EUROPEAN COMMISSION
HEALTH & CONSUMER PROTECTION DIRECTORATE-GENERAL

Directorate C - Scientific Opinions

Scientific Steering Committee

OPINION ON:

THE IMPLICATIONS OF THE HOUSTON *ET AL* PAPER IN *THE LANCET* OF 16 SEPTEMBER 2000 ON THE TRANSMISSION OF BSE BY BLOOD TRANSFUSION IN SHEEP. (THE LANCET, VOL. 356, PP 999-1000; 955-956; 1013)

ADOPTED BY THE SCIENTIFIC STEERING COMMITTEE

AT ITS MEETING OF 26-27 OCTOBER 2000

OPINION

On 16 September 2000, Houston *et al* reported in *The Lancet* on the experimental sheep-to-sheep transmission of the BSE agent by blood transfusion. (The Lancet, 2000, Vol. 356, pp 999-1000). The European Commission invited the Scientific Steering Committee (SSC) to:

1. Evaluate the preliminary results presented in *The Lancet* paper and assess whether it contains important new scientific evidence and/or information that are relevant for public health.
2. Consider the relevance of these results to available scientific opinions on the safety of human and animal blood and blood products.

The SSC established a multi-disciplinary working group. The Working Group met on 11 October 2000. In addition to the above mandate, it also addressed the question "W*hat risk consumers have of acquiring an infection (vCJD), resulting from the consumption of bovine meat products, taking into account the fact that sheep blood has been shown to be infectious during the incubation period of BSE."*

The TSE/BSE *ad hoc* Group at its meeting of 12 October 2000 further discussed the issue, where it also received a verbal account of the Working Group meeting.

On the basis of the summary account of the meeting of the Working Group (attached), of the verbal report on the discussions of the TSE/BSE *ad hoc* Group provided at the SSC meeting, and of its own discussions, the SSC concluded as follows.

Confirmation is needed on two major points i.e. identification of the agent (BSE or not) and the origin of the transmission. Pending confirmation, the data in this experiment are new to the extent that they show that the exchange by transfusion of (400 ml of) whole blood taken during the incubation period of a sheep infected with the BSE agent can transmit BSE to a healthy sheep. This ovine model adds to data obtained in mouse and hamster models of scrapie and human TSE.

As these preliminary data still lack results from the controls and do not confirm the identity of the strain (scrapie or BSE) in both the donor and recipient animals, they can only be considered a tentative evidence of the transmissibility of the BSE agent through blood. If confirmed, the result will support already published European Commission (SANCO) SSC, SC MPMD, and EMEA opinions and recommendations on blood safety. Therefore, although the transmission of infectivity through blood in vCJD urgently needs further study, the data presented in this paper neither justify nor add arguments for the introduction of new methods or approaches to the assessment of blood safety.

Although this information does not change the basis of risk assessment, it does reinforce the substance of previous opinions by the scientific committees. The scientists expressed their hope that the Commission would take comprehensive action on all of the recommendations of the Scientific Committee opinions, including the ones on further research listed in the attached report of the Working Group. The SSC would welcome the Scientific Committee Medicinal Products and Medical Devices to examine whether donors who previously received transfusions should be exclude from donating blood.

The SSC finally invites the Houston *et al* research team to provide, as soon as available, access to the data needed to clarify the questions listed in this opinion and in the report of the Working Group. The SSC could the possibly amend its opinion on the basis of an update of the Working Group's report.

SUMMARY ACCOUNT OF A WORKING GROUP MEETING ON:

THE IMPLICATIONS OF THE HOUSTON *ET AL* PAPER IN *THE LANCET* OF 16 SEPTEMBER 2000 ON THE TRANSMISSION OF BSE BY BLOOD TRANSFUSION IN SHEEP. (THE LANCET, VOL. 356, PP 999-1000; 955-956; 1013)

I. MANDATE

On 16 September 2000, Houston *et al* reported in *The Lancet* on the experimental sheep-to-sheep transmission of the BSE agent by blood transfusion. (The Lancet, 2000, Vol. 356, pp 999-1000). The European Commission invited the Scientific Steering Committee to:

1. Evaluate the preliminary results presented in *The Lancet* paper and assess whether it contains important new scientific evidence and/or information that are relevant for public health.
2. Consider the relevance of these results to available scientific opinions on the safety of human and animal blood and blood products, including:
   - Opinion on the Risk quantification for CJD transmission via substances of human origin Adopted on 21 October 1998 by the Scientific Committee on Medicinal Products and Medical Devices
   - Update of the Opinion on The Risk Quantification For CJD Transmission Via Substances of Human Origin, adopted On 16 February 2000 by the Scientific Committee on Medicinal Products and Medical Devices.
   - Opinion on Quality and Safety of Blood, adopted on 16 February 2000 by the Scientific Committee on Medicinal Products and Medical Devices.
   - Opinion on The Safety of ruminant blood with respect to TSE risks, adopted by the Scientific Steering Committee at its meeting of 13-14 April 2000.
   - The Opinion on specified risk materials of small ruminants, adopted on 13-14 April 2000 by the Scientific Steering Committee.
   - The report of the EMEA Expert Workshop *15-16 May 2000* on human TSEs and plasma-derived medicinal products.

The SSC established a multi-disciplinary working group composed as indicated in the section IV "Acknowledgements". The Working Group (WG) met on 11 October 2000. In addition to the above mandate, it also addressed the question "W*hat risk consumers have of acquiring an infection (vCJD), resulting from the consumption of bovine meat products, taking into account the fact that sheep blood has been shown to be infectious during the incubation period of BSE."*

The summary account of the meeting follows hereafter.

II. REPORT OF THE WORKING GROUP

II.1. On the preliminary results presented in Houston *et al (*2000)

Summary of Houston *et al* (2000): 400 ml of whole blood was taken from each of 19 sheep thus far that had each been fed 5 grams of BSE-affected cattle brain. This blood was transfused into healthy scrapie susceptible sheep. One recipient sheep transfused 318 days after the oral challenge of the donor sheep and 311 days before the onset of a BSE like illness in the donor sheep showed signs of a BSE-like

illness 610 days later. The donor sheep itself developed disease 629 days after oral challenge. Tests on the recipient sheep that developed a BSE type illness, revealed widespread deposition of modified prion ("PrP^{sc} ") throughout the brain and the peripheral nerves. All the other sheep which received blood were still healthy at the time of the redaction of the paper, but in all but one case the observation time is shorter than 610 days. In the other case with a longer observation period, blood was transfused after one third of the incubation time in the donor animal.

The data in this experiment, if confirmed, are new in that the experiment apparently shows how a high volume blood transfusion from sheep to sheep can transmit a BSE-like illness within the same species and that infectivity can be transmitted from blood taken during the asymptomatic incubation period of the disease of the donor sheep. In a comment to the paper, P.Brown (in: The Lancet, 2000, Vol. 356, pp 955-956) considers these observations to be consistent with previous reports on blood borne infectivity in experimentally infected rodents.

The Working Group considered that the available data on infectivity in the blood of animals infected with a TSE agent show no consistently reproducible patterns and little is known about inoculum size or infectivity levels. This single case of successful transmission within a single species should therefore be considered as additional justification for assessing the possible impact of the transmissibility of TSE agents via blood.

The Working Group members were not convinced that the evidence presented established beyond doubt that the agent causing a BSE like illness in the recipient sheep was the same BSE agent to which the donor sheep had been exposed orally. The Working Group therefore considered that it was not established beyond doubt that the BSE like illness observed in the recipient sheep was actually the result of a transmission of BSE by i/v blood transfusion and not natural scrapie occurring in the flock from which the recipient sheep was taken. In this flock the sheep are of a scrapie-susceptible genotype but spontaneous scrapie is rare.

Convincing evidence would consist of strain-typing as well as clear Western Blot results applied both to the original brain material, and to brain material from the donor and recipient sheep. The main element that contributed to questioning whether the TSE agent in both donor and recipient were the same BSE agent was that the Western Blot presented in the paper was of poor technical quality.

Assuming that the questions concerning the TSE strain identity (and hence transmissibility) could be resolved, then, the Working Group considered that the findings would be (i) the first published evidence for intra-species transmission of BSE agent by blood-transfusion and (ii) in line with what is currently known on TSE infectivity in blood[1] (see Annex 1; courtesy P.Brown).

The Working Group noted that studies published since October 1988 indicate that in rodents, blood is regularly infectious throughout the entire incubation period and the clinical phases of disease. It noted that the Houston et al (2000) finding does not (yet) apply to blood taken in the late stage of incubation, but to the mid-incubation

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[1] The SC-MPMD Opinion on *The Risk quantification for CJD transmission via substances of human origin Adopted on 21 October 1998 by the Scientific Committee on Medicinal Products and Medical Devices* contains an extensive compilation of published papers and their results.

period. The experiment does not yet tell about the percentage of BSE-infected donor sheep whose 400ml blood taken at mid-incubation transmit: i) to single recipient and ii) to the number out of 10 recipients. It also does not answer what would be the effect on successful transmission rate if transfusion volume were 200ml or 20ml versus 400ml, or if transfusion is carried out at 100 or 500 days versus 300 days post challenge.

II.2. On the possibility to use the "BSE agent in sheep" model as a proxy model for vCJD in humans or BSE in cattle.

The Working Group agreed that there were enough similarities between the pathogenesis of TSE in sheep and vCJD in humans to consider the BSE agent in sheep model as a significant addition to the CJD and scrapie rodent models as a proxy for vCJD in humans. These similarities arise mainly in terms of distribution of tissue infectivity, in particular the involvement of the LRS. (It should be noted that murine models are quite close to human vCJD in terms of dissemination of the pathological protein in the lymphoïd formations; the bovine model is not less pertinent as only the terminal ileum is infectious both during the pre-clinical and the clinical phase).

These findings were therefore considered supportive of the existing opinions on the safety of human blood. However, caution is needed when extrapolating from an experimental model (i.e., BSE agent in sheep) to field conditions (i.e., vCJD in humans) because the conditions are likely to be different (e.g., dose; exposure; controlled environment; genetics; infectivity in blood of host-adapted BSE;…)

The model would also be relevant for assessing the risks for humans and animals, should the BSE agent(s) in sheep be confirmed under field conditions. The Working Group recommended that SSC should finalise as soon as possible its forthcoming *Pre-emptive risk assessment should BSE in small ruminants be found under domestic conditions*.

The Working Group asked whether the finding of infectivity in the blood of sheep infected with the BSE agent had relevance to the risk of consumers acquiring infection (vCJD), from the consumption of *bovine* meat products. The Working Group considered that the finding of infectivity in the blood of sheep could not be extrapolated to BSE in cattle. Indeed, the most recent research results do not support the hypothesis that bovine blood or lean meat constitutes a risk for humans. However, assay limitations have always to be born in mind, e.g., the exposure of animals vs. humans, the exposure dose, probability of infectivity in blood used for challenge, …

- In its opinion of 28-29 October 1999 *On the scientific grounds of the Advice of 30 September 1999 of the French Food Safety Agency (the Agence Française de Sécurité Sanitaire des Aliments, AFSSA), to the French Government on the draft Decree amending the Decree of 28 October 1998 establishing specific measures applicable to certain products of bovine origin exported from the United Kingdom,* the SSC addresses the issue of infectivity being present in (bovine) spleen and muscle.

- G.Wells (pers.comm., October 2000[2]) confirmed that cattle (four per group) inoculated intracerebrally with a ten percent dilution of pooled spleen or lymph nodes from BSE affected cattle[3] did not develop a TSE. If the survival data for these animals (4/4 in the lymph node pool group surviving to 85 months post inoculation and 3/4 in the spleen pool group surviving 74-86 months) is interpreted from the titration[4] of BSE affected brain material in cattle the values suggest that if infectivity were present in these tissues it is at a concentration of less than 0.1 cattle i.c. ID50/g of tissue.

II.3. On the relevancy of the result to available scientific opinions on the safety of human and animal blood and blood products.

The Working Group considered that existing scientific opinions already anticipated the risks resulting from the possible presence of low levels of TSE infectivity in blood.

In fact, the opinion on the *Safety of ruminant blood with respect to TSE risks*, adopted by the Scientific Steering Committee at its meeting of 13-14 April 2000 states, amongst others:

"(…) it is concluded that there could be a risk of the occasional presence of low levels of TSE infectivity in blood collected in abattoirs. Levels of infectivity which might represent a risk to animal or human health are not known. Control measures and/or decontamination standards might need to be developed to potentially TSE-infected blood collected in abattoirs. (…)

The collective data currently available from experimental transmission studies show that there is uncertainty on the presence of infectivity in the blood of TSE-infected ruminants. If PrP^{Sc} has been detected in the blood of clinically normal sheep from scrapie-susceptible flocks using a newly-developed and highly sensitive assay system, infectivity of femtomole amounts remain to be demonstrated.

The relationship between PrP^{Sc} and infectivity is not understood. The two do not always correlate; the presence of PrP^{Sc} does not necessarily imply presence of infectivity. Moreover, the methods for detecting PrP^{Sc} need to be validated for the pre-clinical stage. As far as ruminant blood is concerned, it is considered that the best approach to protect public health at present is to assume that it could contain low levels of infectivity. However, even if this is true, it becomes almost irrelevant compared with the level of contamination that could occur as a result of the methods of stunning used in abattoirs. (…)

Citation from the October 1998 SC-MPMD opinion:

"(…) Studies on the infectivity in blood of patients with nvCJD have not yet been performed.

An evaluation of all animal experiments [on all TSEs, not only vCJD - rapporteur] has to take into account, that the results depend on several factors: strain and sometimes breed of the host animal, type of TSE agent, its dose and its route of administration (Asher 1976). Therefore, an extrapolation from animal experiments onto the situation in men may be difficult. A conservative conclusion may be, that in animal models, if at all, a low infectivity in blood may be measurable in late stages of the incubation period and during clinical stages.

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[2] The study has been reported on at the 2nd Cambridge Healthtech Institute Annual TSE Conference, Alexandria, Virginia, 3-4 October 2000

[3] The donor cattle were 5 field cases of BSE, the same five from which brain was taken for the comparison of a titration of BSE affected brain material in cattle and mice

[4] There are reservations about the interpretation of titres of non CNS tissues from titrations of CNS tissues but this can be used as an approximation. A paper on these results has yet to be prepared so a more detailed interpretation is not yet available.

The Houston *et al* finding does not bring a new scientific concept to the consideration of BSE in terms of risk assessment of vCJD and does not provide reason to change the scientific bases of the risk assessments carried out so far. However, the Houston *et al* (2000) finding, if the TSE agent in the recipient sheep is in fact due to transfusion, does provide additional support to the opinions listed in Section I and strengthens the recommendations made in these opinions. A selection of these recommendations is as follows:

- From the SSC opinion on the safety of ruminant blood:

  "The SSC also recommends that intraspecies recycling of ruminant blood and blood products should be avoided in situations when a TSE risk exists."

- From the SC-MPMD Update of the Opinion given by the Scientific Committee on Medicinal Products and Medical Devices on The Risk Quantification For CJD Transmission Via Substances of Human Origin:

  "(…) the SCMPMD cannot make a clear-cut recommendation with respect to the general introduction of leukodepletion, unless a number of studies has been performed to answer the open questions. The SCMPMD recommends supporting of such research. (…) In the meantime, it might be advisable to introduce leukofiltration as a precautionary step, as it is assumed that it will contribute to diminishing infectivity in blood. (…)

  (…) The SCMPMD repeats its recommendation to support efforts in the development of easily applicable screening tests for CJD/vCJD."

  (…) the SCMPMD recommends a careful consideration whether the exclusion of donors who stayed for a defined period of time in areas with increased risk of exposure to the BSE agent would provide an increase in safety balanced to its negative impact on supply and donor population. In order to be able to make the optimal decision three sets of data have to be collected and evaluated:

  1. The travel pattern of European donors which may differ between Member States.
  2. The exposure to UK bovine derived material in food between 1980 and 1996 in different Member States.
  3. The prevalence of HIV, HBV and HCV in first time donors in different Member States."

  From the February 1998 CPMP recommendations:

  "Given the lack of specific information on nvCJD, as a precautionary measure it would be prudent to withdraw batches of plasma-derived medicinal products from the market if a donor to a plasma pool is subsequently strongly suspected, by de reference centre, of having nvCJD.

  Since a recall involving albumin used as excipient has the potential to cause major and widespread supply difficulties for essential products, manufacturers should avoid using, as an excipient , albumin derived from countries where a number of nvCJD cases have occurred."

- From the report of the EMEA Expert Workshop *15-16 May 2000* on human TSEs and plasma-derived medicinal products: See Annex 2.

III. PROPOSALS FOR FURTHER RESEARCH

The Working Group, in the course of its discussions, identified the following areas for further research (not exhaustive list):

- identification of the components of blood in sheep - or other species - that carry the source of infectivity. It should be researched whether prion infectivity is present in plasma, in the cellular part of blood, or in both. (This research has direct bearing on leucodepletion.. Also, cellular blood components [platelets, erythrocytes] have completely different therapeutic usage than plasma derived components, most of which (with the exception of fresh frozen plasma) are used for the manufacturing of stable blood products (immunoglobulin preparations and so on) and are actually easier to decontaminate from many agents.
- diagnostic testing;
- if feasible, challenge of sheep with blood from a vCJD victim and verification of infectivity in the recipient sheep blood;
- challenge of sheep with brain material from a vCJD victim and verification of infectivity in the blood of these sheep;
- broadening the Houston *et al* (2000) protocol to:
    i) a much larger sample of sheep, so as to obtain a quantitative idea of the statistical frequency of infectivity transmission via blood.
    ii) a larger range of volumes of transfused blood, for example from 20 to 400 ml.
    iii)infectivity titration of the donor sheep brain.
- species-barrier determination between cow and sheep.

As a first step, a comprehensive paper should be prepared, critically setting out all the experiments on transmissibility of blood a) in cattle, b) in sheep.

IV. SUMMARY CONCLUSIONS

Confirmation is needed on two major points i.e. identification of the agent (BSE or not) and the origin of the transmission. Pending confirmation, the data in this experiment are new to the extent that they show that the exchange by transfusion of (400 ml of) whole blood taken during the incubation period of a sheep infected with the BSE agent can transmit BSE to a healthy sheep. This ovine model adds to data obtained in mouse and hamster models of scrapie and human TSE.

As these preliminary data still lack results from the controls and do not confirm the identity of the strain (scrapie or BSE) in both the donor and recipient animals, they can only be considered a tentative evidence of the transmissibility of the BSE agent through blood. If confirmed, the result will support already published European Commission (SANCO) SSC, SC MPMD, and EMEA opinions and recommendations on blood safety. Therefore, although the transmission of infectivity through blood in vCJD urgently needs further study, the data presented in this paper neither justify nor add arguments for the introduction of new methods or approaches to the assessment of blood safety.

Although this information does not change the basis of risk assessment, it does reinforce the substance of previous opinions by the scientific committees. The scientists expressed their hope that the Commission would take comprehensive action on all of the recommendations of the Scientific Committee opinions, including the ones on further research listed in the present report.

With respect to the risks resulting from the possible presence of the BSE agent in sheep, should it be found in domestic flocks, the Working Group recommends that the forthcoming *Pre-emptive risk assessment should the BSE agent in small ruminants be found under domestic conditions* should be finalised as soon as possible.

Finally, the Working Group members recommend that the ethical aspects of the question of informing recipients of vCJD blood should be addressed.

V. ACKNOWLEDGEMENTS

The following scientists contributed to the preparation of the present report:

Prof.Dr.K.Jones (chairperson), Dr.E.Vanopdenbosch (rapporteur), Prof.Dr.S.Bird, Dr.P.Brown, Prof.Dr.H.Budka, Prof.Dr.D.Dormont, Dr R.Geertsma, Dr N.Hunter, Prof.Dr.H.Kretzchmar, Dr.F.Lantier, Prof.Dr.J.Löwer, Dr.J.Schlatter, Dr.G.Silvester, Dr D.Taylor, Prof.Dr.J.H.Trouvin, Prof.Van Aken, Prof.Dr.M.Vanbelle, Mrs.E.Voets, Prof.Dr.G.Wells, Prof.Dr.M.Wierup.

V. REFERENCES

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Annex 1: Summary of research findings on TSE infectivity in blood.

Table 1. Attempts to detect infectivity in the blood of animals with TSE

Species Donor	Assay	Inoculum[1]	Route of Inoculation	Pos./total donors	Reference
Scrapie (natural)					
Goat	Mouse	Blood clot/serum	ic	0/3	Hadlow 1980
Sheep	Mouse	Blood clot/serum	ic	0/18	Hadlow 1982
BSE (natural)					
Cow	Mouse	Blood clot/serum/	ic + ip	0/2	Fraser, 1994, cited
		Buffy coat	ic + ip	0/2	in Bradley 1999
Scrapie (experimental)					
Goat	Goat	Whole blood	ic	0/14	Pattison 1962
Mouse	Mouse	Whole blood	ic	0/39	Eklund 1967
Goat	Mouse	Blood clot	ic or sc	0/20	Hadlow 1974
Sheep	Mouse	Serum	ic	1/1	Gibbs 1965
Rat	Rat	Serum	ic	1/1 (pool)	Clarke 1967
Mouse	Mouse	Serum	ic	1/1 (pool)	Clarke 1967
Mouse	Mouse	Whole blood	ic	3/13	Dickinson 1969
Hamster	Hamster	Whole blood	ic	0/9	Diringer 1984
Hamster	Hamster	Blood extract	ic	5/5 (pools)	Diringer 1984
Hamster	Hamster	Blood extract	ic	10/11 (pools)	Casaccia 1989
Hamster	Hamster[2]	All blood components	ic	1/1 (large pool)	Rohwer 1999
		Whole blood	ic	25-50%	Rohwer 1999
		Whole blood	iv	<1%	Rohwer 1999
Mink encephalopathy (experimental)					
Mink	Mink	Serum	ic	0/1	Marsh 1969
Mink	Mink	Whole blood, plasma, red cells, white cells, platelets	ic	0/8 (pools)	Marsh 1973
BSE (experimental)					
Cow	Mouse	Buffy coat	ic + ip	0/11 (pools)	Wells 2000
	Cow[2]	Buffy coat	ic	0/4 (pools)	Wells 2000
Mouse	Mouse	Plasma	ic	4/48	Taylor 2000
Sheep	Sheep[2]	Whole blood	iv	1/19	Houston 2000
CJD (experimental)					
Guinea pig	Guinea pig	Buffy coat	ic,sc,im,ip	10/28	Manuelidis 1978
GSS (experimental)					
Mouse	Mouse	Buffy coat	ip	4/7 (pools)	Kuroda 1983
Mouse	Mouse	Buffy coat/plasma	ic	5/5 (pools)	Brown 1999
		Buffy coat/plasma	iv	2/2 (pools)	Brown 1999

[1]In several of the studies, assays were conducted on serial specimens obtained during both the incubation and clinical phases of disease. [2]Ongoing experiments.

Table 2. Attempts to detect infectivity in the blood of humans with CJD

Diagnosis	Pos./total subjects	Assay Animal	Inoculum	Route of inoculation	Pos./total Animals	Reference[1]
Sporadic CJD	1/1	Guinea pig	Buffy coat	ic	2/2	Manuelidis 1985
Sporadic CJD	1/1	Guinea pig	Buffy coat	ic	0/5	
		Hamster	Buffy coat	ic	2/2	
Sporadic CJD	1/3	Mouse	Whole blood	ic	2/13	Tateishi 1985
Sporadic CJD	1/1	Mouse	Leukocytes	ic	0/10	Tamai 1992
		Mouse	Plasma conc. X3	ic	3/8	
Sporadic CJD	0/3	Chimpanzee	Whole blood units	iv	0/3	Gajdusek/Gibbs/
Sporadic CJD	0/1	Guinea pig	Whole blood	ic,ip	0/2	Brown 1994
Sporadic CJD	0/1	Spider monkey	Whole blood	ic,iv,ip	0/3	
Sporadic CJD	0/1	Squirrel monkey	Whole blood	ic,ip,im	0/1	
Sporadic CJD	0/4	Squirrel monkey	Buffy coat	ic,iv	0/4	
hGH iatro. CJD	1/1	Hamster	Whole blood	ic	1/4	Deslys 1994
Sporadic CJD	0/13	Transgenic mouse	Buffy coat	ic	0/106	Safar 2000
	0/7		Plasma	ic	0/56	

[1]Publication citations can be found in ref. 1 of this article (the transgenic mouse data has not been published).

Annex 2: Summary of the Report of the EMEA Expert Workshop of *15-16 May 2000* on human TSEs and plasma-derived medicinal products

An EMEA Expert Workshop was held on 15-16 May 2000 to provide an update on the latest information on human transmissible spongiform encephalopathies (TSEs) in relation to plasma-derived medicinal products. In the light of this information, consideration is given to whether further precautionary measures, with respect to variant Creutzfeldt-Jakob disease (vCJD), would be appropriate for plasma-derived medicinal products. The outcome of the meeting can be summarised as follows:

- It is still too early to predict the eventual number of cases of vCJD that will occur.
- There continues to be no evidence that CJD (sporadic, familial and iatrogenic) is transmitted via blood or plasma-derived medicinal products.
- Results are awaited from on-going studies investigating whether infectivity is present in blood of patients who have developed vCJD.
- Accumulating data from a variety of studies are increasing the understanding of TSEs in relation to plasma-derived medicinal products.
- From the evidence available so far, it is not clear that leucodepletion would be a significant measure to reduce infectivity in plasma for fractionation since some of the infectivity may be in a cell-free form. There is a need for further studies before any recommendation for or against systematic leucodepletion for plasma for fractionation can be made.
- A considerable number of spiking studies have been undertaken to investigate the partitioning and removal of the abnormal prion protein (PrP^{sc}) or infectivity during the fractionation process. The results are broadly consistent and suggest that a number of steps contribute to removal of the TSE agent, including ethanol fractionation, precipitation steps, chromatographic procedures, nanofiltration and depth filtration. The extent of removal depends on the processing conditions. There is still uncertainty about the relevant spiking agent to represent the infective agent, if it were present in blood.
- Several types of tests are used for assaying the presence of PrP^{sc}. These tests are still in their development and validation stages. Collaborative studies using appropriate reference materials are essential for the evaluation of assays and the WHO is undertaking an important programme in this respect. It is difficult to foresee to what extent these tests could be applicable in the future for routine screening of blood donations and/or as a confirmatory tool in early diagnosis of vCJD.
- The risk factors for vCJD include residence in the UK. This raises the question of whether exclusion of donors who have spent some time in the UK should be considered as a precautionary measure. Data are being gathered on the travel patterns of European donors to the UK so that the cumulative exposure to BSE risk from UK travel and the impact on the number of donors that would be excluded can be estimated.

On the basis of the current information, the recommendations in the CPMP Position Statement on “New variant CJD and plasma-derived medicinal products” (CPMP/201/98) are still appropriate. The considerable efforts and resources invested to answer the many questions in this area are acknowledged.