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CHMP POSITION STATEMENT ON CREUTZFELDT-JAKOB DISEASE and PLASMA-DERIVED AND URINE-DERIVED MEDICINAL PRODUCTS

This is the first revision of the CPMP[a] Position Statement on "Creutzfeldt-Jakob disease and plasma-derived and urine-derived medicinal products" (EMEA/CPMP/BWP/2879/02) published in February 2003, which replaced the CPMP Position Statement on "New variant CJD and plasma-derived medicinal products" (CPMP/201/98) issued in February 1998.

SUMMARY

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

Variant CJD (vCJD) is an emerging disease and the eventual number of cases of the disease is uncertain. There is a wider distribution and higher level of infectivity/abnormal prion protein in peripheral tissues than is seen with sporadic CJD. It is not known whether or not infectivity is present in human blood; however, a possible transmission of vCJD by blood transfusion in man has recently been reported.

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

Available data indicate that the manufacturing processes for plasma-derived medicinal products would reduce vCJD infectivity if it were present in human plasma. Manufacturers are now required to estimate the potential of their specific manufacturing processes to reduce infectivity using a step-wise approach. It is recommended that manufacturers consult the relevant competent authorities at each of the milestones in this estimation. CHMP and its Biotechnology Working Party (BWP) will keep progress with these recommendations and the actions to be taken under review.
In support of this recommendation, CHMP and BWP, with the involvement of external experts, is developing guidance on how to investigate manufacturing processes with regard to vCJD risk and CHMP and BWP will be available to discuss issues that might arise.
The rationale for this position is that if, in the future, further cases of vCJD occur in countries collecting blood and plasma for the manufacture of plasma-derived medicinal products, a process previously shown to be able to reduce TSE infectivity will provide reassurance on the safety of past products, and could help to justify continuing fractionation.

The detection of an abnormal prion protein in the urine of animals and humans suffering from transmissible spongiform encephalopathies (TSEs) was reported in 2001. While information is awaited

[a] In May 2004 there was a change in the name of the EMEA's scientific committee for human medicines from CPMP to CHMP.

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from on-going research work in this area, further information has been gathered on the manufacturing processes for urine-derived medicinal products. This general review indicates that it is feasible to apply donor selection criteria when a product is derived from a relatively small and well-defined donor population. In addition, it indicates that manufacturing processes have at least one step that might be theoretically capable of reducing TSE infectivity if it were present in the starting material. It is noted that urine-derived medicinal products are not sourced from urine collected in the UK.

On the basis of this review and other considerations, the use of exclusion criteria for selection for a urine donor panel is 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 but, unlike blood/plasma donors, these criteria would not be checked at each donation. Manufacturers of urine-derived medicinal products, who have not yet undertaken a theoretical evaluation of the potential of their manufacturing processes to reduce infectivity, should carry this out and report the outcome to the relevant competent authorities.

1. Introduction

Creutzfeldt-Jakob disease (CJD) is a rare neurodegenerative disease causing the death of approximately 1.5 to 2 persons per million population per year. Cases can arise spontaneously (sporadic), may arise at higher frequency in families with certain genetic mutations (familial) or can result from medical exposure to infectious material (iatrogenic). In 1996, a variant form of CJD (vCJD) was identified.[1] There is strong evidence that vCJD is caused by the agent responsible for bovine spongiform encephalopathy (BSE) in cattle.[2,3,4] The most likely hypothesis is that vCJD has occurred through exposure to BSE contaminated food.

Human transmissible spongiform encephalopathies (TSEs), including in particular vCJD, were addressed in expert meetings/workshops at the EMEA in January 1998, January 1999, December 1999, May 2000, and December 2000. A CPMP Position Statement on variant CJD and plasma-derived medicinal products was issued in February 1998[5f] and the outcome of the subsequent meetings was published on the EMEA website.[5] An EMEA Expert Workshop on Human TSEs and Medicinal Products was held on 19-21 June 2002. This provided the scientific basis for a new CPMP Position Statement issued in 2003.[5b] A further EMEA Expert Workshop was held in January 2004 to review the current state of knowledge of vCJD, in the light of the recent report of a possible human transmission by blood transfusion.[6] In addition, the Workshop discussed the CPMP Discussion document on the investigation of manufacturing processes with respect to vCJD.[5a] A report of the January 2004 meeting will be published on the EMEA website.

Blood and blood components for transfusion are outside the scope of this Position Statement. Recommendations on the suitability of blood and plasma donors and the screening of donated blood in the European Community are described in Council Recommendation 98/463/EC.[7c] European legislation on human blood and blood components entered into force on 8 February 2003 and Member States have until 8 February 2005 for its transposition into national law.[7a] Under this legislation, a Commission Directive on certain technical requirements for blood and blood components, including eligibility criteria for donors, entered into force in April 2004.[7b]

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

The Scientific Steering Committee (SSC) and the Scientific Committee on Medicinal Products and Medical Devices (SCMPMD) of the European Commission have published a number of opinions relating to TSEs, which are of relevance to blood and blood components for transfusion, as well as to plasma-derived medicinal products.[8] WHO Guidelines on TSE in relation to biological and

pharmaceutical products is also of relevance to both blood components for transfusion and plasma-derived medicinal products.[9] The Council of Europe has made recommendations for blood and blood components for transfusion.[10]

2. Variant CJD current status

The official UK figures for vCJD at the beginning of June 2004 were a total of 146 definite or probable vCJD cases.[11] (One case in Hong Kong was a UK case and is included in the UK figures.) Outside of the UK, there has been one case in Ireland, one in the USA, and one in Canada, who were probably infected while in the UK.[12] However, none of the 6 cases in France[13] and 1 case in Italy had spent time in the UK. The possibility of cases occurring in other countries cannot be excluded.
All cases, who have been genotyped so far, are Met-Met homozygotes at codon 129 of the prion protein (PrP) gene.

Analysis of the UK figures for the quarterly incidence of deaths indicates that vCJD incidence in the UK is currently in decline. However, interpretation requires caution as there may be a long tail or more than one peak to the epidemic.[14]

A UK study screening specimens from surgically removed appendices and tonsils for accumulation of prion protein in the lymphoreticular system has been carried out in order to try and obtain some estimation of the number of people that might be incubating vCJD in the UK.[15] Three positive appendix specimens have been found as a result of the screening of 12,674 appendix and tonsil specimens. However, the pattern of lymphoreticular accumulation in two of these samples was dissimilar from that seen in known cases of vCJD, raising the possibility that they may be false positives. With respect to this possibility, the authors comment that although it is uncertain whether immunohistochemical accumulation of prion protein in the lymphoreticular system is specific for vCJD, it has not been described in any other disease, including other forms of human prion disease or a range of inflammatory and infective conditions.

Statistical analysis on this finding of 3 positive specimens gives the following estimations of numbers who may be incubating vCJD:
237 infections per million population (95% confidence interval (CI): 49-692 per million)
Assuming that this estimate relates to those aged 10-30 years[b]:
3,808 individuals (CI 785-11 128) aged 10-30 years may be incubating vCJD.

These estimations are higher than the most recent predictions from modelling of the clinical data (upper 95% confidence interval of 540 future cases).[16] It is not known whether those incubating vCJD will eventually develop clinical disease. However, estimates of numbers possibly incubating are important with respect to any potential for secondary transmission (e.g. by blood donation, surgical instruments) while individuals are in the incubation phase. It should be noted that plasma-derived medicinal products are not manufactured from donations collected in the UK.

A larger study will now be undertaken, involving the establishment and testing of a national prospective archive of tonsil tissue from 100,000 people of all ages removed during routine tonsillectomies.[17]

3. Human tissue distribution of infectivity/abnormal prion protein.

Tissue distribution has been investigated by detection of the abnormal prion protein (PrP^{sc}/PrP^{res})[c] or by infectivity assays. Until now, detection of PrP^{sc} in tissues has always been associated with

[b] The reason the age range of 10-30 years is specified is because 83% of the samples were from individuals in this age range.

[c] PrP^{sc} is an abnormal isoform of the natural protein PrP^{c}, which is anchored to the surface of many cells in mammals. PrP^{c} and PrP^{sc} have a different resistance towards proteinase K treatment: the endogenous PrP^{c} is completely degraded by proteinase K, whereas PrP^{sc} is partly resistant (giving rise to PrP^{res}).

infectivity, however it should be noted that animal studies show that, in some circumstances, infectivity can also be present without detection of PrP^{sc}. This may be related to limitations of assay methods for PrP^{sc}, however, in some cases the reason for this finding is not known. It is thus recommended that any study on tissue or fluid distribution of the abnormal prion protein be confirmed with an infectivity assay.
A wider distribution and higher level of PrP^{sc} in human peripheral tissues, including the lymphoreticular system, has been found in vCJD compared with sporadic CJD.[18,19,20] Limited data from infectivity assays of tissues are consistent with the PrP^{sc} findings. [21]

4. Infectivity in blood and transmissibility via blood

4.1 Animal blood

Low levels of infectivity have been found in the blood of rodents experimentally infected with TSE agents.[22,23,24,25] Experiments indicate that approximately half the infectivity is in the cellular components, mainly the buffy coat, and the remainder in the plasma. Experimental studies indicate that the vCJD agent behaves in a similar way (qualitatively and quantitatively) to a familial CJD agent[d] when adapted to RIII/Fa/Dk mice.[25] Infectivity has also been detected in buffy coat of a prosimian microcebe experimentally infected with a macaque-adapted BSE strain.[26]

The infectivity in rodent blood was transmitted by intravenous inoculation, but 5-7 fold less efficiently than by the intracerebral route.[23] In one study with mouse-adapted vCJD agent, the intravenous and intracerebral routes were found to be equally efficient for the buffy coat fraction but not for the plasma fraction.[25] However, studies in primates show that survival times were similar after intravenous or intracerebral inoculation of infected brain material.[27,28] Furthermore, information from an on-going intra-species transfusion experiment indicates that experimental BSE in orally infected sheep or natural scrapie infection in sheep can be transmitted to sheep by blood transfusion.[29,30] The level of infectivity in sheep blood cannot be established from these experiments.

The European Union has provided funding for animal transmission projects, including still on-going studies.

4.2 Human blood

In the UK, a surveillance system was established to see whether any cases of vCJD occurred in recipients of blood donations from donors who later developed vCJD. As of 18 December 2003, there were 17 living recipients of blood transfusions where the donations were given by individuals who later developed vCJD. [6]

This tracing of recipients of blood transfusion from UK donors who have subsequently developed vCJD has revealed one possible case of secondary transmission.[6] The individual had received a transfusion of red cells from a donor who developed symptoms of vCJD 3 years 4 months later. Six and a half years after the blood transfusion, the recipient developed the first clinical symptoms of vCJD. This case is the second oldest one (late 60s) of vCJD identified. The individual was a methionine homozygote at codon 129 of the prion protein gene. It is not possible to exclude that infection in the recipient was due to dietary exposure but statistical analysis suggests that this is unlikely. This possible case is consistent with the findings from sheep transfusion studies that infectivity in blood can be transmitted during the pre-clinical phase of infection.
Twenty units of plasma from individuals who later developed vCJD were included in pools for the production of fractionated products before 1998, at which time a policy was introduced to source plasma for fractionation from outside the UK. As of February 2004, no case of vCJD had been identified with a history of exposure to fractionated blood products. [6]

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[d] Mouse-adapted Fukuoka-1 strain of human TSE (brain tissue obtained from a case of Gerstmann-Sträussler-Scheinker syndrome).

The surveillance described above emphasises the importance of national databases of blood donors and the maintenance of traceability from donor to recipient and vice versa. Without a national database of blood donors it becomes very difficult to establish whether a vCJD case has been a blood donor. (UK experience has shown that questioning of family members is unreliable for establishing whether a patient has been a blood donor.) Traceability is a specific requirement in Article 14 of Directive 2002/98/EC.[7a]

Infectivity or PrP^{sc} were not detected in blood of vCJD cases using methods capable of detecting infectivity/PrP^{sc} in peripheral tissues such as tonsil or spleen, indicating that if infectivity is present it is at levels below the sensitivity of these methods.[21, 18] A review of transmission studies to detect infectivity in the blood of humans with CJD (sporadic, iatrogenic and variant) shows that although transmissions have occasionally been reported, the majority of studies failed to detect infectivity.[31] Infectivity was not detected in blood from patients with sporadic CJD using human PrP - transgenic mice for the detection of infectivity. Further experiments to detect infectivity in human blood are on-going.

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

5. Detection techniques

Several techniques are under development for the detection of PrP^{sc} in blood. Approaches based on surrogate markers are also under investigation. Development and validation of all methods is on-going but there is no screening test yet.
Several WHO reference preparations are available and further materials are under development[e]. These reference preparations will allow calibration of assays versus infectivity bioassays, and can be used for collaborative studies to compare the performance of different assays to see whether they are sufficiently sensitive and specific to justify further evaluation for screening blood.

6. Leucoreduction

Leucoreduction is used in transfusion medicine to reduce the level of white blood cells in blood and blood components.
The rationale for considering leucoreduction as a precautionary measure is:

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

The SCMPMD opinion on leucoreduction[8a, 8b] for blood and blood components for transfusion states that it might be a precautionary step to remove white blood cells as completely as possible. For plasma for fractionation the opinion states the following:
'Taken together, there is no compelling scientific evidence to date for the introduction of leucoreduction of plasma for fractionation, or other methods aiming at removal of cells and debris, as a precaution against vCJD transmission. The question should be further explored by suitable experiments.'
For plasma-derived medicinal products, there is a theoretical concern that leucoreduction of blood might encourage dissociation of infectivity from white blood cells resulting in an increase in infectivity in the plasma compartment.

[e] Standards are developed by the WHO Working Group on International Reference Materials for Diagnosis and Study of TSEs (http://www.who.int/biologicals).

Reassuringly, results of UK studies on leucoreduction, reported at the 2002 EMEA Workshop, show that it does not provoke fragmentation of cells and lysis.

At the present time, there are no data to support the effectiveness of leucoreduction to reduce infectivity of plasma for fractionation.[23] In one study in hamsters, reported at the 2004 EMEA Workshop, there was a reduction in infectivity of about 50 percent after leucoreduction of whole blood. There is a need for further studies investigating leucoreduction of infected blood using infectivity assays. A project investigating leucoreduction is currently being funded by the European Union.

7. Manufacturing processes for plasma-derived medicinal products

Many investigational studies have now been carried out with different strains of agent and spiking materials of different nature and purity, and using different assays to follow the partition of PrP^{res} and/or infectivity. *In vitro* assays can be useful for spiking experiments to investigate manufacturing processes but it is important to correlate such results with those from infectivity assays, as has already been reported in publications in this area.

These studies have investigated the contribution of the various manufacturing steps to reduction of infectivity (including precipitation followed by centrifugation or depth filtration, chromatography and nanofiltration). Data support the removal of infectivity by steps that are commonly used in the manufacture of plasma-derived medicinal products. However, caution is needed in the interpretation of data since the effectiveness of a given step is dependent on a number of variables (including the process conditions and state of the agent in the sample). Consequently, effectiveness of removal may vary from one manufacturer to another.

Animal studies using blood from rodents infected by intracerebral inoculation indicate that the fractionation process contributes to the removal of endogenous plasma infectivity.[22,23] Preliminary information reported at the EMEA Workshops in 2002 and 2004 suggests that endogenous infectivity might persist further through the fractionation process than would be expected from spiking studies. There is a need for further research in this area to investigate the partition and removal of endogenous infectivity and the extent to which this is comparable with data from spiking studies.

8. Infectivity in urine

Shaked *et al.*[32] have reported the detection of a protease resistant PrP isoform ($UPrP^{sc}$) in the urine of hamsters, cattle and humans suffering from TSEs. However, it is noteworthy that intracerebral inoculation of hamsters with $UPrP^{sc}$ did not cause clinical signs of prion disease in this study. These findings are yet to be confirmed and additional studies are on-going.

Epidemiological evidence in the last 25 years, when urinary-derived medicinal products and particularly gonadotrophins have been widely used, does not suggest a risk from sporadic CJD. Since epidemiological evidence has identified the few cases of iatrogenic transmission of CJD through the use of pituitary-derived gonadotrophins, it could be expected that transmission from urinary-derived gonadotrophins would have been detected if it had occurred.

9. Recommendations and proposals

9.1 Sporadic, familial and iatrogenic CJD and plasma-derived medicinal products

Cumulative epidemiological evidence does not support transmission of sporadic, familial and iatrogenic CJD by blood, blood components or plasma-derived medicinal products.[31, 33] Nevertheless, donor selection criteria include criteria to exclude donors who might be at higher risk of developing CJD. The following permanent deferral criteria are specified in Commission Directive 2004/33/EC:

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.[7b] Precautionary recalls of batches of plasma-derived medicinal products after post-donation reports of CJD or CJD risk factors in a donor contributed to severe shortages of certain products. [9]

On the basis of the current epidemiological evidence, the CPMP recommendation that recall of plasma-derived medicinal products is not justified where a donor is later confirmed as having sporadic, familial or iatrogenic CJD is maintained. Further epidemiological studies are recommended.

9.2 Variant CJD and plasma-derived medicinal products

Variant CJD is a new emerging agent. Uncertainties still exist concerning the number of cases of vCJD that will occur and whether infectivity is present in blood. Variant CJD has a different peripheral distribution to sporadic CJD. Epidemiological experience is too limited, in terms of timescale and number of cases, to reach conclusions on whether or not vCJD could be transmitted by blood, blood components or plasma-derived medicinal products. However, there is now one possible case of human transmission by blood transfusion.

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

9.2.1 Exclusion Criteria

a) Consideration of Country-based exclusions

Variant CJD sufferers with overt disease will be too ill to present for donation or would be disqualified at the point of donor screening. However, there is no screening test to detect donors who may be incubating the disease or in the early clinical stages. Therefore, other approaches are considered in order to try and identify donors who may present a higher risk.

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

Exclusion of donors based on cumulative period of time spent in the UK
Since UK donors are excluded from donating plasma for the manufacture of plasma-derived medicinal products in the UK, it is consistent to exclude donors who have spent long periods in the UK. This is supported by the finding of vCJD cases, which have a risk factor of long periods spent in the UK, in other countries[f].

It is, therefore, recommended that donors who have spent a cumulative period of 1 year or more in the UK between the beginning of 1980 and the end of 1996 are excluded from donating blood/plasma for fractionation. Countries are highly encouraged to choose their national cumulative period limit for plasma-derived medicinal products according to a nationally calculated benefit/risk balance, which will take into account the endogenous risk of BSE and the risk of shortages of blood and plasma for the manufacture of medicinal products. The national limit is recommended to be of cumulative periods in the UK below or equal to 1 year, since for plasma-derived medicinal products, there is very little difference in effectiveness of the measure between an exclusion of 3 months, 6 months or 1 year in the UK.

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

[f] One case in each of Ireland, US and Canada associated with long periods spent in the UK.

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

The safety of batches of product manufactured from blood/plasma collected before the implementation of the measure is not in question. Therefore, such batches can stay on the market and are not subject to any batch recall.

French plasma
France is currently the only country outside the UK that has had a number of vCJD cases, which are not linked to stays in the UK. France has estimated a risk of 1/20 of that in the UK for dietary exposure of the population to BSE. France published an analysis of the risk of transmission of vCJD by blood and its derivatives sourced from French plasma in December 2000.[34d] This concluded that plasma collected in France could continue to be used for fractionation. The safety margin for plasma-derived medicinal products was considered to be sufficient. However, a further increase in the safety margin of some products was recommended (e.g. nanofiltration of Factor VIII introduced in January 2001). Leucodepletion for plasma for fractionation, as for plasma for transfusion, was also recommended as a precautionary measure.
The subsequent analyses published in 2002, 2003 and 2004 re-confirmed these conclusions.[34]

Donors who have spent a cumulative period of time in France
Exclusion of donors who have spent a cumulative period of time in France is not recommended because of the lower risk associated with time spent in France compared with time spent in the UK. On the basis that the risk in France is 1/20 of that in the UK, a donor spending a cumulative period of one year in the UK would be equivalent to a donor spending 20 years in France during the risk period.

Concluding remarks
Country-based exclusions are inefficient, as the vast majority of donors who will be excluded will not develop the disease. There is a lack of spare plasma capacity to make up for shortfalls if countries that are major producers of plasma-derived medicinal products discontinue the use of nationally collected plasma for fractionation.

b) Other possible exclusion criteria

Commission Directive 2004/33/EC indicates that further deferral criteria for vCJD may be recommended as a precautionary measure.[7b]
Other possible exclusion criteria that could be considered include permanent exclusion of recipients of blood transfusion (general exclusion or exclusion of recipients of transfusion in UK[g]), transplant recipients, and donors who have undergone neurosurgery.
Caution is needed because of the risk of loss of donors and consequent supply problems. Since such criteria could apply to both blood and blood components, and plasma-derived medicinal products, it was appropriate to consider this further within the scope of Directive 2002/98/EC.[7a] The technical meeting of blood experts, convened by the European Commission in January 2004, considered exclusion criteria, as well as blood component preparation and processing, recipient tracing and surveillance, and optimal use of blood.[7e]

9.2.2 Leucoreduction

For plasma-derived medicinal products, results would be needed from studies investigating the effect of leucoreduction on infectivity in plasma (recovered plasma or apheresis plasma) before making any recommendation. (See Section 6 for further discussion of this aspect.)

[g] 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. The numbers of donors outside the UK who have spent a cumulative period of less than one year in the UK but have received a blood transfusion within the UK is expected to be very small and it may not be worthwhile to have a specific measure.

9.2.3 Manufacturing processes for plasma-derived medicinal products

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

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

Whereas the general information available on manufacturing processes provides useful background information, the actual effectiveness of a manufacturing process might be dependent on the specific process conditions. Manufacturers should consider the relevance of the published data to their specific manufacturing processes and whether the removal capacity can be expected to be comparable.

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

Investigations using biochemical assays may be sufficient if a clear correlation with infectivity data has already been established for similar processes (e.g. ethanol fractionation). If such a correlation is not established (e.g. a novel step) and the step is considered critical for 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). *(Flow diagram, step 3)*

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

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

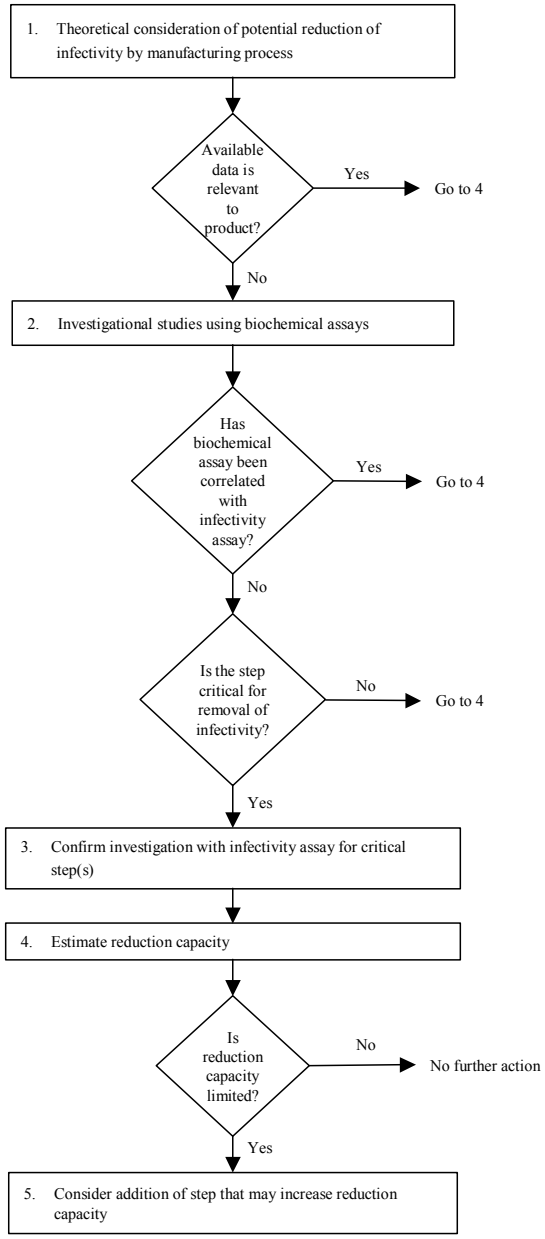
The outcome of the estimates of the theoretical potential of manufacturing processes to reduce infectivity and the results of product-specific investigational studies should be reported to the relevant competent authorities for the medicinal products concerned, as information becomes available. Applicants submitting new marketing authorisation applications for plasma-derived medicinal products will be expected to include such information in the application dossier. If product-specific investigational studies are not available at the time of submission, the proposed investigations and timescales should be described or justification provided for not performing further studies. The outcome of the estimation of the theoretical potential to reduce infectivity should always be included in the application.

CHMP and its Biotechnology Working Party will keep progress with these recommendations and the actions to be taken under review.

In support of these recommendations, CHMP's Biotechnology Working Party, with the involvement of external experts, is developing guidance on how to investigate manufacturing processes with regard to vCJD risk.[5a]

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.



9.2.4 Recall of batches where information becomes available post-donation

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

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.

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

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

9.2.5 Albumin used as an excipient or in manufacturing processes

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

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

9.2.6 Substitution with alternative products

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

9.2.7 Optimal Use

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

9.3 Urine-derived medicinal products

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

- Epidemiological evidence does not suggest a risk for urine-derived medicinal products from sporadic CJD
- Intracerebral inoculation of hamsters with $UPrP^{sc}$ did not cause clinical signs of prion disease[32]
- There is still uncertainty about whether infectivity is present in urine and results of further studies are needed
- The review of manufacturing processes described below.

CPMP's Biotechnology Working Party has co-ordinated a review of the manufacturing processes for urine-derived medicinal products. This indicates that 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. It is noted that urine-derived medicinal products are not sourced from urine collected in the UK.

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.

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 but, unlike blood/plasma donors, these criteria would not be checked at each donation. Manufacturers who have not yet undertaken a theoretical evaluation of the potential of their manufacturing processes to reduce infectivity, should carry this out and report the outcome to the relevant competent authorities.

The situation will be kept under review as information becomes available from further studies investigating whether infectivity can be found in urine.

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