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研究報告の概要

○複数ルートに曝露された患者のvCJD リスク評価算定
変異型クロイツフェルトーヤコブ病(vCJD)を発症しておらず、vCJDとは関係ない疾患により死亡した血友病患者の剖検時に、脾臓よりvCJD異常プリオンタンパク質が検出された。血友病患者または血漿分画製剤の治療を受けた患者に、vCJD異常プリオンタンパク質が見つかったのはこれが初めてである。
患者は、当該患者は、内視鏡手術、赤血球輸血、英国の血漿由来血液凝固第VIII因子製剤頻回投与等、複数のvCJD感染ルートに暴露された。vCJDに関する血液安全性改善のための措置が導入された1999年以前に英国内で供血された血液由来の凝固因子製剤による治療を受けたことが判明している。また、1996年に血漿の供血を行ってから6か月後にvCJDの症状を発現した供血者に由来する血漿から製造された第VIII因子製剤1ロットの投与を受けている。英国の供血者の潜在的なvCJD感染リスク(有病率約1:10000)を考慮すると、患者はvCJD発症ドナーが関連していない第VIII因子製剤によってvCJDに感染した可能性が最も高いと考えられた。

使用上の注意記載状況・その他参考事項等

赤十字アルブミン20
赤十字アルブミン25
赤十字アルブミン20%静注4g/20mL
赤十字アルブミン20%静注10g/50mL
赤十字アルブミン25%静注12.5g/50mL

血液を原料とすることに由来する感染症伝播等

報告企業の意見	今後の対応
変異型クロイツフェルトーヤコブ病(vCJD)を発症しておらず、vCJDとは関係ない疾患により死亡した血友病患者の剖検時に、脾臓よりvCJD異常プリオンタンパク質が検出され、vCJD発症ドナーが関連していない第VIII因子製剤によって感染した可能性が最も高いと考えられたとの報告である。	プリオン病の原因とされる異常プリオンが分画製剤製造工程で効果的に除去されるとの成績と併せて、これまでの疫学研究では如何なるプリオン病も、血漿分画製剤を介して伝播するという証拠は無かった。しかし、原因が特定されていないものの、本報告で初めて、第VIII因子製剤を介してvCJDに感染する可能性が示唆された。引き続きプリオン病に関する新たな知見及び情報を収集するとともに、血漿分画製剤の製造工程における病原因子の除去・不活化技術の向上に努める。なお、日本赤十字社は、CJD、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)、CJDの既往歴(本人、血縁者)、hGH製剤投与の有無を確認し、該当するドナーを無期限に献血延期としている。

(32)

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Department of Health

vCJD Risk Assessment Calculations for a Patient with Multiple Routes of Exposure

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Preface

This paper was developed in response to a request from the CJD Incidents Panel following the finding of abnormal prion protein in the spleen of a patient with haemophilia. Assuming that the abnormal protein represents a marker of vCJD infection, the paper sets the various possible routes through which such infection could have occurred, and considers their relative likelihood in various scenarios. As well as dealing with this specific "incident", the paper sets out a more general methodology for assessing multiple possible infection routes. The analysis was considered by the Panel at its meeting on 20th May 2009, and informed the advice subsequently issued. This version of the paper repeats the analysis presented to the Panel, while giving slightly more background information for other readers, and is placed here for public record.

Introduction

1. This paper offers an analysis of the recent finding of abnormal prion protein in the spleen of a haemophilic. This involves a patient exposed to a large number of potential vCJD infection routes (including multiple blood component transfusions, repeated receipt of UK-sourced fractionated plasma products including some units linked to a donor who later went on to develop clinical vCJD, and several invasive biopsies) who was found post mortem to have abnormal prion protein in a spleen sample.

2. If this finding is interpreted as an instance of asymptomatic vCJD infection, this raises questions as to the operational meaning of the "prevalence" of infection. The discovery of abnormal protein in a single spleen sample was the only positive result after exhaustive investigation of tissues taken at autopsy of an elderly haemophilia patient who died of other causes with no symptoms of vCJD or other neurological condition. All other tissues from this patient tested for the presence of abnormal prion protein – fixed samples of brain, heart, liver, blood vessel, appendix, spleen and lymph node and frozen samples of frontal lobe, occipital lobe, cerebellum, lymph node and 23 other samples from the spleen – were negative. This individual would not have tested "positive" on any of the vCJD prevalence tests conducted so far, and possibly not even in a post mortem spleen survey (depending on the size of spleen sample used). Nor do we know whether someone with this limited distribution of abnormal prion protein would be infective - and if so, by what routes of transmission.

3. For present purposes, however, these issues of interpretation are ignored. We simply assume that the abnormal prion protein found in this patient is a marker for asymptomatic vCJD infection: the task is then to investigate the relative likelihood of the infection having come from the various possible routes. This is done in order to inform discussion by the CJD Incidents Panel ("the Panel") as to the implications of the finding, and in particular whether the new evidence warrants any change to the "at risk" status of any individuals or groups.

4. The ideal would be to quantify these likelihoods in a robust way. However, this is not possible due to the multiple uncertainties involved. These are well-rehearsed. We do not know the prevalence of infectious donors – and in this instance, some of the potential routes are dependent on prevalence while others are not, so the relativities change. The probability of an infected blood component transmitting infection is uncertain - though on the precautionary approach adopted by the Panel, it is presumed to be substantial. The risks of an implicated plasma derivatives transmitting infection are even more uncertain. However, they can be estimated using methods suggested in an existing assessment by independent consultants DNV (DNV, 2003), which have been used in drawing up Panel recommendations to date. These calculations have also been regarded as "precautionary", i.e. giving a pessimistic view of the levels of infectivity likely to be present.

5. Given these unknowns, we make no attempt at definitive probability calculations, though illustrative examples are provided. Instead, we concentrate on the more limited task of determining whether different groups in the complex chain of contacts associated with the index patient can be robustly placed under or above

the additional 1% (over the UK population risk derived from consumption of beef and beef products) "risk threshold" used by the CJD Incidents Panel to trigger decisions on notification of increased risk status. We also consider the wider implications for groups that are or might be classed as "at risk". Although the analysis does throw some light on these questions, it also highlights some conundrums for our understanding of vCJD prevalence and transmissibility.

Summary of findings

6. Specifically, we conclude that on the evidence available:

   (i) **The chance of the patient having been infected via an endoscopic procedure is very small**, probably comparable to that of having been infected via primary (dietary) exposure. The potential risk associated with the endoscopies can be disregarded in assessing the risks associated with the possible blood-borne transmission routes, and no specific action is called for with regard to other patients on whom those endoscopes may have been used.

   (ii) Comparing the blood-borne routes, **the patient is much more likely to have been infected through receipt of plasma products, rather than any of the 14 units of red cells known to have been received.** The implied risk of each of these 14 donors being infected appears to lie below the 1% threshold that would trigger "at risk" status.

   (iii) Given the large pool sizes involved (of the order of 20,000 donations per pool), **the risk differential between "implicated" and "non-implicated" batches of blood product is not marked.** Unless the prevalence of infection is very low, there is a strong possibility of *any* given batch of blood products prepared from large pools sourced from UK donors in the period 1980-2001 containing at least one infected donation. This reinforces the logic of the CJD Incidents Panel's 2004 decision to consider all haemophilia and blood disorder patents exposed to such UK-sourced plasma products as an "at risk" group. There is no strong case for differentiating between sub-groups.

   (iv) Given the precautionary assumptions in the DNV risk assessment, any patient exposed to substantial quantities of UK plasma product (as this haemophilia patient was) would almost certainly have received a substantial infective dose, *whether or not* any of the batches were "implicated" (i.e. traceable to a donor who later went on to develop clinical vCJD). In fact, this patient may have been **more likely to have been infected by receipt of large quantities of "non-implicated" plasma, than by the smaller quantities of "implicated".**

   (v) The lack of any clinical vCJD cases to date amongst patients with haemophilia may suggest that the DNV infectivity scenario is overly-pessimistic. Risk assessments carried out elsewhere assume that a greater proportion of the infectivity would be removed during the manufacturing processes. This raises issues beyond the scope of this paper. Nevertheless, we have re-run the analysis using a markedly lower infectivity assumption with regard to plasma products, and the conclusions listed in (ii) – (iv) above still hold.

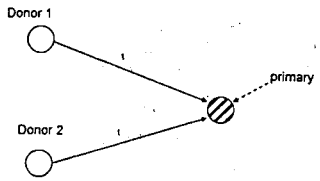
Method

7. The following analysis starts from the "reverse risk assessment" previously used by the Panel to assess the implied risks of donors to vCJD clinical cases being infected (DH, 2005a; Bennett, Dobra and Gronlund, 2006), and extends it to deal with this much more complex incident. We start with a simple example and then build up the analysis step-by-step. This is both to demonstrate how the conclusions are reached in this case, and to show how the same approach can be used to handle other complex incidents that may arise.

Example 1

8. We therefore start with a simple incident as shown in Figure 1(a). Here, a patient has received two single-unit Red Cell transfusions, one from each of two donors. The recipient goes on to develop vCJD, and the timing of the transfusions does not rule either of the donors out as the route of infection. What is the chance of each of these donors carrying vCJD infection?

Figure 1 (a) Two component donors, neither known to be infected



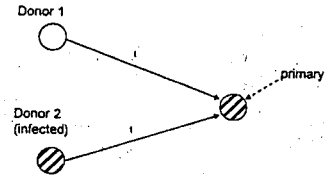
9. The answer to this depends primarily on the chance of transmission occurring *if* one of the donors were to be infected – i.e. the transmission probability, t. By definition, this lies between 0 and 1: if t = 1, transmission would be certain. In that case, and all else being equal[1], the patient's disease would be equally likely to have come from primary infection, or from either of the two donors having been infected. So by implication, each donor would have a 1 in 3 chance of being infective.[2] More generally, if there are n donors, the chance of each being infective would be 1/(n+1).

10. The implied risks to the donors clearly diminish if t <1. However, the CJD Incidents Panel has used a precautionary approach, concentrating on scenarios in which t is at least 0.5. With t in this range, the implied risk to donors remains high unless the number of donors to the vCJD case is large. For example, if t = 0.5, then with two donors the chance of either being infected would be roughly 0.25. Note that none of these calculations depend on the underlying prevalence of infection, provided this is the same for donors and recipients.

Example 2

11. The situation would clearly be very different if one of the donors was later diagnosed with vCJD, as in Figure 1(b).

Figure 1 (b) Two component donors, one known to be infected



This creates a marked asymmetry between the infection routes, dependent on the prevalence of infection in the donor population. Whilst Donor 2 is now known to be infected, Donor 1's prior probability of infection is simply the prevalence of infection (p), unknown but assumed to be small. This situation provides an exemplar for analyses in which some routes are prevalence-dependent and others are not.

Let:

P(D1) be the probability of the recipient's infection having come via Donor 1

[1] "All else being equal" essentially means that there is no prior reason to suppose that donors or recipient were particularly likely or unlikely to have been infected with vCJD, e.g. through "high risk" surgery, or conversely not having lived in the UK during years of high BSE exposure.

[2] The arguments expressed here can be expressed more formally using Bayes' Theorem to update probabilities in the light of new information. However, this is presentationally more clumsy, especially in the more complex examples considered below.

P(D2) be that of the infection having come via Donor 2

and P(prim) be the probability of the recipient having a primary infection

- For simplicity, suppose that the chance of the patient being infected by more than one route is negligible. Then (given that infection has occurred) P(D1), P(D2) and P(prim) must add up to 1.

- Furthermore, the "balance" between the three probabilities will be governed by t and p. Specifically:
    - P(D1) will be proportional to both p (prevalence of infection) and t (transmission probability)
    - P(D2) will only be proportional to t
    - and P(prim) will only be proportional to p

12. Provided p is small (e.g. 1/4,000 or 1/10,000) and t is not, P(D2) will be *much* larger than either of the other two probabilities. To a very close approximation, P(D2) = 1 and P(D1) and P(prim) are zero. We can be virtually certain that the infection came from Donor 2. In practical terms, this new information about Donor 2 means that Donor 1 need not be considered as "at risk" according to CJD Incidents Panel criteria.

Example 3

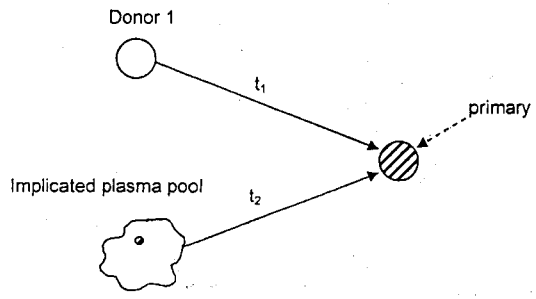
13. In the last two examples, the two secondary routes had the same transmission probability, t. But suppose now that there are routes with different values of t – e.g. transfusion of blood components and receipt of fractionated blood products. Figure 2 below shows a situation in which the calculations need to balance two contrasting secondary routes:

    - a blood component transfusion, associated with a high transmission probability (t_1) *if* the donor (D1) is infected, but with no reason to believe that this is the case, and
    - a plasma product pool with a contributing donor (D2) now known to be infected , but with a low transmission probability (t_2)

    As before, the three probabilities P(D1), P(D2) and P(prim) must add up to 1, and now:

    - P(D1) will be proportional to p and t_1
    - P(D2) will be proportional to t_2
    - and P(prim) will be proportional to p

Figure 2: One component donor, not known to be infected: plasma pool, containing an implicated donation



14. To illustrate numerically, suppose p is 10^{-4} i.e. prevalence of infection is 1 in 10,000, that $t_1 = 1$ and $t_2 = 10^{-3}$ (that is, transmission via the product pool is less efficient than via the transfused component by a factor of 1,000).

    In that case, it can be shown that:

    P(D1) = 1/12 P(D2) = 10/12 and P(prim) = 1/12

    The infected plasma pool is thus clearly the most likely transmission route, by a factor of 10 over each of the other two possibilities.

15. The principles used to analyse these simple cases are now extended to consider the case of the haemophilic patient with a finding of abnormal prion protein in the spleen.

Analysis

16. Potential secondary transmission routes in this instance consisted of the following (where an "implicated" donor means one for which there is now evidence of having been infected with vCJD):

    - 5 invasive endoscopic procedures (biopsies) and a larger number of endoscopies without biopsy.
    - exposure to 14 units of Red Cells, each from different ("non-implicated") donors
    - exposure to just over 9,000 units of Factor VIII made from two plasma pools with an "implicated" contributing donor (8,025 units from one batch and 1,000 from the other)

- exposure to many other units of UK-sourced pooled products, including nearly 400,000 units of Factor VIII, with no *known* links to "implicated" donors

To simplify the subsequent discussion, we consider the relative risks from each of these routes in turn.

Transmission risks from the endoscopies

17. vCJD transmission risks from endoscopy have been examined by an ACDP TSE WG subgroup, informed by an outline risk assessment. It is important to appreciate that these procedures involve a very small instrument (head) being passed down a very long, thin, channel. The possible "mechanics" of infection therefore differs from other surgical procedures. The group considered that any significant risk of onward transfer of infective material to a receptive site would require the procedure to be invasive, as distinct from examinations that involve the instrument sliding against the wall of the gut. On that argument, the relative risk from endoscopic procedures *not* involving biopsy would be negligible.

18. So concentrating on procedures involving biopsy, the question arises of whether the heads used would have been single-use. This would reduce the transmission risks considerably, but not eliminate them (due to the possibility of the new head being contaminated on its way down the endoscopy channel. Although we do not know whether the heads involved in these procedures were single-use, let us suppose they were not.

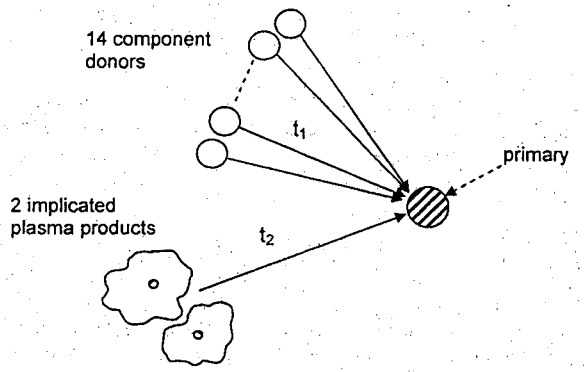
19. For endoscopy with re-useable heads, the best existing analogy is with the current surgical risk assessment as applied to procedures encountering lymphoid tissue. Depending on assumptions on the efficacy of decontamination, the "standard" model suggests that indefinite re-use of a set of instruments might cause 1 – 10 secondary infections per operation on an infective patient. The infection risk to a random patient resulting from all previous re-uses of the instruments would be in the same range multiplied by the prevalence of infection (p). However, the surgical model considers the transmission risks from a set of 20 instruments, rather than just one (very small) biopsy head. For the latter, it therefore seems reasonable to reduce the estimated risk by a factor of at least 10. Even on pessimistic assumptions, therefore, the risk of infection from a "random" biopsy would be in the range (0.1 – 1)p. In other words, the chance of the patient being infected via any of 5 such biopsies would be similar to the risk of having been infected through the "primary" route of dietary exposure.

20. As will be seen below, the chance of this particular patient having been infected by the primary route are very small (in all scenarios) as compared to that of infection through a blood-borne route. On the above argument, the same applies to the endoscopic route. For simplicity, this route will therefore be disregarded in the following calculations. It should be noted that even if the risks of transmission via endoscopy were much greater than suggested here, the only effect on subsequent calculations would be to reduce the probabilities associated with all the blood-borne routes slightly.

Blood components and "implicated" plasma products

21. We now consider the relative probability of the patient's infection having come from the implicated plasma products, versus the 14 Red Cell transfusions. As discussed in the "methods" section, we need to balance the greater transmission probability for blood components (Red Cells in this instance) against the existence of an implicated donor contributing to the pooled plasma products. The situation is shown schematically in Figure 3, omitting for now the other "non implicated" plasma products.

Figure 3: 14 component donors, none known to be infected; 2 plasma products, each from a pool containing an implicated donation



22. The key additional variable here is t_2 – the chance of transmission from an implicated pool. This can be quantified using the infectivity assumptions originally generated in DNV's risk assessment (DNV, 2003). As discussed further below, the calculations initially use the more pessimistic of alternative infectivity scenarios considered by DNV.

23. For the present, we also suppose that the *only* infected donation in the plasma pools came from the identified infected donor – though this is reconsidered below. As detailed in the first part of Annex A, calculations then suggest that this one infected donor would have resulted in the Factor VIII received by the patient containing a total infective dose of about 0.2 ID_{50} (0.16 via one pool and 0.05 via the other). Using the simple linear dose-response model that has informed Panel recommendations to date, this implies a transmission probability t_2 of approximately 0.1.

24. We can then use the approach set out before to assign probabilities to the possible infection routes in different scenarios. Table 1 below shows the results, using this value for t_2 and alternatives of 1 and 0.5 for t_1 and 1 in 4,000 and 1 in

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, t1	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 seen, the previous conclusions still hold, in particular regarding the small implied risk to each of the 14 red cell donors.

[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.

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 x 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 x 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。

(33)

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.*

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