寄生虫症	C型肝炎	日本	男	73	2006/9/27	②軽快	症例報告	当該製品	2006/10/24 提出、識別番号 1-06000141 未完了報告
2	感染症および寄生虫症	B型肝炎	日本	女	64	2006/9/26	⑥不明	症例報告	当該製品	2006/10/26 提出、識別番号 1-06000143 未完了報告
3	感染症および寄生虫症	B型肝炎	日本	男	66	2006/9/22	⑥不明	症例報告	当該製品	2006/10/13 提出、識別番号 1-06000136 未完了報告
4	感染症および寄生虫症	B型肝炎	日本	女	34	2006/9/21	③未回復	症例報告	当該製品	2006/10/11 提出、識別番号 1-06000132 未完了報告
5	感染症および寄生虫症	C型肝炎	日本	女	65	2006/9/21	③未回復	症例報告	当該製品	2006/10/18 提出、識別番号 1-06000139 未完了報告
6	感染症および寄生虫症	C型肝炎	日本	男	82	2006/9/17	⑥不明	症例報告	当該製品	2006/10/18 提出、識別番号 1-06000138 未完了報告
7	感染症および寄生虫症	C型肝炎	日本	男	50	2006/9/15	①回復	症例報告	当該製品	2006/10/11 提出、識別番号 1-06000134 未完了報告
8	感染症および寄生虫症	細菌感染	日本	男	76	2006/9/1	⑤死亡	症例報告	当該製品	2006/9/14 提出、識別番号 1-06000118 未完了報告
9	感染症および寄生虫症	多型滲出性紅斑感染	日本	男	72	2006/9/1	⑥不明	症例報告	当該製品	2006/9/21 提出、識別番号 1-06000120 未完了報告
10	感染症および寄生虫症	B型肝炎	日本	女	80	2006/8/21	③未回復	症例報告	当該製品	2006/9/14 提出、識別番号 1-06000116 未完了報告
11	感染症および寄生虫症	C型肝炎	日本	男	69	2006/8/8	③未回復	症例報告	当該製品	2006/10/24 提出、識別番号 1-06000140 未完了報告
12	感染症および寄生虫症	B型肝炎	日本	女	74	2006/8/7	①回復	症例報告	当該製品	2006/8/22 提出、識別番号 1-06000106 未完了報告
13	感染症および寄生虫症	細菌感染	日本	男	76	2006/8/7	①回復	症例報告	当該製品	2006/8/23 提出、識別番号 1-06000107 未完了報告
14	感染症および寄生虫症	細菌感染	日本	女	66	2006/8/7	①回復	症例報告	当該製品	2006/8/23 提出、識別番号 1-06000108 未完了報告
15	感染症および寄生虫症	敗血症性ショック	日本	男	93	2006/8/4	①回復	症例報告	当該製品	2006/8/18 提出、識別番号 1-06000105 未完了報告
16	感染症および寄生虫症	C型肝炎	日本	女	73	2006/8/3	②軽快	症例報告	当該製品	2006/8/28 提出、識別番号 1-06000109 未完了報告
17	感染症および寄生虫症	B型肝炎	日本	女	63	2006/8/2	②軽快	症例報告	当該製品	2006/10/13 提出、識別番号 1-06000135 未完了報告
18	感染症および寄生虫症	細菌感染	日本	男	78	2006/7/28	②軽快	症例報告	当該製品	2006/8/11 提出、識別番号 1-06000098 未完了報告
19	感染症および寄生虫症	細菌感染	日本	女	70	2006/7/26	③未回復	症例報告	当該製品	2006/8/11 提出、識別番号 1-06000097 未完了報告
20	感染症および寄生虫症	細菌感染	日本	女	75	2006/7/26	①回復	症例報告	当該製品	2006/8/15 提出、識別番号 1-06000102 未完了報告
21	感染症および寄生虫症	C型肝炎	日本	男	64	2006/7/26	③未回復	症例報告	当該製品	2006/8/15 提出、識別番号 1-06000103 未完了報告
22	感染症および寄生虫症	敗血症	日本	男	81	2006/7/25	③未回復	症例報告	当該製品	2006/8/11 提出、識別番号 1-06000099 未完了報告
23	感染症および寄生虫症	B型肝炎	日本	男	53	2006/7/25	③未回復	症例報告	当該製品	2006/8/15 提出、識別番号 1-06000101 未完了報告
24	感染症および寄生虫症	B型肝炎	日本	女	31	2006/7/25	③未回復	症例報告	当該製品	2006/8/18 提出、識別番号 1-06000104 未完了報告
25	感染症および寄生虫症	B型肝炎	日本	女	76	2006/7/20	⑥不明	症例報告	当該製品	2006/9/4 提出、識別番号 1-06000111 未完了報告
26	感染症および寄生虫症	C型肝炎	日本	男	57	2006/7/20	②軽快	症例報告	当該製品	2006/9/4 提出、識別番号 1-06000112 未完了報告
27	感染症および寄生虫症	B型肝炎	日本	女	52	2006/7/20	③未回復	症例報告	当該製品	2006/9/22 提出、識別番号 1-06000122 未完了報告
28	感染症および寄生虫症	B型肝炎	日本	男	61	2006/7/19	③未回復	症例報告	当該製品	2006/8/10 提出、識別番号 1-06000096 未完了報告
29	感染症および寄生虫症	敗血症	日本	女	72	2006/7/14	①回復	症例報告	当該製品	2006/8/2 提出、識別番号 1-06000085 未完了報告
30	感染症および寄生虫症	B型肝炎	日本	女	82	2006/7/13	⑥不明	症例報告	当該製品	2006/8/2 提出、識別番号 1-06000084 未完了報告
31	感染症および寄生虫症	B型肝炎	日本	女	82	2006/7/13	②軽快	症例報告	当該製品	2006/8/29提出、識別番号1-06000084 追加報告 (30番と同一症例)
32	感染症および寄生虫症	B型肝炎	日本	女	82	2006/7/13	②軽快	症例報告	当該製品	2006/10/20提出、識別番号1-06000084 取り下げ (30番、31番と同一症例)

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感染症発生症例一覧

33	感染症および寄生虫症	B型肝炎	日本	男	82	2006/7/7	⑥不明	症例報告	当該製品	2006/9/14 提出、識別番号 1-06000114 未完了報告
34	感染症および寄生虫症	B型肝炎	日本	男	44	2006/6/30	⑥不明	症例報告	当該製品	2006/8/18 提出、識別番号 1-06000083 未完了報告
35	感染症および寄生虫症	C型肝炎	日本	男	39	2006/6/30	④回復したが後遺症あり	症例報告	当該製品	2006/9/22 提出、識別番号 1-06000121 未完了報告
36	感染症および寄生虫症	C型肝炎	日本	男	71	2006/6/29	②軽快	症例報告	当該製品	2006/8/10 提出、識別番号 1-06000095 未完了報告
37	感染症および寄生虫症	C型肝炎	日本	男	10	2006/6/27	⑥不明	症例報告	当該製品	2006/7/24 提出、識別番号 1-06000080 未完了報告
38	感染症および寄生虫症	C型肝炎	日本	男	53	2006/6/26	②軽快	症例報告	当該製品	2006/7/20 提出、識別番号 1-06000075 未完了報告
39	感染症および寄生虫症	C型肝炎	日本	女	35	2006/6/22	⑥不明	症例報告	当該製品	2006/7/6 提出、識別番号 1-06000063 未完了報告
40	感染症および寄生虫症	C型肝炎	日本	男	71	2006/6/22	⑥不明	症例報告	当該製品	2006/9/14 提出、識別番号 1-06000115 未完了報告
41	感染症および寄生虫症	B型肝炎	日本	男	77	2006/6/20	③未回復	症例報告	当該製品	2006/7/18 提出、識別番号 1-06000072 未完了報告
42	感染症および寄生虫症	B型肝炎	日本	男	59	2006/6/20	③未回復	症例報告	当該製品	2006/8/2 提出、識別番号 1-06000086 未完了報告
43	感染症および寄生虫症	細菌感染	日本	女	43	2006/6/16	①回復	症例報告	当該製品	2006/6/30 提出、識別番号 1-06000059 未完了報告
44	感染症および寄生虫症	B型肝炎	日本	女	81	2006/6/10	②軽快	症例報告	当該製品	2006/7/27 提出、識別番号 1-06000081 未完了報告
45	感染症および寄生虫症	B型肝炎	日本	男	85	2006/6/7	③未回復	症例報告	当該製品	2006/7/6 提出、識別番号 1-06000061 未完了報告
46	感染症および寄生虫症	B型肝炎	日本	女	75	2006/6/2	②軽快	症例報告	当該製品	2006/7/20 提出、識別番号 1-06000074 未完了報告
47	感染症および寄生虫症	B型肝炎	日本	女	75	2006/6/2	②軽快	症例報告	当該製品	2006/8/29提出、識別番号1-06000074 取り下げ (46番と同一症例)
48	感染症および寄生虫症	B型肝炎	日本	女	75	2006/6/2	②軽快	症例報告	当該製品	2006/10/20提出、識別番号1-06000074 取り下げ (46番、47番と同一症例)
49	感染症および寄生虫症	C型肝炎	日本	男	48	2006/6/1	③未回復	症例報告	当該製品	2006/6/23 提出、識別番号 1-06000057 未完了報告
50	感染症および寄生虫症	B型肝炎	日本	女	56	2006/5/23	③未回復	症例報告	当該製品	2006/7/12 提出、識別番号 1-06000066 未完了報告
51	感染症および寄生虫症	B型肝炎	日本	男	76	2006/5/22	③未回復	症例報告	当該製品	2006/7/24 提出、識別番号 1-06000079 未完了報告
52	感染症および寄生虫症	B型肝炎	日本	男	82	2006/5/19	⑤死亡	症例報告	当該製品	2006/6/16 提出、識別番号 1-06000049 未完了報告
53	感染症および寄生虫症	B型肝炎	日本	男	82	2006/5/19	⑤死亡	症例報告	当該製品	2006/7/6提出、識別番号1-06000049 追加報告 (52番と同一症例)
54	感染症および寄生虫症	B型肝炎	日本	男	57	2006/5/19	②軽快	症例報告	当該製品	2006/8/2 提出、識別番号 1-06000087 未完了報告
55	感染症および寄生虫症	B型肝炎	日本	男	81	2006/5/17	③未回復	症例報告	当該製品	2006/6/5 提出、識別番号 1-06000039 未完了報告
56	感染症および寄生虫症	C型肝炎	日本	女	51	2006/5/16	⑥不明	症例報告	当該製品	2006/6/5 提出、識別番号 1-06000038 未完了報告
57	感染症および寄生虫症	真菌血症	日本	男	75	2006/5/16	⑤死亡	症例報告	当該製品	2006/8/8 提出、識別番号 1-06000089 未完了報告
58	感染症および寄生虫症	B型肝炎	日本	男	70	2006/5/15	⑥不明	症例報告	当該製品	2006/7/31 提出、識別番号 1-06000082 未完了報告
59	感染症および寄生虫症	B型肝炎	日本	男	46	2006/5/12	③未回復	症例報告	当該製品	2006/6/5 提出、識別番号 1-06000041 未完了報告
60	感染症および寄生虫症	細菌感染	日本	男	70	2006/5/11	①回復	症例報告	当該製品	2006/6/20 提出、識別番号 1-06000051 未完了報告
61	感染症および寄生虫症	B型肝炎	日本	男	77	2006/5/10	③未回復	症例報告	当該製品	2006/6/1 提出、識別番号 1-06000036 未完了報告
62	感染症および寄生虫症	伝染性紅斑	日本	男	59	2006/5/10	①回復	症例報告	当該製品	2006/6/5 提出、識別番号 1-06000040 未完了報告
63	感染症および寄生虫症	B型肝炎	日本	男	73	2006/5/9	⑤死亡	症例報告	当該製品	2006/6/22 提出、識別番号 1-06000054 未完了報告
64	感染症および寄生虫症	B型肝炎	日本	男	72	2006/5/4	⑥不明	症例報告	当該製品	2006/5/29 提出、識別番号 1-06000033 未完了報告
65	感染症および寄生虫症	細菌感染	日本	男	45	2006/5/3	③未回復	症例報告	当該製品	2006/5/23 提出、識別番号 1-06000028 未完了報告

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66	感染症および寄生虫症	B型肝炎	日本	女	80	2006/5/2	②軽快	症例報告	当該製品	2006/6/9 提出、識別番号 1-06000043 未完了報告
67	感染症および寄生虫症	C型肝炎	日本	男	21	2006/5/2	③未回復	症例報告	当該製品	2006/6/13 提出、識別番号 1-06000045 未完了報告
68	感染症および寄生虫症	細菌感染	日本	女	68	2006/5/1	②軽快	症例報告	当該製品	2006/5/23 提出、識別番号 1-06000026 未完了報告
69	感染症および寄生虫症	敗血症	日本	男	70	2006/5/1	⑤死亡	症例報告	当該製品	2006/5/17 提出、識別番号 1-06000023 未完了報告
70	感染症および寄生虫症	C型肝炎	日本	女	79	2006/5/1	③未回復	症例報告	当該製品	2006/5/25 提出、識別番号 1-06000031 未完了報告
71	感染症および寄生虫症	B型肝炎	日本	男	71	2006/5/1	⑥不明	症例報告	当該製品	2006/5/25 提出、識別番号 1-06000032 未完了報告
72	感染症および寄生虫症	B型肝炎	日本	女	90	2006/4/26	③未回復	症例報告	当該製品	2006/5/17 提出、識別番号 1-06000024 未完了報告
73	感染症および寄生虫症	B型肝炎	日本	女	90	2006/4/26	③未回復	症例報告	当該製品	2006/6/26提出、識別番号1-06000024 追加報告 (72番と同一症例)
74	感染症および寄生虫症	B型肝炎	日本	女	90	2006/4/26	③未回復	症例報告	当該製品	2006/10/26提出、識別番号1-06000024 取り下げ (72番、73番と同一症例)
75	感染症および寄生虫症	B型肝炎	日本	女	53	2006/4/25	⑥不明	症例報告	当該製品	2006/5/17 提出、識別番号 1-06000025 未完了報告
76	感染症および寄生虫症	B型肝炎	日本	女	50	2006/4/25	②軽快	症例報告	当該製品	2006/6/26 提出、識別番号 1-06000058 未完了報告
77	感染症および寄生虫症	敗血症	日本	女	4	2006/4/23	②軽快	症例報告	当該製品	2006/5/23 提出、識別番号 1-06000027 未完了報告
78	感染症および寄生虫症	B型肝炎	日本	男	70	2006/4/18	②軽快	症例報告	当該製品	2006/5/2 提出、識別番号 1-06000014 未完了報告
79	感染症および寄生虫症	細菌感染	日本	女	77	2006/4/18	②軽快	症例報告	当該製品	2006/5/8 提出、識別番号 1-06000018 未完了報告
80	感染症および寄生虫症	C型肝炎	日本	女	77	2006/4/17	③未回復	症例報告	当該製品	2006/7/6 提出、識別番号 1-06000062 未完了報告
81	感染症および寄生虫症	敗血症	日本	女	65	2006/4/15	①回復	症例報告	当該製品	2006/5/2 提出、識別番号 1-06000016 未完了報告
82	感染症および寄生虫症	C型肝炎	日本	男	82	2006/4/15	③未回復	症例報告	当該製品	2006/5/11 提出、識別番号 1-06000019 未完了報告
83	感染症および寄生虫症	B型肝炎	日本	男	49	2006/4/14	③未回復	症例報告	当該製品	2006/5/8 提出、識別番号 1-06000017 未完了報告
84	感染症および寄生虫症	B型肝炎	日本	女	67	2006/4/14	③未回復	症例報告	当該製品	2006/5/29 提出、識別番号 1-06000034 未完了報告
85	感染症および寄生虫症	C型肝炎	日本	女	63	2006/4/12	③未回復	症例報告	当該製品	2006/6/16 提出、識別番号 1-06000048 未完了報告
86	感染症および寄生虫症	B型肝炎	日本	女	72	2006/4/11	⑥不明	症例報告	当該製品	2006/7/12 提出、識別番号 1-06000068 未完了報告
87	感染症および寄生虫症	B型肝炎	日本	男	56	2006/4/10	③未回復	症例報告	当該製品	2006/5/2 提出、識別番号 1-06000015 未完了報告
88	感染症および寄生虫症	C型肝炎	日本	男	92	2006/4/5	⑥不明	症例報告	当該製品	2006/5/25 提出、識別番号 1-06000030 未完了報告
89	感染症および寄生虫症	B型肝炎	日本	男	69	2006/4/4	⑥不明	症例報告	当該製品	2006/7/12 提出、識別番号 1-06000067 未完了報告
90	感染症および寄生虫症	B型肝炎	日本	男	69	2006/4/4	⑥不明	症例報告	当該製品	2006/8/24 提出、識別番号 1-06000067 追加報告
91	感染症および寄生虫症	B型肝炎	日本	男	69	2006/4/4	⑥不明	症例報告	当該製品	2006/10/20提出、識別番号1-06000067 取り下げ (90番と同一症例)
92	感染症および寄生虫症	B型肝炎	日本	女	33	2006/3/23	⑥不明	症例報告	当該製品	2006/8/2提出、識別番号1-06000012 追加報告 第7回症例番号92は前回報告における第6回症例番号6において報告したものの追加報告
93	感染症および寄生虫症	B型肝炎	日本	女	33	2006/3/23	⑥不明	症例報告	当該製品	2006/10/26提出、識別番号1-06000012 取り下げ (92番と同一症例) 第7回症例番号93は前回報告における第6回症例番号6において報告したものの追加報告
94	感染症および寄生虫症	E型肝炎	日本	男	56	2006/3/20	②軽快	症例報告	当該製品	2006/5/12 提出、識別番号 1-06000020 未完了報告

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95	感染症および寄生虫症	B型肝炎	日本	男	78	2006/3/13	⑤死亡	症例報告	当該製品	2006/6/30 提出、識別番号 1-06000060 未完了報告
96	感染症および寄生虫症	C型肝炎	日本	女	78	2006/2/24	②軽快	症例報告	当該製品	2006/10/26 提出、識別番号 1-06000142 未完了報告
97	感染症および寄生虫症	B型肝炎	日本	男	78	2006/2/3	③未回復	症例報告	当該製品	2006/5/29 提出、識別番号 1-06000035 未完了報告
98	感染症および寄生虫症	細菌感染	日本	男	83	2006/1/20	②軽快	症例報告	当該製品	2006/6/29提出、識別番号1-05000246 完了報告 第7回症例番号98は前回報告における第6回症例番号29、30において報告したものの追加報告
99	感染症および寄生虫症	B型肝炎	日本	女	67	2005/12/26	②軽快	症例報告	当該製品	2006/5/23 提出、識別番号 1-06000029 未完了報告
100	感染症および寄生虫症	B型肝炎	日本	男	70	2005/12/9	⑤死亡	症例報告	当該製品	2006/7/18 提出、識別番号 1-06000070 未完了報告
101	感染症および寄生虫症	B型肝炎	日本	女	50	2005/12/2	①回復	症例報告	当該製品	2006/6/29提出、識別番号1-05000236 追加報告 第7回症例番号92は前回報告における第6回症例番号56において報告したものの追加報告
102	感染症および寄生虫症	B型肝炎	日本	女	54	2005/11/2	③未回復	症例報告	当該製品	2006/9/14 提出、識別番号 1-06000117 未完了報告
103	感染症および寄生虫症	C型肝炎	日本	男	46	2005/9/17	③未回復	症例報告	当該製品	2006/7/20 提出、識別番号 1-06000073 未完了報告
104	感染症および寄生虫症	B型肝炎	日本	女	1	2005/7/11	③未回復	症例報告	当該製品	2006/6/9 提出、識別番号 1-06000042 未完了報告
105	感染症および寄生虫症	B型肝炎	日本	男	40	2005/6/8	③未回復	症例報告	当該製品	2006/4/28提出、識別番号1-06000007 追加報告 第7回症例番号105は前回報告における第6回症例番号97において報告したものの追加報告
106	感染症および寄生虫症	B型肝炎	日本	男	40	2005/6/8	⑤死亡	症例報告	当該製品	2006/5/24提出、識別番号1-06000007 追加報告 (105番と同一症例) 第7回症例番号106は前回報告における第6回症例番号97において報告したものの追加報告
107	感染症および寄生虫症	B型肝炎	日本	男	63	2005/4/1	①回復	症例報告	当該製品	2006/9/27提出、識別番号1-05000017 完了報告 第7回症例番号107は前々々回報告における第4回症例番号2において報告したものの追加報告
108	感染症および寄生虫症	B型肝炎	日本	女	88	2005/3/22	③未回復	症例報告	当該製品	2006/9/27提出、識別番号1-05000003 完了報告 第7回症例番号108は前々々回報告における第4回症例番号4において報告したものの追加報告
109	感染症および寄生虫症	C型肝炎	日本	女	61	2005/3/17	⑥不明	症例報告	当該製品	2006/9/27提出、識別番号1-05000012 完了報告 第7回症例番号109は前々々回報告における第4回症例番号6において報告したものの追加報告
110	感染症および寄生虫症	B型肝炎	日本	女	4	2005/3/8	②軽快	症例報告	当該製品	2006/9/27提出、識別番号1-05000005 完了報告 第7回症例番号110は前々々回報告における第4回症例番号8において報告したものの追加報告
111	感染症および寄生虫症	C型肝炎	日本	女	77	2005/3/4	③未回復	症例報告	当該製品	2006/9/27提出、識別番号1-05000009 完了報告 第7回症例番号111は前々々回報告における第4回症例番号11において報告したものの追加報告

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112	感染症および寄生虫症	B型肝炎	日本	女	73	2005/2/28	③未回復	症例報告	当該製品	2006/9/26提出、識別番号1-04000344　完了報告 第7回症例番号112は前々々回報告における第4回症例番号12において報告したものの追加報告
113	感染症および寄生虫症	C型肝炎	日本	男	64	2005/2/19	⑥不明	症例報告	当該製品	2006/9/26提出、識別番号1-04000341　完了報告 第7回症例番号113は前々々回報告における第4回症例番号18において報告したものの追加報告
114	感染症および寄生虫症	B型肝炎	日本	女	68	2005/2/15	②軽快	症例報告	当該製品	2006/9/29提出、識別番号1-04000323　完了報告 第7回症例番号114は前々々回報告における第4回症例番号21において報告したものの追加報告
115	感染症および寄生虫症	B型肝炎	日本	女	69	2005/2/9	③未回復	症例報告	当該製品	2006/9/26提出、識別番号1-04000342　完了報告 第7回症例番号115は前々々回報告における第4回症例番号24において報告したものの追加報告
116	感染症および寄生虫症	C型肝炎	日本	女	3	2005/2/4	①回復	症例報告	当該製品	2006/9/29提出、識別番号1-04000322　完了報告 第7回症例番号116は前々々回報告における第4回症例番号27において報告したものの追加報告
117	感染症および寄生虫症	桿菌感染	日本	男	70	2005/2/2	②軽快	症例報告	当該製品	2006/9/26提出、識別番号1-04000324　完了報告 第7回症例番号117は前々々回報告における第4回症例番号28において報告したものの追加報告
118	感染症および寄生虫症	B型肝炎	日本	男	67	2005/2/1	①回復	症例報告	当該製品	2006/9/29提出、識別番号1-04000316　完了報告 第7回症例番号118は前々々回報告における第4回症例番号29において報告したものの追加報告
119	感染症および寄生虫症	C型肝炎	日本	女	70	2005/1/27	①回復	症例報告	当該製品	2006/9/29提出、識別番号1-04000318　完了報告 第7回症例番号119は前々々回報告における第4回症例番号30において報告したものの追加報告
120	感染症および寄生虫症	敗血症	日本	女	60	2005/1/26	②軽快	症例報告	当該製品	2006/9/26提出、識別番号1-04000307　完了報告 第7回症例番号120は前々々回報告における第4回症例番号31において報告したものの追加報告
121	感染症および寄生虫症	敗血症	日本	男	72	2005/1/21	⑥不明	症例報告	当該製品	2006/9/26提出、識別番号1-04000304　完了報告 第7回症例番号121は前々々回報告における第4回症例番号34において報告したものの追加報告
122	感染症および寄生虫症	C型肝炎	日本	女	52	2005/1/17	①回復	症例報告	当該製品	2006/9/29提出、識別番号1-0400321　完了報告 第7回症例番号122は前々々回報告における第4回症例番号38において報告したものの追加報告
123	感染症および寄生虫症	C型肝炎	日本	女	62	2005/1/12	⑥不明	症例報告	当該製品	2006/9/26提出、識別番号1-04000345　完了報告 第7回症例番号123は前々々回報告における第4回症例番号42において報告したものの追加報告

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124	感染症および寄生虫症	B型肝炎	日本	女	48	2004/12/29	①回復	症例報告	当該製品	2006/9/29提出、識別番号1-04000319　完了報告 第7回症例番号124は前々々回報告における第4回症例番号47において報告したものの追加報告
125	感染症および寄生虫症	細菌感染	日本	女	68	2004/12/28	②軽快	症例報告	当該製品	2006/9/26提出、識別番号1-04000293　完了報告 第7回症例番号125は前々々回報告における第4回症例番号48において報告したものの追加報告
126	感染症および寄生虫症	細菌感染	日本	男	67	2004/12/15	⑥不明	症例報告	当該製品	2006/9/13提出、識別番号1-04000274　完了報告 第7回症例番号126は前々々回報告における第4回症例番号51において報告したものの追加報告
127	感染症および寄生虫症	B型肝炎	日本	男	31	2004/12/13	⑥不明	症例報告	当該製品	2006/9/27提出、識別番号1-05000016　完了報告 第7回症例番号127は前々々回報告における第4回症例番号56において報告したものの追加報告
128	感染症および寄生虫症	細菌感染	日本	男	74	2004/11/26	①回復	症例報告	当該製品	2006/9/13提出、識別番号1-04000264　完了報告 第7回症例番号128は前々々回報告における第4回症例番号64において報告したものの追加報告
129	感染症および寄生虫症	C型肝炎	日本	女	66	2004/11/25	②軽快	症例報告	当該製品	2006/9/29提出、識別番号1-04000300　完了報告 第7回症例番号129は前々々回報告における第4回症例番号67において報告したものの追加報告
130	感染症および寄生虫症	菌血症	日本	女	1	2004/11/12	②軽快	症例報告	当該製品	2006/9/13提出、識別番号1-04000257　完了報告 第7回症例番号130は前々々回報告における第4回症例番号72において報告したものの追加報告
131	感染症および寄生虫症	C型肝炎	日本	女	84	2004/10/20	⑥不明	症例報告	当該製品	2006/8/10 提出、識別番号 1-06000094 未完了報告
132	感染症および寄生虫症	細菌感染	日本	男	80	2004/10/7	①回復	症例報告	当該製品	2006/9/13提出、識別番号1-04000234　完了報告 第7回症例番号132は前々々回報告における第4回症例番号93、94において報告したものの追加報告
133	感染症および寄生虫症	細菌感染	日本	男	80	2004/10/7	①回復	症例報告	当該製品	2006/9/13提出、識別番号1-04000234　追加報告 (132番と同一症例) 第7回症例番号133は前々々回報告における第4回症例番号93、94において報告したものの追加報告
134	感染症および寄生虫症	C型肝炎	日本	女	90	2004/9/27	⑥不明	症例報告	当該製品	2006/6/14 提出、識別番号 1-04000225 完了報告
135	感染症および寄生虫症	細菌感染	日本	女	49	2004/9/24	①回復	症例報告	当該製品	2006/9/25 提出、識別番号 1-04000216 完了報告
136	感染症および寄生虫症	細菌感染	日本	男	76	2004/9/13	②軽快	症例報告	当該製品	2006/9/20 提出、識別番号 1-04000211 完了報告
137	感染症および寄生虫症	敗血症性ショック	日本	女	63	2004/9/4	⑤死亡	症例報告	当該製品	2006/9/25 提出、識別番号 1-04000183 完了報告
138	感染症および寄生虫症	C型肝炎	日本	男	15	2004/8/25	③未回復	症例報告	当該製品	2006/6/30 提出、識別番号 1-04000184 完了報告
139	感染症および寄生虫症	B型肝炎	日本	男	74	2004/8/19	⑥不明	症例報告	当該製品	2006/6/30 提出、識別番号 1-04000181 完了報告
140	感染症および寄生虫症	B型肝炎	日本	女	35	2004/8/19	②軽快	症例報告	当該製品	2006/9/20 提出、識別番号 1-04000192 完了報告
141	感染症および寄生虫症	C型肝炎	日本	男	26	2004/8/16	⑥不明	症例報告	当該製品	2006/9/25 提出、識別番号 1-04000172 完了報告
142	感染症および寄生虫症	B型肝炎	日本	男	74	2004/8/5	③未回復	症例報告	当該製品	2006/9/19 提出、識別番号 1-04000207 完了報告

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	143	感染症および寄生虫症	B型肝炎	日本	男	26	2004/8/3	②軽快	症例報告	当該製品	2006/9/19 提出、識別番号 1-04000195 完了報告
	144	感染症および寄生虫症	C型肝炎	日本	女	87	2004/8/2	③未回復	症例報告	当該製品	2006/6/30 提出、識別番号 1-04000178 完了報告
	145	感染症および寄生虫症	敗血症	日本	男	55	2004/7/18	②軽快	症例報告	当該製品	2006/6/14 提出、識別番号 1-04000139 完了報告
	146	感染症および寄生虫症	細菌感染	日本	男	67	2004/7/11	①回復	症例報告	当該製品	2006/9/19 提出、識別番号 1-04000149 完了報告
	147	感染症および寄生虫症	菌血症	日本	男	67	2004/6/25	①回復	症例報告	当該製品	2006/6/14 提出、識別番号 1-04000125 完了報告
	148	感染症および寄生虫症	B型肝炎	日本	男	72	2004/6/10	⑥不明	症例報告	当該製品	2006/9/19 提出、識別番号 1-04000123 完了報告
	149	感染症および寄生虫症	B型肝炎	日本	男	60	2004/6/8	⑤死亡	症例報告	当該製品	2006/9/19 提出、識別番号 1-04000122 完了報告
	150	感染症および寄生虫症	B型肝炎	日本	女	80	2004/5/31	⑥不明	症例報告	当該製品	2006/9/25 提出、識別番号 1-04000210 完了報告
	151	感染症および寄生虫症	C型肝炎	日本	男	57	2004/5/11	③未回復	症例報告	当該製品	2006/9/27提出、識別番号1-05000014 完了報告 第7回症例番号151は前々々回報告における第4回症例番号119において報告したものの追加報告
	152	感染症および寄生虫症	C型肝炎	日本	女	71	2004/4/6	②軽快	症例報告	当該製品	2006/6/30 提出、識別番号 1-04000141 完了報告
	153	感染症および寄生虫症	B型肝炎	日本	女	1	2003/11/12	①回復	症例報告	当該製品	2006/6/14提出、識別番号1-04000275 完了報告 第7回症例番号153は前々々回報告における第4回症例番号137において報告したものの追加報告
	154	感染症および寄生虫症	C型肝炎	日本	男	77	2003/1/6	③未回復	症例報告	当該製品	2006/9/27提出、識別番号1-05000010 完了報告 第7回症例番号154は前々々回報告における第4回症例番号8において報告したものの追加報告
	155	感染症および寄生虫症	B型肝炎	日本	男	55	2002/2/8	⑥不明	症例報告	当該製品	2006/9/20 提出、識別番号 1-04000197 完了報告
	156	感染症および寄生虫症	B型肝炎	日本	女	56	2001/9/5	②軽快	症例報告	当該製品	2006/9/25 提出、識別番号 1-04000144 完了報告
	157	感染症および寄生虫症	B型肝炎	日本	女	67	1997/10/28	②軽快	症例報告	当該製品	2006/9/19 提出、識別番号 1-04000169 完了報告
第6回	6	感染症および寄生虫症	B型肝炎	日本	女	33	2006/3/23	⑥不明	症例報告	当該製品	2006/4/26 提出、識別番号 1-06000012 未完了報告
	29	感染症および寄生虫症	細菌感染	日本	男	83	2006/1/20	②軽快	症例報告	当該製品	2006/2/7 提出、識別番号 1-05000246 未完了報告
	30	感染症および寄生虫症	細菌感染	日本	男	83	2006/1/20	②軽快	症例報告	当該製品	2006/2/21 提出、識別番号 1-05000246 未完了報告
	56	感染症および寄生虫症	B型肝炎	日本	女	50	2005/12/2	③未回復	症例報告	当該製品	2006/1/11 提出、識別番号 1-05000236 未完了報告
	97	感染症および寄生虫症	B型肝炎	日本	男	40	2005/6/8	③未回復	症例報告	当該製品	2006/4/20 提出、識別番号 1-06000007 未完了報告
	2	感染症および寄生虫症	B型肝炎	日本	男	63	2005/04/01	⑧不明	症例報告	当該製品	2005/04/19 提出、識別番号 1-05000017 未完了報告
	4	感染症および寄生虫症	B型肝炎	日本	女	88	2005/03/22	③未回復	症例報告	当該製品	2005/04/06 提出、識別番号 1-05000003 未完了報告
	6	感染症および寄生虫症	C型肝炎	日本	女	61	2005/03/17	⑧不明	症例報告	当該製品	2005/04/12 提出、識別番号 1-05000012 未完了報告
	8	感染症および寄生虫症	C型肝炎	日本	男	79	2005/03/10	③未回復	症例報告	当該製品	2005/04/12 提出、識別番号 1-05000010 未完了報告
	9	感染症および寄生虫症	B型肝炎	日本	女	4	2005/03/08	③未回復	症例報告	当該製品	2005/04/06 提出、識別番号 1-05000005 未完了報告
	11	感染症および寄生虫症	C型肝炎	日本	男		2005/03/04	⑧不明	症例報告	当該製品	2005/04/12 提出、識別番号 1-05000009 未完了報告
	12	感染症および寄生虫症	B型肝炎	日本	女	73	2005/02/28	③未回復	症例報告	当該製品	2005/03/29 提出、識別番号 1-04000344 未完了報告
	18	感染症および寄生虫症	C型肝炎	日本	男	64	2005/02/19	③未回復	症例報告	当該製品	2005/03/23 提出、識別番号 1-04000341 未完了報告
	21	感染症および寄生虫症	B型肝炎	日本	女	68	2005/02/15	①軽快	症例報告	当該製品	2005/03/02 提出、識別番号 1-04000323 未完了報告
	24	感染症および寄生虫症	B型肝炎	日本	女	69	2005/02/09	③未回復	症例報告	当該製品	2005/03/23 提出、識別番号 1-04000342 未完了報告

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第4回	27	感染症および寄生虫症	C型肝炎	日本	女	3	2005/02/04	③未回復	症例報告	当該製品	2005/03/02 提出、識別番号 1-04000322 未完了報告
	28	感染症および寄生虫症	菌血症	日本	男	70	2005/02/02	①軽快	症例報告	当該製品	2005/03/02 提出、識別番号 1-04000324 未完了報告
	29	感染症および寄生虫症	B型肝炎	日本	男	67	2005/02/01	③未回復	症例報告	当該製品	2005/02/18 提出、識別番号 1-04000316 未完了報告
	30	感染症および寄生虫症	C型肝炎	日本	女	70	2005/01/27	⑧不明	症例報告	当該製品	2005/02/23 提出、識別番号 1-04000318 未完了報告
	31	感染症および寄生虫症	敗血症	日本	女	60	2005/01/26	③未回復	症例報告	当該製品	2005/02/10 提出、識別番号 1-04000307 未完了報告
	34	感染症および寄生虫症	敗血症	日本	男	72	2005/01/21	③未回復	症例報告	当該製品	2005/02/08 提出、識別番号 1-04000304 未完了報告
	38	感染症および寄生虫症	C型肝炎	日本	女	52	2005/01/17	①回復	症例報告	当該製品	2005/03/02 提出、識別番号 1-04000321 未完了報告
	42	感染症および寄生虫症	C型肝炎	日本	女	62	2005/01/12	⑧不明	症例報告	当該製品	2005/03/29 提出、識別番号 1-04000345 未完了報告
	47	感染症および寄生虫症	B型肝炎	日本	女	48	2004/12/29	①回復	症例報告	当該製品	2005/02/23 提出、識別番号 1-04000319 未完了報告
	48	感染症および寄生虫症	細菌感染	日本	女	68	2004/12/28	①軽快	症例報告	当該製品	2005/01/19 提出、識別番号 1-04000293 未完了報告
	51	感染症および寄生虫症	細菌感染	日本	男	67	2004/12/15	⑧不明	症例報告	当該製品	2004/12/28 提出、識別番号 1-04000274 未完了報告
	56	感染症および寄生虫症	B型肝炎	日本	男	31	2004/12/13	⑧不明	症例報告	当該製品	2005/04/19 提出、識別番号 1-05000016 未完了報告
	64	感染症および寄生虫症	細菌感染	日本	男	74	2004/11/26	①回復	症例報告	当該製品	2004/12/14 提出、識別番号 1-04000264 未完了報告
	67	感染症および寄生虫症	C型肝炎	日本	女	66	2004/11/25	①軽快	症例報告	当該製品	2005/02/02 提出、識別番号 1-04000300 未完了報告
	72	感染症および寄生虫症	菌血症	日本	女	1	2004/11/12	①軽快	症例報告	当該製品	2004/12/09 提出、識別番号 1-04000257 未完了報告
	93	感染症および寄生虫症	細菌感染	日本	男	80	2004/10/07	①回復	症例報告	当該製品	2004/11/10 提出、識別番号 1-04000234 未完了報告
	94	感染症および寄生虫症	細菌感染	日本	男	80	2004/10/07	①回復	症例報告	当該製品	2004/11/10 提出、識別番号 1-04000234 未完了報告
	119	感染症および寄生虫症	C型肝炎	日本	男	57	2004/05/11	③未回復	症例報告	当該製品	2005/04/19 提出、識別番号 1-05000014 未完了報告
	137	感染症および寄生虫症	B型肝炎	日本	女	1	2003/11/12	①回復	症例報告	当該製品	2004/12/28 提出、識別番号 1-04000275 未完了報告

60186	2006/12/20	日本赤十字社	人赤血球濃厚液	人赤血球濃厚液

MedDRA/J Ver. 9.0J

別紙様式第４

感染症発生症例一覧

	番号	感染症の種類		発現国	性別	年齢	発現時期（年/月/日）	転帰	出典	区分	備考
		器官別大分類	基本語								
第7回	7-1	感染症および寄生虫症	Ｃ型肝炎	ドイツ	男	59歳	2001/1/3	不明	症例報告	外国製品	識別番号：06000023　報告日：2006年11月9日 MedDRA: Version (9.0)
第6回	0*	0	0	0	0	0	0	0	0	0	
第5回	5-1	感染症および寄生虫症	Ｃ型肝炎	ドイツ	男	47歳	2005年	未回復	症例報告	外国製品	識別番号：05000417　報告日：2005年8月26日 MedDRA: Version (8.0)
第4回	1-1	臨床検査	Ｃ型肝炎抗体陽性	日本	男	76歳	2003/9/19	不明	症例報告	当該製品	登録番号：A03-120　報告日：2005年4月28日 第1回症例番号1-1において報告したもの（未完了報告）の取り下げ報告 MedDRA: Version (6.1)
第3回	3-1	感染症および寄生虫症	Ｂ型肝炎	ドイツ	男	55歳	2001年	不明	症例報告	外国製品	識別番号：04000030　報告日：2004年7月29日 MedDRA: Version (7.0)
第2回	2-1	感染症および寄生虫症	Ｃ型肝炎	ドイツ	男	69歳	不明	不明	症例報告	外国製品	識別番号：03000020　報告日：2004年2月10日 MedDRA: Version (6.1)
	2-2	臨床検査	Ｃ型肝炎抗体陽性	フランス	女	87歳	2003/12/18	不明	症例報告	当該製品	識別番号：03000022　報告日：2004年4月9日 MedDRA: Version (7.0)
	2-3	感染症および寄生虫症	Ｃ型肝炎	ドイツ	男	4歳	1998/6/10	不明	症例報告	外国製品	識別番号：04000006　報告日：2004年4月30日 MedDRA: Version (7.0)
第1回	1-1	臨床検査	Ｃ型肝炎抗体陽性	日本	男	76歳	2003/9/19	不明	症例報告	当該製品	登録番号：A03-120　（未完了報告 2003年10月3日） MedDRA: Version (6.1)

＊ 当該調査期間に対象となる感染症報告はなかった。

60191	2006/12/28	バクスター	該当なし

別紙様式第４

感染症発生症例一覧

	番号	感染症の種類		発現国	性別	年齢	発現時期 (年/月/日)	転帰	出典	区分	備考
		器官別大分類	基本語								
第7回	7-1	臨床検査	ＨＩＶ抗体陽性	アメリカ	不明	小児	不明	不明	症例報告	外国製品	識別番号： 06000022 (完了報告) 報告日：2006年8月24日 MedDRA: Version (9.0)
第6回	5-1	感染症および寄生虫症	Ｃ型肝炎	米国	男性	51歳	2005年9月	未回復	症例報告	当該製品	識別番号： 05000456 (追加報告) 報告日：2006年2月15日 第6回症例番号5-1は前回報告における第5回症例番号5-1において報告したものの追加報告 MedDRA: Version (8.1)
第5回	5-1	感染症および寄生虫症	Ｃ型肝炎	米国	男性	51歳	2005年9月	未回復	症例報告	当該製品	識別番号： 05000456 (追加報告) 報告日：2005年11月11日 MedDRA: Version (8.1)
	5-1	感染症および寄生虫症	Ｃ型肝炎	米国	男性	51歳	2005年9月	未回復	症例報告	当該製品	識別番号： 05000456 (完了報告) 報告日：2005年10月27日 MedDRA: Version (8.1)
	1-3	感染症および寄生虫症	Ｃ型肝炎	米国	男性	26歳	2002/11/19	不明	症例報告	当該製品	識別番号：03000006 (追加報告) 報告日：2005年7月4日 第2回症例番号1-3において報告したものの追加報告　MedDRA: Version (8.0)
	1-3	感染症および寄生虫症	Ｂ型肝炎	米国	男性	26歳	2002/10/4	不明	症例報告	当該製品	識別番号：03000006 (追加報告) 報告日：2005年7月4日 第2回症例番号1-3において報告したものの追加報告　MedDRA: Version (8.0)
	4-1	臨床検査	HTLV-1 血清学的検査陽性	フランス	男性	6歳	2005年	不明	症例報告	当該製品	識別番号： 05000001 (追加報告) 報告日：2005年6月27日 第4回症例番号4-1において報告したものの追加報告　MedDRA: Version (8.0)

別紙様式第４

	番号	感染症の種類		発現国	性別	年齢	発現時期（年/月/日）	転帰	出典	区分	備考
		器官別大分類	基本語								
第５回	4-1	臨床検査	HTLV-2 血清学的検査陽性	フランス	男性	6 歳	2005 年	不明	症例報告	当該製品	識別番号： 05000001（追加報告） 報告日：2005 年 6 月 27 日 第 4 回症例番号 4-1 において報告したものの追加報告　MedDRA: Version (8.0)
第４回	4-1	臨床検査	HTLV-1 血清学的検査陽性	フランス	男性	6 歳	2005 年	不明	症例報告	当該製品	識別番号： 05000001（追加報告） 報告日：2005 年 4 月 25 日 MedDRA: Version (8.0)
	4-1	臨床検査	HTLV-1 血清学的検査陽性	フランス	男性	6 歳	2005 年	不明	症例報告	当該製品	識別番号： 05000001（完了報告） 報告日：2005 年 4 月 7 日 MedDRA: Version (8.0)
	4-1	臨床検査	HTLV-2 血清学的検査陽性	フランス	男性	6 歳	2005 年	不明	症例報告	当該製品	識別番号： 05000001（追加報告） 報告日：2005 年 4 月 25 日） MedDRA: Version (8.0)
	4-1	臨床検査	HTLV-2 血清学的検査陽性	フランス	男性	6 歳	2005 年	不明	症例報告	当該製品	識別番号： 05000001（完了報告） 報告日：2005 年 4 月 7 日 MedDRA: Version (8.0)
	4-2	感染症および寄生虫症	C 型肝炎	フランス	男性	不明	不明	不明	症例報告	外国製品	識別番号： 04000129 報告日：2005 年 3 月 31 日） MedDRA: Version (8.0)

別紙様式第4

感染症発生症例一覧

	番号	感染症の種類		発生国	性別	年齢	発現時期	転帰	出典	区分	備考
		器官別大分類	基本語								
第7回	1	感染症および寄生虫症	B型肝炎	ドイツ	女	27	2006年6月	不明	その他	外国製品	弊社血漿分画製剤と原料血漿が同様の可能性のある症例
	1	臨床検査	B型肝炎表面抗原陽性	ドイツ	女	27	2006年6月	不明	その他	外国製品	弊社血漿分画製剤と原料血漿が同様の可能性のある症例
	1	臨床検査	抗HBs抗体陽性	ドイツ	女	27	2006年6月	不明	その他	外国製品	弊社血漿分画製剤と原料血漿が同様の可能性のある症例
	1	臨床検査	抗HBcIgG抗体陽性	ドイツ	女	27	2006年6月	不明	その他	外国製品	弊社血漿分画製剤と原料血漿が同様の可能性のある症例
	1	臨床検査	抗HBe抗体陽性	ドイツ	女	27	2006年6月	不明	その他	外国製品	弊社血漿分画製剤と原料血漿が同様の可能性のある症例
	2	感染症および寄生虫症	C型肝炎	ドイツ	男	37	不明	不明	その他	外国製品	弊社血漿分画製剤と原料血漿が同様の可能性のある症例
	3	感染症および寄生虫症	C型肝炎	ドイツ	女	41	2006/11/21	不明	その他	外国製品	弊社血漿分画製剤と原料血漿が同様の可能性のある症例 識別番号3-06000029　提出日2006年12月7日
	3	臨床検査	C型肝炎抗体陽性	ドイツ	女	41	2006/11/21	不明	その他	外国製品	弊社血漿分画製剤と原料血漿が同様の可能性のある症例 識別番号3-06000029　提出日2006年12月7日
	3	臨床検査	C型肝炎RNA陽性	ドイツ	女	41	2006/11/21	不明	その他	外国製品	弊社血漿分画製剤と原料血漿が同様の可能性のある症例 識別番号3-06000029　提出日2006年12月7日
	3	感染症および寄生虫症	C型肝炎	ドイツ	女	41	2006/11/21	不明	その他	外国製品	弊社血漿分画製剤と原料血漿が同様の可能性のある症例 識別番号3-06000029　追加報告提出日2006年12月20日
	3	臨床検査	C型肝炎抗体陽性	ドイツ	女	41	2006/11/21	不明	その他	外国製品	弊社血漿分画製剤と原料血漿が同様の可能性のある症例 識別番号3-06000029　追加報告提出日2006年12月20日
	3	臨床検査	C型肝炎RNA陽性	ドイツ	女	41	2006/11/21	不明	その他	外国製品	弊社血漿分画製剤と原料血漿が同様の可能性のある症例 識別番号3-06000029　追加報告提出日2006年12月20日
第6回	1	感染症および寄生虫症	C型肝炎	米国	不明	不明	2006年	不明	その他	外国製品	弊社血漿分画製剤と原料血漿が同様の可能性のある症例
	2	感染症および寄生虫症	C型肝炎	ドイツ	女	63	2005年11月	不明	症例報告	外国製品	弊社血漿分画製剤と原料血漿が同様の可能性のある症例 識別番号:3-06000004 提出日:2006/4/25
	2	感染症および寄生虫症	C型肝炎	ドイツ	女	63	2005年11月	不明	症例報告	外国製品	弊社血漿分画製剤と原料血漿が同様の可能性のある症例 識別番号:3-06000004 追加報告提出日:2006/4/27
	2	感染症および寄生虫症	C型肝炎	ドイツ	女	63	2005年11月	不明	症例報告	外国製品	弊社血漿分画製剤と原料血漿が同様の可能性のある症例 識別番号:3-06000004 追加報告提出日:2006/5/18

60200	2007/01/24	ZLBベーリング	ペプシン処理人免疫グロブリンG

別紙様式第4

感染症発生症例一覧

別紙(5)

	番号	感染症の種類		発生国	性別	年齢	発現時期	転帰	出典	区分	備考
		器官別大分類	基本語								
第7回	1	感染症および寄生虫症	B型肝炎	ドイツ	女	27	2006年6月	不明	その他	外国製品	弊社血漿分画製剤と原料血漿が同様の可能性のある症例
	1	臨床検査	B型肝炎表面抗原陽性	ドイツ	女	27	2006年6月	不明	その他	外国製品	弊社血漿分画製剤と原料血漿が同様の可能性のある症例
	1	臨床検査	抗HBs抗体陽性	ドイツ	女	27	2006年6月	不明	その他	外国製品	弊社血漿分画製剤と原料血漿が同様の可能性のある症例
	1	臨床検査	抗HBcIgG抗体陽性	ドイツ	女	27	2006年6月	不明	その他	外国製品	弊社血漿分画製剤と原料血漿が同様の可能性のある症例
	1	臨床検査	抗HBe抗体陽性	ドイツ	女	27	2006年6月	不明	その他	外国製品	弊社血漿分画製剤と原料血漿が同様の可能性のある症例
	2	感染症および寄生虫症	C型肝炎	ドイツ	男	37	不明	不明	その他	外国製品	弊社血漿分画製剤と原料血漿が同様の可能性のある症例
第6回	1	感染症および寄生虫症	C型肝炎	米国	不明	不明	2006年	不明	その他	外国製品	弊社血漿分画製剤と原料血漿が同様の可能性のある症例
	2	感染症および寄生虫症	C型肝炎	ドイツ	女	63	2005年11月	不明	症例報告	外国製品	本剤 識別番号:3-06000004 提出日:2006/4/25
	2	感染症および寄生虫症	C型肝炎	ドイツ	女	63	2005年11月	不明	症例報告	外国製品	本剤 識別番号:3-06000004 追加報告提出日:2006/4/27
	2	感染症および寄生虫症	C型肝炎	ドイツ	女	63	2005年11月	不明	症例報告	外国製品	本剤 識別番号:3-06000004 追加報告提出日:2006/5/18

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60202	2007/01/24	ZLBベーリング	乾燥濃縮人アンチトロンビンⅢ

別紙様式第４

	番号	感染症の種類		発現国	性別	年齢	発現時期 (年/月/日)	転帰	出典	区分	備考
		器官別大分類	基本語								
第3回	3-1	感染症および寄生虫症	C型肝炎	米国	女性	37歳	2004/5/21	不明	症例報告	当該製品	識別番号：04000023 報告日：2004年6月30日 MedDRA: Version (7.0)
	3-2	臨床検査	B型肝炎抗体陽性	米国	女性	63歳	2004/7/27	不明	症例報告	当該製品	識別番号：04000059 報告日：2004年9月7日 MedDRA: Version (7.0)
	3-2	臨床検査	A型肝炎抗体陽性	米国	女性	63歳	2004/8/16	不明	症例報告	当該製品	識別番号：04000059 報告日：2004年9月7日 MedDRA: Version (7.0)
	3-3	臨床検査	B型肝炎抗体陽性	米国	女性	50歳代	2004/9月	不明	症例報告	当該製品	識別番号：04000082 報告日：2004年10月20日 MedDRA: Version (7.1)
	3-3	臨床検査	A型肝炎抗体陽性	米国	女性	50歳代	2004/9月	不明	症例報告	当該製品	識別番号：04000082 報告日：2004年10月20日 MedDRA: Version (7.1)

別紙様式第４

	番号	感染症の種類		発現国	性別	年齢	発現時期（年/月/日）	転帰	出典	区分	備考
		器官別大分類	基本語								
第２回	1-3	感染症および寄生虫症	Ｃ型肝炎	米国	男性	26 歳	2003/8/30	軽快	症例報告	当該製品	識別番号：03000006 報告日：2004 年 1 月 7 日 第 1 回症例番号 1-3 において報告したもの（FAX 報告）の完了報告 MedDRA: Version(6.1)
	2-2	感染症および寄生虫症	Ｃ型肝炎	ドイツ	女性	6 歳	1994/6/21	未回復	症例報告	外国製品	識別番号：04000013 報告日：2004 年 5 月 27 日 MedDRA: Version(7.0)
第１回	1-1	臨床検査	Ｃ型肝炎ウイルス	米国	男性	不明	不明	未回復	症例報告	外国製品	識別番号：Ｄ03-31 報告日：2003 年 8 月 6 日 MedDRA: Version(6.1)
	1-2	臨床検査	Ｃ型肝炎ウイルス	米国	男性	不明	不明	未回復	症例報告	外国製品	識別番号：Ａ03-32 報告日：2003 年 8 月 6 日 MedDRA: Version(6.1)
	1-3	感染症および寄生虫症	Ｃ型肝炎	米国	男	26 歳	2003/8/30	軽快	症例報告	当該製品	FAX 報告 報告日：2003 年 11 月 19 日 （識別番号：03000006 2003 年 11 月 28 日） MedDRA: Version(6.1)

60196	2006/12/28	バクスター	乾燥イオン交換樹脂処理人免疫グロブリン

別紙様式第4

感染症発生症例一覧

	番号	感染症の種類		発生国	性別	年齢	発現時期	転帰	出典	区分	備考
		器官別大分類	基本語								
第7回	1	感染症および寄生虫症	B型肝炎	ドイツ	女	27	2006年6月	不明	その他	外国製品	弊社血漿分画製剤と原料血漿が同様の可能性のある症例
	1	臨床検査	B型肝炎表面抗原陽性	ドイツ	女	27	2006年6月	不明	その他	外国製品	弊社血漿分画製剤と原料血漿が同様の可能性のある症例
	1	臨床検査	抗HBs抗体陽性	ドイツ	女	27	2006年6月	不明	その他	外国製品	弊社血漿分画製剤と原料血漿が同様の可能性のある症例
	1	臨床検査	抗HBcIgG抗体陽性	ドイツ	女	27	2006年6月	不明	その他	外国製品	弊社血漿分画製剤と原料血漿が同様の可能性のある症例
	1	臨床検査	抗HBe抗体陽性	ドイツ	女	27	2006年6月	不明	その他	外国製品	弊社血漿分画製剤と原料血漿が同様の可能性のある症例
	2	感染症および寄生虫症	C型肝炎	ドイツ	男	37	不明	不明	その他	外国製品	弊社血漿分画製剤と原料血漿が同様の可能性のある症例
	3	感染症および寄生虫症	C型肝炎	ドイツ	女	41	2006/11/21	不明	その他	外国製品	弊社血漿分画製剤と原料血漿が同様の可能性のある症例 識別番号3-06000029　提出日2006年12月7日
	3	臨床検査	C型肝炎抗体陽性	ドイツ	女	41	2006/11/21	不明	その他	外国製品	弊社血漿分画製剤と原料血漿が同様の可能性のある症例 識別番号3-06000029　提出日2006年12月7日
	3	臨床検査	C型肝炎RNA陽性	ドイツ	女	41	2006/11/21	不明	その他	外国製品	弊社血漿分画製剤と原料血漿が同様の可能性のある症例 識別番号3-06000029　提出日2006年12月7日
	3	感染症および寄生虫症	C型肝炎	ドイツ	女	41	2006/11/21	不明	その他	外国製品	弊社血漿分画製剤と原料血漿が同様の可能性のある症例 識別番号3-06000029　追加報告提出日2006年12月20日
	3	臨床検査	C型肝炎抗体陽性	ドイツ	女	41	2006/11/21	不明	その他	外国製品	弊社血漿分画製剤と原料血漿が同様の可能性のある症例 識別番号3-06000029　追加報告提出日2006年12月20日
	3	臨床検査	C型肝炎RNA陽性	ドイツ	女	41	2006/11/21	不明	その他	外国製品	弊社血漿分画製剤と原料血漿が同様の可能性のある症例 識別番号3-06000029　追加報告提出日2006年12月20日
第6回	1	感染症および寄生虫症	C型肝炎	米国	不明	不明	2006年	不明	その他	外国製品	弊社血漿分画製剤と原料血漿が同様の可能性のある症例
	2	感染症および寄生虫症	C型肝炎	ドイツ	女	63	2005年11月	不明	症例報告	外国製品	弊社血漿分画製剤と原料血漿が同様の可能性のある症例 識別番号：3-06000004 提出日：2006/4/25
	2	感染症および寄生虫症	C型肝炎	ドイツ	女	63	2005年11月	不明	症例報告	外国製品	弊社血漿分画製剤と原料血漿が同様の可能性のある症例 識別番号：3-06000004 追加報告提出日：2006/4/27
	2	感染症および寄生虫症	C型肝炎	ドイツ	女	63	2005年11月	不明	症例報告	外国製品	弊社血漿分画製剤と原料血漿が同様の可能性のある症例 識別番号：3-06000004 追加報告提出日：2006/5/18

60227	2007/02/23	ZLBベーリング	人C1-インアクチベーター