THE EUROPEAN AGENCY FOR THE
EVALUATION OF MEDICINAL PRODUCTS (EMEA)

FINAL

Ad hoc working party on Creutzfeldt-Jakob disease and blood derivatives

(13 February 1995)

At the request of the CPMP, a meeting was held in Brussels, on February 13th 1995 to discuss the risk of CJD transmission via blood derivatives.

The composition of the group was the following:

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J. Lower, Paul Ehrlich Institut, Langen, Germany,

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CPMP: G. Vicari, Istituto superiore di Sanita, Roma, Italy, - Chairman

J-H Trouvin, French Medicines Agency, Paris, France, Rapporteur.

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An assessment report, prepared by the rapporteur was circulated two weeks in advance. This assessment report has been extensively discussed and used as a basis for the following report to the CPMP.

Risk of Creutzfeldt-Jakob disease transmission via medicinal products derived from human plasma"

1- INTRODUCTION

As a precautionary measure, since March 1994, France has been recalling from the market a large number of batches of plasma-derived medicinal products for which blood donors have been identified as at risk for Creutzfeldt-Jakob disease (CJD) (see below). Already, mid 1991, batches of immunoglobulins and factor VIII preparations were withdrawn in Germany for the same reasons.

Some US companies, recently initiated, "at the recommendation from the US FDA", worldwide market withdrawal of batches of clotting factors, albumin and immunoglobulins because, post donation, a blood donor was diagnosed as having CJD. These withdrawals call into doubt the safety of plasma-derived products and, in addition to problems of demand and supply, create a great deal of anguish for patients receiving products that are later recalled from the market.

There is thus a need to harmonize the European position on the risk of CJD transmission via medicinal products derived from human plasma.

The main points are to decide whether or not there is a risk of CJD transmission via plasma-derived products and, if necessary, to propose additional measures for blood donor selection and/or recall of batches.

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2 SCIENTIFIC BACKGROUND

2-1 Creutzfeldt-Jakob disease

Creutzfeldt-Jakob disease (CJD) is a transmissible subacute spongiform encephalopathy (TSE). It is a progressive degenerative disease of the central nervous system characterized by dementia (and/or cerebellar syndrome), and is invariably fatal. The pathophysiology of the disease is not yet clearly understood but involves an accumulation in the brain of a protein classically named PrPCJD (or PrPsc or PrPres); this is an abnormal conformation of a normal host cell-surface protein, PrPc, that is mainly found in neurones.

The causative agent of CJD is being intensively investigated. Several hypotheses have been proposed involving either an unknown virus or a new class of transmissible agent. Infectivity is resistant to standard means of sterilization, including heat, formaldehyde, 70% ethanol, UV light and ionization. The infectious agent is generally considered to be associated with cellular material.

Spontaneous cases are very rare; the incidence - ca. 1 case per million inhabitants per year - is evenly distributed worldwide and has remained stable for many years, with the exception of iatrogenic cases.

Most spontaneous cases are sporadic, the disease generally develops in patients over 60. Familial cases, with autosomal inheritance, develop in younger patients (ca. 45-50-year old) and represent 5 to 10% of natural cases. There is no clear demonstration of horizontal transmission of sporadic or familial CJD.

2-2 Iatrogenic transmission

Iatrogenic cases have involved transferral of infectious human material (extracted pituitary hormones, cornea or dura-mater) or neurosurgery using contaminated instruments. All cases of iatrogenic transmission have involved the central nervous system.

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In iatrogenic CJD, the form of the disease (mental deterioration or cerebellar syndrome) and the incubation period depend on the source of infection. When contamination occurs by a peripheral route, the clinical features of iatrogenic cases are distinct from most of sporadic cases.

The different types of animal TSE, particularly ovine scrapie, have been studied using various experimental models. The different tissues have been classified according to the concentration of the infectious material. The central nervous system is considered to have the highest infectivity titer (the agent accumulates in the brain).

There is general agreement on the similarity between experimental animal models and human TSEs. The EC classification could thus also apply to human tissues. White blood cells can be placed in category III (low infectivity), whereas plasma is in category IV (no detectable infectivity). The lack of accumulation of the infectious agent in body fluids could account for the lack of reported infectivity.

2-3 Risk of transmission via blood and plasma-derived products

Even though this assessment report deals only with the plasma derivatives, the blood transfusion data must be taken into account. There have been no reports of CJD transmission via blood products (transfusion) and/or plasma-derived medicinal products (e.g. albumin and coagulation factors) and it is not known whether CJD can be transmitted by blood. However, the small number of observations is a limiting factor and all that can be said is that the risk, if it exists, is extremely remote.

No data on CJD transmission via plasma-derived products are available in the literature, despite the extensive use of such products i) in well-identified groups of patients, ii) in many cases, for long-term treatment and iii) in patients under close medical surveillance. For instance, many haemophiliacs have been

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receiving blood transfusions and, more recently, coagulation factor concentrates since childhood.

There is no report of CJD cases in the hemophiliac population. One should remind that in other situations, such as pituitary-derived human growth hormone in children or pituitary-derived gonadotrophins in women, transmission and infection have been detected (a number of young adults -fewer than 60 worldwide- treated with human extracted pituitary growth hormone, have developed CJD).

The absence of reported CJD cases among haemophiliacs is in favour of the safety of plasma-derived products. Despite increasing use of blood products in medical practices the CJD prevalence has remained stable in those EC countries where a surveillance system is active.

Whole blood and buffy coats from clinically diagnosed CJD patients have been reported to transmit infection to animals but only when administered directly into the brain. In contrast, all attempts at transmission via blood from CJD patients to chimpanzees or other non human primates via peripheral routes have been unsuccessful.

In conclusion, there is no evidence that CJD can be transmitted via plasma-derived products. There are insufficient data, however, to rule out the risk completely.

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3- Questions addressed and conclusions

The following questions regarding the risk of CJD transmission via plasma-derived products were addressed by the group:

a) Should the following subjects, who are at a higher risk of developing CJD, be excluded from blood donation ?

- donors having been treated with extracted human pituitary hormones
- donors with a family case of CJD (familial or sporadic)
- donors having received a human tissue transplant (dura-mater graft or embolism, cornea, other).

b) Is there evidence for a risk of CJD transmission via plasma medicinal products ?

c) Should batches of plasma-derived products be withdrawn whenever post-donation information indicates that a donor

- has been treated with extracted human pituitary hormones
- has a family case of CJD (familial or sporadic)
- has received a human tissue transplant (dura-mater graft or embolism, cornea, other)
- has developed a CJD

a) With respect to exclusion criteria for donor, it has been suggested that reliance be placed on the decision of the Council of Europe which includes *"all individuals who have in the past been treated with extract derived from human pituitary glands or who have a family history of CJD are debarred from donation"*. However, further reflection should be conducted regarding the exclusion of donors having received graft or embolism with dura-mater or cornea-gratt. It is noteworthy that

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such criterion would be difficult to apply in daily practice. Results of the discussion should be transmitted to Council of Europe for coordination.

b) With respect to the question of evidence on the risk of transmission, the group concluded that regarding plasma and plasma-derived products, i) no epidemiologic evidence is available about the risk of transmission ii) experimental data do not support the risk of transmission.

c) With reference to the recall of batches of plasma-derived products from plasma pools incorporating a donation considered as at risk, the group concluded that there was no reason for recall, whatever the origin of the risks.

Finally, the group stated that the issues should be re-evaluated at regular intervals, depending on the evolution of epidemiological and scientific data.

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