23 June 2011
EMA/CHMP/BWP/782508/2010 - Corr.
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on 'CHMP position statement on Creutzfeldt-Jakob disease and plasma-derived and urine-derived medicinal products' (EMEA/CHMP/BWP/303353/2010)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	Baxter Innovations GmbH
2	Neil R. Cashman
3	Margaret Dow
4	FDA
5	GE Healthcare
6	IPFA
7	Dr. Y. Kuwabara (sent by Merck Serono)
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1. General comments – overview

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6	1. The CHMP position statement of June 2004 provides a measured and factual description of the status of vCJD as a potential threat to these products, so far as this could be established at the time of publication.	N/A
6	**2.** Since the publication of this statement, despite considerable scientific endeavour, progress has been disappointing in some important areas of TSE research. However, sufficient new information has become available during the last six years, to warrant updating the position statement. Much of this has been captured very usefully by the draft revision of this document. This new information has mixed implications for the potential TSE safety of plasma derived products. However, **IPFA does feel that such an amount of reassuring information is not taken enough into consideration in the draft position paper.** a. On the debit side, there have been a further three cases of vCJD in the recipients of blood components, provided by donors who subsequently developed vCJD. There is therefore no reasonable doubt, that the threat to labile blood components is real rather than theoretical. The detection of abnormal prion in only one of 26 samples of the spleen, but in no other tissues, of a haemophiliac who received a plasma-derived product from a donor who later developed vCJD is a further concern, although a causal relationship remains unproven, it is considered by the UK Department of Health to be probable.	The comment is acknowledged. Is is agreed that BSE continues to decline worldwide and the probability of further primary infections is diminishing. However, it is still difficult predict the future trend from the few cases that occurred in the very recent years in UK and other European countries. Considering the size of large plasma pools for fractionation and the number of plasma products produced from such pools, even very rare cases might implicate a large number of recipients. It is noted that a distinction between the possible numbers of the vCJD cases in the future and the prevalence of asymptomatic vCJD infections should be made. The figures for these two groups are not necessarily equivalent and there may well be large numbers of asymptomatic infections in the UK and other countries. We have no means at present of identifying these individuals and the prevalence rate in the UK in particular is difficult to calculate – an estimate of around 1/10,000 in the UK population appears to be reasonable.

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	b. On the credit side, cases of vCJD have continued to decline, and the epidemiological predictions continue to be refined. There remains the possibility of a second wave, involving genetically less susceptible individuals, but there is now general agreement that the final total is very unlikely to be as high as the most pessimistic estimates available in 2004. BSE continues to decline worldwide, so the probability of further primary infections is diminishing. It may be concluded that, although vCJD may present a genuine risk, at least to blood components, the magnitude of that risk to both blood and to plasma products produced today, has receded as the incidence of vCJD has declined.	
6	3. A donor screening test could provide an improved level of safety. Despite initial interest, and some promising developments, it now appears unlikely that a credible test will be available in the near future. The technical challenges involved in validating such a test remain formidable. The potential problems that would be introduced by any test of inadequate specificity would be daunting. In our opinion, a good confirmatory test would be an essential prerequisite to introducing a screening test for vCJD.	Agreed. The problem of few available samples from clinically affected patients has already been outlined in section 5.
6	4. One issue which remains as contentious as it was six years ago is the methodology of demonstrating TSE clearance. There has been a continued controversy over the relative methods of quantifying prion removal. There are essentially three options. - The first of these involves the use of an endogenous spike. This has been claimed by some to offer the most realistic	N/A (see point 5 below).

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	approach, and indeed this is implied in the draft revision of the 2004 position paper (line 372 – 374). The low titre associated with an endogenous spike means that the only possible quantification method is a bioassay. This approach will be discussed further (5). - The second involves spiking the model process stream with an exogenous prion protein, typically a mouse adapted CJD or a rodent adapted scrapie. The quantification method is a bioassay using the donor species. - The third, and the most widely used, involves spiking the model process step with an exogenous prion, often a hamster adapted scrapie. The quantification used is a biochemical method, typically a Western blot.	
6	5. The bioassay is more sensitive than the Western blot, and it measures infectivity based on pathogenicity rather than the presence of an immunologically reactive protein. Despite these advantages, there is little evidence that it is any more predictive of the ability of a process step to remove human vCJD than a biochemical assay. Indeed, equivalent results have been recurrently obtained in numerous comparative instances. A bioassay is extremely expensive and time consuming (sample processing takes 12 – 24 months). Since it provides little more assurance of vCJD safety than an in-vitro assay, its use is ethically highly questionable. The availability of suitably accredited facilities to carry out these assays is also limited. In our view, there has been no development to tilt the balance from biochemical methods, to the infectivity method for the purpose of routine	Agreed. The proposed text (lines 349-353) recognises that "*in most cases, the correlation between the capacity to partition PrP^{TSE} and infectivity has been demonstrated for the spiking preparations used until now (mainly brain homogenates of various strain*)". It is further stated in line 350 to 353: "*It is now confirmed that biochemical assays can be useful for spiking experiments to investigate manufacturing processes in a reasonable timeframe and less costly protocols than the in vivo bioassay*." However, there might be manufacturing steps where a correlation between biochemical assay and infectivity has not yet been investigated or remains unclear.

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	clearance studies.	Proposed modification (line 354): *However it is still necessary to correlate such results with those from infectivity assays in animals <u>in cases of novel assays, novel process elimination steps based on new mechanism or any other process step or detection method where such correlation is unclear.</u>*
6	6. Consequently, we welcome the changes to section 7 of the draft revision of the 2004 position paper. The new text (lines 349-353) recognises that "in most cases, the correlation between the capacity to partition PrP^{TSE} and infectivity has been demonstrated for the spiking preparations used until now (mainly brain homogenates of various strains)". The new text also confirms the value of biochemical assays in spiking experiments. In this context, we wonder if the original text (lines 353-354) might be better qualified to clarify that it is only novel biochemical assays or novel process elimination steps based on new mechanism, which are required to be correlated to infectivity assays in animals.	See above
6	7. We note the expansion of the section describing the need for further TSE research (lines 372 – 375). The two new research needs are "to investigate the partition and removal of endogenous infectivity" and "to gain better knowledge of the form of infectivity present in blood".	See comment no 9 below
6	8. These are legitimate ambitions for TSE research. However, there are severe problems associated with the use of an endogenous model. The amount of prion protein present is very small, so the clearance that can be demonstrated is very low. The approach involves using non-human plasma in the process models, consequently the credibility of the model (a key requirement of	See comment no 9 below

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	the CHMP guideline on the investigation of manufacturing processes) is highly questionable. It is completely unsuitable for modelling downstream processes, many of which offer the greatest potential for prion clearance.	
6	9. Consequently, it may be helpful to clarify that these new "needs" represent research ambitions, not requirements for the investigation of the clearance of TSE by manufacturer's processes.	Agreed, The text in section 7 has been modified and states: "There is a need to investigate the partitioning or removal capacities of the various fractionation steps used in the preparation of the plasma-derived medicinal products. (….) There is further need for research to gain better knowledge of the form of infectivity present in blood in order to confirm the relevance of the spiking material used in the validation studies.
6	10. The vCJD risk in France is now estimated to be 1/10 of that in the UK (line 499). In the 2004 document this risk was estimated as 1/20 of that in the UK. It may be helpful to clarify this, in view of the 2009 French Risk Assessment statement "these observations do not entail to revise upwards the current epidemiological estimations in France, nor the hypotheses on the asymptomatic vCJD agent carriers reservoir, whatever the genotype of these healthy carriers."[1].This is acknowledged in the position paper itself (line 489).	Epidemiological estimates and ratio of exposure between UK and France have been debated in the 2007 Expert Report (referred as 83b in the list of references). At this occasion, the ratio of exposure has been revised to 1/10. The 2009 Afssaps Report (ref. 83a) deals with the epidemiologic situation and case number estimation in France. The conclusions are reminded in the section "French Plasma and plasma from other BSE-exposed European conuntries". There is no contradiction between an upward revision of the ratio of exposure and a downward revision of the epidemiologic estimates.
6	11. As far as we are aware, PRP^{TSE} has still not been detected in the blood of vCJD cases, and this may have implications for the successful development of a screening test.	N/A

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6	12. The mandatory recall policy for medicinal products containing plasma derived products as excipients (line 573) could have (and has had) huge consequences for the provision of essential medicinal products. The introduction of risk assessment to the recall policies, in the case of a vCJD donor contributing to a pool, might be a very useful tool for decision making. It seems the position paper makes a categorical statement when, despite all reassuring evidence regarding robustness of prion elimination in the manufacturing process of plasma-derived excipients, (typically albumin) even a very small amount of albumin in a vaccine would still be considered as justifying withdrawal. An IPFA position paper on the issue of product recall will be submitted separately, to the BWP. This position paper is intended to amplify these comments, and to set out the IPFA position on the important issue of product recall. This paper addresses in particular section 9.2.4. "Recall of batches where information becomes available post donation".	The recommendation of batch recall when post donation information confirms vCJD donor is maintained. The number of vCJD cases is decreasing and the chance of a vCJD case to be a blood donor is relatively rare. Therefore the impact of the recommendation is limited. Plasma derived medicinal products used as excipients are incorporated in the final stages of the manufacturing process after the specific removal steps of TSE infectivity. The recommendation is maintained. In the case of albumin used as an excipient, a recall should be considered. However, a careful case-by-case risk analysis taking into account the prion reduction data and the amount of albumin incorporated in the medicinal product could justify not needing a recall. The document already states that: *A case-by-case consideration would be appropriate where plasma-derived products have been used in the manufacture of other medicinal products. This consideration would include the nature of the product, the amount used, where it is used in the manufacturing process and the downstream processing.*
6	13. The revised position statement otherwise retains the measured, science-based approach which distinguished the original 2004 document. Our suggested amendments to the text are listed below, in the format required by the template.	N/A
7	There seems to be no major problems with the content of this statement. It is important to manufacture the medical products	N/A

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	following this kind of statement.	
8	Since the last version of the CHMP Position statement, the following information has been collected on the risk of urine-derived product on transmitting prions. - Low levels of infectivity have been detected in urine of scrapie-infected rodents by several research groups and in the urine of deer with Chronic Wasting Disease[i]; - In view of these new data, the WHO tables on tissue infectivity[ii] has been updated in 2010 and urine was moved from the category of "tissues with no detectable infectivity" to the category of "lower-infectivity tissues". This last category is the same category as blood-derived products; - Furthermore, according to National CJD Surveillance Unit (UK) in a letter to editors[iii], 143 cases of vCJD have been reported in UK, of which 63 were females. One case with history of treatment for infertility (four cycles of urinary hMG and urinary hCG, and three cycles of recombinant FSH and urinary-hCG) was reported. It was concluded that there was not strong evidence the CJD has been acquired through the use of urinary gonadoptropins; - At that time, there was no evidence of prion presence in urinary gonadotropin products. However, recently, presence of human prions in some urinary hMG finished products have been detected, suggesting a potential risk for developing prion disease in using urinary hMG preparations (Kuwabara Y, et al. J Reprod Med 2009)[iv]; - Prion protein was also detected for the first time in two commercial urinary hCG preparations. These findings demonstrate that different purification processes for different	A reference that presence of PrP protein in urine has been reported has been included. While this is a necessary condition for the presence of the abnormal, infectious form, it is not evidence that infectivity is present, which derives from transmission experiments (refs 3.4 Position Statement).

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	urinary-derived preparations are unable to remove prion proteins from the source material and the process controls employed do not permit the identification of this major contaminant[v]; Furthermore, as mentioned in the draft position statement, the strength of evidence excluding transmission by urinary derived medicinal products is less secure compared to plasma products. In view of the above recent data, the risk of using urinary gonadotropins should be reconsidered.	
8	In view of the above described risks and since a great variety of non-gonadotropin urinary protein contaminants were identified in some urinary preparations that may affect the properties of these preparations[vi, vii, viii, ix] , the Company proposes that a unified warning statement for medicinal products sourced from human urine, covering all transmissible agents (and not only CJD) should be considered (in line with the Note for guidance on the warning on transmissible agent in SPC and PL for Plasma derived medicinal products – CPMP/BPWG/BWP/561/03). The warning statement could be as follows (similar as in France, Italy, Canada and Switzerland): "The drug substance of this medicinal product is sourced from human urine. Therefore the risk of transmitting infectious agents of known and unknown nature can not be totally excluded."	At the moment, the request for inclusion of any warning statement for urine derived medicinal products is done at a national level. This topic will be discussed in the revision of guidance on urine products, as reflected on BWP Working programme 2011.
8	Risk minimisation plan to prevent transmissible agents in urine-derived products should be described in the Risk Management Plan of the product (source, process and follow-up of patients).	

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2	This comment will be on the safety of injectable pharmaceuticals derived from urine donors. Recent data from many laboratories have demonstrated infectious prions in animal models of prion disease. Moreover, the commenter is in process of submitting a manuscript (near-final draft attached) demonstrating that prion protein and peptides are detectable by mass spectrometry in urinary derived fertility hormones, but not in recombinant product.	
9	i) The ability of established process steps (routinely used in the manufacture of plasma and urine derived products) to remove CJD infectivity is based almost entirely upon studies conducted with preparations (spikes) of infectious brain material. Brain derived infectivity is highly aggregated in the native state and infectious brain tissue has to be mechanically processed to yield a material that can be manipulated in liquid form. There is strong evidence from animal studies that the form of infectivity in homogenised brain-spike preparations may be in different (more aggregated) in comparison to soluble endogenous infectivity found in blood and plasma. In view of these findings, it cannot be assumed that established process steps found to be effective for the removal of TSE infectivity derived from crude brain homogenates will also be effective for removal of endogenous infectivity from plasma or urine. This is particularly true for process steps based on mechanical removal (such as centrifugation, depth filtration and nano-filtration) as opposed to methods based on specific prion capture (affinity ligands). ii) Existing processes used to manufacture plasma and urine derived products may not be safe with regard to the removal of potential CJD contamination. This has been brought into focus by the recent finding	i) The problems in using appropriate experimental spike preparations and interpretation of data have been outlined in this document and in Guideline CPMP/BWP/5136/03. A need for further research on this topic has been stipulated in this document. However, the data from characterization of so-called 'endogenous' infectious agent in human or animal plasma (e. g. aggregation status) is still limited. Further, prion aggregation status in starting plasma might be different to the aggregation status in a respective down-stream production intermediate, especially at steps involving protein precipitations or at manufacturing stages following such precipitation steps. Guideline CPMP/BWP/5136/03 proposed to investigate spiked material which has been pre-processed through such preceding precipitation steps (so called coupled steps studies). Such an approach might not be feasible using infectious plasma from rodents because the amount of infectivity in the animal plasma is too limited.

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	of a UK haemophiliac found to be incubating vCJD with the strong suspicion this was contracted from a contaminated plasma-derived product (Factor VIII). Whilst UK sourced plasma is no longer used for the manufacture of plasma products, this case demonstrates that CJD infectivity can pass from plasma to the final purified product. Consequently existing and new processes should be critically appraised for their ability to remove vCJD and the adoption of process steps specifically designed to reduce prions should be encouraged. A recent expert review publication concludes "further research is required to define the safety of plasma products" [Reference: J. Coste, C. Prowse, R. Eglin, C. Fang; A report on Transmissible Spongiform Encephalopathies and Transfusion Safety, Vox Sanguinis, Vol.96, Issue 4, pp 284–291, May 2009]. iii) It is concerning that the agency is advocating a very different approach to prions in comparison to the universally accepted procedures to minimise viral transmission. All plasma protein manufacturing processes are expected to have robust measures to minimise the risk of viral transmission and each process has to be validated for its ability to remove/inactivate virus to a safe and acceptable level. The agency position proposed for CJD suggests that processes for plasma derived products do not need to be validated for prion removal provided published data exists to suggest "the [CJD] removal capacity can be expected to be comparable". Virtually all of the published data relating to prion removal from plasma products is derived from a very artificial situation (homogenised brain infectivity) and there is strong evidence from animal studies to suggest processes which remove brain derived TSE infectivity may not necessarily remove the form of TSE infectivity present in plasma. NB: leucofiltration was originally thought to safeguard blood against vCJD	ii) The need for careful characterization or the prion reduction capacity of manufacturing processes is a central topic of this document. iii) The step-wise approach was chosen considering the various practical experimental limitations (e.g. laboratory capacity for validation of all products and process steps using a bio-assay would be too limited and such an approach would be very time consuming) as well as the uncertainties about the appropriate experimental design and interpretation of such data. Therefore, prion reduction studies have been termed "investigational studies" rather than "validation studies" and cannot be regarded equivalent to validation studies on virus reduction. However, the approach proposed by CHMP includes a specific case by case assessment of ALL plasma-derived medicinal products on the market or applications for marketing authorisation which is considered in line with a precautionary principle. iv) The importance of reliable prion reduction capacity is recognised. In the step-wise approach as outlined in fig. 1 of the document, implementation of additional process steps which may increase reduction capacity has already been included as the ultimate requirement if the overall reduction capacity of the manufacturing process is found limited. v) See comment above

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	contamination but was subsequently found not to be effective for the removal of soluble (endogenous) plasma infectivity. The proposed strategy set-forth in Figure 1 poses a risk of CJD contaminated plasma products in the event a plasma unit from a donor incubating vCJD is incorporated into a plasma pool used for the manufacture of plasma products. The proposed strategy appears inconsistent with the application of the Precautionary Principle (a statutory requirement under European Law) and a disincentive to manufacturers to develop safer plasma products. We strongly urge the Agency to adopt the position that ALL processes used to manufacture plasma and urine products should be validated for their ability to reduce TSE's to a safe level and the validation methods used should incorporate a form of TSE infectivity spike which represents as closely as possible the form of TSE infectivity encountered in plasma (endogenous infectivity). The infectivity spike used should have a known TSE infectivity titre established by bioassay. Also, the use of highly aggregated brain-spike materials as a source of infectivity should be discouraged as the resulting data may be highly unreliable as an indicator of the removal of endogenous infectivity. iv) Throughout the draft position paper there is a presumption that prion removal by use of specific chromatography resins/membranes is somewhat experimental in nature and not proven or reduced to practice. In this respect the referenced literature is out of date as proven prion-reduction technologies exist which are now used routinely in connection with the manufacture regulated blood and plasma products. In particular, a prion binding affinity resin has been incorporated into	

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	the P-Capt® filter designed for prion-filtration of red cells. This product received CE Mark approval in 2006 and has been extensively investigated in multiple efficacy and safety (clinical trial) studies. In November 2009, the UK Advisory Committee on the Safety of Blood, Tissues and Organs (SaBTO) recommended adoption of the P-Capt filter to the UK Department of Health for prion filtration of red cells transfused to children. This recommendation was based in-part upon the successful completion of an independent efficacy study sponsored by the UK National Blood Service. Secondly, a prion-binding affinity resin has been successfully incorporated into the manufacturing process for a solvent-detergent treated plasma product (Octaplas® LG) where it has been proven to provide a substantial increase in product safety with respect to TSE agents. Octaplas LG has been approved for clinical use in individual European states including Germany and Switzerland. Given these advances, we urge the Agency to amend the way in which the status of prion-reduction technology is described in the draft position paper. Furthermore, we urge that serious consideration is given to the incorporation of specific prion-reduction steps in manufacturing processes for plasma and urine-derived products to provide a robust defence against the possibility of CJD contamination. v) Available evidence suggests sporadic CJD is infectious but not transmissible by transfusion so of lesser concern in comparison to vCJD. However there are still many aspects of human prion diseases that are poorly understood. In particular, virtually all confirmed cases of vCJD to date have been individuals with MM genotype at codon 129. Very few individuals of MV or VV genotype have been linked with	

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	vCJD, though it is known from similar prion diseases such as Kuru that individuals of MV or VV genotype are susceptible to prion disease; though perhaps with a longer incubation time (which creates the possibility of a silent carrier state passing on infection to the next generation by secondary transmission). However, it remains a mystery that more MV and VV cases have not been identified to date which has led to speculation that individuals of non-MM genotype may present different symptoms or pathology leading to miss-diagnosis and potential confusion with sCJD (http://www.prion.ucl.ac.uk/research/mrc-research-groups/transgenics/). Data published by the CJD Surveillance Unit (Edinburgh, UK) indicates a progressive and unexplained increase in sCJD cases at a time when vCJD cases have risen and declined. Given the potential for confusion between vCJD and other neuropathological diseases, it would be prudent to exercise caution with respect to sCJD, particularly in situations where a plasma or urine donor is subsequently diagnosed with sCJD and their plasma or urine was incorporated into a pool used for the manufacture of therapeutic products. The development of robust manufacturing processes with a proven ability to deplete a wide range of human and animal prions should be encouraged. This would also afford protection against new human or animal-derived prion diseases in the future.	
4	The document repeatedly refers to "genetic" CJD. Although that terminology is often used, others use the term "familial" CJD. The term "genetic" seems to accept the prion hypothesis, positing that the familial disease represents a spontaneous misfolding of the prion protein induced by one of several mutations and that the misfolded protein becomes an infectious TSE agent/prion. An alternative hypothesis--that the mutations found in families with CJD and similar	The term “genetic” CJD is widely used to cover a range of prion diseases associated with mutations or pathogenic insertions in the human prion protein gene. Many of these individuals are identified only as a consequence of clinical diagnosis and genetic analysis since a clear cut family history is not always obtained. For this reason, the term “familial” CJD is not considered appropriate.

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	diseases confer a greatly increased susceptibility to infection with an exogenous agent--remains tenable. Introduction of mutations into the PrP-encoding genes of engineered cells and mice does not appear to generate a true infectious agent. The term "familial" avoids the controversy.	

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
49-52	10	Comment: Absence of evidence is not evidence of absence. Epidemiology also provides little reassurance that transmissions do not occur. Sentence 2, "There is no change…" implies that the justification for rescinding recalls is based on a lack of epidemiological evidence for transmission. To the contrary, the rational is that for plasma pools of 100,000 donors or more the frequency of donation by a CJD infected donor must be nearly 1. This is based on an annual incidence of $1/10^6$ an incubation time of ten years or so and a resulting prevalence of incubating cases of at least $1/10^5$. There is currently no way to differentiate pools with recognized CJD donors from those without. Since it is likely that most are exposed, claiming one pool is safer than another on the basis of having circumstantially recognized an infected donor in one but not the other is misleading to both recipients of from the recalled pool and to those receiving product from un-recalled pools. Neither is at any more or less risk than the other and yet the individuals that are notified of an exposure are sometimes devastated by this information.	The wording is maintained. The (limited) epidemiological studies have been outlined in the respective section of the document. Sentence 2: Agreed. It is noted that the usual size of plasma pools is about 10,000 donations rather than 100,000 donations.
57	4	The vCJD agent was not detected in the patient of concern; the abnormal form of prion protein (PrPTSE) generally taken as a surrogate marker for vCJD infection was detected in his spleen. Infectivity studies would be needed to confirm the	Term is changed to abnormal prion protein.

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		presence of "agent" and those have not been reported.	
60	9	Comment: SABTO have recommended that UK sourced plasma (FFP) should no longer be used for transfusion (SABTO meeting minutes dated 14/15th July 2009). Proposed change (if any): "fractionate from UK plasma *and the UK Advisory Committee on the Safety of Blood Tissues and Organs (SaBTO) to recommend that UK sourced plasma should no longer be used for transfusion*."	Fresh frozen plasma (FFB) from single donations is outside the scope of this document.
64-65	10	Comment: The rational for not recalling after post donation discovery of a donor with greater geographical exposure than the limit allowed, has nothing to do with this deferral being "a very conservative precautionary measure." The geographical exposure limits have been established statistically on the basis of person/days of exposure. Six persons spending 2 months each in the UK contribute the same risk as 1 person spending 1 year. Since deferring all persons with any level of exposure (the hamburger in Heathrow scenario) would have too great an impact on supply, the permitted residence times were adjusted so as to obtain the greatest reduction in exposure from the fewest number of deferrals. This is accomplished by deferring those with the longest exposures first. However, the residual exposure remains about 10% of the total, i.e. geographical exposures remove 90% of the risk. Occasional missing a deferral will have only an incremental effect on the residual risk.	Agreed. Proposed modification: "*There is no recommendation to recall batches if information that would have excluded a donor based on his/her stay in the UK becomes available post-donation~~, since this is a very conservative precautionary measure~~.*"

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67	9	Comment: See General Comments (i) and (iii). Proposed change (if any): "Available data *from studies conducted with brain-derived TSE infectivity* indicate that .."	Not agreed. The proposed wording excludes the findings in which Plasma from GSS infected mice is used (e.g. P. Brown et al. 1998 and 1999).
76-79	6	This statement seems to suggest that we can rely on the results of the investigational prion removal studies. This conclusion is corroborated by lines 543-546, where apparently such studies are given much weight. So, the general CPMP's position for mandatory recalls is a bit ambivalent. A demonstration of effective prion removal capability by specific investigational prion removal studies is incompatible with mandatory recall.	The limitations of prion reduction studies have been outlined at the end of section 7 as well as in the Guideline CPMP/BWP/5136/03 mentioned here.
76 - 79	9	Comment: A process previously shown to be able to reduce TSE infectivity will only provide reassurance on safety if that process has been validated for removal of TSE infectivity to a safe and acceptable level using a prion assay incorporating an infectivity spike which resembles as closely as possible the form of TSE infectivity found in plasma (endogenous infectivity). Animal studies and an occurrence in humans demonstrate that endogenous infectivity can pass through processes to contaminate the final plasma product. Proposed change (if any): Revise with more cautionary wording.	See comments above.

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80-87	10	Comment: Again, absence of evidence is not evidence of absence; and there are at least as many caveats associated with correlations with urine hormone use as for plasma derivatives as acknowledged in line 149. This qualification needs to appear here as well.	Agreed
81-87	8	Comment: As per the 2007 EMEA expert report, the Company proposes to precise that for vCJD, the epidemiological experience is too limited, given the long incubation periods[x], to reach conclusions on whether or not vCJD could be transmitted. Furthermore, in line with the first comment above, the Company proposes the following changes: Proposed change: Line 81-87: "However, there is no epidemiological evidence of CJD or vCJD transmission by urine derived medicinal products. *For vCJD, the epidemiological experience is too limited, given the long incubation periods, to reach conclusions on whether or not vCJD could be transmitted.* *Epidemiological data should be categorized according to age groups of donors for any particular drug product. For some products the age group are young individuals whereas for others like hMG, FSH, the donors are postmenopausal women and the incidence of CJD is higher than in the general population.* *Recently it has been described the presence of human prion in*	See general comments stakeholder 8. A reference to the reclassification of Urine in the WHO tables of Tissue infectivity distribution in TSE has been inserted in section 9.

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		a urinary-derived hMG product suggesting a potential risk for developing prion disease in using urinary hMG preparations (Kuwabara Y, et al. J Reprod Med 2009). Prion protein was also detected for the first time in two commercial urinary hCG preparations. These findings demonstrate that different purification processes for different urinary-derived preparations are unable to remove prion proteins from the source material and the process controls employed do not permit the identification of this major contaminant (Matrangeli R et al. J Reprod Med 2010). *The risk of urinary-derived products should be reconsidered also in view of 2010 updated WHO Tables on Tissue Infectivity Distribution in Transmissible Spongiform Encephalopathies where urine moved from the category of ''tissues with no detectable infectivity'' to the category of ''lower-infectivity tissues". This last category is the category containing blood. Accordingly, urine-derived medicinal products should conform to the same criteria used for blood-derived products."*	
88-89	8	Comment: According the previous comment it might be recommended to use the same exclusions criteria for selection of urine donors as used for blood/plasma donors. Proposed change Line 88: Delete the sentence "use of exclusion criteria for selection for a urine donor panel is encouraged, as a precautionary measure, where feasible."	The principle to apply the same exclusion criteria as applies for blood/plasma donors with respect to CJD and vCJD has been revised and is outlined in the main text (section 9.3)
92-94	8	Comment: The seeding hypothesis posits that PrPC is in equilibrium with PRPSc, the equilibrium is largely in favour of	The statement in the summary section is considered adequate. The proposed change is

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		PrPC[xi]. In addition, Prion variants constantly arise in a particular population[xii]. These variants are believed to differ in the way the prion protein is folded. As some urinary-derived medicinal products are now known to contain human prion and other human impurities, as a precautionary measure the manufacturing process should be able to remove human prion as well as human prion-binding molecules i.e. plasminogen and clusterin[xiii,xiv] that might potentially alter conformational equilibrium of the prion. Clusterin has been also reported to shorten incubation and alter histopathology of BSE in mice[xv]. Furthermore, as per the 2007 EMEA expert report[i], the physicochemical form of the spiking agent can affect the measured reduction capacity. The preconditioning of the spike should be described in detail. It has a great influence on the experimental findings as shown for plasma-derived medicinal products (e.g. treatment with detergents). The importance of the aggregation state has also to be taken into account particularly when investigating nanofiltration. If inactivation processes are investigated (e.g. heat, alkali), the selection of strains of TSE agent should take into account strain differences in resistance to the inactivation process under investigation. In addition, reference should be made to CHMP guideline on the investigation of manufacturing processes for plasma derived medicinal product with regards to VCJD risk.	too extensive for a summary section The *in vitro* formation of infectious prion needs to bring together a number of specific conditions which are not met in the manufacturing process of urine derived products from urine to finished product.

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		Finally, as per the current version of the CHMP Position statement, the Company proposes that the outcome of the manufacturing process evaluation should be reported to the relevant competent authorities. Proposed change: "Manufacturers of urine-derived medicinal products are recommended to evaluate the capacity of the manufacturing process to reduce/eliminate TSE agents by following a similar approach to that for plasma-derived medicinal products *(in line with the CHMP guideline on the investigation of manufacturing processes for plasma derived medicinal product with regards to VCJD risk). The preconditioning of the spike should be described in detail. In addition, as a precautionary measure the manufacturing process should be able to remove human prion as well as human prion-binding molecules. Outcomes of the evaluation should be reported to the relevant competent authorities."*	
103-104	10	Proposed change (if any): "The most likely hypothesis…' to "A favored hypothesis…"	Modification is not necessary
141-142	10	Comment: All of these studies admit the formidable challenge of demonstrating a correlation over a lifetime of incubation and a dearth of adequate records. This statement, made without qualification misrepresents the quality of these observations.	Modification is not necessary

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163-164	6	In 2009 a possible case of v-CJD was reported in the UK with an heterozygous codon 129 genotype. However, as its stands, it cannot be totally excluded that this case was a sCJD [18]. [18] J-P Brandel *et al*. Lancet, 375 pg 889-890	No modification of text necessary The term "possible" here has a precise meaning in relation to the current diagnostic criteria for vCJD. This term does not imply that the diagnosis of vCJD is in anyway confirmed and the possibility of sCJD cannot be excluded as things stand.
165-166	10	Comment: The point here is that without certain knowledge of the prevalence rate, we can not know what the current decline in vCJD cases represents - was this some outlier group of unusually susceptible persons, or who had an unusually virulent exposure, where as the bulk of the infection has taken a different course, perhaps presenting differently both clinically and pathologically.	No modification of text necessary
168-181	10	Comment: It is important to recognize that for neither the Hilton study or the follow up is there any knowledge of the ascertainment rate for discovery of positives by the methods used. It is certainly not 100% and could be as low as 1% or .1%. The actual prevalence would be proportionately higher. Alan Dickinson provided us with plenty of examples in animal TSEs of varying presentations and clinical courses based on host genotype. The danger here is that valine homozygotes may be life long carriers and the problem will not be recognizable for another 20 years.	The text is not changed. The clinical and pathological features of variant CJD in other codon 129 genotypes are not known and it is not assumed that these would necessarily be the same as current vCJD cases. It has never been assumed that the Hilton Study had an ascertainment rate of 100%, since the use of immunohistochemistry on fixed tissues to detect disease-associated prion protein is not as sensitive as western blot examination. It is not possible, however, to calculate the ascertainment rate for the

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			discovery of positives by this method and given the uncertainty.
181	9	Comment: Addition of new sentence (see General Comment (v) above) Proposed change (if any): "*It has been speculated that individuals with MV or VV genotypes may present different disease phenotypes which may have implications for accurate diagnosis of vCJD and potential confusion with other neuropathological diseases.*" [references: (i) D Kaski, S Mead, H Hyare, J Collinge, P Rudge, S Cooper, R Jampana, J Overell and R Knight Lancet 2009; 374: 2128. (ii) Transgenic modelling of human prion disease, intermammalian transmission barriers and assessment of candidate therapeutics; MRC Prion Unit website (http://www.prion.ucl.ac.uk/research/mrc-research-groups/transgenics)]	See above.
185-186	10	Comment: It must be emphasized that the core measurement of 3 is a minimum value for the actual prevalence in this group.	No modification of text necessary.
187-192	10	Comment: The easiest explanation for inconsistencies between a mathematical model and data, is that the model is inadequate.	No modification of text necessary.
193-201	4	The draft is already somewhat out of date. In August 2010 a tonsil sample containing abnormal PrP was detected in the UK, suggesting a (minimal point) prevalence of 109 pre-clinically	Agreed. The publication in the Journal of Pathology

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		vCJD-agent-infected individuals per million people in the highest-risk UK cohort born 1961 to 198 (M Fernandez de Marco et al). Large-scale immunohistochemical examination for lymphoreticular prion protein in tonsil specimens collected in Britain. J Pathol 2010 (thejournalofpathology.com).	is now included and discussed in the revised CJD Position Statement.
207-208	10	Comment: "….infectivity can be present without detection of PrP^{TSE} or PrP^{TSE} be present in the absence of infectivity.[23]" This is a crucial point that has not carried through to the consideration of biochemical validation and other uses of the Western blot later in this document. This discrepancy has shown up in many other studies besides Piccardo et al. Lasmezas et al. reported this disconnect during adaptation of bovine BSE to mice. It has also been seen in first passage adaptations in the Manuelidis and Caughey laboratories. The kinetics of production of PrP amyloid and the appearance of TSE infectivity seem to be disconnected in the PMCA reaction, at least in some species. The contrary is also true. GPI anchorless transgenics and the recently described synthetic SSLOW strain produce huge amounts of PrP amyloid with minimal disease in the case of GPI- animals, or a non-fatal disease in the case of SSLOW. Biochemical assay is a useful tool for screening out steps that are not worth validating. However, it cannot at present be used as a substitute for infectivity assay.	The need for correlation between infectivity assay and biochemical assay has been outlined in section 7
214	6	Limited data from infectivity assays of vCJD tissues are	No modification of text necessary

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		consistent with the PrPTSE findings.27 Please clarify	
226-227	4	Strictly speaking, half the TSE agent infectivity is not found in the "cellular components, mainly the buffy coat" of experimentally infected animals. That statement implies that erythrocytes are intrinsically infected with some agent, while the studies themselves suggest that infectivity detected in red cell concentrates probably comes from contaminating nucleated cells and plasma.	No modification of text necessary.
226	10	Comment: The most precise measurements of the titre of whole blood are in references 58 and 59 that should be included here. Proposed change (if any): add references 58 and 59	Agreed.
227	10	Proposed change (if any): "..in the plasma." to "…in the plasma.[58, 59]"	See above.
230	10	Comment: Admittedly it is difficult to present prior to publication, however the Macaque studies being conducted at the CEA under the direction of Comoy and Deslys should be summarized here. They show clear evidence of blood borne infectivity and transfusibility in a primate model.	The referred studies have not been published on a peer reviewed article by the time of the publication of the position statement. Once published they can be considered in future updates of this document.
242	9	Comment: More recent data available Proposed change (if any): "level of infectivity in sheep blood	Agreed. The text of the guideline has been revised.

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		cannot be established from these experiments*. Experiments with BSE infected sheep demonstrate all blood components, including plasma, contain transmissible TSE infection and all components remain infectious after leucoreduction".* [reference: S. McCutcheon, The Effect of Leucodepletion on Transmission of BSE by Transfusion of Sheep Blood Components; Transmissible Spongiform Encephalopathies, Pullman Hotel, Cologne, Germany, 10-11th June 2010]	
245-253	10	Comment: An important limitation of the TMER study has been the lack of comprehensive autopsies on any deceased recipients except the 3 clinically affected cases and the one incubating case. Nearly half of the recipients died within two or three years of their transfusions from underlying causes. Some proportion of those may, like the incubating case, have also been infected by their transfusions. Even without these cases the infection rate based on recipients that have lived long enough to develop symptomatic disease is around 20% consistent with the transmission rate in BSE and scrapie infected sheep and not inconsistent with the CEA macaque studies.	The comment is acknowledged. No modifications of the text are necessary.
252	9	Comment: More recent data available Proposed change (if any): "129 of the PRNP gene. *A further two potential cases of secondary transmission have been identified but cannot be proven.* Taken together …" [reference: R. Will; Will there be a Second Wave of Variant CJD?, Transmissible Spongiform Encephalopathies, Pullman	The text is not modified. There is significant uncertainty that the two cases were caused by blood transfusion (Ref.: Chohan et al. Transfusion, May 2010, 50 (5), 1003-1006).

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		Hotel, Cologne, Germany, 10-11th June 2010]	
256	5	Comment: Are there any data available upon specific plasma fractions?	The text has been updated as follows: *"The patient, who died of unrelated pathology, had received large quantities of UK-sourced fractionated plasma products (i.e. FVIII) , including some units derived from plasma pools which contained plasma from a donor who later developed variant CJD."*
259	4	A more recent report (Peden A et al. Variant CJD infection in the spleen of a neurologically asymptomatic UK adult patient with haemophilia. Haemophilia 2010;16:296-304) described 1 of 26 spleen samples as positive for abnormal PrP by a highly sensitive Western blot assay. The document should cite that report.	Agreed. The reference has been inserted. Recently, another presumed case of prion infection was identified in an elderly haemophilic patient who was heterozygous at codon 129 in the prion protein gene (ref 46).
259-262	6	Finding in one organ does not imply presence in blood.	This is not relevant for the question whether the recipient had been infected by plasma product. It has already been stated that "Whether someone with this limited distribution of PrP^{TSE} would be infectious is unknown…" No modification of text necessary.
259	10	Comment: The spin as written is impugning the result as if it is less significant because it was difficult to discover. The implication is that if this same level of diligence were applied to all autopsies, we might discover a prevalence rate far	Current wording seems appropriate

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		greater than expected. The very difficulty with which this case was discovered, justifies a strong skepticism of epidemiological claims based on "lack of evidence". Proposed change (if any): "although only" to "where"	
269-271	6	Comment: See general comments paragraph 11 Proposed change (if any): Infectivity in the blood of asymptomatic vCJD cases has been demonstrated by the probable incidents of transfusion-transmitted vCJD. PrP^{TSE} has not yet been identified in the blood of such cases, indicating that if present, it is below the sensitivities of the detection methods. This may have implications for the development of a suitable screening test. PrP^{TSE} has been detected in certain peripheral tissues such as the spleen.	The text has been modified and reference to PrP^{TSE} has been removed.
269-271	10	Comment: Our measurements in hamster demonstrate that blood infectivity concentrations are 100,000 to 1,000,000 fold lower than in spleen. This result is not surprising. In fact after 15 years of intense effort, by at least 20 commercial firms and possibly as many academic laboratories, will still lack any assay capable of detecting PrP^{res} in blood. The only convincing evidence that it is there is from infectivity measurements.	Agreed. No modification of text necessary
274	6	Comment: missing word	See below.

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		Proposed change (if any): possible case of sporadic CJD linked to blood transfusion. However, current data are insufficient to	
274	10	Proposed change (if any): "…are scanty…" to "…are too scanty…"	Agreed. The text states: *"…possible case of sporadic CJD linked to blood transfusion. However, current data are <u>too</u> scanty to unequivocally exclude …"*
277-281	10	Comment: Blood infectivity concentrations are, by our measurements in hamsters and mice, around 10 infectious doses/ml. If there is any dilution or processing of the sample the concentration can be even lower. If the transmission attempt is between species, the efficiency will be reduced also reducing the likelihood of detection. All of these factors are at play in one or more of these studies easily accounting for the variable results. It is especially important to realize that species barriers exist even between closely related species such as humans and monkeys, and even between strains of the same species. Transgenic mice carrying the donor host transgene can be more efficiently infected than wild type mice but they are still mice and it should not be presumed that there is no barrier effect. "It remains possible that PrPTSE is present at low levels in blood of clinically affected cases of sCJD". As stated the implication is that "low levels" of infectivity may be of no consequence. This might be true for a tissue used in	Agreed on the principle. No modification of text necessary

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		microgram quantities. However, blood and plasma are typically collected and administered 250 to 500 mls at a time. Even a 0.1 ID/ml sample would contain 50 ID per dose, fifty times the quantity required to initiate an infection by the definition of ID. Urine could pose a similar risk if infectivity were concentrated with the product. The plausibility of this scenario is supported by a presentation at Prion 2010, Salzburg in which mass spectroscopy was used to demonstrate a significant contamination of urine derived fertility hormones assayed in the final packaged product.	
289-297	10	Comment: This paragraph is out of date. The last high profile commercial effort to develop a blood - based diagnostic was abandoned earlier this year. While there may be other efforts underway they are not being presented at conferences, and the most telling point is the large number of failures. There are also serious reservations about deploying a screening test for such a rare disease. The best hope for a test with the requisite sensitivity to detect PrP^{TSE} in blood or urine is PMCA. There have been major obstacles to making the assay reproducible, quantitative and compatible with blood proteins. However, there do not seem to be any theoretical limitations to prevent its adaptation to this use.	The section has been updated.
290	6	Several techniques have been under development for the detection of PrP^{TSE} in blood including methods based on epitope protection [53/54] and PrP^{TSE} specific antibodies [55,	This section has been modified.

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		[54] press release on vCJD test update on http://www.amorfix.com/pr_2010.php	
292	6	Comment: see general comments paragraph 6 Proposed change (if any): Development and validation of all methods is on-going but there is no screening test yet. A suitable confirmatory test is likely to be an essential component of any vCJD screening system. Confirmatory tests that have been proposed include Protein Mis-folding Cyclic	The section has been modified
303	9	Comment: More recent data available Proposed change (if any): "to be given access to the available samples[56]. *One assay has been granted access to human vCJD plasma but failed to detect vCJD in samples from three different patients*." [Reference: Amorfix (TSX:AMF) press release dated 29th December 2009].	see above.
315-317	10	Comment: Leukoreduction does not affect risk, however it is a prerequisite for removing TSE infectivity from the plasma component of blood. It is therefore an essential component in the implementation of TSE removal by affinity ligands.	No modification of text necessary.
322-323	10	Comment:The original statement implies that there might be some protection from leucoreduction. In fact, it could only be effective if there was 1 ID or less per the whole unit. To have an impact a removal strategy has to reduce the infectivity by	This document is about plasma-derived medicinal products. Considering that one contaminated donation would be diluted into a pool of 1000 to 1000 donations and that the

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		at least 100 to 1000 fold. A 72 % reduction is less than 4 fold. Proposed change (if any): " Infectivity data from hamster studies indicate that leucoreduction alone is not totally protective against prion transmission, with between 42 to 72 percent reduction in infectivity of whole blood." **to** " Hamster studies using endogenously infected whole blood have shown that leucoreduction removes only 42 to 72 percent of the infectivity from whole blood resulting in no significant reduction in the risk of transmission from whole blood."	recipients would receive only a small part of an affected batch, even a limited reduction capacity (4 fold) could prevent a number of patients receiving an infectious dose. The text has been revised as follows: "*Studies with blood from infected hamsters have shown that leucoreduction removes only 42 to 72 percent of the infectivity of whole blood.* ~~*Infectivity data from hamster studies indicate that leucoreduction alone is not totally protective against prion transmission, with between 42 to 72 percent reduction in infectivity of whole blood"*~~
323	6	Comment: missing word Proposed change (if any): prion transmission, with between 42 to 72 percent reduction in the infectivity of whole blood58,59.	See above.
323	9	Comment: Include reference to recent work with BSE infected sheep Proposed change (if any): "… infectivity of whole blood[58,59]. *Similarly, leucoreduction was found to be ineffective for the removal of TSE infectivity from the blood of BSE infected sheep*." [reference: S. McCutcheon, The Effect of	Agreed. To be modified accordingly.

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		Leucodepletion on Transmission of BSE by Transfusion of Sheep Blood Components; Transmissible Spongiform Encephalopathies, Pullman Hotel, Cologne, Germany, 10-11th June 2010]	
324	9	Comment: See General Comment (iv) above. Proposed change (if any): "Specific affinity ligands that bind prion proteins *have been shown* to reduce TSE"	See General Comment (iv) above. Validation of suitability of ligand-media and pooled plasma has still not yet been completed. No modification of text necessary.
324-325	10	Comment: As written this statement is five years out of date and does not reflect the advanced state of this product. Proposed change (if any): "Specific affinity ligands that bind prion proteins are being evaluated for their ability to reduce TSE infectivity present in blood and plasma." to "Specific affinity ligands that bind prion proteins have now been extensively characterized and have been found both efficacious and safe by the UK advisory committee for the Safety of Blood, Tissues and Organs (SaBTO) for use in filters to remove TSE infectivity from red blood cell units. These resins have also been approved for use and are being used to remove TSE infectivity from pooled plasma.	The text in lines 324-325 is maintained. Efficacy of ligand-media for pooled plasma has still not been fully demonstrated. However the section has been reworded. In October 2009 the UK Advisory Committee on the Safety of Blood, Tissues and Organs recommended the use prion filtration of red cell components administered to children born since 1 January 1996. The recommendation is subject to the satisfactory completion on the PRISM clinical trial to evaluate the safety of prion filtered red blood cells. A reference has been inserted. http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@ab/docu

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			ments/digitalasset/dh_108860.pdf
326-328	9	Comment: The prion filter described in the referenced study was later found to give incomplete removal of endogenous infectivity which resulted in this filter being withdrawn by the manufacturer and the Irish Blood Transfusion Service terminating a clinical trial. Consequently the Agency may wish to reconsider the inclusion of this reference (60). Proposed change (if any):	No proposed change at present.
326-328	10	Comment: The filter described in this study failed to remove endogenous infectivity to the limit of detection and has to my knowledge been abandoned. The percentages are erroneous as used here. Proposed change (if any): Remove paragraph	See above.
326-335	6	Comment: Missing or incorrect words, punctuation Proposed change (if any): A study in hamsters showed that a leucocyte-reduction filter, based on modified polyester fibres, exhibited a prion clearance capability of between 99.0 to 99.9 percent of the endogenous and exogenous infectivity of red cell concentrates60. Initial studies using leucoreduced human red blood cell concentrates, spiked with hamster brain-derived scrapie infectivity, indicate that some ligands immobilised on a	Agreed to revise punctuation.

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		chromatographic resin matrix, are capable of removing 3 to 4 log ID50 per ml59. A further study, using scrapie-infected hamster whole blood, demonstrated an overall reduction of infectivity of more than 1.22 log ID61. 10/25 The prion binding capacity of an affinity ligand chromatography step, has been investigated during the processing of a plasma medicinal product, using hamster brain derived spiking material62. These preliminary data require further evaluation before conclusions can be drawn about possible efficacy.	
329	9	Comment: (See General Comment (iv) above). Proposed change (if any): The word "Initial" to be deleted.	Agreed.
329-332	10	Comment: These changes better reflect the current state of this product. Proposed change (if any): Change first sentence to: "Studies using leucoreduced human red blood cell concentrates spiked with hamster brain-derived scrapie infectivity demonstrated removals of 3 to 4 $log_{10}ID_{50}$ per ml by several designer ligands immobilized on a chromatographic matrix.[59] Change "…infectivity of more than 1.22 log ID" to "infectivity to the limit of detection equivalent to more than 1.22 log ID".	Agreed. Studies using leucoreduced human red blood cell concentrates spiked with hamster brain-derived scrapie infectivity demonstrated removals of 3 to 4 $log_{10}ID_{50}$ per ml by several designer ligands immobilized on a chromatographic matrix (ref 36). A further study using scrapie-infected hamster whole blood demonstrated an overall reduction of infectivity of more than 1.22 log ID (ref 64).
330	9	Comment: All ligands tested in this work gave ≥3 log	See above.

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		reduction of infectivity. Proposed change (if any): "scrapie infectivity indicate that *specific* ligands immobilised on a …"	
332	9	Comment: Incomplete information given (See General Comment (iv) above). Proposed change (if any):"blood demonstrated an overall reduction of *endogenous infectivity to beyond the limit of bioassay detection (≥1.22 log_{10} ID[61]). This affinity resin has been incorporated into a prion reduction device for red cell filtration. The P-Capt® filter was CE Marked in 2006 and has been shown to remove TSE infectivity from leucoreduced human red cells [reference A], does not cause any changes to red cell quality [references B & C] and does not result in any adverse events when filtered red-cells are transfused into humans [references D & E]". In late 2009 the UK Advisory Committee on the Safety of Blood, Tissues and Organs (SaBTO) noted there was sufficient evidence that this particular filter reduces infectivity and recommended its use for the filtration of red cells transfused to children [reference F]."* **Reference A**: N. Lescoutra-Etchegaray, E. Comoy, C. Sumian and J-P. Deslys. Removal of exogenous prion infectivity in leukoreduced red blood cells by macopharma P-Capt filter. Poster presented at Prion 2009, Thessalonica, Greece, 2009.	See above.

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		Reference B: C. V. Murphy, E. Eakins, J. Fagan, H. Croxon & W. G. Murphy. In vitro assessment of red-cell concentrates in SAG-M filtered through the MacoPharma P-CAPT prion-reduction filter. Transfusion Medicine, 2009, 19, 109–116. **Reference C**: M. Wiltshire, S. Thomas, J. Scott, V. Hicks, M. Haines, P. Cookson, M. Garwood, and R. Cardigan. Prion reduction of red blood cells: impact on component quality. Transfusion, Vol. 50, pp. 970-979, 2010. **Reference D**: Edwardson, P., Sumian, C. and Walicka, I. Pharmacovigilance clinical studies with P-Capt prion capture filter in human volunteers. Poster presented at ISBT, June 7-12 2009, Macao, China. **Reference E**: M. R. Cahill, T. Murphy, M. Khan, J. Fagan & W. G. Murphy. Phase I / II safety study of transfusion of prion-filtered red cell concentrates in transfusion-dependent patients. Vox Sanguinis (2010) 99, 174–176. **Reference F**: SaBTO meeting minutes, Summary of the Eighth Meeting, 27 October 2009.	
334-335	9	Comment: Incomplete information given (See General Comment (iv) above). On the basis of the considerable body of information demonstrating the effectiveness of prion filtration and associated product approvals, the statement "this preliminary data requires further evaluation before conclusions can be drawn on possible efficacy" should be	See above. Inclusion of reference not necessary

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		deleted. Proposed change (if any): "… derived spiking material[62]. *This technology has been incorporated into the manufacture of a solvent-detergent treated plasma product which has gained regulatory approval in Germany and Australia [Ref]. These examples demonstrate specific prion reduction steps can be safely incorporated into manufacturing processes to provide enhanced removal of TSE infectivity and increased product safety*." [Ref: Neisser-Svae, A. Case study on the implementation of a novel prion protein removal technology into the manufacturing process of a human plasma product - Octaplas®. Transmissible Spongiform Encephalopathies 2009, Cologne, Germany, 26th June 2009].	
335	10	Comment: This ligand has been extensively characterized in reference 59, and this study should not be considered preliminary. Proposed change (if any): Strike: "This preliminary…possible efficacy."	See above. No modification necessary.
352-354	6	Comment: see general comments paragraph 6 Proposed change (if any): investigate manufacturing processes in a reasonable timeframe and less costly protocols than the *in vivo* bioassay. However, where the conclusions of	See proposed modification at general comments above.

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		such investigations are based on the results of novel biochemical assays, it is still necessary to correlate such results with those from infectivity assays in animals. Cell-based assays may also be useful if properly validated for this purpose.	
355-358	9	Comment: This knowledge is based upon the results of infectivity studies conducted with brain homogenate which, depending upon the method of preparation, may not reflect the situation for endogenous plasma infectivity. By way of example, Leucofilters were initially thought to be effective for the removal of TSE infectivity from blood but investigations subsequently revealed only the insoluble (cell associated) infectivity was trapped and a substantial proportion of soluble plasma-associated infectivity was not removed. Consequently caution should be exercised in relation to the interpretation of results (and the potential extent of prion removal) for separation techniques based upon exploitation of differences in size or mass (eg. precipitation, centrifugation, depth filtration, nano- filtration etc.) and it should not be assumed that these techniques are effective for the removal of endogenous plasma infectivity in the absence of proof. Proposed change (if any): Consider revision with more precautionary wording.	See general comments above.
360-363	6	Comment: Typographical errors? Proposed change (if any): conditions typically cause PRP^{TSE} to	The text has been modified to state: *"In many cases, downstream steps using*

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		partition into the precipitate phase. In those precipitates which are waste fractions, this may provide a useful reduction in potential infectivity. The reduction levels achieved may vary according to the specific manufacturing process, and probably depend on the concentrations of the precipitating agent and salts, and the pH. Chromatographic steps, classically used in the separation of coagulation factors but also in the purification of other plasma derivatives have been demonstrated to remove TSE	*various precipitating agents or conditions allow to discard PrP^{TSE} in the precipitates. The reduction level achieved may vary according to the specific manufacturing process, and probably depend on the concentration of the precipitating agent and salts, and the pH."*
371	5	Comment: The importance of the use of a well established fractioning process and the compliance with Eur. Ph Monograph, when available, could also be mentioned in this context. Reference to CPMP/BWP/269/95 may be referenced with this regard. Examples may include what is stated in section 5.2.1e) iii pg 16, viral inactivation/Removal for albumin: Albumin manufactured by an established fractioning process with terminal pasteurisation as specified in Eur Pharmacopoeia, has an excellent viral safety records. Proposed change (if any):	The Ph. Eur does not specify any fraction step. Reference to viral safety record of albumin is not appropriate because viral safety is based on the pasteurization step. No modification of text is necessary.
372-375	6	Comment: see general comments paragraph –7 - 8 Proposed change (if any): order to confirm the relevance of the spiking material used in the validation studies. The last two needs (ii and iii) represent current research requirements, and are not requirements for the investigation of the clearance of TSEs by manufacturer's processes.	The paragraph has been reworded in order to clarify requirements for investigations of manufacturing processes and requirements for research.

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380	4	Please note the misspelling of Luisa Gregori's name on page 11/25 line 380. Her name is spelled correctly in the reference list.	Agreed. Corrected.
380-385	8	Comment: In line with the information provided for Gonzales-Romero et al/Murayama et al, the Company proposes to provide the information of infectivity in urine compared to blood. Proposed change: "Gregory et al. demonstrated that the disease could be transmitted by intracerebral inoculation of pooled urine from scrapie-sick hamsters. The infectivity titre of the urine was calculated to be around 3.8 infectious doses/ml ***and is similar to the levels calculated for plasma (6 ID/ml) in the same hamster model***. Titration of kidney and urinary bladders from the same animals gave 20,000-fold greater concentrations…"	Modification not necessary.
408-409	8	Proposed change : Insert a sentence between line 408 and 409 such as : "Based on the above consideration, in 2010 WHO updated the Tables on Tissue Infectivity Distribution in Transmissible Spongiform Encephalopathies moving urine from the category of ''tissues with no detectable infectivity'' '' to the category of ''lower-infectivity tissues.''	Reference to WHO reclassification added to Section 8.
409-413	7	Comment: I think it will be better to refer our paper showing that prion protein was actually detected in human gonadotrophine preparations by mass spectrometry.	The protein detected is very likely "normal" cellular prion protein. The data provided is limited and no relationship has been

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		(Kuwabara Y et al, J Reprod Med 2009;54 (8):459–466. August 2009). This result strongly suggests that there is a potential risk of developing prion disease through using urine-derived medical products, no matter how strict the manufacturing processes may be. Although there is no reason to doubt the safety of commercially available urine-derived medical products at present, the introduction of available recombinant alternative medical products should be constantly considered. Proposed change (if any):	established between the presence of the PrP and TSE/CJD infectivity that would sustain the assumptions made by the stakeholder. A sentence has been included in the section stating the report of presence of PrP in urine.
409-413	8	See comment on lines 81-87	See above.
424	9	Comment: Proposed change (if any): "vCJD. *The possibility that unusual strains of vCJD might be confused with sCJD cannot be discounted*."	It has been already stated that "There is a potential for diagnostic confusion between sporadic and variant CJD, particularly in younger age groups" A reference has been included.
435-437	9	Comment: The implementation of specific prion reduction steps with a broad selectivity for different strains of TSE would provide increased protection against TSE infection of plasma products and support the argument that product recalls are not justified if there is evidence plasma pools may contain units donated by a donor later confirmed as having CJD. Proposed change (if any):	Agreed.

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488-490	6	Comment: missing words Proposed change (if any): 2003, 2004, 2005, 2007 and 2009 re-confirmed these conclusions and acknowledged that the estimated size of the epidemic had been reduced by more recent modeling, and the risk associated with collecting blood from vCJD-incubating donors was lower than previously estimated. 78	Agreed. The text ahs been modified accordingly: *"2003, 2004, 2005, 2007 and 2009 re-confirmed these conclusions and acknowledged that the estimated size of the epidemic had been reduced by more recent modelling, and the risk associated with collecting ~~to collect~~ blood from vCJD-incubating donors was lower than previously estimated. "*
499	6	Comment: see general comments paragraph 10 Proposed change (if any): The risk in France is estimated to be 1/10 of that in UK (this has been increased from the 1/20 estimated in the 2004 guideline,). Since the previous version of the Position Contradictory to the French Risk Assessment 2009 (see general comment 15)	See general comment 6.10. A reference to the 2007 Expert Report has been included.
506-509	9	Comment: The implementation of specific prion reduction steps with a broad selectivity for different strains of TSE would provide increased protection against TSE infection of plasma products. If such measures were adopted the need for country-based exclusions may become unnecessary which would help to preserve plasma supplies. Country based exclusions should be maintained where there is a risk of vCJD contamination entering the plasma supply and where	See above.

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		processes for the manufacture of plasma proteins have not been validated for their ability to reduce soluble TSE infectivity to a safe level. Proposed change (if any):	
527	9	Comment: See General Comment (iv) above. Line 527 is outdated and needs revision. Proposed change (if any): "*Specific affinity media/filters have been shown to be safe and effective for the removal of TSE infectivity from blood, plasma and plasma products*."	No modification necessary (see comment on lines 324-325).
533-535	9	Comment: This guidance appears discourage innovation and provides a disincentive to manufacturers to develop safer plasma products. Where there is an un-quantifiable risk the Precautionary Principle should be applied in conformance with European Law. Proposed change (if any): Delete "A decision to undertake an infectivity assay ….."	The text has been modified.
536-546 and Figure 1	9	Comment: We urge the Agency to re-consider the proposed policy regarding reliance on available published data as an alternative to undertaking prion-reduction validation studies for each process. See General Comment (iii) above. Proposed change (if any): Revise to include the following points: ALL processes used to manufacture plasma and urine products should be validated for their ability to reduce TSE's	See general comments above. No modification necessary.

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		to a safe level and the validation methods used should incorporate a form of TSE infectivity spike which represents as closely as possible the soluble form of TSE infectivity encountered in plasma (endogenous infectivity). The infectivity spike used should have a known TSE infectivity titre established by bioassay. The use of highly aggregated brain-spike materials as a source of infectivity should be discouraged as the resulting data may be highly unreliable as an indicator of the removal of endogenous infectivity.	
538	5	Comment: Reference to the compliance with Eur. Ph Monograph, when available, may be mentioned. Proposed change (if any):	Not applicable.
543	6	We welcome the CHMP acknowledgment that the use of published data would serve as pivotal results, based on comparability of manufacturing process steps.	See general comments above.
547-551	6	Comment: see general comments paragraph 6 Proposed change (if any): Investigations using biochemical assays may be sufficient, if a clear correlation with infectivity data has already been established using a similar assay method. If such a correlation is not established (e.g a novel biochemical method has been used) and the step is considered critical for the removal of infectivity for the specific product (e.g. it is the only step for removal), the investigations should be confirmed using an infectivity assay for the critical step(s).	See general comments above. No modification of text (and diagram necessary).

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		(Flow diagram, step3 -would need to be amended accordingly)	
558-563	6	*Comment:* Please clarify the term "such information". The EMEA 2004 position paper (page 9; bottom 3rd paragraph),allowed to further submit results of validation studies to the MAA, as stated: "The outcome of estimates.....if product specific investigational studies are not available at the time of submission, the proposed investigations and timescales should be described..." This option does not appear anymore in the 2010 position paper. Please restore this possibility, since prion validation studies are quite long term and should not impact on the timing of the marketing authorisation evaluation process.	No modification necessary. It is meant to provide an estimation on the prion reduction. This term did not cause confusion in the past years. Therefore, no modification is considered necessary. The need to perform evaluation of prion reduction is known since several years.
571-575	6	This section needs clarification on the word "prudent", and the meaning of "careful consideration with competent authority". Please, also clarify who is meant by "competent authority". (National? EMA?)	No clarification necessary.
573	6	See general comments 12 "Recall should also include medicinal products containing plasma-derived products as excipients" This needs to be stated in a very different manner since such affirmation would have huge consequences for the supply of essential medicinal products. Based on available knowledge, risk assessment provides a useful tool for considering the need to withdraw or not batches of essential medicinal	See general comment 6.12. Section 6.2.5. regarding albumin used as excipient has been updated as follows: "Where a donor to a plasma pool subsequently develops vCJD in the case of albumin used as an excipient, a recall should be considered. However, a careful case-by-case risk analysis

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		products containing plasma-derived products as excipients.	taking into account the estimated capacity of the process to remove infectivity and the amount of albumin incorporated in the medicinal product could justify not needing a recall."
584	6	Comment: typographical error Proposed change (if any): would have excluded a donor based on his/her stay in the UK since this donation exclusion criterion is a	Agreed.
593-595		See general comments 12 *Nevertheless, in the case of albumin used a excipient, recall is still recommended as a precautionary principle …* Comment: The introduction of risk assessment in the recall policies in case of vCJD donor contributing to a pool might be a very useful tool for decision making. It seems the position paper makes categorical statement when despite all reassuring evidence regarding robustness of prion elimination in the manufacturing process of albumin (manufactured by ethanol fractionation) even a very low amount of albumin in a vaccine (as few as 1 ml) would still be considered as justifying withdrawal	See general comment 6.12 and comment on line 573.
596-599	1	Comment: The sentence „Development of substitutes for plasma-derived albumin used as an excipient or in manufacturing processes is	See general comment 6.12 and comment on line 573.

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		encouraged…" are found in the two CHMP guidelines CPMP/BWP/2879/02/rev 1 and CPMP/BWP/269/95 rev. 3. Both Guidelines are currently under revisions. But whereas in the draft version of CPMP/BWP/269/95 rev. 4 the sentence is no longer present, it is still included in the draft version of guideline EMEA/CPMP/BWP/2879/02/rev 2. Please note that a similar sentence was found in the original WHO guideline "Transmissible Spongiform Encephalopathies in relation to Biological and Pharmaceutical Products" from the year 2003 which was later removed for the revised guideline in the year 2006. Proposed change (if any): Plasma-derived albumin has a proven safety record with no evidence of any transmission of vCJD. Therefore, I propose to remove this sentence as it was done in the above mentioned EMA and WHO guidelines.	
601-602	8	The update of the CHMP position statement on CJD and plasma-derived and urine-derived medicinal products should also take into consideration whether alternative drugs to urine-derived product with safer processes (and potentially better safety profile) for the same indications are available. Proposed change : "Use of alternative products to plasma-derived ***and urine-derived*** medicinal products could be considered, where these are available."	No modification made. This will be considered along with the planned revision of the guidance on urine products.

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603-604	6	It should be noted that plasma-derived products such as albumin may be used in the manufacture of recombinant products. What is the meaning for such a statement? Please, clarify.	Albumin may be used as a reagent; e.g a component in the cell culture media at production of a recombinant protein.
608-648	11	Comment: With regard to section 9.3 *Urine-derived medicinal products* we propose the following: The recommendations for urine-derived medicinal products are based on the following considerations: - There is no epidemiological evidence of CJD and vCJD transmission by urine-derived medicinal products. - Traceability back to donor has not been warranted for urine-derived medicinal products. - TSE infectivity in urine has been reported in some animal models. Manufacturers are required to estimate the potential of their specific manufacturing processes to reduce infectivity and to consider exclusion criteria for selection for a donor panel where feasible. The outcome of the estimates of the theoretical potential of manufacturing processes to reduce infectivity, the results of product-specific investigational studies and the exclusion criteria for selection for a donor panel should be reported to the relevant competent authorities for the medicinal products concerned, as information becomes available. Applicants	The text has been reworded. The regulatory aspects related to the dossier submission to competent authorities are not considered necessary in the frame of this position statement and have not been mentioned in the text.

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		submitting new marketing authorisation applications for urine-derived medicinal products will be expected to include such information in the application dossier. The outcome of the estimation of the theoretical potential to reduce infectivity should always be included in the application. General review of the manufacturing processes indicates that, in each manufacturing process, there is at least one step that might be theoretically capable of reducing infectivity if it were present in the starting material. In cases where the reduction capacity is limited, manufacturers should consider the addition of steps that may increase the overall removal capacity. Investigational studies of infectivity reduction by the manufacturing processes should be done following the same general, stepwise approach as recommended for plasma derived medicinal products (see Section 9.2.3). The studies should address potential accumulation of prions on chromatographic columns or a potential batch to batch contamination due to carry-over of prions. For inactivation studies, investigation of different TSE strains should be considered as they may vary in resistance. Bibliographic data could be acceptable as additional supportive data to the investigational studies provided. Similarity of the compared process and materials should be established. Extrapolation of results for plasma-derived medicinal products is not justified particularly for chromatographic steps at the beginning of the manufacturing process because of the high protein content in plasma. Urine should be collected from countries where there is a surveillance system for both human and animal TSEs. It is	

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		noted that urine-derived medicinal products are not sourced from urine collected in the UK. Based on the limited data on human exposure to BSE-risk materials in other European countries it is still difficult to estimate the epidemiological risk in those countries which have small number of vCJD cases or have not yet reported any vCJD cases. The use of exclusion criteria for selection for a donor panel is encouraged. The same exclusion criteria should be applied with respect to CJD and vCJD as used for blood/plasma donors providing starting material for the manufacture of plasma-derived medicinal products. Manufacturers should follow up the donor criteria at defined intervals. The exclusion of donors with known inflammation of kidney and/or chronic renal inflammatory diseases is encouraged. For particular products, such as hormones from a relatively small well-defined donor population, some manufacturers have put in place limited exclusion criteria for the selection of a donor for inclusion in a donor panel. For other products manufactured from very large donor pools (e.g. urokinase), such measures are more difficult to apply.	
610-611	2	Comment: an epidemiological "spike" in classical CJD caused by urinary pharmaceuticals may be unrecognized considering dose (and consequent incubation time) in comparison with pituitary derived growth hormone. Proposed change (if any):	Agreed.
610-611	8	See comment on lines 81-87	See above.

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612-613	8	Proposed change : Insert a sentence between line 612 and 613 such as : "2010 updated WHO Table on Tissue Infectivity Distribution in Transmissible Spongiform Encephalopathies moved urine from the category of ''tissues with no detectable infectivity'' '' to the category of ''lower-infectivity tissues.''	Agreed. A reference to the change has been included in the text.
614-616	8	Same comment on line 92-94.	See above.
614-624	2	Comment: such studies are not published for inspection of the academic community. Moreover, our detection of prion protein as a major contaminant in final endproduct indicates that depletion strategies for urinary pharmaceuticals are ineffective – indeed our data suggests that contaminants such as prion protein are co-purified with active hormone. Proposed change (if any): if the studies exist, they should be made available in a public forum.	It is under the manufacturer's choice to consider the publication of such studies. No modification necessary.
632	8	After line 632: Proposed change : Infectivity of transmissible agent should be a parameter tested as part of the drug substance specifications, using state-of-the-art technologies.	Testing of drug substance is not considered an appropriate stage. Sensitivity of detection methods is to low in order to exclude an infectious risk
634 and 640	2	Comment: "limited exclusion criteria" for urine donors will not exclude presymptomatic but still prion-infectious donors from contributing to urine pools.	See 601-602 above.

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		Proposed change (if any): Encourage use of recombinant product.	
637-638	8	Comment: "Surveillance system" should be clarified. Are these audited systems? Proposed change : "Urine should be collected from countries where there is a surveillance system for both human and animal TSEs. ***These surveillance organisations should liaise with collaborating centres and use standard surveillance methods, both established by the World health Organisation[xvi]"***	Not agreed. "Surveillance system" here refers to official surveillance system for animal and human TSEs. Such surveillance systems are part of the OIE`s assessment for the classification of countries into the risk categories. The requirements for surveillance system are outside the scope this Position statement.
637-639	3	Comment: This statement will currently preclude the sourcing of urine from the People's Republic of China (PR China) for the manufacture of urine-derived medicinal products. This will affect the supply of the majority, if not all, of the urine-derived medicinal products currently registered and marketed in the EU. It is understood that PR China has been actively implementing several strategies to enhance BSE risk analysis and assessment as well as BSE surveillance in order to submit a dossier for the OIE (World Organisation for Animal Health) BSE risk status recognition. (Ref: Fourth OIE/FAO-APHCA	Agreed. "unless otherwise justified" has been included in the text.

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		Regional Workshop and Working Group Meeting on BSE and Other Prion Diseases, 24-26 February 2010). However, official BSE risk status recognition for PR China could take some considerable time. According to the risk assessment scheme of the European Scientific Steering Committee (SSC), the importation of animals or meat and bone meal (MBM) from the UK or other countries with BSE between 1980 and 2000 is the most important risk factor for the occurrence of BSE. Taking into account the political situation in PR China and also for reasons of economy it is unlikely that animals or MBM would have been imported into PR China during that period. Therefore, the risk of BSE and vCJD occurrence in PR China at this present time is likely to be extremely low. Proposed change (if any): The sentence at line 637 should be changed to: "Urine should be collected from countries where there is a surveillance system for both human and animal TSE's, **unless otherwise justified**". In view of the fact that there are no CHMP Guidelines on the manufacture and control of urine-derived medicinal products, it might also be prudent to state that urine should not be collected from public toilets, hospitals or military establishments.	
640-648	8	Comment: In view of the potential risk described as a first general	It has been considered that the classification of urine in the same category of tissue infectivity

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		comment and based on the variability of the donors and their clinical profile which add to the potential risk of great variety of possible contamination, there is a need for a unified framework in order to ensure high standards of quality and safety with respect to the procurement, testing, processing, storage and distribution of urine raw materials and donors used as sources for pharmaceutical products. Thus, the Company considers that the section on donation should be clarified. In particular, in line with the WHO table in which urine is classified as blood in term of infectivity, there should be more precision made on donation in the model of the Directive 2004/33/EC[xvii] related to blood. In particular, there may be a need to set: • Requirements for the accreditation, designation, authorisation or licensing of establishments • Information required from donors; • Eligibility of donors • Laboratory tests required for donors and frequency • Traceability through a donor identification system (ethnic and geographical origin, age, sex, general physical condition, results of tests for pathogenic agents) In addition, in line with the CHMP guidance for plasma-derived products[xviii], it should be recommended that every time that a urine-derived product is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product.	as blood in the 2010 WHO tables does not suffice to apply the same requirements on urine donations than those defined in the Directive 2004/33/EC for blood donations. The requirements in the reworded text refer clearly to the requirements for blood donations and are considered in proportion with the risk linked to urine-derived products.

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		Proposed change: "On the basis of these considerations~~, the use of exclusion criteria for selection for a donor panel are encouraged, as a precautionary measure, where feasible.~~ The same exclusion criteria should be applied with respect to CJD and vCJD as used for blood/plasma donors providing starting material for the manufacture of plasma-derived medicinal products[xvii]. ***These exclusion criteria are as follows: persons who have a family history which places them at risk of developing a TSE, or persons who have received a corneal or dura mater graft, or who have been treated in the past with medicines made from human pituitary glands. For variant Creutzfeldt Jakob disease, further precautionary measures may be recommended. In addition, donors with known inflammation of kidney and/or chronic renal inflammatory diseases should be excluded. Manufacturers are required to review their donors screening questionnaires and donor follow-up procedures to ensure that they adequately manage any potential risk of prion transmission.*** Although these criteria would not be checked at each donation unlike blood/plasma donors, ***manufacturers should apply these criteria to each donor and*** follow up the donor criteria at defined intervals. ~~The exclusion of donors with known inflammation of kidney and/or chronic renal inflammatory diseases is encouraged.~~ Record keeping for traceability is recommended for products ~~where it is possible~~ to trace back to donor level. ***It should be***	

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		recommended that every time that a urine-derived product is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product."	
647	2	Record keeping for traceability will not be helpful if an infected donor contributes urine to a pool. Proposed change: withdrawal of product from market if any donor develops a syndrome consistent with CJD.	Withdrawal of product in case of post donation CJD-diagnosis is at present not recommended for plasma-derived medicinal products based on the current epidemiological evidence. In consequence this does not seem to be justified for the urine-derived products.
654-655	2	Renal inflammation is not essential for prion excretion in animal models. Proposed change: encourage use of recombinant product	Not agreed. Even if renal inflammation has not been shown to be essential in part of the animal experiments, data from some experiments have shown that it may have an effect on transmission of infectivity.(Seeger et al, 2005) Therefore this recommendation is appropriate and may add further safety.

[i] Expert Workshop on CJD risk and urine-derived medicinal products, EMEA, London -12-13 July 2007.
[ii] WHO tables on Tissue infectivity distribution in transmissible spongiform encephalopathies (WHO/EMP/QSM/2010.1) – Updated 2010
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