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3 Committee for Medicinal Products for Human Use (CHMP)

4 **CHMP position statement on Creutzfeldt-Jakob disease**  
5 **and plasma-derived and urine-derived medicinal products**  
6 **Draft<sup>1</sup>**

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<sup>1</sup> Delete once the reflection paper is adopted.



12 CHMP position statement on Creutzfeldt-Jakob disease  
13 and plasma-derived and urine-derived medicinal products

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42 **This is the second revision of the CPMP<sup>2</sup> Position Statement on “Creutzfeldt-Jakob disease**  
43 **and plasma-derived and urine-derived medicinal products” (EMA/CPMP/BWP/2879/02)**  
44 **published in February 2003 and revised in June 2004 and XXX 2010, which replaced the**  
45 **CPMP Position Statement on “New variant CJD and plasma-derived medicinal products”**  
46 **(CPMP/201/98) issued in February 1998.**

47

## 48 **Summary**

49 Cumulative epidemiological evidence does not support transmission of sporadic, familial and iatrogenic  
50 Creutzfeldt-Jakob disease (CJD) by plasma-derived medicinal products. There is no change to the  
51 previous CHMP position that recall of plasma-derived medicinal products is not justified where a donor  
52 is later confirmed as having sporadic, familial or iatrogenic CJD.

53 Variant CJD (vCJD) is an emerging disease and the eventual number of cases of the disease is  
54 uncertain. There is a wider distribution and higher level of infectivity/abnormal prion protein in  
55 peripheral tissues than is seen with sporadic CJD. Four instances of apparent iatrogenic vCJD infection  
56 by blood transfusion in man in the UK provide strong evidence that vCJD is transmissible through blood  
57 transfusion. In 2009, the agent was detected in a haemophilia A patient who received intermediate  
58 purity FVIII prepared from pooled plasma sourced in the UK before 1998.

59 Residence in the UK is a recognised risk factor for vCJD and has led to the UK deciding to no longer  
60 fractionate from UK plasma. It is consistent with this decision to exclude donors who have spent long  
61 periods in the UK during the risk period from donating blood/plasma for fractionation. It is  
62 recommended that donors who have spent a cumulative period of 1 year or more in the UK between  
63 the beginning of 1980 and the end of 1996 are excluded from donating blood/plasma for fractionation.

64 There is no recommendation to recall batches if information that would have excluded a donor based  
65 on his/her stay in the UK becomes available post-donation, since this is a very conservative  
66 precautionary measure.

67 Available data indicate that the manufacturing processes for plasma-derived medicinal products would  
68 reduce vCJD infectivity if it were present in human plasma. Manufacturers are required to estimate the  
69 potential of their specific manufacturing processes to reduce infectivity using a step-wise approach. It  
70 is recommended that manufacturers consult the relevant competent authorities at each of the  
71 milestones in this estimation. CHMP and its Biotechnology Working Party (BWP) will keep progress with  
72 these recommendations and the actions to be taken under review.

73 In support of this recommendation, CHMP and BWP, with the involvement of external experts, have  
74 developed guidance on how to investigate manufacturing processes with regard to vCJD risk and CHMP  
75 and BWP are available to discuss issues that might arise.

76 The rationale for this position is that if, in the future, further cases of vCJD occur in countries collecting  
77 blood and plasma for the manufacture of plasma-derived medicinal products, a process previously  
78 shown to be able to reduce TSE infectivity will provide reassurance on the safety of past products, and  
79 could help to justify continuing fractionation.

80 Low levels of infectious TSE agents have been detected in the urine of scrapie-infected rodents and in  
81 the urine of deer with Chronic Wasting Disease. However, there is no epidemiological evidence of CJD  
82 or vCJD transmission by urine derived medicinal products. A general review of manufacturing

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<sup>2</sup> In May 2004 there was a change in the name of the EMA's scientific committee for human medicines from CPMP to CHMP.

83 processes for urine-derived medicinal products indicates that it is feasible to apply donor selection  
84 criteria when a product is derived from a relatively small and well-defined donor population. In  
85 addition, it indicates that manufacturing processes have at least one step that might be theoretically  
86 capable of reducing TSE infectivity if it were present in the starting material. It is noted that urine-  
87 derived medicinal products are not sourced from urine collected in the UK.

88 On the basis of this review and other considerations, the use of exclusion criteria for selection for a  
89 urine donor panel is encouraged, as a precautionary measure, where feasible. The same exclusion  
90 criteria should be applied with respect to CJD and vCJD as used for blood/plasma donors providing  
91 starting material for the manufacture of plasma-derived medicinal products but, unlike blood/plasma  
92 donors, these criteria would not be checked at each donation. Manufacturers of urine-derived medicinal  
93 products are recommended to evaluate the capacity of the manufacturing process to reduce/eliminate  
94 TSE agents by following a similar approach to that for plasma-derived medicinal products.

95

## 96 **1. Introduction**

97 Creutzfeldt-Jakob disease (CJD) is a rare neurodegenerative disease belonging to the group of human  
98 Transmissible Spongiform Encephalopathies (TSEs) or prion diseases. Mortality rate of TSEs ranges  
99 approximately from 1.5 to 2 persons per million population per year. TSEs can occur sporadically  
100 (sporadic CJD (sCJD) and sporadic fatal insomnia), be associated with mutations of the prion protein  
101 gene (genetic TSEs (gTSE)), or result from medical exposure to infectious material (iatrogenic CJD  
102 (iCJD)). In 1996, a variant form of CJD (vCJD) was identified.<sup>1</sup> There is strong evidence that vCJD is  
103 caused by the agent responsible for bovine spongiform encephalopathy (BSE) in cattle.<sup>2,3,4</sup> The most  
104 likely hypothesis is that vCJD has occurred through exposure to BSE contaminated food.

105 Human TSEs, including in particular vCJD, were addressed in expert meetings/workshops at the EMEA  
106 in January 1998, January 1999, December 1999, May 2000, and December 2000. A CPMP Position  
107 Statement on variant CJD and plasma-derived medicinal products was issued in February 1998<sup>5f</sup> and  
108 the outcome of the subsequent meetings was published on the EMEA website.<sup>5</sup> An EMEA Expert  
109 Workshop on Human TSEs and Medicinal Products was held on 19-21 June 2002. This provided the  
110 scientific basis for a new CPMP Position Statement issued in 2003.<sup>5b</sup> A further EMEA Expert Workshop  
111 was held in January 2004 to review the current state of knowledge of vCJD, in the light of the recent  
112 report of a possible human transmission by blood transfusion.<sup>6</sup> In addition, the Workshop discussed  
113 the CPMP Discussion document on the investigation of manufacturing processes with respect to vCJD.<sup>5a</sup>  
114 In October 2005, a follow-up workshop was held to discuss the number of vCJD cases reported in  
115 France and other European countries and the potential effect of additional donor exclusion measures.  
116 Urine-derived medicinal products were specifically discussed at an EMEA expert workshop in July  
117 2007<sup>5g</sup> after publication of experiments indicating transmission of prions via urine using a hamster  
118 model.

119 Blood and blood components for transfusion are outside the scope of this Position Statement.  
120 Recommendations on the suitability of blood and plasma donors and the screening of donated blood in  
121 the European Community were described in Council Recommendation 98/463/EC.<sup>7c</sup> European  
122 legislation on human blood and blood components entered into force on 8 February 2003<sup>7a</sup> Under this  
123 legislation, a Commission Directive on certain technical requirements for blood and blood components,  
124 including eligibility criteria for donors, entered into force in April 2004.<sup>7b</sup> In addition, Council of Europe  
125 Recommendation No. R (95) 15 contains a technical appendix on the use, preparation and quality  
126 assurance of blood components and details the current requirements for donors.<sup>79</sup>

127 In December 2003, following the announcement of a possible case of vCJD transmission by blood  
128 transfusion, Commissioner Byrne made a statement highlighting EU activities in the area of vCJD and  
129 announcing a meeting of the Working Group of the Blood Regulatory Committee to consider the latest  
130 information available from the UK.<sup>7d</sup> The meeting took place in January 2004 and a summary  
131 statement was produced.<sup>7e</sup>

132 The Scientific Steering Committee (SSC) and the Scientific Committee on Medicinal Products and  
133 Medical Devices (SCMPMD) of the European Commission have published a number of opinions relating  
134 to TSEs, which are of relevance to blood and blood components for transfusion, as well as to plasma-  
135 derived medicinal products.<sup>8</sup> WHO Guidelines on TSEs are also of relevance to both blood components  
136 for transfusion and plasma-derived medicinal products.<sup>9</sup> The Council of Europe has made  
137 recommendations for blood and blood components for transfusion.<sup>10</sup>

138

## 139 **2. Human TSEs current status**

### 140 ***2.1. Sporadic, genetic and iatrogenic forms of human TSEs***

141 There is no evidence that sporadic, genetic or iatrogenic forms of human TSEs have been transmitted  
142 from person to person through exposure to plasma products or urinary derived medicinal products.  
143 Systematic surveillance for CJD of all types has been undertaken in a number of countries, including a  
144 collaborative study in the EU since 1993,<sup>11,12</sup> and no case of sporadic, genetic or iatrogenic CJD has  
145 been causally linked to prior treatment with plasma products. Cases of sporadic CJD with a history of  
146 drug treatment for infertility have not been identified but there is uncertainty about the validity of this  
147 observation. (See the report of the 2007 EMA expert meeting for further details.<sup>5g</sup>) Although there is  
148 evidence that plasma products have not been implicated in transmission of sporadic, genetic or  
149 iatrogenic CJD, the strength of the evidence excluding transmission by urinary derived medicinal  
150 products is less secure.

### 151 ***2.2. Variant CJD***

152 The official UK figures for vCJD at the beginning of April 2010 were a total of 172 definite or probable  
153 vCJD cases.<sup>13</sup> (One case diagnosed in Hong Kong was classified as a UK case and is included in the UK  
154 figures.) Outside of the UK, there have been 25 cases in France<sup>15</sup>, 5 in Spain, 4 in the Republic of  
155 Ireland, 3 in the Netherlands, 3 in the USA, 2 in Portugal and Italy and single cases in Canada, Saudi  
156 Arabia and Japan. 2 of the Irish cases, 2 of the US cases, 1 French case and the Canadian case had  
157 spent more than 6 months in the UK during the period 1980-1996 and were probably infected while in  
158 the UK.<sup>14</sup> The third US case has been reported as most likely infected when living in Saudi Arabia. The  
159 possibility of cases occurring in other countries cannot be excluded.

160 Two cases of vCJD identified in Spain occurred in the same family. No family links have been reported  
161 in any other vCJD cases to date.

162 All definite and probable cases, which have been genotyped so far, are Met-Met homozygotes at codon  
163 129 of the prion protein (PrP) gene.<sup>16</sup> In 2009 a possible case of variant CJD was reported in the UK  
164 with a heterozygous codon 129 genotype.<sup>17</sup>

165 Analysis of the UK figures for the quarterly incidence of deaths indicates that vCJD incidence in the UK  
166 is currently in decline. However, interpretation requires caution as there may be a long tail or more  
167 than one peak to the epidemic.<sup>18</sup>

168 A UK study screening specimens from surgically removed appendices and tonsils for accumulation of  
169 prion protein in the lymphoreticular system has been carried out in order to try and obtain some  
170 estimation of the number of people that might be incubating vCJD in the UK.<sup>19</sup> Three positive appendix  
171 specimens have been found as a result of the screening of 12,674 appendix and tonsil specimens.  
172 However, the pattern of lymphoreticular accumulation in two of these samples was dissimilar from that  
173 seen in known cases of vCJD, raising the possibility that they may be false positives. With respect to  
174 this possibility, the authors comment that although it is uncertain whether immunohistochemical  
175 accumulation of prion protein in the lymphoreticular system is specific for vCJD, it has not been  
176 described in any other disease, including other forms of human prion disease or a range of  
177 inflammatory and infective conditions. Subsequent genetic analysis of residual tissue samples from  
178 these 2 cases found that both were valine homozygotes at codon 129 in the prion protein gene<sup>20</sup> This  
179 finding might account for the immunohistochemical features in these cases; all patients who have  
180 developed vCJD and have undergone a comparable genetic analysis have been methionine  
181 homozygotes at codon 129 in the prion protein gene.

182 Statistical analysis on this finding of 3 positive specimens gives the following estimations of numbers  
183 who may be incubating vCJD:

184 237 infections per million population (95% confidence interval (CI): 49-692 per million)

185 Assuming that this estimate relates to those aged 10-30 years<sup>3</sup>, 3,808 individuals (CI 785-11 128)  
186 aged 10-30 years may be incubating vCJD in the UK.

187 These estimations are higher than predictions from modelling of the clinical data (upper 95%  
188 confidence interval of 540 future cases).<sup>21</sup> It is not known whether those incubating vCJD will  
189 eventually develop clinical disease. However, estimates of numbers possibly incubating are important  
190 with respect to any potential for secondary transmission (e.g. by blood donation, surgical instruments)  
191 while individuals are in the incubation phase. It should be noted that plasma-derived medicinal  
192 products have not been manufactured from donations collected in the UK since 1998.

193 A larger study of an archive of tonsil tissue from 63,007 people of all ages removed during routine  
194 tonsillectomies has been published.<sup>22</sup> 2,753 samples were from the 1961- 1985 birth cohort in which  
195 most cases of vCJD have arisen and 19,808 were from the 1986-1995 birth cohort that may also have  
196 been orally exposed to bovine spongiform encephalopathy. None of the samples were unequivocally  
197 reactive to two enzyme immunoassays and none of the initial reactives were positive for PrP<sup>TSE</sup> by  
198 immunohistochemistry or immunoblotting. The estimated 95% confidence interval for the prevalence  
199 of PrP<sup>TSE</sup> in the 1961-1995 birth cohort was 0-113 per million and in the 1961-1985 birth cohort 0-289  
200 per million. These estimates are lower than the previous study of appendix tissue, but are still  
201 consistent with this study. Archiving of tonsil tissues continues and further studies are planned.

202

### 203 **3. Human tissue distribution of infectivity/abnormal prion** 204 **protein.**

205 Tissue distribution has been investigated by detection of the abnormal prion protein PrP<sup>TSE</sup> or by  
206 infectivity assays. Detection of PrP<sup>TSE</sup> in tissues has often been associated with infectivity, however it  
207 should be noted that, in some circumstances, infectivity can be present without detection of PrP<sup>TSE</sup> or  
208 PrP<sup>TSE</sup> be present in absence of infectivity.<sup>23</sup> This may be related to limitations of assay methods for  
209 PrP<sup>TSE</sup>, however, in some cases the reason for this finding is not known. It is thus recommended that

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<sup>3</sup> The reason the age range of 10-30 years is specified is because 83% of the samples were from individuals in this age range.

210 any study on tissue or fluid distribution of the abnormal prion protein be confirmed with an infectivity  
211 assay.

212 A wider distribution and higher level of PrP<sup>TSE</sup> in human peripheral tissues, including the  
213 lymphoreticular system, has been found in vCJD compared with sporadic CJD.<sup>24,25,26</sup> Limited data from  
214 infectivity assays of vCJD tissues are consistent with the PrP<sup>TSE</sup> findings.<sup>27</sup> In clinical vCJD cases high  
215 titres of infectivity are found in the brain and spinal cord and lower levels in spleen and tonsil<sup>27</sup>. While  
216 PrP<sup>TSE</sup> and infectivity are occasionally found in the spleen of sporadic CJD, the levels of PrP<sup>TSE</sup> are lower  
217 than in vCJD.<sup>81</sup> It is also suspected that lymphoid tissue involvement in sCJD is associated with a  
218 relatively long duration of clinical illness whereas it occurs preclinically in vCJD. PrP<sup>TSE</sup> accumulations  
219 have been observed in muscles of some patients with both sporadic and variant CJD.<sup>28</sup>

220 It is likely that the distribution of PrP<sup>TSE</sup> and infectivity in iCJD is more similar to sCJD than vCJD.<sup>29</sup>  
221 Data are lacking for gCJD.

222

## 223 **4. Infectivity in blood and transmissibility via blood**

### 224 **4.1. Animal blood**

225 Low levels of infectivity have been found in the blood of rodents experimentally infected with animal  
226 and human TSE agents.<sup>30,31,32,33</sup> Experiments indicate that approximately half the infectivity is in the  
227 cellular components, mainly the buffy coat, and the remainder in the plasma. Experimental studies  
228 indicate that the vCJD agent behaves in a similar way (qualitatively and quantitatively) to a genetic  
229 TSE agent<sup>4</sup> when adapted to RIII/Fa/Dk mice.<sup>33</sup> Infectivity has also been detected in buffy coat of a  
230 prosimian microcebe experimentally infected with a macaque-adapted BSE strain.<sup>34</sup>

231 The infectivity in rodent blood was transmitted by intravenous inoculation, but 5-7 fold less efficiently  
232 than by the intracerebral route.<sup>31</sup> In one study with mouse-adapted vCJD agent, the intravenous and  
233 intracerebral routes were found to be equally efficient for the buffy coat fraction but not for the plasma  
234 fraction.<sup>33</sup> However, studies in primates show that survival times were similar after intravenous or  
235 intracerebral inoculation of infected brain material.<sup>35,36</sup> Unpublished studies presented at scientific  
236 meetings<sup>37,38</sup> indicate that blood of primates experimentally infected with human TSE agent is  
237 infectious from about half way through the incubation period.

238 Furthermore, information from intra-species transfusion experiments indicates that experimental BSE  
239 in orally infected sheep or natural scrapie infection in sheep can be transmitted to sheep by blood  
240 transfusion.<sup>39,40</sup> Transmission efficiency was high for both BSE and natural scrapie, and the majority of  
241 transmissions resulted from blood collected more than half way through the incubation period<sup>41</sup>. The  
242 level of infectivity in sheep blood cannot be established from these experiments.

243 The European Union has provided funding for animal transmission projects.

### 244 **4.2. Human blood**

245 The tracing of recipients of blood transfusion from UK donors who have subsequently developed vCJD  
246 (the TMER study) has revealed four instances of secondary transmission.<sup>42</sup> These individuals had  
247 received transfusion of non-leucodepleted red cells from donors who were clinically healthy at the time  
248 of donation but subsequently (17–40 months later) developed variant CJD. Three of the four patients  
249 developed disease after incubation periods ranging from 6.5 to 8.5 years; the fourth died 5 years after

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<sup>4</sup> Mouse-adapted GSS strain of human TSE (brain tissue obtained from a case of Gerstmann-Sträussler-Scheinker syndrome).

250 transfusion of an illness unrelated to prion disease but tested positive for PrP<sup>TSE</sup> in the spleen and  
251 lymph nodes. This asymptomatic prion-infected patient was heterozygous (methionine/valine) at codon  
252 129 of the *PRNP* gene. Taken together, these instances are strong evidence that vCJD is transmissible  
253 through blood transfusion.

254 Recently, another presumed case of prion infection was identified in an elderly haemophilic patient who  
255 was heterozygous at codon 129 in the prion protein gene.<sup>43</sup> The patient, who died of unrelated  
256 pathology, had received large quantities of UK-sourced fractionated plasma products, including some  
257 units derived from plasma pools which contained plasma from a donor who later developed variant  
258 CJD. This patient was identified through an intensive search for PrP<sup>TSE</sup> positivity in all post-mortem  
259 tissues, although only 1 of 24 samples taken from the spleen tested positive. Whether someone with  
260 this limited distribution of PrP<sup>TSE</sup> would be infectious is unknown, but from a public health perspective,  
261 this patient represents a warning that some plasma-derived products might contain residual prion  
262 infectivity.

263 The surveillance described above emphasises the importance of the TMER study for identifying the risk  
264 of blood transfusion in transmitting vCJD. Moreover, national databases of blood donors and the  
265 maintenance of traceability from donor to recipient and vice versa are essential to establish whether a  
266 vCJD case has been a blood donor (UK experience has shown that questioning of family members is  
267 unreliable for establishing whether a patient has been a blood donor). Traceability is a specific  
268 requirement in Article 14 of Directive 2002/98/EC.<sup>7a</sup>

269 Infectivity or PrP<sup>TSE</sup> were not detected in blood of vCJD cases using methods capable of detecting  
270 infectivity/PrP<sup>TSE</sup> in peripheral tissues such as tonsil or spleen, indicating that if infectivity is present it  
271 is at levels below the sensitivity of these methods.<sup>27,24</sup>

272 There is no epidemiological evidence that blood of sporadic CJD may transmit disease.<sup>44,45</sup> Prospective  
273 studies, similar to the TMER study, are in progress in the UK and USA and have not yet revealed any  
274 possible case of sporadic CJD linked to blood transfusion. However, current data are scanty to  
275 unequivocally exclude the possibility that such an event could occur in a small number of cases with a  
276 long (10 or more years) incubation period.<sup>46</sup>

277 A review of transmission studies to detect infectivity in the blood of humans with CJD (sporadic,  
278 iatrogenic and variant) shows that although experimental transmissions to animal models have  
279 occasionally been reported<sup>47-50</sup>, other studies failed to detect infectivity.<sup>51,27</sup> It remains possible that  
280 PrP<sup>TSE</sup> is present at low levels in the blood of clinically affected cases of sCJD. Data are lacking for gCJD  
281 but the assumption is that the tissue distribution of infectivity will be more similar to sCJD than vCJD.

282 For the purpose of risk assessments, it is recommended that, as a worst case assumption, a relative  
283 efficiency of the intravenous and intracerebral routes of 1:1 should be used.<sup>52</sup> This is because the  
284 accumulated information now available from animal studies indicates that the intravenous route can be  
285 an efficient route of transmission and in certain cases can give a transmission rate and/or an  
286 incubation period similar to the intracerebral route (see also 4.1).

287

## 288 **5. Detection techniques**

289 Several techniques are under development for the detection of PrP<sup>TSE</sup> in blood including methods based  
290 on epitope protection<sup>53</sup> and PrP<sup>TSE</sup> specific antibodies<sup>54</sup>. Approaches based on surrogate markers are  
291 also under investigation. Development and validation of all methods is on-going but there is no  
292 screening test yet. Confirmatory tests that have been proposed include Protein Mis-folding Cyclic  
293 Amplification (PMCA)<sup>55</sup> which is extremely sensitive, but has not yet been validated.



294 Several WHO reference preparations are available and further materials are under development<sup>9b</sup>.  
295 These reference preparations will allow calibration of assays versus infectivity bioassays, and can be  
296 used for collaborative studies to compare the performance of different assays to see whether they are  
297 sufficiently sensitive and specific to justify further evaluation for screening blood.

298 PrP<sup>TSE</sup> detection methods for screening human blood for evidence of infection are being considered for  
299 inclusion as Annex II List A devices under the IVD Directive. There are very few samples of blood or  
300 plasma from clinically affected patients or from individuals known to have been infected at a particular  
301 time. This contrasts with other blood borne agents such as viruses. Alternative development and  
302 evaluation strategies have been proposed to assess whether a candidate assay is sufficiently promising  
303 to be given access to the available samples.<sup>56</sup>

304

## 305 **6. Leucoreduction and specific prion affinity filters**

306 Leucoreduction is used in transfusion medicine to reduce the level of white blood cells in blood and  
307 blood components. It was implemented in the UK in 1999.

308 The rationale for considering leucoreduction as a precautionary measure is:

309 - The lymphoreticular involvement in vCJD

310 - The detection of low levels of infectivity, in studies with rodents, in the buffy coat (associated  
311 with white blood cells).

312 The SCMPMD opinion on leucoreduction<sup>8a, 8b</sup> for blood and blood components for transfusion states  
313 that it might be a precautionary step to remove white cells as completely as possible. For plasma for  
314 fractionation the opinion states the following:

315 'Taken together, there is no compelling scientific evidence to date for the introduction of leucoreduction  
316 of plasma for fractionation, or other methods aiming at removal of cells and debris, as a precaution  
317 against vCJD transmission. The question should be further explored by suitable experiments.'

318 Results reported at the 2002 EMEA Workshop, suggested that leucoreduction does not provoke  
319 fragmentation of cells and lysis. Results of a comprehensive study involving a number of different  
320 filters and procedures indicate that leucodepletion is not detrimental in terms of the generation of  
321 microvesicles or the release of prion proteins<sup>57</sup>.

322 Infectivity data from hamster studies indicate that leucoreduction alone is not totally protective against  
323 prion transmission, with between 42 to 72 percent reduction in infectivity of whole blood<sup>58,59</sup>.

324 Specific affinity ligands that bind prion proteins are being evaluated for their ability to reduce TSE  
325 infectivity present in blood and plasma.

326 A study in hamsters showed that a leucocyte-reduction filter based on modified polyester fibres  
327 exhibited a prion clearance capability between 99.0 to 99.9 percent on the endogenous and exogenous  
328 infectivity of red cell concentrates<sup>60</sup>.

329 Initial studies using leucoreduced human red blood cell concentrates spiked with hamster brain-derived  
330 scrapie infectivity indicate that some ligands immobilised on a chromatographic resin matrix are  
331 capable of removing 3 to 4 log ID<sub>50</sub> per ml<sup>59</sup>. A further study using scrapie-infected hamster whole  
332 blood demonstrated an overall reduction of infectivity of more than 1.22 log ID<sup>61</sup>.

333 The prion binding capacity of an affinity ligand chromatography step has been investigated in the  
334 processing of a plasma medicinal product using hamster brain derived spiking material<sup>62</sup>. This  
335 preliminary data requires further evaluation before conclusions can be drawn on possible efficacy.

336

## 337 **7. Manufacturing processes for plasma-derived medicinal** 338 **products**

339 Taking account of the available data concerning blood infectivity, it is of utmost importance to  
340 investigate the capacities of the manufacturing process (fractionation) to eliminate/inactivate the  
341 infectious material potentially present in the plasma pool used as the starting material for preparation  
342 of plasma-derived products. Initial results from animal studies, using blood from rodents infected by  
343 intracerebral inoculation, indicated that the fractionation process contributes to the removal of  
344 endogenous plasma infectivity.<sup>30,31</sup> Information reported at the EMEA Workshops in 2002 and 2004  
345 suggested that endogenous infectivity might persist through the fractionation process to a greater  
346 extent than would be expected from spiking studies,

347 Many investigational studies have now been carried out with different strains of agent and spiking  
348 materials of different nature and purity, and using different assays to follow the partition of PrP<sup>TSE</sup>  
349 and/or infectivity. In most cases, the correlation between the capacity to partition PrP<sup>TSE</sup> and infectivity  
350 has been demonstrated for the spiking preparations used until now (mainly brain homogenates of  
351 various strains). It is now confirmed that biochemical assays can be useful for spiking experiments to  
352 investigate manufacturing processes in a reasonable timeframe and less costly protocols than the *in*  
353 *vivo* bioassay. However it is still necessary to correlate such results with those from infectivity assays  
354 in animals. Cell-based assays may also be useful if properly validated for this purpose.

355 Studies aimed at investigating the contribution of the various manufacturing steps to reduction of  
356 infectivity (including precipitation followed by centrifugation or depth filtration, chromatography and  
357 nanofiltration) have accumulated convergent data supporting the removal of infectivity by steps that  
358 are commonly used in the manufacture of plasma-derived medicinal products.<sup>62-68</sup> For coagulation  
359 factors derived from cryoprecipitate, downstream fractionation using various precipitating agents or  
360 conditions allow to discard PrP<sup>TSE</sup> in the precipitates. Reduction level achieved may vary according to  
361 the specific manufacturing process and probably depends on the concentration of the precipitating  
362 agent and salts, and the pH. Chromatographic steps, classically used in the separation of coagulation  
363 factors but also in the purification of other plasma derivatives have been described to remove TSE  
364 infectivity or PrP<sup>TSE</sup>. Again, the reduction factors may be variable according to the fraction eluted.  
365 However, caution is still needed in the interpretation of those data since the effectiveness of a given  
366 step is dependent on a number of variables including the process conditions and the state/nature of  
367 the agent in the spiking preparation sample and in the spiked product intermediate. Consequently,  
368 effectiveness of removal may vary from one manufacturer to another. In addition, recent studies have  
369 highlighted the fact that removal capacity may be variable according to the state of dispersion of the  
370 agent in the spiking preparation particularly for steps based on retention mechanisms.

371 Overall, there is a need i) to investigate the partitioning or removal capacities of the various  
372 fractionation steps used in the preparation of the plasma-derived medicinal products, ii) to investigate  
373 the partition and removal of endogenous infectivity and the extent to which this is comparable with  
374 data from spiking studies, iii) to gain better knowledge of the form of infectivity present in blood in  
375 order to confirm the relevance of the spiking material used in the validation studies.

376

## 377 **8. Infectivity in urine**

378 Low levels of infectivity have been detected in urine of scrapie-infected rodents by several research  
379 groups and in the urine of deer with Chronic Wasting Disease.<sup>59, 9c</sup>

380 Gregory *et al.*<sup>69</sup> demonstrated that the disease could be transmitted by intracerebral inoculation of  
381 pooled urine from scrapie-sick hamsters. The infectivity titre of the urine was calculated to be around  
382 3.8 infectious doses/ml. Titration of kidney and urinary bladders from the same animals gave 20,000-  
383 fold greater concentrations. Histologic and immunohistochemical examination of these tissues showed  
384 no indication of inflammation or other pathologic changes, except for occasional deposits of disease-  
385 associated prion protein in kidneys.

386 Kariv-Inbal *et al.*<sup>70</sup> have observed transmission of the disease after intraperitoneal (i.p.) administration  
387 of enriched urine fractions from scrapie sick hamsters. Transmission via the oral route was also  
388 investigated. The recipient hamsters remained without symptoms but secondary transmission was  
389 observed after inoculation of brain extract from an asymptomatic hamster.

390 Seeger *et al.*<sup>71</sup> have studied transmission via urine using mouse models of chronic inflammation. They  
391 have detected prionuria in scrapie infected mice with coincident chronic lymphocytic nephritis.  
392 Transmission has been shown upon intracerebral inoculation of purified proteins from pooled urine  
393 collected from scrapie sick or presymptomatic mice. In contrast, prionuria was not observed in scrapie  
394 infected mice displaying isolated glomerulonephritis without interstitial lymphofollicular foci or in  
395 scrapie infected wild type mice lacking inflammatory conditions.

396 Prionuria was also detected in chronic wasting disease (CWD) of deer. Experiments by Haley *et al.*<sup>72</sup>  
397 provided evidence that concentrated urine from deer at the terminal stage of the disease, that also  
398 showed mild to moderate nephritis histopathologically, was infectious when inoculated into transgenic  
399 mice expressing the cervid PrP gene. In addition, the urine collected from the CWD sick deer that was  
400 used for mouse inoculation, showed positive results when assayed for PrP<sup>TSE</sup> by serial rounds of protein  
401 misfolding cyclic amplification (PMCA) assay. The concentration of abnormal prion protein was very low  
402 as indicated by undetectable PrP<sup>TSE</sup> by traditional assays and prolonged incubation periods and  
403 incomplete TSE attack rates in the transgenic mice.

404 Using the highly sensitive PMCA technology Gonzalez-Romero *et al.*<sup>73</sup> and Murayama *et al.*<sup>74</sup> have  
405 detected PrP<sup>TSE</sup> in urine of scrapie sick hamsters. The results by Gonzalez-Romero *et al.* suggest that  
406 the concentration of PrP<sup>TSE</sup> in urine is in average 10-fold lower than in blood. Animal experiments have  
407 demonstrated that *in vitro* generated PrP<sup>TSE</sup> by PMCA starting from urine produced a disease  
408 indistinguishable from the one induced by infected brain material.<sup>73</sup>

409 Epidemiological evidence in the last 25 years, during which urinary-derived medicinal products and  
410 particularly gonadotrophins have been widely used, does not suggest a risk from sporadic CJD. Since  
411 epidemiological evidence has identified the few cases of iatrogenic transmission of CJD through the use  
412 of pituitary-derived gonadotrophins, it is possible that transmission from urinary-derived  
413 gonadotrophins would have been detected if it had occurred.

414

## 415 **9. Recommendations and proposals**

### 416 ***9.1. Sporadic, genetic and iatrogenic CJD and plasma-derived medicinal*** 417 ***products***

418 Cumulative epidemiological evidence does not support transmission of sporadic, genetic and iatrogenic  
419 CJD by blood, blood components or plasma-derived medicinal products.<sup>75, 76, 12</sup> Nevertheless, rigorous  
420 epidemiological studies for tracing blood-related sCJD cases have not yet reached sufficient statistical  
421 power to formally exclude the possibility of blood transmission in a small number of cases. Moreover,  
422 the experimental evidence of peripheral tissue infectivity in various subtypes of sCJD is very limited  
423 but available data show presence of infectivity in spleen and lymph nodes in human TSEs other than  
424 vCJD.

425 The implementation of appropriate actions in relation to CJD depends on accurate diagnosis in  
426 suspected cases. There is a potential for diagnostic confusion between sporadic and variant CJD,  
427 particularly in younger age groups.

428 Donor selection criteria include criteria to exclude donors who might be at higher risk of developing  
429 CJD. The following permanent deferral criteria are specified in Commission Directive 2004/33/EC:  
430 Persons who have a family history which places them at risk of developing a TSE, or persons who have  
431 received a corneal or dura mater graft, or who have been treated in the past with medicines made  
432 from human pituitary glands.<sup>7b</sup> Precautionary recalls of batches of plasma-derived medicinal products  
433 after post-donation reports of CJD or CJD risk factors in a donor contributed to severe shortages of  
434 certain products.<sup>9a</sup>

435 On the basis of the current epidemiological evidence, the CHMP recommendation that recall of plasma-  
436 derived medicinal products is not justified where a donor is later confirmed as having sporadic, genetic  
437 or iatrogenic CJD or CJD risk factors is maintained.

### 438 ***9.2. Variant CJD and plasma-derived medicinal products***

439 Uncertainties still exist concerning the number of cases of vCJD that will occur although the number of  
440 cases is in decline in the UK and France. Variant CJD has a different distribution of infectivity in tissue  
441 outside the central nervous system to sporadic CJD.

442 There is now strong epidemiological evidence of human to human transmission of vCJD by blood  
443 transfusion (see Section 4.2). In addition, one vCJD infection was detected in a patient with  
444 haemophilia treated with high doses of intermediate purity factor VIII. Estimates of the relative risks of  
445 exposure through diet, surgery, endoscopy, blood transfusion and receipt of UK-sourced plasma  
446 products suggest that the most likely route of infection in the patient with haemophilia was receipt of  
447 UK plasma products. At least one batch came from a pool containing a donation from a donor who later  
448 developed vCJD.<sup>43,77,</sup>

449 The following measures are aimed at minimising the risk of transmission of the agent by plasma-  
450 derived medicinal products.

#### 451 **9.2.1. Exclusion Criteria**

##### 452 **a) Consideration of Country-based exclusions**

453 There is currently no screening test to detect donors who may be incubating the disease or in the early  
454 clinical stages. Therefore, other approaches are considered in order to try and identify donors who may  
455 present a higher risk.

456

457 ***UK plasma***

458 Residence in the UK is a recognised risk factor for vCJD and has led to the UK deciding no longer to  
459 fractionate from UK plasma.

460

461 ***Exclusion of donors based on cumulative period of time spent in the UK***

462 Since UK donors are excluded from donating plasma for the manufacture of plasma-derived medicinal  
463 products in the UK, it is consistent to exclude donors who have spent long periods in the UK. This is  
464 supported by the finding of vCJD cases, which have a risk factor of long periods spent in the UK, in  
465 other countries<sup>5</sup>.

466 It is, therefore, recommended that donors who have spent a cumulative period of 1 year or more in  
467 the UK between the beginning of 1980 and the end of 1996 are excluded from donating blood/plasma  
468 for fractionation. Countries are highly encouraged to choose their national cumulative period limit for  
469 plasma-derived medicinal products according to a nationally calculated benefit/risk balance, which will  
470 take into account the endogenous risk of BSE exposure (and introduction in the food chain) and the  
471 risk of shortages of blood and plasma for the manufacture of medicinal products. The national limit is  
472 recommended to be of cumulative periods in the UK below or equal to 1 year.

473 Countries may still apply a stricter limit than 1 year for exclusion of donors for blood/plasma collected  
474 for fractionation within the country (e.g. 6 months) but will accept plasma-derived medicinal products  
475 from other countries provided that at least the one-year time limit is applied.

476 The rationale for this recommendation is to exclude donors who have the highest individual risk from  
477 stays in the UK and to be consistent with the UK decision to no longer fractionate from UK plasma. This  
478 is further explained in the first version of this Position Statement published in February 2003.<sup>5b</sup>

479

480 ***French plasma and plasma from other BSE-exposed European countries***

481 France published an analysis of the risk of transmission of vCJD by blood and its derivatives sourced  
482 from French plasma in December 2000.<sup>78g</sup> This concluded that plasma collected in France could  
483 continue to be used for fractionation. The safety margin for plasma-derived medicinal products was  
484 considered to be sufficient. However, introduction of additional steps to further increase the safety  
485 margin of some products was recommended (e.g. nanofiltration of Factor VIII introduced in January  
486 2001). Leucodepletion for plasma for fractionation, as for plasma for transfusion products, was also  
487 recommended in 2001 as a precautionary measure. The subsequent risk-analyses published in 2002,  
488 2003, 2004, 2005, 2007 and 2009 re-confirmed these conclusions and acknowledged that the size of  
489 epidemic was revised to a lower estimate by more recent modeling, and the risk to collect blood from  
490 vCJD-incubating donors lower than previously estimated.<sup>78</sup>

491 Based on the limited data on human exposure to BSE-risk materials in other European countries it is  
492 still difficult to estimate the epidemiological risk in those countries which have small number of vCJD  
493 cases or have not yet reported any vCJD cases.

494

495 ***Donors who have spent a cumulative period of time in France and other BSE-exposed***  
496 ***countries***

497 Exclusion of donors who have spent a cumulative period of time in France is not recommended  
498 because of the lower risk associated with time spent in France compared with time spent in the UK  
499 (the risk in France is estimated to be 1/10 of that in UK). Since the previous version of the Position  
500 Statement, endogenous vCJD cases occurred in some other countries (see Section 2. Human TSEs  
501 current status) placing them close to or lower than France in terms of incidence and ratio of risk in

---

<sup>5</sup> Two cases in Ireland, two cases in US, one case in UK, and the Canadian case associated with long periods spent in the UK.

502 comparison to UK. Exclusion of donors who have spent time in other European countries having a risk  
503 ratio in the same order of magnitude as France is not recommended.

504  
505 **Concluding remarks**

506 Country-based exclusions may appear unjustified in the sense that the vast majority of donors who will  
507 be excluded will not develop the disease. There is a lack of spare plasma capacity to make up for  
508 shortfalls if countries that are major producers of plasma-derived medicinal products discontinue the  
509 use of nationally collected plasma for fractionation.

510  
511 **b) Other possible exclusion criteria**

512 Commission Directive 2004/33/EC indicates that further deferral criteria for vCJD may be  
513 recommended as a precautionary measure.<sup>7b</sup>

514 Other possible exclusion criteria that could be considered include permanent exclusion of recipients of  
515 blood transfusion (general exclusion or exclusion of recipients of transfusion in UK<sup>6</sup>), transplant  
516 recipients, and donors who have undergone neurosurgery.

517 Caution is needed because of the risk of loss of donors and consequent supply problems. Since such  
518 criteria could apply to both blood and blood components, and plasma-derived medicinal products, it  
519 was appropriate to consider this further within the scope of Directive 2002/98/EC.<sup>7a</sup> The technical  
520 meeting of blood experts, convened by the European Commission in January 2004, considered  
521 exclusion criteria, as well as blood component preparation and processing, recipient tracing and  
522 surveillance, and optimal use of blood.<sup>7e</sup>

523 **9.2.2. Leucoreduction and specific prion affinity filters**

524 The benefit of inclusion of leucoreduction to improve the safety of plasma has not been demonstrated.

525 At present it is not appropriate to recommend the introduction of leucoreduction for the safety of  
526 plasma-derived products.

527 Efficacy of introducing recently developed affinity media / filters is still under investigation.

528 **9.2.3. Manufacturing processes for plasma-derived medicinal products**

529 The available data support the reduction of infectivity by steps in the manufacturing process.  
530 Manufacturers are required to estimate the potential of their specific manufacturing processes to  
531 reduce infectivity. This should follow a step-wise approach as described below and illustrated in the  
532 accompanying flow diagram. It is recommended that manufacturers consult the relevant competent  
533 authorities at each of the milestones in this estimation. A decision to undertake an infectivity assay  
534 and/or to add a further manufacturing step(s) to increase reduction capacity should only be made after  
535 a careful consideration of all benefit-risk factors for a certain product.

536 Firstly, manufacturers should compare their own processes to those with published data on reduction  
537 of infectivity in order to estimate the theoretical potential of their specific manufacturing processes to  
538 reduce infectivity. (*Flow diagram, step 1*)

539 Whereas the general information available on manufacturing processes provides useful background  
540 information, the actual effectiveness of a manufacturing process might be dependent on the specific

---

<sup>6</sup> In April 2004, the UK implemented exclusion of persons who have previously received transfusions of whole blood components since January 1980, as a precautionary approach.

541 process conditions. Manufacturers should consider the relevance of the published data to their specific  
542 manufacturing processes and whether the removal capacity can be expected to be comparable.

543 If it cannot be concluded that the removal capacity would be expected to be comparable, it is  
544 recommended that manufacturers undertake product-specific investigational studies on key steps in  
545 their manufacturing processes using biochemical assays. Priority should be given to studies on  
546 products with the lowest potential removal capacity. (*Flow diagram, step 2*)

547 Investigations using biochemical assays may be sufficient if a clear correlation with infectivity data has  
548 already been established for similar processes (e.g. ethanol fractionation). If such a correlation is not  
549 established (e.g. a novel step) and the step is considered critical for removal of infectivity for the  
550 specific product (e.g. it is the only step for removal), the investigations should be confirmed using an  
551 infectivity assay for the critical step(s). (*Flow diagram, step 3*)

552 The above steps will allow manufacturers to estimate the reduction capacity of their manufacturing  
553 processes. (*Flow diagram, step 4*)

554 In cases where the overall reduction capacity is limited, manufacturers should consider the addition of  
555 steps that may increase the removal capacity where this is feasible without compromising the safety,  
556 quality and availability of the existing products. Discussion with the relevant competent authorities is  
557 recommended. (*Flow diagram, step 5*)

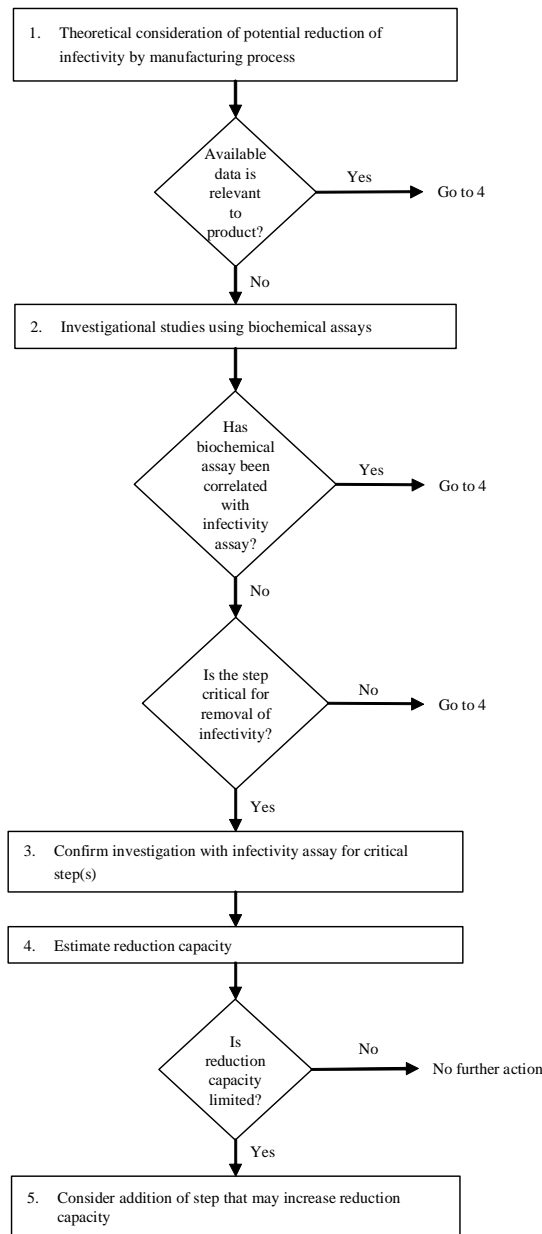
558 The outcome of the estimates of the theoretical potential of manufacturing processes to reduce  
559 infectivity and the results of product-specific investigational studies should be reported to the relevant  
560 competent authorities for the medicinal products concerned, as information becomes available.  
561 Applicants submitting new marketing authorisation applications for plasma-derived medicinal products  
562 will be expected to include such information in the application dossier. The outcome of the estimation  
563 of the theoretical potential to reduce infectivity should always be included in the application.

564 In support of these recommendations, CHMP's Biotechnology Working Party, with the involvement of  
565 external experts, has developed guidance on how to investigate manufacturing processes with regard  
566 to vCJD risk.<sup>5a</sup>

567

Figure 1: Plasma-Derived Medicinal Products: estimation of potential reduction capacity of specific manufacturing processes

**Important Note:** this flow diagram should be read in conjunction with the preceding text in 9.2.3. It is recommended to consult the relevant competent authorities at the milestones in this estimation. Give priority to studies on products with the lowest potential removal capacity.



568

569 **9.2.4. Recall of batches where information becomes available post-**  
 570 **donation**

571 In view of the lack of adequate information on vCJD, it is prudent to recall batches of plasma-derived  
 572 medicinal products where a donor to a plasma pool subsequently develops vCJD. Recall should also  
 573 include medicinal products containing plasma-derived products as excipients. However, in both cases,  
 574 consequences for essential medicinal products where alternatives are not available will need careful  
 575 consideration by the competent authorities.



576 A case-by-case consideration would be appropriate where plasma-derived products have been used in  
577 the manufacture of other medicinal products. This consideration would include the nature of the  
578 product, the amount used, where it is used in the manufacturing process and the downstream  
579 processing.

580 Look-back to identify the fate of donations should be taken as far as possible. Regulatory authorities,  
581 Official Medicines Control Laboratories, surveillance centres and the supply chain should be informed of  
582 all batches of product and intermediate implicated whether or not supplies of the batch are exhausted.

583 There is no recommendation to recall batches if information becomes available post-donation, which  
584 would have excluded a donor based on his/her stay in the UK since this donation exclusion criteria is a  
585 very conservative precautionary measure (see 9.2.1).

#### 586 **9.2.5. Albumin used as an excipient or in manufacturing processes**

587 The available data on the removal of infectivity during the fractionation process used in the  
588 manufacture of albumin indicates that the risk of transmission of infectivity by albumin would be  
589 particularly low. Nevertheless, in the case of albumin used as an excipient, recall is still recommended  
590 as a precautionary measure where a donor to a plasma pool subsequently develops vCJD. A single  
591 batch of albumin may be used to produce a number of batches of a medicinal product because of the  
592 small amounts that are typically used as an excipient. As a consequence, a recall could affect complete  
593 stocks of a product and create severe shortages. Therefore, to avoid a negative impact on supply,  
594 companies should consider the origin of plasma and select countries where the probability of having to  
595 recall batches is as limited as possible.

596 Development of substitutes for plasma-derived albumin used as an excipient or in manufacturing  
597 processes is encouraged although it is recognised that this can be difficult (requiring development and  
598 validation and usually non-clinical and clinical investigations) and should thus be considered as a long-  
599 term approach.

#### 600 **9.2.6. Substitution with alternative products**

601 Use of alternative products to plasma-derived medicinal products could be considered, where these are  
602 available. It is felt that this choice should remain with users, taking into account the needs of the  
603 individual patient. It should be noted that plasma-derived products such as albumin may be used in  
604 the manufacture of recombinant products.

#### 605 **9.2.7. Optimal Use**

606 Optimal use of plasma-derived medicinal products is encouraged, as this will maximise the benefits of  
607 the products compared with any potential risk.

### 608 ***9.3. Urine-derived medicinal products***

609 The recommendations for urine-derived medicinal products are based on the following considerations:

610 There is no epidemiological evidence of CJD and vCJD transmission by urine-derived medicinal  
611 products.

612 TSE infectivity in urine has been reported in some animal models.

613 The review of manufacturing processes described below.

614 Investigational studies of infectivity reduction by the manufacturing processes should be done following  
615 the same general, stepwise approach as recommended for plasma derived medicinal products (see  
616 Section 9.2.3).<sup>5a</sup>

617 Results from different assay systems are not necessarily directly comparable (Western blot, cell based  
618 assays, bioassay). The approach recommended for plasma-derived medicinal products would be  
619 applicable (i.e. confirm reduction capacity using infectivity assays for steps critical for reduction of  
620 infectivity if a clear correlation between data from biochemical assays and infectivity assays has not  
621 been established for similar process steps). For inactivation studies, investigation of different TSE  
622 strains should be considered as they may vary in resistance.

623 Potential accumulation of prions on chromatographic columns or a potential batch to batch  
624 contamination due to carry-over of prions should be addressed in the studies.

625 Bibliographic data could be acceptable as additional supportive data to the investigational studies  
626 provided. Similarity of the compared process and materials should be established. Extrapolation of  
627 results for plasma-derived medicinal products is not justified particularly for chromatographic steps at  
628 the beginning of the manufacturing process because of the high protein content in plasma.

629 General review of the manufacturing processes indicates that, in each manufacturing process, there is  
630 at least one step that might be theoretically capable of reducing infectivity if it were present in the  
631 starting material. In cases where the reduction capacity is limited, manufacturers should consider the  
632 addition of steps that may increase the overall removal capacity.

633 For particular products, such as hormones from a relatively small well-defined donor population, some  
634 manufacturers have put in place limited exclusion criteria for the selection of a donor for inclusion in a  
635 donor panel. For other products manufactured from very large donor pools (e.g. urokinase), such  
636 measures are more difficult to apply.

637 Urine should be collected from countries where there is a surveillance system for both human and  
638 animal TSEs. It is noted that urine-derived medicinal products are not sourced from urine collected in  
639 the UK.

640 On the basis of these considerations, the use of exclusion criteria for selection for a donor panel are  
641 encouraged, as a precautionary measure, where feasible. The same exclusion criteria should be applied  
642 with respect to CJD and vCJD as used for blood/plasma donors providing starting material for the  
643 manufacture of plasma-derived medicinal products. Although these criteria would not be checked at  
644 each donation unlike blood/plasma donors, manufacturers should follow up the donor criteria at  
645 defined intervals. The exclusion of donors with known inflammation of kidney and/or chronic renal  
646 inflammatory diseases is encouraged.

647 Record keeping for traceability is recommended for products where it is possible to trace back to donor  
648 level.

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