10,000 for the prevalence, p. The successive rows show the probability of infection having come from the implicated plasma products, from any *one* of the 14 component (Red Cell) donors, and from the primary outbreak. It can be seen that in all scenarios, the first route strongly dominates. Note that these are illustrative figures, using assumptions subject to much uncertainty. Nevertheless, they do suggest that the infection is much more likely to have come from the plasma products, with the implied risk to the component donors remaining clearly below 1%.

Table 1: Relative probabilities of potential infection routes (omitting "non implicated plasma" products)

Prevalence, p	1 in 4,000		1 in 10,000	
Transmission probability, t1	0.5	1	0.5	1
Probability implicated plasma products	98%	97%	99%	99%
Probability of each of the 14 component donors	<0.3%	<0.3%	<0.1%	<0.1%
Probability primary	<0.3%	<0.3%	<0.1%	<0.1%

Note: these are illustrative calculations only. All figures are rounded to the nearest %, or (for small probabilities) indicate an upper bound.

Implicated and "Non-implicated" plasma products

25. Although the above analysis provides some robust conclusions about the infection routes considered so far, the calculations ignore one further factor: the chance of the infection having come from the "non-implicated" plasma products – i.e. those manufactured from plasma pools not *known to have* an infected contributing donor. The problem here is that because the pool sizes are so large (of the order of 20,000 donations each), there is a high probability that many of them did, in fact, contain infective donors even if one has not been identified. Crudely, if the prevalence were 1 in 10,000, one would expect each pool to contain about 2 infected donations.[3]

26. This argument does not entirely remove the distinction between implicated and non-implicated pools. Where there is known to be an infected contributing donor (and nothing is known about the rest), the other donors to that pool also have the same probability p of being infected. So with a prevalence of 1 in 10,000 and typical pool sizes of 20,000, one would reasonably expect a "non-implicated" pool to contain 2 infected donations and an "implicated" pool to contain 3. Nevertheless, this is not a great differential. The calculation suggests that unless the prevalence of infection is very low - much lower than considered here, there is only a modest difference in the risks posed by receipt of implicated and non-implicated plasma. This observation supports the existing policy of considering recipients of UK-sourced plasma products as a group, rather than

[3] More strictly, the expected number of infected donations in each pool will be subject to a binomial distribution. However, the distribution is not essential to the argument, especially for patients receiving high volumes of product sourced from many different pools, when these statistical fluctuations will tend to even out.

applying additional measures to those with known exposure to implicated batches.

27. This specific haemophilia patient had received such large quantities of Factor VIII – almost 400,000 units, the majority since 1980)] - that on these calculations, the cumulative risk from the "non-implicated" batches may well have exceeded that from the smaller number of "implicated" ones. This can be illustrated by considering the expected number of ID_{50} received via each route. This is illustrated in the second part of Annex A. In summary:

- If the two "implicated" pools contained 3 infected donations, this route would have exposed the patient to a total dose of 0.6 ID_{50}.
- If the other "non-implicated" pools each contained 2 infected donations, this route would have exposed the patient to an expected total of 24 ID_{50}.

28. Simple application of the linear dose-response model would then suggest that whereas Factor VIII from the two "implicated" pools would have contained a dose liable to transmit infection with a probability of 0.3, the large number of units sourced from "non-implicated" pools would have contained more than enough infectivity to transmit. Crudely, this suggests that the "non-implicated" pools represent the more probable source of infection, by a factor of just over 3.[4]

29. This last calculation is reflected in Table 2 below, for prevalence scenarios of both 1 in 10,000 and 1 in 4,000. However, we stress that this is very simplistic. It rests on accepting the linear model uncritically, and assuming that doses received on successive occasions can simply be added together in calculating an overall risk of infection. Nevertheless, the comparison between "implicated" and "non-implicated" routes is instructive, in showing how the sheer number of exposures may come to dominate the presence of a known infection.

Table 2: Relative probabilities of potential infection routes (including "non implicated plasma" products)

Prevalence, p	1 in 4,000		1 in 10,000	
Transmission probability, 11	0.5	1	0.5	1
Probability implicated plasma products	38%	38%	24%	24%
Probability of each of the 14 component donors	<0.03%	<0.03%	<0.02%	<0.02%
Probability primary	<0.03%	<0.03%	<0.02%	<0.02%
Probability non-implicated plasma products	61%	61%	76%	76%

Note: these are illustrative calculations only. All figures are rounded to the nearest %, or (for small probabilities) indicate an upper bound.

[4] Note that the differential between *infectious doses* is much greater, but the practical effect is limited by infection being regarded as certain once the dose reaches 2 ID_{50}. As seen in following paragraphs, the risk differential between routes is therefore more pronounced in lower-infectivity scenarios.

30. As can be seen, the previous conclusion about the low implied risk to each of the 14 component (red cell) donors still applies, with even greater force. However, these results also highlight something of a paradox. Combined with the infectivity scenario taken from the DNV assessment, the pool size / prevalence calculations suggest that many recipients of plasma products would have received very high infectious doses, *whether or not* they had received any "implicated" units with known linkage to an infected donor. This opens the question of why no clinical vCJD cases have been seen in the population of haemophilia / blood disorder patients designated as "at risk" because of their exposure to UK sourced blood products.[5] It might therefore be argued that the infectivity assumptions applied to plasma products are overly pessimistic.

31. Although this question is impossible to answer definitely, and in any case raises issues beyond the scope of this paper, it is appropriate to check that the conclusions we have already suggested about relative likelihoods would not be overturned were we to assume lower levels of infectivity in plasma derivatives. The DNV report itself suggests two possible methods for calculating the infectivity present in each plasma derivative, using different assumption about the effect of the various manufacturing steps. In line with the generally precautionary approach adopted by CJD Incidents Panel, the calculations so far use figures based on the more pessimistic of these. The less pessimistic alternative suggested by DNV (using the "highest single clearance factor" in the manufacturing process) leads to an infectivity estimate for Factor VIII that is lower by a factor of 4. However, it should also be noted that risk assessments carried out elsewhere take the clearance factors achieved at different stages to be at least partly additive, which would lead to much smaller infective loads.

32. In fact, reducing the assumed infectivity *increases* the relative chance of infection via "non-implicated" as compared to "implicated" plasma. For example, suppose the presumed infectivity in all the Factor VIII received was reduced by a factor of 100 (2 logs). Modifying the calculations in paragraph 27, this patient would then have received an expected:

- 0.006 ID_{50} from the two "implicated" pools (representing a transmission risk of 0.003)
- 0.24 ID_{50} from all the other "non-implicated" pools (representing an infection risk of 0.12).

33. Albeit with the same caveats as before about using the linear model to quantify the cumulative risks from successive doses, this suggests that the latter risk would outweigh the former by a factor of 40. Table 3 shows how the previous results for this patient would change, under this revised infectivity scenario. As can be

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5 *Possible* explanations include the following: that prevalence of infection amongst donors is much lower than in the scenarios considered here; that much more infectivity is removed during processing of plasma products than suggested by the DNV analysis; and/or there is a threshold dose-response effect and most recipients fall below this. Genotype effects may also be relevant (in providing resistance to infection or extending the time to clinical disease), but one would expect a substantial proportion of this group to be MM homozygotes – the most susceptible genotype.

seen, the previous conclusions still hold, in particular regarding the small implied risk to each of the 14 red cell donors.

Table 3: Relative probabilities of potential infection routes (including "non implicated plasma" products and using lower infectivity estimates for plasma products)

Prevalence, p	1 in 4,000		1 in 10,000	
Transmission probability, t1	0.5	1	0.5	1
Probability implicated plasma products	2%	2%	3%	3%
Probability of each of the 14 component donors	<0.05%	<0.09%	<0.05%	<0.09%
Probability primary	<0.09%	<0.09%	<0.09%	<0.09%
Probability non-implicated plasma products	97%	97%	97%	96%

Note: these are illustrative calculations only. All figures are rounded to the nearest %, or (for small probabilities) indicate an upper bound.

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Annex A: Application of DNV Risk Calculation to Factor VIII Units

(a) Implicated Donations

Key points: FHB4547

- There was one implicated (presumed infective) donation in a start pool of 26,303 donations (pool size supplied by Professor Frank Hill via email)
- Factor VIII is derived from cryoprecipitate, which has an estimated infectivity of 60 ID_{50}s / donation of infected whole blood according to the DNV model
- 70.45kg of cryoprecipitate was made from the start pool, of which 21.58kg was used in the FHB4547 batch
- This implies that (21.58kg / 70.45kg) of the 60 ID_{50}s made its way into the FHB4547 batch (18.38 ID_{50}s)
- 1,844 vials each of 500 units (iu) were made from the batch, which results in an estimate of 0.00997 ID_{50}s per vial or 1.99×10^{-5} ID50s per iu

Professor Frank Hill's report indicates that the index case received 8,025 units from this batch, giving an estimated 0.16 ID_{50} from the implicated donation.

Key points: FHC4237

- There was one implicated (presumed infective) donation in a pool of 21,330 donations (pool size again supplied by Professor Frank Hill)
- Factor VIII is derived from cryoprecipitate, which has an estimated infectivity of 60 ID_{50} / donation of whole blood
- 67.6kg of cryoprecipitate was made from the start pool, of which all was used in the FHC4237 batch
- This implies that the full dose of 60 ID_{50} made its way into the FHC4237 batch
- 5,074 vials each of 250 iu were made from the batch, resulting in an estimate of 0.0118 ID_{50} per vial or 4.73×10^{-5} ID_{50} per iu

Professor Frank Hill's report indicates that the index case received 1,000 units from this batch, giving an estimated dose of 0.05 ID_{50}.

Conclusion

In total, these calculations suggest that index case would have received an estimated 0.21 ID_{50} from the "implicated" donor. Using a linear dose-response model (where 1 ID_{50} translates into a transmission probability of 0.5 and 2 ID_{50} or more translates into transmission probability of 1) this represents a transmission probability of 0.104 or 10.4%.

(b) Non-implicated Donations

In addition to the implicated donations, we have also to consider the possibility of other donors contributing to a pool being infective. With pool sizes of the order of 20,000 donations, each pool will be likely to contain contributions from one or more infected donors by chance, unless p is very small. For implicated pools, these will be *in addition to* the "known" implicated donor.

With a prevalence of 1 in 10,000, one might therefore expect the two implicated pools to contain two *further* infected donations, taking the total from 1 to 3 per pool.

This would make the infective dose received via the implicated units three times that calculated above, i.e. a total of roughly 0.6 ID_{50}, yielding a transmission probability of 0.3.

This patient also received approximately 391,000 iu of UK-sourced Factor VIII plasma treatment *not* known to be associated with any infected donor. In round figures, this can be visualised in terms of 20 exposures to pools of 20,000 donors, each typically containing 2 donations from infected donors. The exact infective dose passed on to the patient will vary from batch to batch. However, the two examples given in part (a) suggest an eventual dose of 2-5 x 10^{-5} ID_{50} per unit, per infected donor. For illustration, therefore, suppose that each unit exposed the recipient to 6 x 10^{-5} ID_{50}, 400,000 such units would therefore have exposed the recipient to 24 ID_{50}.

別紙様式第 2-1

医薬品
医薬部外品　研究報告　調査報告書
化粧品

別紙 3-6

識別番号・報告回数		回	報告日 年　月　日	第一報入手日 2009 年 8 月 3 日	新医薬品等の区分 該当なし	総合機構処理欄
一般的名称			研究報告の公表状況	CONCEPT PAPER ON THE NEED TO UPDATE THE CHMP POSITION STATEMENT ON CJD AND PLASMA-DERIVED AND URINE-DERIVED MEDICINAL PRODUCTS (EMEA/CPMP/BWP/2879/02 REV. 1) http://www.emea.europa.eu/pdfs/human/bwp/25324609en.pdf	公表国 英国	
販売名（企業名）						

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
本報告では，欧州医薬品委員会（CHMP）のクロイツフェルト・ヤコブ病（CJD）と血漿・尿由来製剤に関する現行ガイダンスは 2004 年 6 月に発表されており，ヒト組織由来製剤と CJD および変異型 CJD（vCJD）について具体的には記載されていない。そのため，2004 年 6 月以降に得られたヒト組織中の感染性の異常プリオン蛋白に関連する，あるいは血漿・尿由来製剤による vCJD 感染リスクに関連する最新疫学データと新しい知見を踏まえてガイダンスを改訂する必要があることを発表している。2004 年から現在までに，白血球非除去赤血球輸血による vCJD 感染が 4 例報告されており，また，現在調査中ではあるが，ｖCJD に感染した供血者からの血漿製剤を投与された血友病患者 1 名の脾臓から異常プリオン蛋白が検出された事例についても考慮すべきであると述べている。血漿・尿由来製剤のメーカーは，製造過程でどの程度感染性を減弱することができるかを予測し，その情報を関係当局へ報告することが義務付けられているが，これらのデータに基づき必要ならばガイダンス中の提言を再検討するべきであり，また，2005 年および 2007 年に欧州医薬品審査庁（EMEA）で開催された CJD 感染リスクと血漿・尿由来製剤に関する会議での決定事項も新たなガイダンスに盛込む必要があることを報告している。さらに，血漿由来製剤のリスク評価に影響を与える可能性のある今後の状況についても考慮する必要性にも触れている（例として，献血時の vCJD スクリーニングテストの有用性について）。更新された提言は，3 ヶ月間の意見公募の後 2010 年に適用する予定である。	BYL-2009-0392 http://www.emea.europa.eu/pdfs/human/bwp/47271709en.pdf

報告企業の意見	今後の対応
この報告に沿い，現行ガイダンスの改訂が行われることで，更なる生物由来製剤の安全性の確保が保障されるものと考えられる。なお，弊社の血漿分画製剤の製造工程におけるプリオン除去能は 4log を上回ることが確認されており，弊社製剤による vCJD 感染リスクは極めて低いと考えられる。	現時点で新たな安全対策上の措置を講じる必要はないと考える。

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European Medicines Agency
Pre-authorisation Evaluation of Medicines for Human Use

London, 23 July 2009
Doc. Ref. EMEA/CHMP/BWP/253246/2009

COMMITTEE OF HUMAN MEDICINAL PRODUCTS (CHMP)

CONCEPT PAPER ON THE NEED TO UPDATE THE CHMP POSITION STATEMENT ON CJD AND PLASMA-DERIVED AND URINE-DERIVED MEDICINAL PRODUCTS (EMEA/CPMP/BWP/2879/02 REV. 1)

AGREED BY THE BIOLOGICS WORKING PARTY	June 2009
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	23 July 2009
END OF CONSULTATION (DEADLINE FOR COMMENTS)	31 October 2009

The proposed document will replace the CHMP Position Statement on Creutzfeld-Jakob Disease and Plasma-derived and Urine-derived Medicinal Products (EMEA/CPMP/BWP/2879/02 rev 1)

Comments should be provided using this template to alberto.ganan@emea.europa.eu

KEYWORDS	*Creutzfeldt-Jakob disease, vCJD, plasma-derived medicinal products, urine-derived medicinal products, prion infectivity reduction*

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1. INTRODUCTION

The last revision of the "CHMP position statement on CJD and plasma-derived and urine-derived medicinal products" (EMEA/CHMP/BWP/2879/02/rev.1) was published in June 2004.

The document is the current EMEA/CHMP guidance on CJD and vCJD and plasma-derived and urine-derived medicinal products. It includes recommendations for these products based on the knowledge on CJD and vCJD epidemiology, human tissue distribution of infectivity/abnormal prion protein and infectivity in blood.

2. PROBLEM STATEMENT

The current position statement dates from 2004. Additional information has been accrued in this field since 2004 including the finding of four cases of vCJD infection associated with blood transfusion of non-leucodepleted red blood cells.[1,2] TSE infectivity has also been detected in urine in some animal models[3,4,5,6] in the clinical phase of the disease.

The CHMP opinion and recommendations reflected in the position statement were based on the knowledge on CJD and vCJD at the time of publishing. The progress in the field during the subsequent years reinforces the need to update the content of the document and to review the recommendations for these products.

The current position statement covers plasma-derived medicinal products and urine-derived medicinal products. Currently, there is no specific guidance on CJD and vCJD and advanced therapy medicinal products based on human tissues.

3. DISCUSSION

The position statement needs to include the latest epidemiological data and to reflect any new findings regarding the distribution of infectivity/abnormal prion protein in human tissues and the risk of infectivity and transmissibility of vCJD by plasma-derived and urine-derived medicinal products.

The position statement should revise some of the statements, which were uncertain in June 2004 but where further evidence has now accumulated (e.g. the presence of vCJD infectivity in human blood). It should also take into account the outcome of the ongoing investigations following the detection of abnormal prion protein in the spleen of a haemophiliac patient who received a plasma-derived medicinal product from a donor that later developed vCJD.[7]

Manufacturers of plasma-derived and urine-derived medicinal products were required to estimate the potential of their specific manufacturing processes to reduce infectivity and provide this information to the relevant Competent Authorities. Based on the experience in the evaluation of these data, the recommendations should be re-discussed and revised if necessary.

The main conclusions of the two meetings regarding CJD risk and plasma-derived and urine-derived medicinal products held at EMEA in 2005 and 2007 respectively should also be incorporated in the current revision. Additionally, there is a need to update some of the references to the additional relevant EMEA guidance published (e.g. the guidance on the Investigation of Manufacturing Processes for Plasma-Derived Medicinal Products with Regard to vCJD Risk).

Furthermore, the updated position statement should also consider possible future situations which may have an impact on the risk assessment of plasma-derived medicinal products (e.g. the availability of a possible screening test for vCJD in blood donations).

The vCJD risk of medicinal products based on human cells and tissues will also be considered for discussion. A decision on whether the guidance and recommendations of the Position Statement should also cover these products will be discussed during the revision.

4. RECOMMENDATION

As already announced in the Biologics Working Party (BWP) work programme, an update of the CHMP position statement on CJD and plasma-derived and urine-derived medicinal products is recommended.

5. PROPOSED TIMETABLE

The appointment of the drafting group members and chairperson took place during the June BWP meeting. The updated CHMP Position Statement is intended to be adopted in 2010 following a 3 months' public consultation.

6. RESOURCE REQUIREMENTS FOR PREPARATION

A dedicated drafting group will be involved in the preparation of the revision of the CHMP position statement. Initially, the drafting group will meet by teleconference or virtual meeting system. Meetings at the EMEA involving the drafting group members and some co-opted members for specific topics may be needed at a later stage. A meeting with interested parties may be needed.

7. IMPACT ASSESSMENT (ANTICIPATED)

The updated position statement will have an impact on the recommended measures for human plasma-derived and urine-derived medicinal products.

8. INTERESTED PARTIES

Other EMEA Committees and Working Parties (including the Committee on Advanced Therapies (CAT), the Working Parties on Blood Products (BPWP), Cell-Based Products (CPWP) and on Gene Therapy Products (GTWP)) will be involved during the preparation. There will be liaison with the European Commission (DG Sanco) and ECDC. Internationally, there will be liaison with the WHO and with regulatory authorities in other regions. Interested parties with specific interest in this topic will be consulted, including EHC, EPPIC, IPFA and PPTA.*

9. REFERENCES

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* EHC: European Haemophilia Consortium
EPPIC: European Patients Primary Immunodeficiency Collaboration
IPFA: International Plasma Fractionation Association
PPTA: Plasma Protein Therapeutics Association

別紙様式第 2-1
番号 14

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 2009 年 6 月 18 日	新医薬品等の区分	厚生労働省処理欄

一般的名称	①②③④人血清アルブミン ⑤乾燥濃縮人血液凝固第Ⅷ因子 ⑥⑦乾燥濃縮人血液凝固第Ⅸ因子	研究報告の公表状況	FDA(Advisory Committee)/2009/06/16	公表国 アメリカ
販売名 (企業名)	①献血アルブミン 25%静注 5g/20mL「ベネシス」　(ベネシス) ②献血アルブミン 25%静注 12.5g/50mL「ベネシス」　(ベネシス) ③献血アルブミン 5%静注 5g/100mL「ベネシス」　(ベネシス) ④献血アルブミン 5%静注 12.5g/250mL「ベネシス」　(ベネシス) ⑤コンコエイトーHT　(ベネシス) ⑥クリスマシン M 静注用 400 単位　(ベネシス) ⑦クリスマシン M 静注用 1000 単位　(ベネシス)			

221 研究報告の概要

vCJD に関連した凝固Ⅷ因子製剤で 11 年前に治療をうけた英国の血友病患者の vCJD 感染についての最新の報告により、FDA は米国で承認されている凝固Ⅷ因子製剤のレシピエントのリスクと、それら製剤のリスク管理戦略を再評価した。FDA は 2006/12/15 の TSEAC の会議で「米国で採血された血漿から製造された米国承認の人血漿由来凝固Ⅷ因子製剤に関連した潜在性 vCJD リスク評価の素案」の前回版を公表した。2006 年以降、新しい情報が現れ、我々をリスク評価の更新へと刺激した。結果は、米国許可施設で製造された血液凝固第Ⅷ因子製剤を使用された重症型血友病 A あるいは重症フォン・ヴィルブランド病（3 型 vWD)患者における、vCJD 原因因子への曝露確率、曝露レベル及び vCJD 感染の可能性のあるリスクの見積もりの修正である。2006 年の FDA のリスク評価は、英国での vCJD 保有率予想は 1.8 人/100 万であり、2009 年の英国での vCJD 保有率の予想は 4.5 人／100 万であった。

最新のリスク評価の結果：年当りの曝露と vCJD リスクについての FDA の 2009 年の最新リスク評価の結果は、第Ⅷ因子インヒビターがなく、出血の治療を受けている血友病患者では、おおよそは 1.7×10^{-7} ivID50 /人/年（1/1200 万のリスク）と低く、第Ⅷ因子インヒビターがあり、免疫寛容療法の治療を受けていて予防的治療レジメに従っている血友病患者では、おおよそは 1.6×10^{-4} ivID50/人/年（1/12000 のリスク）と潜在的な曝露量はより高い。これは vCJD 感染因子を合計 4-6 Log 低減させる工程で製造された凝固Ⅷ因子製剤を使用された全ての血友病 A 患者の年当たりの潜在曝露推定値の比較である。推定値（2009 年 vs2006 年）の最も大きい差はⅧ因子インヒビターがあり、免疫寛容療法を必要とする予防療法を受ける患者においてであり、年当たりの曝露リスクは約 4.5 倍違った（7.3×10^{-6}vs1.57×10^{-6}）。

2009 年の FDA の vCJD 血液由来Ⅷ因子製剤リスト評価モデルの結果は、米国で承認されている凝固Ⅷ因子製剤からの vCJD 感染のリスクはおそらく非常に小さいだろうが、ゼロではないだろうというものであった。

英国 Health Protection Agency からの最近の報告を受けての再評価においても、FDA はリスクは極めて小さいと信じているとし、以下の点について TSEAC（海綿性脳症諮問委員会）に諮問した。1) FDA はこのリスク評価を変更すべきか？ 2) FDA は製剤のリスク低減のための手段の追加の推奨する考慮すべきか？、血漿分画製剤の警告ラベルを変更の推奨を考慮すべきか？、FDA が承認した血漿分画製剤を使用した患者の vCJD リスクに関連した FDA の広報（例えば、ウェブ）の変更の推奨を考慮すべきか？

使用上の注意記載状況・
その他参考事項等

代表として献血アルブミン 25%静注 5g/20mL「ベネシス」の記載を示す。

2. 重要な基本的注意

(1) 略

1) 略

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

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報告企業の意見	今後の対応	
英国Health Protection Agencyからの最近の報告を受けてFDAが行ったvCJD感染リスクの再評価についての報告である。 血漿分画製剤は理論的なvCJD伝播リスクを完全には排除できないため、投与の際には患者への説明が必要である旨を2003年5月から添付文書に記載している。2009年2月17日、英国健康保護庁(HPA)はvCJDに感染した供血者の血漿が含まれる原料から製造された第Ⅷ因子製剤の投与経験のある血友病患者一名から、vCJD異常プリオン蛋白が検出されたと発表したが、弊社の原料血漿採取国である日本及び米国では、欧州滞在歴のある献（供）血希望者を一定の基準で除外し、また国内でのBSEの発生数も少数であるため、原料血漿中に異常型プリオン蛋白が混入するリスクは1999年以前の英国に比べて極めて低いと考える。また、製造工程においてプリオンが低減される可能性を検討するための実験を継続して進めているところである。	本報告は本剤の安全性に影響を与えるものではないと考えるので、特段の措置はとらない。	

Transmissible Spongiform Encephalopathies Advisory Committee
21st Meeting, June 12, 2009

Holiday Inn
2 Montgomery Village Avenue
Gaithersburg, MD 20879

Topic I:

Modified FDA Risk Assessment for Potential Exposure to the Infectious Agent of Variant Creutzfeldt-Jakob Disease (vCJD) in US-licensed Plasma-Derived Factor VIII (pdFVIII)

ISSUE:

Plasma-derived Factor VIII (pdFVIII) products are used by blood clotting disorder patients with von Willebrand disease and some patients with hemophilia A. The announcement in February 2009 by health authorities in the United Kingdom that a vCJD infection had been recognized in a person with hemophilia treated with a UK manufactured "vCJD-implicated" pdFVIII 11 years earlier has prompted FDA to review the potential vCJD risk for US users of US-licensed pdFVIII products and current risk management strategies for such products.

Results from an updated FDA risk assessment model continue to indicate that the estimated risk of the potential for US-licensed pdFVIII products to transmit the agent of vCJD, the human form of "Mad Cow Disease," is highly uncertain but is most likely to be extremely small.

FDA seeks the advice of the Committee on whether additional risk reducing measures are needed (e.g. modifications to current donor deferral policies) to maintain the safety of plasma-derived biologic products and whether FDA should change its communications concerning the risks of vCJD associated with plasma derivatives.

BACKGROUND:

In February 2009 the Health Protection Agency of the United Kingdom (UK) reported a probable case of pre-clinical variant Creutzfeldt-Jakob Disease (vCJD) infection in a man over 70 years of age with hemophilia (http://www.hpa.org.uk/webw/HPAweb&HPAwebStandard/HPAweb_C/1195733818681). Post-mortem examination of the brain found no neuropathological changes suggestive of vCJD, however, examination of the spleen revealed abnormal accumulations of prion protein (PrP) typical of vCJD and not of other forms of CJD. The man, who was in his 70s at death, had been treated 11 years earlier with UK-sourced plasma-derived Factor VIII (pdFVIII) from a "vCJD-implicated" lot, i.e., a lot of pdFVIII manufactured from pooled plasma containing at least one donation from a person who later died of confirmed or probable vCJD.

Variant CJD is a fatal human neurodegenerative disease acquired through infection with the agent that causes bovine spongiform encephalopathy (BSE). vCJD infection is most often acquired by consumption of beef products from infected cattle. The first human cases of vCJD were reported in the UK in 1996 (Will 1996); as of May 2009, 211 definite or probable clinical cases of vCJD have been reported worldwide, 168 of them in the UK (http://www.cjd.ed.ac.uk/). In addition to food-borne cases, four presumptive "secondary" transfusion-transmitted infections with the vCJD agent have also been reported in the UK since 2003 (Llewelyn 2004, Peden 2005, Hewitt 2006, http://www.hpa.org.uk/webw/HPAweb&HPAwebStandard/HPAweb_C/1195733711457?p=1171991026241). Three of the transfusion recipients died of vCJD, while one had vCJD infection detected after death from an unrelated cause. Each person with a secondary vCJD infection had been transfused with red blood cells from donors who were asymptomatic at the time of donation but who later died from vCJD. The probable transmission of vCJD via transfusion of red blood cells in the UK increased the concern that products manufactured from the plasma component of human blood might also pose a risk of vCJD transmission. (Plasma of animals with scrapie—a transmissible spongiform encephalopathy [TSE] used to model vCJD—contains approximately 50% of the total infectious agent present in blood [Gregori 2004].)

After the first descriptions of vCJD, UK authorities, recognizing a possible risk of transmitting vCJD by products derived from human plasma, stopped using UK plasma in their manufacture and began to obtain plasma from the US (http://www.transfusionguidelines.org.uk/docs/pdfs/dl_ps_vcjd_2008-09.pdf). After the first reports of transfusion-transmitted vCJD, UK authorities took the additional step of notifying recipients of a number of plasma derivatives, such as coagulation factors VIII, IX, and XI, as well as antithrombin and intravenous immune globulins, that they might be at increased risk of vCJD and reminded surgeons and dentists to take reasonable precautions to prevent iatrogenic transmission of vCJD (http://www.advisorybodies.doh.gov.uk/acdp/tseguidance/tseguidance_annexj.pdf http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_081170?IdcService=GET_FILE&dID=155914&Rendition=Web).

In 1999, prior to the identification of transfusion-transmitted vCJD, FDA recognized a potential though unknown risk of transmitting vCJD by contaminated blood products. Therefore, consistent with advice from TSEAC, FDA recommended precautionary deferrals of blood and plasma donors who had traveled or lived for six 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. FDA added certain other measures to reduce potential risk, such as deferring any donor with a history of blood transfusion in the UK after 1979 (http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/BloodSafety/ucm095138.ht

m;
http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/BloodSafety/ucm095143.htm). Taken together, these steps were estimated to have excluded donors representing slightly more than 90% of the potential 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 since 1980. FDA has issued draft guidance containing such recommendations (FDA 2006).

Because BSE has been detected in so few US cattle (only three reported cases: two in US-born cattle and one in a cow imported from Canada [http://www.ars.usda.gov/research/publications/publications.htm?SEQ_NO_115=197033]), and because none of the three cases of vCJD recognized in the US appears likely to have resulted from exposure here (two cases in long-time UK residents and a third in a recent immigrant from Saudi Arabia), the risk that US plasma donors might have acquired vCJD infection from US beef is thought to be extremely low. (Because the likelihood of exposure of US donors to the BSE agent in US beef products was judged to be so much lower than likelihood of exposure in UK, its estimated contribution to overall risk seems negligible and—while not ignored in developing FDA Risk Assessments—was not included in the model summarized here.) However, it is possible that a few US donors might have been exposed to the BSE agent during travel or residence in the UK, France, or certain other countries of Europe; such donors are at an uncertain but increased risk for vCJD. A subset of such vCJD-infected donors might have contributed to plasma pools used to manufacture pdFVIII in the US. The FDA-recommended donor deferral policy probably eliminates most of the risk associated with vCJD-infected individuals; however, there could be residual risk from eligible donors who were nonetheless infected during brief stays in foreign countries (Yamada 2006) or from donors who should have been deferred by the screening process, but, for an unknown reason, were not.

FDA Risk Assessment for vCJD and pdFVIII

The recent report from the UK attributing vCJD infection in a person with hemophilia to treatment 11 years earlier with pdFVIII from an implicated batch prompted FDA to re-examine the potential vCJD risk for recipients of US-sourced pdFVIII. FDA presented a previous version of 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*" at the December 15, 2006 meeting of the TSEAC.

Since 2006, new information has emerged, prompting us to update the risk assessment. FDA is presenting an update of its 2006 computer-based simulation model to estimate the potential risk, to elucidate the most important factors determining the risk, and to identify feasible actions that might reduce the risk. The results are modified estimates of the probability of exposure, possible levels of exposure to the vCJD agent and the possible risk of vCJD infection in several types of patients with severe hemophilia A (HA) or with a severe form of von Willebrand disease (type-3 vWD) who have used pdFVIII product manufactured in US-

licensed facilities. The following overview briefly describes key elements of the FDA risk assessment for vCJD and pdFVIII as first presented and posted online in 2006 (FDA, 2006).

I. Overview of FDA 2006 Risk Assessment Model for vCJD and pdFVIII

Module 1. Estimates of vCJD Prevalence in UK

In our 2006 model, we used the possible UK prevalence of vCJD to estimate the possible prevalence in US plasma donors. The model assumed that the major source of vCJD infection in the US would probably be from plasma donors who traveled or lived in the UK, France or elsewhere in Europe since 1980 and were infected with the BSE agent during their stays.

Two different sources of information were used to estimate possible prevalence of UK vCJD:

- One estimate was based on epidemiological modeling predictions of the number of vCJD cases diagnosed in the UK and a number of assumptions (e.g., incubation period, time of infection, effectiveness of feed ban). The model estimated a prevalence of approximately ~1.8 cases per million persons of the genetically most susceptible genotype (homozygous for methionine at codon 129 of the gene encoding PrP [*PRNP* gene]) and allowed for the possibility that some infected people might have very long asymptomatic incubation periods or never become symptomatic (Clarke and Ghani 2005). The model relied on reports of overt clinical cases of vCJD—all of which, at the time of our FDA 2006 risk assessment, had been in persons homozygous for methionine at codon 129 of the *PRNP* gene. The number of expected cases was therefore restricted to the approximately 40% of the UK population having that genotype; no prediction was offered for the rest of the population.

- A second estimate for UK vCJD infection prevalence was generated using data from a survey of abnormal TSE-associated PrP (recently designated as PrP^{TSE} by a WHO Consultation (http://www.who.int/bloodproducts/cs/TSEPUBLISHEDREPORT.pdf)) in lymphoid tissues reported in 2004 (Hilton 2004), yielding a mean estimate of 1 case per 4,225 persons. The prevalence estimate was further adjusted to account for the difference in age distributions of patients whose tissues were surveyed and of blood donors.

Module 2. Estimates of vCJD Prevalence in US Donors and US Plasma Pools

This module estimated the number of US plasma donors potentially infected with the agent that is responsible for vCJD and, from that, the number and percentage of plasma pools potentially including donations containing the vCJD agent. This module used results of a travel survey of US donors to determine numbers of US plasma donors expected to be at increased risk for vCJD, including those with history of:

- Dietary exposure to BSE-contaminated beef during long-term travel or residence in UK, France and other European countries (since 1980);
- US military service in European countries where beef was obtained from the UK, including US military personnel and associated civilian employees and dependents posted on or residing near military facilities in Europe during certain years; and
- Transfusion with blood collected in Europe ("EuroBlood").

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

- Country of travel or residence,
- Specific duration of travel or residence,
- Years of travel or residence,
- Age of donor,
- Rate and frequency of plasma donation,
- Number of donations per pool, and type of plasma pool (Source Plasma or recovered plasma), and
- Effectiveness of donor deferral policies.

Module 3. pdFVIII Manufacturing and Processing

This part of the model calculated the likelihood and number of plasma pools potentially containing vCJD agent and the quantity of agent per plasma pool and FVIII vial based on:

- Probability of and predicted quantities of vCJD infectivity (as animal intravenous 50%-infecting doses [i.v. ID_{50}]) per donation and per pool,
- Reduction in quantity of 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 with hemophilia A to vCJD agent in pdFVIII was estimated in the model based on:

- Total quantity of pdFVIII used per year, and
- Estimated potential quantity of vCJD agent predicted to be present in the pdFVIII product.

The quantity of pdFVIII utilized by an individual patient depends on the severity of hemophilia and the treatment regimen employed. Those were estimated using data from a study sponsored by the US Centers for Disease Control (CDC) involving patients with hemophilia A in six states from 1993 through 1998. The FDA 2006 Risk Assessment provided outputs that estimated the annual exposures for several subpopulations of patients with severe hemophilia A in the following five clinical treatment groups:

- Patients requiring FVIII prophylaxis but having no FVIII inhibitor and no immune-tolerance treatment;
- Patients requiring FVIII prophylaxis but having FVIII inhibitor (i.e., needing more FVIII to maintain desired coagulation status);
- Patients requiring prophylaxis and having both inhibitor and immune-tolerance treatment;
- Patients requiring only episodic treatments and having no inhibitor; and
- Patients requiring only episodic treatments but having FVIII inhibitor.

Additional Module. VonWillebrand disease (vWD) in Adults (>15 yrs of age) and Young Persons (≤15 yrs of age)

We estimated risk for adult and juvenile patients with vWD in two clinical treatment groups, those requiring:

- Prophylaxis or
- Episodic treatments only.

II. FDA Modified Risk Assessment Model for vCJD and pdFVIII: Updates and Changes in Model Inputs of June 2009

Recently, new scientific information has emerged concerning susceptibility to infection with the vCJD agent. To date, only persons homozygous for methionine at codon 129 of the *PRNP* gene have developed symptomatic vCJD illness that meets the case definition for vCJD. Successful sequencing of the *PRNP* genes from two of the three PrP^{TSE}-positive appendix samples detected during the survey described above (Hilton 2004) found them to be from persons homozygous for valine (VV) at codon 129 (Ironside 2006). The fate of these two persons with *PRNP* codon-129 VV genotypes is not known, although no definite or probable cases of vCJD in persons with that genotype have been reported. One of the four transfusion-transmitted vCJD infections reported since 2003 was in a patient heterozygous for methionine and valine (MV) at that codon (Peden 2004). Furthermore, one individual with the *PRNP* codon-129 MV genotype—apparently not a transfusion recipient—was reported in the UK popular press (Telegraph, December 18, 2008) to have died with CJD suspected "...on a clinical basis only... [but] it does look more likely to be variant CJD than another form of prion disease."
(http://www.telegraph.co.uk/health/healthnews/3815384/Hundreds-could-die-as-scientists-identify-first-case-of-second-wave-vCJD.html).

Taken together, these recent findings suggest that it is now more reasonable to assume that the entire general UK population is at risk for vCJD infection, and this assumption has been incorporated throughout the FDA 2009 updated Risk Assessment. Unfortunately, there is still little information available on the duration of the incubation periods for vCJD-infected persons with *PRNP*-129 non-MM genotypes. We assumed that the incubation periods and duration of that part of the incubation period in which vCJD agent is present in blood of infected *PRNP*-129 non-MM individuals is potentially much longer than for *PRNP*-129 MM individuals.

Several inputs have been updated or added to modules 1 and 2 of the model since 2006. Three input parameters, listed below, have been updated since 2006, and three new inputs were recently added to the model to improve assumptions for susceptibility of recipients to vCJD infection.

Updated Inputs:

1. Prevalence estimation of UK vCJD infection
2. Prevalence of UK vCJD infection: Age of susceptible population
3. Time during incubation period when infectivity is present in blood

New Inputs:

4. *PRNP*-129 genotype susceptibility and genotype proportions in US population
5. Distributions of vCJD incubation periods for persons of different *PRNP*-129 genotypes
6. Age distribution of persons with asymptomatic vCJD infections

1. Prevalence Estimation of UK vCJD Infection (updated input)

A key assumption of the FDA vCJD Risk Assessment Model is that most infected donors in the US would probably have become infected through exposure to the BSE agent from consumption of BSE-contaminated beef products during travel to the UK, France and other countries in Europe since 1980. Because prevalence of vCJD infection is highest in the UK, the model used prevalence in the UK population and a relative-risk approach to estimate vCJD exposure, and therefore prevalence of vCJD infection, for US donors who traveled to the UK, France and other European countries. The actual prevalence of vCJD infection in the UK remains unknown and difficult to estimate because of the long incubation periods and because clinical illness appears only during the last few months or years of infection. Because of the uncertainties, the FDA 2006 Risk Assessment used the two different sources of information described above for estimating possible UK prevalence of vCJD infection: a high estimate based on a lymphoid-tissue survey (infection prevalence) and a lower vCJD case prevalence estimate based on registered overt vCJD cases. We still do not know which of the two estimates of UK prevalence of vCJD is better to estimate the possible prevalence of US donors having vCJD agent in their blood at the time of donation. We modified the lower vCJD prevalence estimate (Clarke-Ghani case-based estimate) for this 2009 update of the FDA Risk Assessment to assume that the entire population is susceptible to vCJD infection, including persons with all three possible *PRNP*-129 genotypes: MM, MV and VV. As noted above, the lower vCJD case prevalence estimate was derived using epidemiological modeling of actual reported cases to estimate probable future clinical vCJD cases in the UK (Clarke and Ghani 2005). This estimate of approximately 1.8 vCJD cases per million was used by FDA for the 2006 Risk Assessment. It had a number of limitations associated with its simplifying assumptions; those contributed to considerable uncertainty in final case estimates. Those simplifying assumptions included the intensity of human exposure to the BSE agent, influence of genetics and other factors on susceptibility to infection with BSE agent, length of vCJD incubation periods, and influence of age on exposure to the agent. An

additional limitation is the possibility that the prevalence of vCJD infection in the UK is higher than this estimate if there are people infected but who never develop the disease while still potentially spreading the infection, or—as seems increasingly likely—if some infected individuals become ill but only after an extremely long time.

The higher vCJD infection prevalence was estimated from testing results of a relatively small survey of tonsil and appendix tissue samples saved from UK patients; the samples were examined by immunohistochemistry, seeking accumulations of abnormal PrP^{TSE}. (Such accumulations of abnormal PrP^{TSE} were previously found at autopsies of patients who died with vCJD and in tissue fortuitously saved from surgery during the last two years of incubation period [Hilton 2002]). This approach yielded an unadjusted estimate of 1 vCJD-infected person in 4,225 (237 infections per million [Hilton 2004]) that was then adjusted for patient age and the distribution of reported age-specific vCJD rates. A limitation to this study, contributing to uncertainty of the estimate, was its lack of control by testing a statistically adequate number of similar tissues from non-BSE exposed populations, so that false-positive reactions cannot be ruled out, and specificity and positive-predictive values cannot be evaluated. It also remains unknown whether the finding of PrP^{TSE} in lymphoid tissues by immunohistochemistry, assuming reliability of the method for identifying sub-clinical or pre-clinical vCJD infections, accurately predicts the presence of vCJD agent in blood in a quantity sufficient to transmit infection by transfusion—now repeatedly demonstrated for blood during the last one to three years of incubation period for three donors who later became ill with typical vCJD. (This limitation also applies to the lower prevalence estimate.)

After accounting for the age distribution, incubation period, country, year and duration of travel, we used both prevalence estimates to predict the number of vCJD donations that might make their way into US plasma pools of various sizes. A brief summary comparing changes in the UK vCJD infection prevalence estimates between the FDA December 2006 Risk Assessment Model and the FDA June 2009 updated Model is provided in Table 1 below. The lower vCJD prevalence estimate used for the FDA 2006 Risk Assessment Model was ~1.8 per million; it assumed that vCJD-infected individuals would develop clinically overt vCJD only if they had the *PRNP* codon-129 MM (approximately 40% of the total population). The FDA 2009 Risk Assessment Model now assumes 100% of the population to be susceptible to vCJD infection, yielding a higher prevalence of ~4.5 per million (~1.8 per million x 100% / 40% = ~4.5 per million).

Table 1: Changes in UK vCJD infection prevalence estimates between the FDA December 2006 Risk Assessment Model and FDA June 2009 Updated Model

Input Parameter Name and Description	FDA Model December 2006	FDA Updated Model June 2009
UK vCJD Prevalence Estimates	1) LOWER vCJD Case Prevalence estimate: Predictive modeling estimates; implies initial prevalence ~1.8 per million* *Estimate based on Clarke and Ghani (2005), assumed only persons homozygous for methionine (MM) at codon 129 of *PRNP* gene would progress to develop clinically overt vCJD	1) LOWER vCJD Case Prevalence estimate: Predictive modeling estimates; implies initial prevalence ~4.5 per million* *Estimate based Clarke and Ghani (2005), assumes persons of all 3 *PRNP* genotypes to be equally susceptible to vCJD infection and that some might progress to develop clinically overt vCJD
	2) HIGHER vCJD Infection Prevalence estimate: starting prevalence based on PrP^{TSE} immunohistochemical surveillance study of tonsils and appendices of ~ 1 in 4,225# #Estimate based on Hilton et al (2004); assumed persons of all three *PRNP*-129 genotypes (i.e., entire general population)to be susceptible to vCJD infection	2) HIGHER vCJD Infection Prevalence estimate: starting prevalence based on PrP^{TSE} immunohistochemical surveillance study of tonsils and appendices of ~ 1 in 4,225# #Estimate based on Hilton et al (2004); assumed persons of all three *PRNP*-129 genotypes (i.e., entire general population) to be susceptible to vCJD infection

2. Prevalence of UK vCJD Infection: Age of Susceptible Population (updated input)

In the UK, vCJD has most often occurred in relatively young persons; the median age at onset of clinical signs is approximately 30 years. Because of this tendency for infection and clinical disease to occur in the relatively young, the FDA December 2006 Risk Assessment Model adjusted prevalence estimates to account for the age-specific rates of observed clinical cases in the UK, where "age" was the age at the onset of symptoms as described in Hilton (Hilton 2004).

The updated FDA June 2009 Risk Assessment Model incorporates an estimate of the age distribution of the population of persons at risk for or susceptible to vCJD infection. The approach further adjusts the age-specific rates of observed clinical cases in the UK at the onset of symptoms (Hilton 2004) that were used in our previous model (http://www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4271b1-index.htm) by subtracting the median incubation period, which is assumed to have a median duration of approximately 12 years (90% CI= 5-35). The resulting mathematical function effectively shifts the age distribution curve at the time of clinical onset left by approximately 12 years to produce a new distribution that represents the population of persons who are at risk or susceptible to vCJD infection (see Figure 1 below). This overall younger population (a median of

approximately 12 years younger) probably provides a better representation of the age distribution of the UK population most susceptible to vCJD infection.

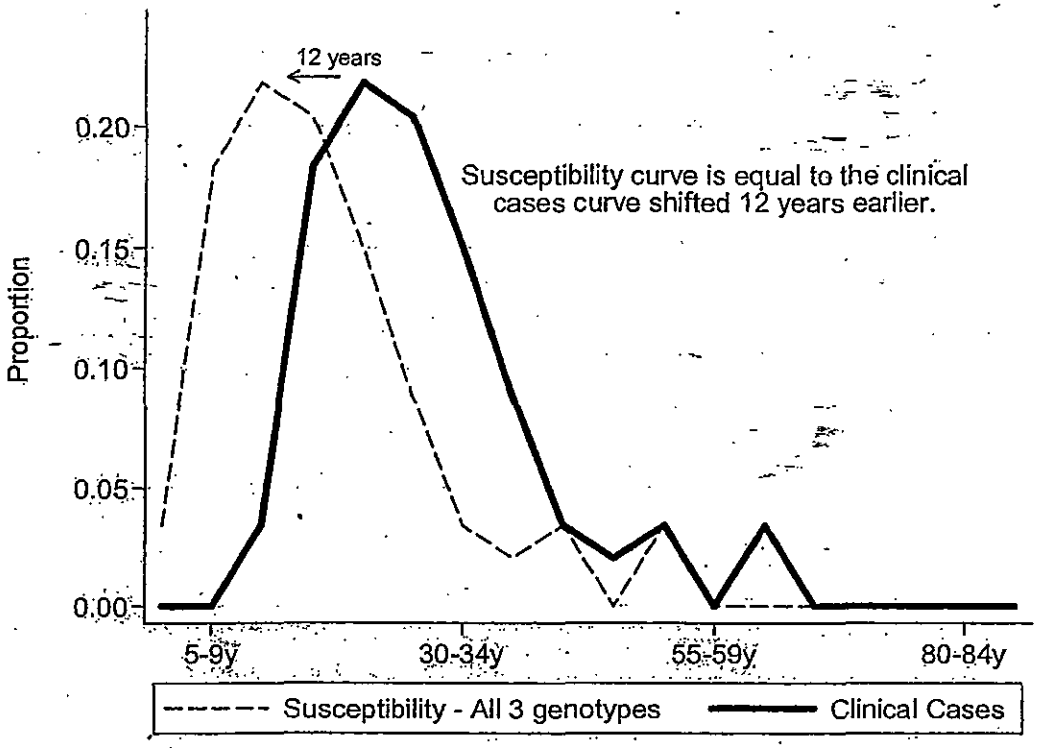

Figure 1. UK vCJD Prevalence: Age of susceptible population. Age of the susceptible population was derived using the distribution for age of persons at the time of clinical onset of vCJD in observed cases (Hilton 2004) and subtracting the median incubation period of approximately 12 years.

3. Time During Incubation Period when vCJD Infectivity Present in Blood (updated input)

The FDA December 2006 Risk Assessment Model assumed that infectious vCJD agent was present in blood of infected persons only during the last half of the incubation period. This assumption was based on a discussion at the October 31, 2005 TSEAC Meeting addressing vCJD risk for plasma derivatives. The updated FDA June 2009 Risk Assessment Model now assumes that infectious vCJD agent is most likely to be present in blood longer—during the last 75% of the incubation period (minimum=50%, maximum=90%). This assumption was updated to reflect results from recent findings from studies in animal models which suggest that TSE agents might appear in blood during the first third of the incubation period (Brown 2007).

4. *PRNP*-129 Genotype Susceptibility and Genotype Proportions in US Population (new input)

The FDA December 2006 Risk Assessment Model assumed that the genetic background of individuals in the population is one factor likely to be associated with susceptibility to vCJD infection. At that time, all known cases of overt vCJD (symptomatic individuals who met the WHO case definition of vCJD) had occurred in individuals with the homozygous *PRNP*-129-MM genotype. Research had revealed presumptive evidence of latent infection in two individuals homozygous for valine at that locus (*PRNP*-129-VV) (Ironside 2006) among the three samples of appendix containing accumulations of PrP^{TSE} reported by Hilton (Hilton 2004). (The third PrP^{TSE}-positive appendix tissue could not be genotyped.) However, because clinical vCJD had never been identified in any individual with a *PRNP*-129-non-MM genotype (*PRNP*-129-MV or *PRNP*-129-VV genotypes), it was impossible to estimate incubation periods for non-MM infected persons—except to conclude that they would be longer than those of *PRNP*-129-MM persons. Furthermore, it was even unclear whether these individuals would ever develop clinical illness or transmit infection. Therefore, to calculate the lower vCJD Case Prevalence estimate, the model assumed that only persons with the *PRNP*-129-MM genotype were susceptible and would—if they lived long enough—eventually develop clinical vCJD. MM persons were assumed to represent approximately 40% of the total donor population in the UK. Persons with *PRNP*-129-non-MM genotypes were not included in the calculation of the LOWER vCJD case prevalence estimate. For the higher vCJD Infection Prevalence estimate (based on the Hilton tissue survey), we assumed that persons of all *PRNP*-129 genotypes—MM, MV and VV—representing 40%, 50% and 10% of the total donor population, respectively were equally susceptible to vCJD infection.

The updated FDA June 2009 Risk Assessment Model now assumes for both the LOWER vCJD Case Prevalence estimate and the HIGHER vCJD Infection Prevalence estimate (based on the tissue survey) that all persons are equally susceptible to vCJD infection. We have also modified our 2006 assumption that only persons with the *PRNP*-129-MM genotype would develop overt vCJD, and our updated 2009 model assumes for the LOWER vCJD Case Prevalence estimate that at least some persons with *PRNP*-129-non-MM genotypes may eventually progress to develop overt vCJD but that many will probably remain asymptomatic for life. We again assume, for modeling purposes, that persons with the *PRNP*-129- MM, -MV, and -VV genotypes comprise 40%, 50% and 10% of the total donor population, respectively, in both the UK and US.

5. Distributions of vCJD Incubation Periods for Persons of Different *PRNP*-129 Genotypes (new input)

The FDA December 2006 Risk Assessment Model assumed a vCJD median incubation period of 13 years and mean incubation of 14 years for persons with the *PRNP*-129-MM genotype. Because little information was available on the incubation period for persons with the *PRNP*-129-MV and -VV genotypes, we assumed their incubation periods to be the same as for persons of the *PRNP*-129-MM genotype. The updated FDA June 2009 Risk Assessment Model assumes a median incubation period of 12 years (90% CI = 5-35) for persons with the *PRNP*-129-MM genotype.

Additional reports of *PRNP*-129-non-MM genotype individuals with immuno-histochemical evidence of vCJD infection detected post-mortem have been published in the literature (Peden 2004, Ironside 2006). Although no case reports of definite or probable vCJD in such

persons have been officially announced, a prudent assumption must be that some of them will eventually develop overt disease and that their blood may contain the infectious vCJD agent for a portion of the incubation period. However, the estimation of incubation periods for people with *PRNP*-129-non-MM genotypes remains complicated and more uncertain than for persons with the *PRNP*-129-MM genotype. Given this considerable uncertainty, we made simplifying assumptions to establish a distribution for the incubation periods of vCJD-infected people with the *PRNP*-129-non-MM genotype. Our updated model assumes the distributions for the incubation periods for vCJD infection to be the same for persons with *PRNP*-129-MV and -VV genotypes with a median of 32 years (90%CI; 25-55 years) and to be normally distributed. The high value of 55 years (95th percentile) was estimated based on the maximum incubation period for kuru (Collinge 2006).

6. Age distribution of persons with asymptomatic infection (new input)

The December 2006 FDA Risk Assessment Model assumed that the age distribution for persons with asymptomatic vCJD infections was the same as the distribution of ages of onset of clinical cases. The updated FDA June 2009 Risk Assessment Model calculates an "Age Distribution of Incubation Periods" (period of asymptomatic infections) by combining the "UK vCJD Prevalence: Age of susceptible population" (input #2, described above) and "Distribution of incubation periods" (input #5 described above).

Model Uncertainty

The ranges of uncertainty and variability in the input parameters of the risk assessment are great, resulting in very large uncertainty in the outputs that estimate potential risk. Uncertainty can result from lack of information or limited information, while variability is usually the inherent difference observed for a particular input parameter. Because scientific data regarding 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 risk of infection generated in the assessment may not be accurate. For those 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.

FDA believes it is nonetheless appropriate to share with the general public both the findings of possible risk and the uncertainties in our assessment for pdFVIII, because it is possible that the risk is not zero. We are seeking the advice of the TSEAC, meeting in June 2009, concerning the findings of the updated risk assessment and its interpretation, given the very wide range of uncertainty in the estimate of vCJD risk. We will also seek advice on steps that might help to estimate risks better and improve risk reduction.