The European Agency for the Evaluation of Medicinal Products
Evaluation of Medicines for Human Use

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CPMP/906/01

PRESS RELEASE

69th MEETING OF THE COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS

The Committee for Proprietary Medicinal Products (CPMP) held its 69th plenary meeting from 27 to 29 March 2001.

The CPMP appointed the following Vice-Chairpersons:

- Dr Manfred Haase as Vice-Chairperson of the Biotechnology Working Party
- Dr Anne Castot as Vice-Chairperson of the Pharmacovigilance Working Party
- Prof. Fernando de Andrés Trelles as Vice-Chairperson of the Scientific Advice Review Group

The Committee agreed that the appointment of the remaining Working Party Vice-Chairpersons will take place at a future CPMP plenary meeting following the Quality, Safety and Efficacy Working Party meetings which have been scheduled within the next months.

Furthermore the CPMP appointed the following CPMP Ad-Hoc Working Group Chairpersons:

- Dr Per Nilsson as Chairperson of the Ad-Hoc Working Group on Anti-HIV medicinal products
- Prof. Ingemar Persson as Chairperson of the Ad-Hoc Working Group on the Third generation oral contraceptives and cardiovascular risks
- Dr Patrick Salmon as Chairperson of the Ad-Hoc Working Group on the Update of the Guidance on Summary of Products Characteristics
- Dr Hans van Bronswijk as Chairperson of the Ad-Hoc Working Group on Interferons and neutralising antibodies.
- Dr Frances Rotblat as Chairperson of the Ad-Hoc Working Group on the update of the Anticancer Guideline.
- Dr Markku Toivonen as Chairperson of the Ad-Hoc Working Group on comparability of biotechnology products – preclinical and clinical issues.

The following issues were discussed during the meeting:

Product related issues

Centralised procedures

The pre- and post-authorisation centralised procedures finalised during this meeting are summarised in **Annex 1** and an overview of centralised procedures since 1995 is given in **Annex 2**.

For marketing authorisations granted by the European Commission since the last CPMP plenary meeting in February 2001, see **Annex 3**.

Scientific Advice procedures

The CPMP adopted the outcome of the discussions of the Scientific Advice Review Group meeting, which was held on Monday 26 March 2001. For further details, please see **Annex 4**.

One harmonisation procedure was started under article 11 of Council Directive 75/319/EEC, as amended. This referral was initiated by the French National Competent Authority.

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Non-product related issues

CPMP Working Parties and Ad-Hoc Groups

The CPMP adopted the final European Union recommendations for the influenza vaccine composition for the season 2001/2002 (CPMP/BWP/844/01). Such recommendation is provided in **Annex 5.**

The report of the EMEA Workshop on viral safety of plasma-derived medicinal products with particular focus on non-enveloped viruses (CPMP/BWP/BPWG/4080/00) held on 13 September 2000 and the Addendum conclusions and recommendations of BWP and BPWG (CPMP/BWP/BPWG/93/01) were adopted by the CPMP and are attached as **Annex 6**. The summary report of the EMEA Expert meeting on human TSEs and medicinal products derived from human blood and plasma (CPMP/BWP/450/01) held on 1 December 2000 was adopted by the CPMP and is attached as **Annex 7**.

An overview of guidance documents adopted during the meeting or released for consultation to Interested Parties is attached as **Annex 8**.

Organisational Matters

The second CPMP Ad-Hoc Group on Organisational Matters (ORGAM) was held on 26 March 2001 under the Chairmanship of Dr Daniel Brasseur. During the meeting, preliminary discussions on the CPMP Internal Rules of Procedure, the development of a Day 70 Assessment Report template, Transparency proposals, streamlining of Variation activities, the organisation of Cross Working Party Chairpersons meetings, as well as Scientific Advice activities were initiated.

In relation to transparency, it should be noted that summaries of adopted CPMP opinions for initial evaluations (positive and negative) will be published, as an attachment to the CPMP Press Release. This will be effective as of the April 2001 CPMP meeting.

Mutual Recognition procedure

The CPMP noted the report from the Mutual Recognition Facilitation Group (MRFG) meeting held on 26 March 2001, which is circulated together with this Press Release (see **Annex 9**), including the status of the activities of the sub-group on harmonisation of Summary of Product Characteristics.

Next meeting

The 70th plenary meeting of the CPMP will be held from 24 April 2001 until 26 April 2001.

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OUTCOME OF THE MARCH 2001 CPMP MEETING IN RELATION TO CENTRALISED APPLICATIONS

PRE-AUTHORISATION PHASE			
Opinions			
Number of Opinions	**Number of Active Substances**	**Outcome**	**Comments**
8	7(4 Part A/3 Part B)	Positive by consensus	4 Opinions under exceptional circumstances

Withdrawals	
Number of Withdrawals	**Number of Active Substances**
1	1 (1 Part B)

POST-AUTHORISATION PHASE

Opinions for Type I Variation applications following Type II Procedure	
Number of Opinions	**Outcome**
2	Positive by consensus

Opinions for Type II Variation applications	
Number of Opinions	**Outcome**
9 (SPC/PL update)	Positive by consensus
13 (Pharmaceutical aspects)	Positive by consensus

Withdrawals	
Number of Withdrawals	**Scope of Post-Authorisation change**
1 (Extension of indication)	Type II variation application (extension of the indication)

Annex II applications	
Number of Opinions	**Outcome**
1 (New strength) 1 (New pharmaceutical form)	Positive by consensus Positive by consensus

Opinions for Annual Re-Assessment		
Name of Medicinal Product	**Outcome**	**Comments**
Remicade	Positive by consensus	Marketing Authorisation to remain under exceptional circumstances

Opinions for Renewal applications		
Name of Medicinal Product	**Outcome**	**Comments**
Zerit	Positive by consensus	----
Puregon	Positive by consensus	----

EMEA CENTRALISED PROCEDURES

	1995-2000			2001			Overall Total
	Part A	Part B	Total	Part A	Part B	Total	
Scientific Advice	74	122	196	3	16	19	215
Follow-up to scientific advice	15	11	26	3	0	3	29

	1995-2000			2001			Overall Total
	Part A	Part B	Total	Part A	Part B	Total	
Applications submitted	97	182	279	6	8	14	293
Withdrawals	12	37	49	0	4	4	53
Positive CPMP opinions	64	112	176	8	7	15	191[1]
Negative CPMP opinions[2]	1	3	4	0	1	0	5[3]
Marketing authorisations granted by the Commission	56	95	151	6	14	20	171[4]

	1995-2000			2001			Overall Total
	Part A	Part B	Total	Part A	Part B	Total	
Variations type I	265	551	816	64	70	134	950
Positive opinions, variations type II	159	224	383	18	41	59	442
Negative opinions, variations type II	0	2	2	0	1	1	3
Extensions (Annex II applications)	34	20	54	0	2	2	56

[1] 191 positive opinions corresponding to 150 substances
[2] In case of appeal the opinion will not be counted twice
[3] 5 negative opinions corresponding to 3 substances
[4] 171 Marketing Authorisations corresponding to 132 substances

Medicinal products granted a Community Marketing Authorisation under the Centralised Procedure since February 2001 Press Release

Brand name	Rapamune
INN	sirolimus
Marketing Authorisation Holder	Wyeth Europe Ltd
ATC code	L04AA10
Indication	Prophylaxis of organ rejection in patient receiving renal transplants
CPMP Opinion date	16.11.2000
Date of Commission Decision	13.03.2001

Brand name	Vaniqa
INN	eflornithine
Marketing Authorisation Holder	Bristol Myers Squibb Pharma EEIG
ATC code	D11AX
Indication	Treatment of facial hirsutism
CPMP Opinion date	14.12.2000
Date of Commission Decision	20.03.2001

Brand name	Zometa
INN	zoledronic acid
Marketing Authorisation Holder	Novartis Europharm Ltd
ATC code	M05BA08
Indication	Treatment of tumour induced hypercalcaemia
CPMP Opinion date	14.12.2000
Date of Commission Decision	20.03.2001

Brand name	Kaletra
INN	lopinavir/ritonavir
Marketing Authorisation Holder	Abbott Laboratories
ATC code	J05A
Indication	Combination treatment in combination of HIV-1 infected patients
CPMP Opinion date	14.12.2000
Date of Commission Decision	20.03.2001

Brand name	SonoVue
INN	sulphur hexafluoride
Marketing Authorisation Holder	Bracco S.P.A
ATC code	V08DA
Indication	Ultrasound agent to enhance the echogenicity of the blood
CPMP Opinion date	14.12.2000
Date of Commission Decision	26.03.2001

OUTCOME OF THE MARCH 2001 CPMP MEETING IN RELATION TO SCIENTIFIC ADVICE PROCEDURES

Substance	Intended indication(s)	Topic				
		Type of Request		Pharma-ceutical	Pre-Clinical	Clinical
		New	Follow-up			
Chemical	Treatment of chronic obstructive pulmonary disease (COPD) and asthma	**X**				**X**
Chemical	Treatment of depression	**X**				**X**
Chemical	Treatment of Alzheimer's disease	**X**				**X**
Chemical	Treatment of Parkinson's disease	**X**				**X**
Chemical	Prevention and treatment of postmenopausal osteoporosis	**X**			**X**	**X**
Biological	Treatment of emphysema secondary to congenital alpha-1 antitrypsin deficiency		**X**			**X**

In addition to the adoption of the above final Scientific Advice letters, the Committee accepted seven new requests from companies for Scientific Advice of which two are follow-up from previous Scientific Advices.

ANNEX 5 to CPMP March 2001
Press Release
London, 29 March 2001
CPMP/BWP/844/01

COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS (CPMP)

FINAL EU RECOMMENDATION FOR THE INFLUENZA VACCINE COMPOSITION FOR THE SEASON 2001/2002

EU recommendation for the influenza vaccine composition for the season 2001/2002

The meeting of the Ad hoc Influenza Working Group of the BWP was convened in order to implement Part A of the Note for Guidance on harmonisation of requirements for influenza vaccine i.e. the selection of virus strains for the manufacture of influenza vaccine for 2001/2002.

Having considered the information on international surveillance by WHO presented by Dr Alan Hay (WHO collaborating centre, Mill Hill), the CPMP BWP Ad hoc Influenza Working Group, consisting of experts on influenza from the Member States, considered that the WHO recommendation on the composition of vaccines for 2001/2002 should be followed:

Trivalent vaccine containing:

- an A/Moscow/10/99 (H3N2)-like strain
- an A/New Caledonia/20/99 (H1N1)-like strain
- a B/Sichuan/379/99-like strain

On the basis of cross reactivity and growth in eggs, the group agreed that for the purpose of vaccine manufacture, the following strains be accepted:

a) Reassortant virus RESVIR-17, which has been derived from A/Panama/2007/99 as an A/Moscow/10/99-like strain

b) Reassortant virus IVR-116 which is derived from A/New Caledonia/20/99 as an A/New Caledonia/20/99 -like strain

c) B/Johannesburg/5/99, B/Victoria/504/2000 or B/Guangdong/120/2000, which are antigenically similar and are B/Sichuan/379/99-like strains.

Reagents for vaccine standardisation will be prepared by NIBSC, UK and CBER, USA

(see Annex I). Reagents prepared by CBER will be available from NIBSC.

ANNEX I

Reagents for vaccine standardisation

Available from NIBSC, UK

H1N1

A/New Caledonia/20/99 (IVR-116) antigen. A new reagent will be available by mid April 2001.

A/New Caledonia/20/99 antiserum currently available.

H3N2

A/Panama/2007/99 (RESVIR-17) antigen. A new reagent will be available by end of April 2001.

A/Panama/2007/99 antiserum. A new reagent will be available by end of April 2001.

B

B/Johannesburg/5/99 antigen, currently available.

B/Johannesburg/5/99 antiserum, currently available.

Should they be needed:

B/Guangdong/120/2000 antigen will be available by May 2001.

B/Guangdong/120/2000 antiserum will be available by May 2001.

Available from CBER, USA

B

B/Victoria/504/2000/antigen will be available by May 2001.

B/Victoria/504/2000/antiserum will be available by May 2001.

ANNEX 6 to CPMP March 2001
Press Release
London, 28 March 2001
CPMP/BWP/BPWG/4080/00

EMEA WORKSHOP ON VIRAL SAFETY OF PLASMA-DERIVED MEDICINAL PRODUCTS WITH PARTICULAR FOCUS ON NON-ENVELOPED VIRUSES

13 September 2000
REPORT

SUMMARY

In the early 1990's, occasional incidents of transmission of enveloped viruses (hepatitis B (HBV) and C viruses (HCV)) and other blood-borne viruses, including hepatitis A virus (HAV) occurred with plasma-derived medicinal products. As a result, the effectiveness of processes for inactivation/ removal of enveloped viruses was increased. In addition, the Committee on Proprietary Medicinal Products (CPMP) encouraged the development and introduction of effective steps for non-enveloped viruses including hepatitis A and parvovirus B19 (CPMP Note for Guidance on Plasma-Derived Medicinal Products, CPMP/BWP/269/95).

The 1990's also saw the development of Nucleic Acid Amplification Technology (NAT) as a sensitive technique that could be used to detect viral nucleic acid and to exclude contaminated plasma pools from the manufacturing process for plasma-derived medicinal products. CPMP and its Biotechnology Working Party (BWP) recommended NAT testing of plasma pools for HCV RNA as from July 1999. An update meeting on NAT was held by the BWP in September 1999.

The purpose of the current Workshop was to review progress since the CPMP/BWP recommendations in the mid-1990's and to consider whether further measures are needed, taking into account progress in the state of the art. Participants were from patients' organisations, academia, industry, blood transfusion services and regulatory authorities.

Enveloped viruses

Current plasma-derived medicinal products have excellent viral safety with respect to enveloped viruses including HIV, HBV and HCV. Safety is achieved by a combination of approaches i.e. selection of donors, screening of donations and plasma pools for HBsAg (hepatitis B surface antigen) and antibodies to HIV and HCV, testing for HCV RNA on mini-pools and pools, and effective inactivation/removal procedures for enveloped viruses.

Additional testing on mini-pools and pools by NAT for HIV and HBV genomes has been introduced by some manufacturers.

Non-enveloped viruses

Improved viral safety for HAV has been achieved for coagulation factors (e.g. by pasteurisation, heat treatment of lyophilised products or nanofiltration). In the case of immunoglobulins, the presence of HAV neutralising antibodies contributes to safety and there have been no reports of HAV transmission.

There are two aspects to the consideration of parvovirus B19:

- transmission of the virus itself
- surrogate marker for the potential for unknown non-enveloped viruses to be present.

Parvovirus B19 DNA can be detected in many plasma-derived medicinal products and in particular coagulation factors. The correlation with infectivity is not measurable at present. However, there have been a few reports of parvovirus B19 infection in association with the administration of coagulation factors and solvent/detergent treated plasma. In general, product contamination with parvovirus B19 DNA seems not to be a serious problem clinically because of the natural spread of the virus, the presence of neutralising antibodies and the mildness of the symptoms normally associated with infection. Risk groups for parvovirus B19 infection can be identified. Parvovirus B19 is difficult to inactivate, as it is resistant to many of the current inactivation techniques. Inactivation by

pasteurisation or heat treatment of lyophilised products (e.g. coagulation factors) is not or only partly effective. In addition, the small size of parvovirus B19 means that filtration can only be successful with filters of sufficiently small pore size, yet such filters have generally not been practical for the filtration of all blood products (e.g. Factor VIII, immunoglobulins). New inactivation techniques are in development. Testing of plasma mini-pools and pools by NAT for parvovirus B19 DNA in order to reduce virus load on the manufacturing process can diminish product contamination and complement other safety measures.

Neutralising antibodies present in immunoglobulins and in solvent/detergent treated plasma contribute to the safety of these products.

As stated in CPMP Note for Guidance on Plasma-Derived Medicinal Products (CPMP/BWP/269/95), it is an objective to introduce effective viral inactivation/removal steps for non-enveloped viruses for all plasma-derived medicinal products. There is currently no "magic bullet" and different solutions may be needed for different products.

When making changes in the manufacture of plasma-derived medicinal products, there is a need for vigilance for possible adverse consequences on supply and on the product (e.g. modifications leading to inhibitor formation with Factor VIII, reduction in levels of neutralising antibodies).

Conclusions and recommendations

On the basis of the current state of the art, CPMP and its relevant working parties have considered the viral safety of plasma-derived medicinal products with particular focus on non-enveloped viruses, and have reached the conclusions and recommendations presented in the Addendum to this report.

The viral safety of plasma-derived medicinal products will continue to be kept under review.

1. INTRODUCTION

The recognition in the mid-1980's that plasma-derived medicinal products, in particular coagulation factor concentrates, had caused widespread transmission of human immunodeficiency virus (HIV) and non-A non-B hepatitis (now recognised as mainly hepatitis C) resulted in major changes to manufacturing processes, with the introduction of specific steps to inactivate these and other blood-borne viruses. However, occasional incidents of transmission of these and other blood-borne viruses occurred in the early 1990s and as a consequence viral safety requirements were reviewed. This resulted in the revision in the mid-1990s of the Guideline on "Validation of Virus Removal and Inactivation Procedures" as the Note for Guidance on "Virus Validation Studies: The Design, Contribution and Interpretation of Studies Validating the Inactivation and Removal of Viruses" (CPMP/BWP/268/95) and revision of the CPMP "Note for Guidance on Plasma-Derived Medicinal Products" (CPMP/BWP/269/95).

At that time, recommendations for action were made and limitations identified, based on the state of the art.

CPMP and its Biotechnology Working Party (BWP) recommended NAT testing of plasma pools for HCV RNA as from July 1999. In September 1999 the Biotechnology Working Party held an update meeting on the progress with testing for viral nucleic acid by nucleic acid amplification technology (NAT). The current workshop took discussions forward from this update meeting.

The purpose of the current workshop was to review the progress made since the recommendations made during the 1990s and to consider whether further measures are needed taking into account progress in the state of the art. New technical achievements were considered in the light of their impact on product safety. Data on the effect of new viral screening methods on the supply of plasma and any consequent effect on the supply of cellular blood products was reviewed.

This report covers the September 2000 Workshop but also takes into account information from the September 1999 NAT update meeting.

2. VIRAL SAFETY OF THE CURRENT PLASMA-DERIVED MEDICINAL PRODUCTS

2.1 Virologists perspective

The viral safety of the current plasma-derived medicinal products was reviewed by J. Robertson. With the current controls and manufacturing procedures, plasma-derived medicinal products achieve a high level of assurance of viral safety with respect to enveloped viruses including human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV). This is achieved by donor selection, screening of donations, testing of intermediates (plasma pools), virus inactivation/removal procedures in the manufacturing processes, and the application of Good Manufacturing Practice.

In the case of HBV, there is an increasing prevalence of variants with mutations in the "a" determinant of HBsAg. Detection of hepatitis B surface antigen (HBsAg) by current assays may be compromised with these mutants. At present, such mutants are rare in Europe and the US.

Non-enveloped viruses such as hepatitis A virus (HAV) and parvovirus B19 are more difficult to inactivate and/or remove.

HAV is not screened for at the donation stage as antibody testing will not detect viraemic donors and detection by NAT is difficult to achieve for the following reasons. HAV viraemic donations are rare. Plasma pools contaminated with HAV RNA have only been rarely detected and the level of HAV RNA is so low that specific measures (e.g. testing small mini-pools, use of highly sensitive NAT) have to be taken to detect it. There is therefore a question about the ability of routine testing by NAT to detect HAV RNA reliably in plasma pools as a measure to avoid the use of contaminated pools in the manufacture of plasma-derived medicinal products. It is relatively difficult to inactivate HAV but heat treatments can be effective. Transmission events have been reported infrequently and only with coagulation factors without an effective HAV inactivation/removal step in the manufacturing process.

Parvovirus B19 virus is not currently screened for at the donation stage. It can be detected by NAT testing of plasma pools because of the high levels of parvovirus B19 DNA in viraemic donations. Of the known blood-borne viruses, parvovirus B19 is the most resistant virus. It is difficult to inactivate/remove during the manufacture of plasma-derived medicinal products. The disease is usually mild but on rare occasions has severe consequences predominantly in the identified risk groups. Transmission of parvovirus B19 has been associated with the administration of coagulation factors and solvent/detergent treated plasma. The frequency of transmission is not well documented.

From a virological viewpoint, transfusion of viruses should be avoided wherever possible. Technology is rapidly advancing and new developments need to be evaluated for their possible application to plasma-derived medicinal products. Overall benefit/risk balance and effects on supply need to be considered. The object is to avoid transmission of viruses and resultant disease caused by known viruses and to improve inactivation/removal procedures to provide some assurance of effectiveness for viruses that are at present unknown. The approaches currently available are improved inactivation/removal procedures, the application of novel testing methods (e.g. NAT), testing for viruses not currently tested for in order to reduce virus titres, assuring levels of neutralising antibodies in certain products, and the use of alternative products (e.g. products from recombinant DNA technology).

2.2. Clinical significance of parvovirus B19 infection

Parvovirus B19 infection was reviewed by W-D. Ludwig, who addressed the following questions:

What is the exposure rate in the general population to parvovirus B19?

Are any patient populations receiving plasma-derived medicinal products at particular risk of severe B19 infection?

What would be the clinical impact of additional measures for parvovirus B19?

Parvovirus B19 is a common airborne infection but is very rarely a serious problem clinically. The infection leads to life-long immunity. It has a seasonal epidemiology, with infection peaking in the spring, and cycles of epidemic years. Most children come into contact with the disease between the age of 5 and 15. As a result, 60-80% of adults are seropositive and protected from reinfection.

The cellular receptor for parvovirus B19 is the blood group P antigen which is expressed on erythroid cells, megakaryocytes, endothelial cells, placenta, foetal liver and myocardial cells. Parvovirus B19 is dependent on mitotically active cells for replication and is directly toxic to erythroid progenitor cells. The pattern of disease that follows parvovirus infection is the result of the balance between virus, marrow target cell, and the immune response (*Young, 1995*).

In normal individuals the infection is characterised by a short period of viraemia frequently associated with symptoms of fever, chills, headache and myalgia. While most infections are asymptomatic, this viraemic phase can be followed by a rash in children (fifth disease) and/or arthralgia during the immune response phase.

In patients with increased erythropoiesis, the infection leads to a transient aplastic crisis (severe anaemia with reticulocytopenia and absence of precursors in the bone marrow). It is a self-limiting disease (1-2 weeks) treated by blood transfusion. The risk groups are patients with underlying haemolytic disorders (e.g. hereditary spherocytosis, sickle cell anaemia, thalassemia, red cell enzymopathies, autoimmune haemolytic anaemia) or under conditions of erythroid "stress" (e.g. haemorrhage, iron deficiency anaemia, following kidney or stem cell transplantation).

In immunocompromised patients, parvovirus infection can cause pure red cell aplasia, a chronic disease characterised by severe (intermittent) anaemia, which may be associated with intermittent neutro-/thrombocytopenia, and very rarely pancytopenia. This chronic disease is due to persistent infection caused by the failure to mount a neutralising antibody response. The risk groups are those with congenital immunodeficiency, acquired immunodeficiency (e.g. HIV infection), lymphoproliferative disorders during or after therapy with cytotoxic drugs, iatrogenic immunosuppression (e.g. autoimmune diseases, organ transplants, stem cell transplantation). Treatment consists of decreasing the level or temporary cessation of iatrogenic immunosuppression and repeated infusions of intravenous immunoglobulin.

The prevalence of parvovirus B19 infection during pregnancy is approximately <1 in 40,000. In about 10% of infected women it results in *in utero* infection and destruction of erythroblasts in the foetus. The foetus is at particular risk of persistent infection due to the immaturity of the immune response and the erythropoiesis outside the bone marrow. The risk of a fatal outcome is greatest during the first two trimesters (i.e. hepatic period of hematopoietic activity). Severe anaemia and non-immune hydrops fetalis occurs in approximately 20% of infected foetuses and abortion or foetal death in approximately 10% of infected foetuses. Infection is treated by intrauterine red blood cell transfusion. Persistence of parvovirus B19 infection after birth may cause congenital anaemia.

There is a need for improved awareness of the possibility of parvovirus B19 infection in cases of acute haematological syndromes and chronic bone marrow failure. Further studies are needed into the clinical implications of persistent parvovirus B19 infection and whether the virus has a role in other diseases (e.g. neutro/thrombocytopenia, rheumatic diseases, hepatitis).

In conclusion, parvovirus B19 is a common infection and is rarely a serious problem clinically. The patient groups at particular risk of severe parvovirus B19 infection are clearly defined. Interventions for parvovirus B19 need to balance the low risk of infection at a population level with the potential for serious outcomes for particular groups (*Crowcroft, 1999*)

2.3 Patients' Perspective

The views of the European Haemophilia Consortium (EHC) were presented by K. Pappenheim.

The disparity between the standard of treatment available to patients in the European Union and the lack of treatment for patients in developing countries was highlighted.

The haemophilia population is a high-risk population with regard to any infection transmissible through blood products. Even with the levels of safety now achieved with coagulation factors, many consider the potential risk from blood products to be too high and there is pressure for use of recombinant products. The risk for transmission of parvovirus B19 by plasma-derived medicinal products is of concern where products are administered to risk groups for parvovirus infection (e.g. patients with HIV infection, or parvovirus sero-negative pregnant women with bleeding disorders). Furthermore, this risk may also apply to any unknown non-enveloped viruses that might be present. In

the UK, patients are acutely concerned about the possibility of transmission of variant Creutzfeldt-Jakob disease (vCJD) through coagulation factors.

Other issues for patients are the adequacy of supply and the immunogenicity of products. Product recalls cause a great deal of anxiety to patients.

The EHC has a "Common position on the supply, safety and quality of factor concentrates". In essence, this urges governments to ensure that an adequate and safe supply of factor concentrates for the treatment of haemophilia and related diseases is always available without risk of disruption of supply. In order to further reduce the risk of transmission of infective agents, developments of new products or introduction of new screening and inactivation/removal procedures must continue.

The EHC welcomes the opportunity for dialogue with regulators. It wishes to have openness on risks from coagulation factors. Co-operation between FDA and European regulators was urged.

The views of the European Patients Primary Immunodeficiency Collaboration (EPPIC) were presented by D. Watters and T. Wallington. As with haemophilia, the quality of life for patients with primary immunodeficiencies varies very widely between different countries.

Safety and supply are important issues for patients. In the case of immunoglobulins, long experience shows clinically significant infection transmissible by immunoglobulins to be limited to HCV. Protection from the risk of transmission of HCV and other blood borne viruses is achieved by the sum of precautionary steps taken in plasma collection, screening and fractionation. The presence of neutralising antibodies can also contribute to protection from transmission of infection. When making changes aimed at extending protection to additional blood borne viruses, it is important to establish that the change will not impact adversely on overall virus safety (e.g. by diminishing the level of neutralising antibodies present in immunoglobulins).

Normal immunoglobulin is used to treat parvovirus B19 infections and in prophylaxis against hepatitis A infection. If immunoglobulin offers protection due to the presence of these antibodies then it is safe from transmitting these agents. The question is how can this be specified for each product batch.

3. VIRAL SAFETY INFORMATION FROM CLINICAL EXPERIENCE

The view of the CPMP's Ad-Hoc Working Group on Blood Products (BPWG) on viral safety information from clinical experience was described by R. Seitz, a member of the BPWG. Following the transmission of HIV by coagulation factors in the early eighties, clinical studies to assess viral safety of plasma products were advocated. This included studies in previously untreated patients (PUPs), using a battery of repetitive virus marker tests. In the recent revision of the BPWG guidelines on coagulation factors, the requirement to perform formal clinical studies to assess viral safety was discarded. The approach was changed for the following reasons.

Firstly, in the case of enveloped viruses, procedures in place are now considered to be highly effective and ensure the viral safety of the product with respect to enveloped viruses. The few clusters of transmissions of enveloped viruses observed in the last decade were all attributed to certain batches and/or to GMP failure well after licensing. Thus, demonstration of the absence of transmissions by a small number of pre-approval batches in a relatively small number of patients will not prove safety of future batches.

Furthermore, the number of available PUPs is very limited making it difficult to perform PUP studies for all products and leading to incomplete studies failing to reach the PUP numbers required in the old Note for Guidance. It seems wise to restrict the involvement of PUPs (often very small children) to clinical research into relevant problems that cannot be solved by other means. Nevertheless, all experience with PUPs needs to be documented in the dossier and information provided in the product information.

In the case of non-enveloped viruses, the procedures in place may be of limited value e.g. against HAV and parvovirus B19. However, the safety of products with respect to non-enveloped viruses cannot currently be adequately evaluated in clinical studies. There have been cases of clusters of HAV transmission from batches of FVIII products subjected to solvent/detergent treatment only for viral inactivation. However, plasma pool contamination occurs infrequently and vaccination of recipients is recommended and so investigation of safety for HAV through clinical trials is not feasible. Parvovirus

B19 presents different problems for clinical study. In this case, plasma pool contamination with parvovirus B19 with very variable titres is common, inactivation and removal procedures are of limited value, and transmission by plasma-derived medicinal products, and particularly coagulation factors, has been reported. Clinical studies are complicated by the high natural prevalence of immunity and the incidence of parvovirus B19 infection. As a consequence, many recipients of plasma-derived medicinal products are already immune and, where infections do occur in recipients, it is difficult to differentiate natural infection from product-related infection.

The BPWG recommends that viral safety information from clinical experience is gathered using the following approach:

- Investigators should continue using their normal clinical practice for monitoring of patients for viral infections
- All available data gathered on patients treated with the product in clinical trials should be provided and all experience in the treatment of PUPs should be documented
- A pre-treatment serum sample of each patient included in the clinical trial should be stored at -70^{o}C for possible future testing
- Data from the post-marketing study for coagulation factors should be reported
- Pharmacovigilance should have systems in place to collect information on patients treated with the product and to respond rapidly to any reports of infection with a full investigation

4. THE CAPABILITY OF MANUFACTURING PROCESSES TO INACTIVATE/ REMOVE NON-ENVELOPED VIRUSES

The questions to be addressed in this session included:

What is the current state of the art for the inactivation/removal of non-enveloped viruses, including methods in development?

What do validation studies tell us about the ability of the albumin manufacturing process to inactivate/remove hepatitis A, parvovirus B19 and other non-enveloped viruses?

4.1 "Classical methods"

The effect of 'classical' methods to inactivate/remove non-enveloped viruses was addressed by S. Petteway and R. McIntosh. All the methods used are process and product dependent and validation for each method and for each product is necessary. For all these processes the level of inactivation/removal must be evaluated against the product stability (loss of active substance, denaturation of the active substance, formation of neoantigens).

Pasteurisation is used for albumin, and for some immunoglobulins and coagulation factors.

The potential efficacy is dependent upon the nature and concentration of the stabilisers used to protect proteins. Pasteurisation can be effective for the inactivation of HAV, but is generally of limited value in the inactivation of parvovirus B19. Temperature, time, protein concentration and stabilisers are the critical parameters.

Conclusion: The effect of pasteurisation is process and product specific and product stability is a limiting factor.

Heat treatment of lyophilised products is used for some coagulation factors. The effectiveness of this step may vary according to the product formulation, the lyophilisation process, the residual moisture, the duration of the step and the temperature at which the product is heated. Residual moisture is of great importance but can be difficult to control, particularly in terminally heat-treated products.

R. McIntosh presented data to show that terminal heat treatment of lyophilised products (80^{O}C for 72 hours) can be effective for inactivation of HAV in Factor VIII and IX, fibrinogen and thrombin, but parvovirus models (canine parvovirus (CPV) and bovine parvovirus (BPV)) are more resistant. Some inactivation of parvovirus is observed and this increases with the length of heating. The extent of inactivation is product dependent. To ensure robustness, the heating conditions are carefully controlled and specified lower and upper limits for residual water are set. Experiments using different

temperatures suggest that 100 ^{O}C for 0.5 hours may be less effective for parvovirus than 80^{O}C for 72 hours.

This finding with model viruses is consistent with the clinical trial follow up reported by Santagostino et al. (1997) which suggested that parvovirus B19 transmission can still occur with a product subjected to 100°C for 30 minutes.

Conclusion: The effect of heat treatment is process and product dependent and product stability is a limiting factor. Residual moisture is a critical parameter.

Partition processes, such as precipitation or chromatography, can contribute to the removal of viruses in the manufacture of plasma-derived medicinal products. Temperature, pH and the concentration of the precipitating agent are critical parameters for precipitation. The effect of chromatography depends on the type of chromatography and the chromatographic conditions.

Conclusion: The effectiveness of partition processes, such as precipitation and chromatography, for virus removal is process and product dependent, requires stringent process control for reproducibility, and may vary in relation to virus properties.

4.2 Nanofiltration

Nanofiltration is a more recent development that uses technological advances in the manufacture of controlled pore size membranes in the nanometre range for virus removal. Effective removal requires that the pore size of the filter is smaller than the effective diameter of the virus. Careful validation is needed to reveal the potential of the method for specific applications and may utilise NAT testing and studies of the down-scaled process with several virus species.

Three filter producers are on the market: Viresolve 180 and 70 from Millipore, Planova 35N and 15N from Asahi Kasei and Ultipor DV50 and DV20 from PALL. Nanofiltration has been used for the removal of hepatitis A and parvovirus B19 from Factor IX products using the smaller pore size filters (Viresolve 70, Planova 15N and Pall Ultipor DV20). In general, it has not been found possible to filter Factor VIII and immunoglobulins through filters of these pore sizes. However, it was reported by S. Satoh and B. Flan that these limitations for Factor VIII can be overcome and one product is in clinical trials. Furthermore, E-G Graf showed data on filtration of immunoglobulin (0.7% IgG) through an Ultipor DV20 filter and S. Satoh reported that a pepsin treated intravenous immunoglobulin could be filtered with a Planova 15N filter. The larger pore size filters (Viresolve 180, Planova 35N and Ultipor DV50) are not robust for the removal of HAV or parvovirus B19.

H. Hiemstra described the use of "designed experiments" to investigate the effect of a number of parameters simultaneously on the robustness of filtration.

Conclusion: The effectiveness of nanofiltration may be process and product dependent. Operating parameters are of particular importance for virus retention if the size of the target virus is in the pore size range of the filter membranes. Preparation of the virus spike for the evaluation of the process is critical.

4.3 New approaches

Various new approaches for non-enveloped viruses were presented by C. Kempf and R. McIntosh:

UV-C Irradiation: Hitherto this technology was assessed only at laboratory scale but this technique is now being investigated at pilot scale for large volume liquids. This technique could only be used for specific groups of products because some products are sensitive to UV irradiation. Results showing inactivation of parvovirus models without loss of protein activity were presented for 4.5 % albumin and for alpha$_1$-proteinase inhibitor. Flow rate, path length and residence time are important variables.

Inactine^{TM} Technology, Vitex : these are small, electrophilic compounds which selectively bind and irreversibly modify nucleic acid (DNA and RNA), rendering it non-functional, while sparing other biological molecules such as proteins and carbohydrates. Issues to be considered include the toxicology of Inactine^{TM} residues that might be present in products and the possibility that some modifications of proteins might occur.

The effectiveness of ethyleneimine trimer treatment has been investigated using minute virus of mice (MVM) as a model parvovirus (*Kasermann and Kempf, manuscript*). The inactivation process was found to be strongly pH dependent and protein modification was observed.

Chaotropic agents and heat: The extent of inactivation of a picornavirus model, bovine enterovirus (BEV) and a parvovirus model, MVM, depended on time, temperature and the concentration of the chaotropic agent. The active proteins can denature at high temperature. (*Schlegel, Immelmann and Kempf, in press*)

Photodynamic inactivation by singlet oxygen in the presence of C_{60}[1] as a sensitiser has been investigated using MVM. Inactivation was seen in the presence of C_{60} and with a slightly elevated temperature (*Kassermann and Kempf, 1997 and 1998*). The C_{60} compound is easily removed by filtration, because it is water insoluble.

Biocide filter sheets: filtration in the presence of iodine was investigated with an immunoglobulin preparation spiked with MVM. The viral inactivation results seemed promising, but there is a problem in the removal of iodine. Immediately after filtration, the inactivation is incomplete but further inactivation occurs during a post-filtration incubation period.

Conclusion: These approaches are all in the development stage and need further investigation.

4.4 Validation of parvovirus inactivation/removal

R. McIntosh illustrated how NAT testing for parvovirus B19 DNA can be used to study removal and partition processes during production scale manufacture by following the partitioning/removal of measurable parvovirus B19 DNA present in plasma pools. It is an advantage to study the full scale manufacturing process rather than a model spike on a scaled-down process. However it is not known if the DNA found is still infectious or not and this method is, therefore, useful for demonstration of viral removal, including filtration processes, and not for virus inactivation.

Normally animal parvoviruses are used to validate the production process in spiking experiments. As an infectivity assay for parvovirus B19 is not yet available, there is only limited information about the comparability of these animal viruses with parvovirus B19. In addition, there could be some problems with the presence of antibodies to bovine parvoviruses in human plasma. Therefore, other model viruses (porcine, canine or murine parvoviruses) should be used for testing.

The potential for carry-over of parvovirus DNA on reuse of equipment should be considered and investigated in appropriate viral validation studies of sanitisation procedures for equipment.

4.5 Conclusions on the capability of manufacturing processes to inactivate/removal non-enveloped viruses

What is the current state of the art for the inactivation/removal of non-enveloped viruses, including methods in development?

Methods have been validated for HAV inactivation/removal for coagulation factors and albumin. Parvovirus B19 is difficult to inactivate/remove by current methods. Nanofiltration can be used for products such as Factor IX which are filterable through the smaller pore sized filters needed to remove parvovirus. There is currently no single approach that would be applicable for all products. Methods have to be validated for individual products. New methods for inactivation/removal have to be carefully investigated to ensure their effectiveness and the lack of any adverse effect on the efficacy or safety of the product.

The objective remains to have effective steps for the inactivation/removal of non-enveloped viruses for all plasma-derived medicinal products.

What do validation studies tell us about the ability of the albumin manufacturing process to inactivate/remove hepatitis A, parvovirus B19 and other non-enveloped viruses?

Information from validation studies on the manufacturing process for albumin preparations were summarised by PPTA. Albumin is always pasteurised (60°C for 10 hours). A range of results was seen in different viral validation studies. Viral inactivation of 3 – 6.9 logs was found for HAV. Precipitation

[1] C_{60} is composed of 60 carbon atoms and has an icosahedral structure. It is also known as "buckminsterfullerene".

steps contributed to HAV removal (3 – 4 logs). In general, pasteurisation of albumin was of limited value for the inactivation of parvoviruses but parvovirus may also be removed to some extent during fractionation.

5. NAT FOR ENVELOPED VIRUSES

In the EU, it is mandatory to test plasma pools for HCV by NAT. This requirement is based on the long window period of HCV-infection and the high levels of virus during this period. Recently some manufacturers of plasma-derived medicinal products have voluntarily introduced NAT testing of plasma pools and mini-pools for HIV and/or HBV nucleic acid. NAT as a method has advanced in terms of technology and standardisation. New methods of detection and quantitation have been introduced, and standard reference preparations of various viruses (HCV, HIV, HBV, parvovirus B19) are or will soon be in place. Thus, it is reasonable to reassess the need for additional NAT to improve the viral safety of plasma-derived medicinal products.

This session of the workshop examined the extent of testing by the Industry, the results of testing, the progress with the development of standard reference materials, experience with the technology, whether the extension of testing will result in increased safety of plasma-derived medicinal products, and implications for cellular blood components and plasma.

Questions to be addressed included:

What has been the experience of the detection of HIV and HBV positive donations by manufacturers who have introduced pool testing?

Would there be value in introducing pool/mini-pool testing for HBV DNA to detect infected donations not detected by the HBsAg test?

Are there NAT priorities for blood components?

What is the capability of minipool testing for detection of a single infectious donation, especially for HBV?

5.1 Reference Standards

The first HIV-standard for NAT was described by H. Holmes. The standard was established in October 1999 and is based on an HIV-1 subtype B virus-positive plasmapheresis donation. The concentration of the standard is 100,000 IU/vial/ml and it is available from NIBSC. NIBSC is also co-ordinating a study, involving about 25 laboratories, to calibrate seven working reagents against the 1st international HIV-standard. The results are expected to be available in December 2000.

HIV-1 shows great sequence diversity and many subtypes exist. SoGAT (the WHO International Working Group on the Standardisation of Genomic Amplification Techniques for the Virological Safety Testing of Blood and Blood Products) has recommended preparation of a subtype panel. Preliminary characterisation of this panel has shown that subtypes A-F are generally well amplified in all assays tested whereas subtypes G-H, groups N and O show less optimal amplification with certain assays.

An International Standard for HBV was established in 1999. It has a concentration of 10^6 IU/ml and each vial contains 5×10^5 IU.

5.2 Experiences with NAT testing for HIV, HCV and HBV

A. Gröner presented the experience with NAT testing for HIV (primarily HIV-1), HCV and HBV on behalf of the PPTA Viral Safety Group. Experience from testing of over 10 million donations had shown a detection of reactive donations per 100,000 donations of 1.3, 8.5 and 0.4, respectively for HBV, HCV and HIV. (These data include donations from applicant donors and one or more positive donations per donor.)

Data were also presented using HIV repository panels and from identified seroconverting donors to show that HIV-RNA testing of pools can be more sensitive than the HIV-antigen test currently required in the USA.

HBV-DNA was also detected in specimens earlier than HBsAg. When testing single donations, the HBV NAT test was positive approximately 15-32 days earlier than the HBsAg test during the initial phase of infection.

It was concluded by PPTA that NAT testing for HIV-RNA and HBV-DNA is technically feasible utilising the same pooling strategy as for HCV. HBV NAT test has to be developed further (sensitivity, specificity etc.) before its application for routine testing.

T. Krusius, representing the European Blood Alliance (EBA), presented the key issues from the EFPA/NIBSC Workshop on NAT held in May 2000.

The potential additional benefit of testing manufacturing plasma pools for HIV and HBV is very limited since plasma-derived medicinal products have a high level of assurance of viral safety for enveloped viruses through several complementary approaches including the incorporation of effective inactivation/removal steps in manufacturing processes.

In the blood component setting, HCV RNA testing is most commonly done although some collection centres are screening for HIV RNA and HBV DNA. NAT testing of donor samples in mini-pools is demanding due to the large number of samples, the lack of automation, the time needed for testing, insufficiently robust methods, relatively high percentage of invalid test results, and the need for well-trained technicians. These factors are particularly significant for platelet products because of their short shelf life. In order to detect HBV and HIV in individual donations, samples have to be tested in smaller pools than for HCV due to the lower level of viral nucleic acid present. While the risk of transfusion transmitted infections by blood components after implementation of NAT is extremely small, a transmission of HCV RNA has been reported (*Schüttler, 2000*).

In EU countries, the projected yield from NAT testing of donations from voluntary non-remunerated donors is very limited based on data reported by EBA and PPTA (*Müller-Breitkreutz, 2000*). In the case of HIV, approximately 0.22 NAT positive, antibody negative donations per 1,000,000 donations from repeat donors, and in the case of HCV and HBV, approximately 1.0 NAT positive donation per 1,000,000 donations from repeat donors are detected. The incidence of HCV RNA positive, antibody negative donors found by minipool screening has been somewhat smaller than expected from risk calculations. This may be partly due to the "eclipse" period of infection when no viraemia is detected in the blood.

N. Lelie presented results comparing various commercial HIV NAT tests using two different genotypes of HIV (B and E). There were some differences between the tests but generally all tests were performing well with both genotypes. NAT testing was superior to antigen testing in detecting positive samples during the window period.

5.3 Conclusions on NAT testing for enveloped viruses

What has been the experience of detection of HIV and HBV positive donations by manufacturers who have introduced pool testing?

The relative value of NAT testing for the detection of HIV and HBV depends on the epidemiology of the viruses in the population tested.

Would there be value in introducing pool/mini-pool testing for HBV DNA to detect infected donations not detected by the HBsAg test?

There have been reports of HBV variants with mutations in the "a" determinant of HBsAg, which may compromise detection of HBsAg by current assays. However, the presence of these mutants is extremely rare, and although HBV NAT tests are technically feasible and have been implemented by some manufacturers, there is no necessity for a general recommendation to introduce pool/mini-pool testing at present.

Are there NAT priorities for blood components?

The opinion of EBA is that the first priority is to implement HCV NAT testing as a pre-release requirement for blood components.

What is the capability of minipool testing for detection of a single infectious donation, especially for HBV?

Smaller mini-pools and more sensitive NAT tests are needed for HIV and HBV than for HCV because of the lower levels of viral nucleic acid to be detected.

6. TESTING METHODOLOGIES FOR NON-ENVELOPED VIRUSES (HAV AND PARVOVIRUS B19) INCLUDING NAT AND ANTIBODY TESTING

The two important non-enveloped viruses that can be transmitted by certain plasma-derived medicinal products, HAV and parvovirus B19, differ in their characteristics: the frequency of infection and the observed viral load tend to be low for HAV and high for parvovirus B19. Most adults have antibodies to parvovirus B19 whereas the prevalence of antibodies against HAV is decreasing in Europe as the epidemiology of HAV changes. This means that different strategies may have to be applied to ensure safety with respect to these viruses. The purpose of this session was to gather information on the extent of testing for parvovirus B19 and HAV in the industry, the results of testing, standardisation, and experience with the technology, including logistics and pitfalls. Important issues included any evidence of increased safety of plasma-derived medicinal products with these tests, the effect on supply of plasma and any implications for blood components. The following specific questions were posed:

Hepatitis A

Would there be value in introducing pool/mini-pool testing for hepatitis A when the manufacturing process has no/limited capacity for inactivation /removal of such viruses (e.g. immunoglobulins and S/D treated plasma)?

Parvovirus B19

Would there be value in introducing a general recommendation for pool/mini-pool testing for plasma-derived products?

Is a limit test to avoid the highest level of virus in pools acceptable?

Should priority be given to introducing pool/minipool testing for products at particular risk of transmitting parvovirus B19 (e.g. coagulation factors without effective inactivation/removal steps, S/D treated plasma)?

Should anti-D immunoglobulin be considered as a special case in view of its administration to a risk group for parvovirus B19 infection?

Are any actions taken/planned with respect to parvovirus B19 for blood components administered to risk groups?

Antibody testing

Would it be possible and feasible to set minimum levels for protective antibodies when the manufacturing process has no/limited capacity for inactivation removal of non-enveloped viruses (e.g. immunoglobulin products and solvent/detergent treated plasma)?

6.1 Non-enveloped viruses as plasma product contaminants and the human infectious dose

H. Willkommen presented the results of testing pools and products for parvovirus B19 DNA. Over 350 industrial plasma pools were tested and approximately 60% of pools were found positive ($\geq 10^3$ geq/ml), around 30% of these pools had levels above 10^6 geq/ml and less than 5% of pools had levels above 10^8 geq/ml. Ninety-one batches of 7 Factor VIII products were tested for parvovirus B19 DNA and 87% were found positive. Levels up to 10^7 geq/ml were detected. Approximately 70% of Factor IX batches tested (62 batches of 3 products) were found positive with levels up to 10^7 geq/ml. In the case of prothrombin complex products (43 batches/3 products), 88% were found positive with some batches (14%) containing $>10^7$ geq/ml. Parvovirus B19 DNA is seldom detected in batches of albumin, antithrombin and anti-D immunoglobulin and, when detected, the levels are usually low.

Levels of parvovirus B19 DNA in batches of final products were compared with the levels in the corresponding plasma pools to estimate "reduction factors". In a few cases parvovirus B19 DNA was detected in the final product when only low levels were present in the starting pools. It was postulated that this might be due to carry-over from a previous production batch with a higher level of

contamination. It is not known whether parvovirus B19 DNA detected in the final product corresponds to infective virus.

Testing of solvent/detergent treated plasma showed 23% of batches parvovirus B19 positive (66 batches tested) in the period 1997-98 and 13% positive (63 batches tested) in 2000. Levels up to 10^8 geq/ml were detected. The content of parvovirus B19 antibodies found was 47 ± 11 IU/ml (15 batches).

Transmissions of HAV have been observed with coagulation factors. In a transmission episode in Germany in 1997, the HAV RNA concentration in the plasma pool was only 6×10^2 geq/ml and in the FVIII product 3×10^2 geq/ml. The titre in the plasma donor was approx. 10^6 geq/ml (Chudy, 1999). The viral concentration in the asymptomatic phase of infection is of the order of 10^4-10^5 pfu/ml (equivalent to approximately $8x10^5$-$8x10^6$ HAV particles/ml) (Bower, 2000).

M. Chudy described the use of information from the HAV transmission incident described above to estimate the possible human infectious dose. The lowest amount of the Factor VIII batch transfused to a patient that resulted in transmission of HAV was 4,000 units. Thus from the known titre of HAV RNA in the batch, the infectious dose was calculated to be approximately 1.2×10^4 geq.

Similarly, information from HCV transmissions by fresh frozen plasma, from a donor in the window phase of HCV infection, was used to estimate the HCV RNA infectious dose. The minimum HCV RNA titre in the plasma donor that resulted in HCV transmission was >80 geq/ml (<400 geq/ml). The recipient received a transfusion of 540 ml corresponding to a minimal infectious dose of 4.3×10^4 geq.

6.2 Methodological aspects of antibody testing

The presence of protective antibodies to parvovirus B19 and HAV contributes to the viral safety of immunoglobulins and S/D treated plasma. Methodological aspects of antibody testing were addressed by G. Schäffner. Intravenous immunoglobulins (unmodified products) and their plasma pools and anti-D immunoglobulin products were tested for antibodies to parvovirus B19 and HAV. The variability in antibody levels seen was due in part to assay variability and partly to variability in the antibody level in the different products. In the case of parvovirus B19, antibody levels in plasma pools were similar in all the pools tested. However, the intravenous immunoglobulin products differed in the level of parvovirus B19 antibody present.

Comparison of results for HAV antibody testing by the Paul Ehrlich Institut and a manufacturer, using the same test kit, showed significantly different results indicating that both intra-laboratory and inter-laboratory validation of methods is important.

6.3 Reference standards

The work to establish an International Standard for parvovirus B19 NAT assays was described by J. Saldanha. Four candidate materials were tested in 26 laboratories from 14 countries, including control, industrial, diagnostic and academic laboratories. All NAT tests used were in-house tests. From the results obtained, candidate AA is proposed to be suitable as the International Standard. The proposed potency of the sample is 10^6 IU/ml. The ratio of IU:genome equivalents is 1:0.6-0.8. The report and proposal will be considered by WHO at its October 2000 meeting. (Post-meeting note: The International Standard for parvovirus B19 DNA was established in October 2000.)

6.4 Experiences with NAT testing for HAV and parvovirus B19

NAT testing for parvovirus B19 DNA in plasma pools has been initiated by some manufacturers. Members of PPTA have adopted a voluntary strategy to introduce testing as a means to eliminate donations with a high parvovirus B19 burden and limit the potential parvovirus B19 load in plasma pools for manufacture. Strategies for testing plasma minipools for parvovirus B19 DNA were described by H. Igel and B. Flan.

Both manufacturers use a cut-off value for the level of parvovirus B19 DNA since it is not feasible to completely remove parvovirus B19 DNA positive material because of the frequency of positive donations.

H. Igel described a strategy of testing minipools of 512 samples. The limit has been set at approx. 10^4 geq/ml, and all minipools above that are rejected. Looking at minipools over a one-year period (March 99-April 2000), about 4% contained > 10^4 geq/ml. Where possible, the positive donations were

identified and the number of donations rejected was 0.5/1000 donations. Prior to the introduction of this screening, 11% of plasma pools for manufacture had parvovirus B19 DNA levels $>10^4$ geq/ml. Significant reductions in the viral loads in manufacturing pools are achieved by this approach. The anti-parvovirus B19-antibody concentration in plasma pools (10-30 IU/ml) remained unaltered following the introduction of this NAT screening strategy.

B. Flan described a strategy of testing plasma mini-pools of maximum 100 donations for parvovirus B19 DNA by NAT. If the 100 donation pool is positive, sub-pools of maximum 50 donations are tested. All positive sub-pools of 50 donations are discarded. Samples of manufacturing pools are tested by the same method. The qualitative assay has a sensitivity of 10^3-10^4 copies/ml (95% hit rate). In the collaborative study to establish the International Standard for parvovirus B19 DNA, approximately 5×10^4 geq/ml of the proposed standard were detected using this assay. This qualitative testing excludes donations that contain $\geq 10^6$geq/ml of parvovirus B19 DNA and, by calculation, this results in manufacturing pools (2,800 l) containing ≤100 geq/ml.

Testing has been in place for more than 4 years. During this time the average frequency of detection of parvovirus B19 positives has been 1/6,170 donations (~1/3,600 donors) and an average of 0.81% of mini-pools were positive. The maximum frequency has been 1/1,400 donation (~1/820 donors) during a spring epidemic. Viral load was measured by a quantitative assay in 100 consecutive positive mini-pools of maximum 50 donations between August and December 1997. These mini-pools contained between 10^2-10^{11} copies/ml which corresponds to a maximum of $5x10^{12}$ copies/ml at the donation level.

This testing strategy gives a significant reduction in the viral load in manufacturing pools. It is used as a complementary strategy to viral inactivation/removal steps in manufacturing processes. There have been no pharmacovigilance reports of parvovirus B19 conversions associated with plasma-derived products manufactured from tested plasma.

The European Blood Alliance view is that NAT testing for all blood donations is not warranted for blood components. Since the incidence of parvovirus B19 infections is high, parvovirus B19 NAT testing would have a major impact on the complexity of testing of mini-pools and availability of blood components as well as on costs. For blood components, a simpler approach would be to use blood components from parvovirus B19 antibody positive blood donors for risk groups for parvovirus B19 infection (e.g. immunocompromised patients and parvovirus B19 sero-negative pregnant women). The advantage of this approach is that testing of blood donors does not have to be repeated and that in many geographical regions about half of the donors are seropositive.

6.5 Conclusions on testing methodologies for non-enveloped viruses (HAV and parvovirus B19) including NAT and antibody testing

Would there be value in introducing pool/mini-pool testing for hepatitis A when the manufacturing process has no/limited capacity for inactivation /removal of such viruses (e.g. immunoglobulins and S/D treated plasma)?

The value of HAV NAT is questionable since low levels of HAV contamination in plasma pools (~10^2 geq/ml) have been associated with contaminated products. This may be difficult to detect by routine screening.

Parvovirus B19

Would there be value in introducing a general recommendation for pool/mini-pool testing for plasma-derived products?

Is a limit test to avoid the highest level of virus in pools acceptable?

Information has been gathered concerning parvovirus B19 DNA levels and antibody concentrations in plasma pools and products, and on reduction factors achieved during manufacturing processes. NAT testing can be used to reduce the viral load in the starting material and the introduction of testing does not alter the parvovirus B19 antibody content of plasma pools. (Post meeting note: An International Standard for parvovirus B19 DNA was established in October 2000.)

Some manufacturers are already applying a plasma pool limit test for parvovirus B19. In principle, a limit test for parvovirus B19 DNA is acceptable in order to avoid too great a loss of plasma. While

establishing a limit for parvovirus B19 DNA in the starting plasma pool will diminish the viral load challenging the manufacturing process, it cannot be assumed that this will automatically assure that the final product will not transmit parvovirus B19. This will depend upon the capacity of the manufacturing process to inactivate/remove virus and the effectiveness of sanitisation procedures. The content of antibody to parvovirus B19 DNA will also be relevant in the case of immunoglobulins and solvent/detergent treated plasma. Research into effective concentrations of neutralising parvovirus B19 antibodies would be valuable in this respect.

Should priority be given to introducing pool/minipool testing for products at particular risk of transmitting parvovirus B19 (e.g. coagulation factors without effective inactivation/removal steps, solvent/detergent treated plasma)?

Solvent/detergent treated plasma has been reported to transmit parvovirus B19 and, therefore, the introduction of a limit for parvovirus B19 DNA is expected to be beneficial given the presence of protective antibodies in the plasma. Coagulation factors have also transmitted parvovirus B19 and a limit for parvovirus B19 DNA in the plasma pools would be a complementary measure to inactivation/removal steps in the manufacturing process.

Should anti-D immunoglobulin be considered as a special case in view of its administration to a risk group for parvovirus B19 infection?

There have been no reports of transmission of parvovirus B19 by immunoglobulins presumably due to the presence of protective antibodies. However, as anti-D immunoglobulin is administered to a risk group for parvovirus B19 infection, additional measures to ensure safety with regard to parvovirus B19 transmission should be considered. Since anti-D immunoglobulin is manufactured from a small dedicated donor panel, the use of plasma from anti-B19-positive donors or from donations tested for parvovirus B19 DNA is a possible option.

Are any actions taken/planned with respect to parvovirus B19 for blood components administered to risk groups?

The approach favoured by EBA would be the preparation of components from parvovirus B19 antibody positive donors.

Antibody testing

Would it be possible and feasible to set minimum levels for protective antibodies when the manufacturing process has no/limited capacity for inactivation removal of non-enveloped viruses (e.g. immunoglobulin products and solvent/detergent treated plasma)?

In the case of immunoglobulins and solvent/detergent treated plasma, the presence of protective antibodies in plasma pools contributes to viral safety. This raises the question of whether limits for antibodies should be set. There are currently insufficient data on the levels of antibodies needed for product safety and further research is needed into immune-neutralisation mechanisms. In addition, appropriate assays would need to be defined and standards established.

7. FINAL SUMMING UP BY SPEAKERS

The speakers from the session on "Viral safety of the current plasma-derived medicinal products" and representatives of PPTA, EPFA and EBA were invited to sum up their views on the viral safety of plasma-derived medicinal products with particular focus on non-enveloped viruses. Questions to be addressed included:

Taking into account the current viral safety and state of the art for the manufacture of plasma-derived medicinal products, is there a need to recommend

a) New virus inactivation/removal steps for manufacturing processes

b) The extension of pool/mini-pool testing by NAT?

If extension of NAT testing is recommended, which viruses have priority? How would this impact on blood components?

J. Robertson concluded that promising information had been presented to the workshop particularly in the area of inactivation/removal of non-enveloped viruses. Such inactivation/removal steps are also

important to deal with unknown viruses. The introduction of NAT testing for parvovirus B19 is to be welcomed as a means to avoid high titre pools. To what extent this introduction of a limit on the level of parvovirus B19 DNA in the pools will increase safety of final plasma-derived medicinal products is currently unclear.

While he understood the approach of targeting patients at risk, as a virologist, his aim would be to strive to inactivate or remove any virus that causes infection.

In the case of parvovirus B19, W-D. Ludwig emphasised the importance of correctly defining the risk, assessing the impact of new measures, and finding the right solutions. For blood components, he was in agreement with the view of T. Krusius that the best approach would be to have products from antibody positive donors available for the clearly defined risk populations.

K. Pappenheim was encouraged by the many strategies for viral safety that are being employed and developed. More education of patients and doctors is needed about the choice of products for special patient groups. In the case of parvovirus B19, there was a need to focus on at risk groups and provide an appropriate strategy for their treatment. Parvovirus B19 was also a marker for the potential of products to transmit unknown viruses and inactivation/removal procedures were needed to address this.

For patients there is always the issue of supply as well as safety. Within the EU, the supply situation is good but this was not the case worldwide and the EHC supported increased access to products. There is always concern that safety measures might reduce supply and add to cost.

Concluding for EPPIC, T. Wallington indicated that the biggest current concern for primary immunodeficiency patients was supply. There is an increasing use of immunoglobulin and demand keeps rising. The generic approach to viral inactivation/removal was very interesting and the progress reported at the Workshop was heartening. In the case of immunoglobulins there is the added protection provided by the specific antibodies in the preparations.

T. Krusius concluded for the EBA. Taking into account the probability of a window period donation in voluntary and non-remunerated blood donors in Europe and the virus inactivation and removal capacity of the current state of the art manufacture for plasma-derived medicinal products, there is no need to extend mandatory NAT testing in minipools in geographical regions with low incidence of HIV and HBV infections. Extension of NAT minipool testing would increase the costs and complexity of testing, increase the probability of errors, and in the blood transfusion setting, slow down the availability of blood components for transfusion.

T. Snape summarised the position of EPFA. The association encompassed a diversity of manufacturers collecting donations from voluntary, unpaid donors and mostly fractionating nationally sourced blood. In considering approaches to viral safety the importance of Good Manufacturing Practice should not be forgotten.

Considering the individual viruses, the prevalence of HCV in the donor population is low and HCV is more significant for cellular components. EPFA members have introduced or are introducing HCV testing for cellular components. Taking into account the very low projected yield of NAT testing of donations from voluntary non-remunerated donors and the very high viral inactivation/removal factors for manufacturing processes, NAT testing for HIV and HBV is not needed for plasma-derived medicinal products. Some EPFA member organisations have voluntarily introduced or may voluntarily introduce NAT testing for HIV and HBV for reasons of further reducing the very low residual risk of virus transmission for blood components that do not have viral inactivation/removal steps.

The clinical impact of known non-enveloped viruses (HAV, B19) is comparatively small. Nevertheless, most manufacturers are targeting the inclusion, for every product, of at least one process step effective for inactivation/removal of non-enveloped viruses. The presence of protective antibodies in some products contributes to viral safety provided that an adequate level of protective antibodies is maintained. In addition, this approach would need further knowledge about the level of antibodies that are protective and the development/use of appropriate assay methods. The clinical benefit of NAT testing for HAV for plasma-derived medicinal products is uncertain due to the need for very sensitive assays to detect the low but infective levels of HAV.

In the case of parvovirus B19, the principal approach is the development and introduction of inactivation/removal processes. Because of the high viral loads that can challenge manufacturing processes, a strategy of using NAT to control the maximum load on the process may be useful as a complementary approach.

C. Kempf, concluding for PPTA, stated that there is no "magic bullet" to inactivate/remove non-enveloped viruses. All the known techniques are product, process and virus specific. Inactivation and removal processes can impact on product characteristics and yield. Industry experience shows that NAT reduces the potential risk of viral transmission by plasma derived products.

8. CONCLUDING REMARKS FROM THE RAPPORTEUR P. KURKI

The viral safety of plasma-derived medicinal products, including epidemiology of viral infections and developments in technology, are kept under review by the CPMP and its Biotechnology Working Party. Optimal viral safety is achieved through a combination of approaches with the objective to optimise "viral quality" without adversely affecting the clinical safety and efficacy or supply of plasma-derived medicinal products. In this context, specific tests for individual viruses can be seen as complementary to viral inactivation/removal techniques which have a broader range of action. This Workshop has provided the opportunity to bring together the latest information on technical developments and consider their potential clinical benefit for plasma-derived medicinal products.

The information from this Workshop will form the basis for conclusions and recommendations from the Biotechnology Working Party and the Blood Products Working Group to the CPMP on the viral safety of plasma-derived medicinal products. (See Addendum to the report.)

In addition, the Workshop identified several issues related to clinical practice that could have an impact on safety at the patient level, such as education of physicians and patients, optimum use of plasma-derived medicinal products, use of alternative products and vaccination.

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WORKSHOP ON VIRAL SAFETY OF PLASMA-DERIVED MEDICINAL PRODUCTS WITH PARTICULAR FOCUS ON NON-ENVELOPED VIRUSES

Wednesday 13 September, 10am to 4.30pm
7 Westferry Circus, Canary Wharf, E14 4HB
EMEA, 4th floor (Meeting Room B)

List of Participants

Chairman:	**G. Vicari** Ministero della Sanità, Medicines Evaluation and Pharmacovigilance Department, Italy	
Rapporteur	**P. Kurki** National Agency for Medicines Pharmacological Department, Finland	
Speakers:	**M. Chudy** Paul-Ehrlich Institut, Germany	EPFA/LFB
	E-G. Graf PALL	**A. Gröner** PPTA/Aventis Behring
		H. Igel
	C. Kempf PPTA/ZLB Bioplasma AG EPFA/CLB/Sanquin	**T. Krusius** EBA/Finnish Red Cross BTS
		W. Ludwig Robert Rössle Klinik Humboldt University, Germany
	H. Lutz Millipore	EPFA/SNBTS
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	J. Robertson NIBSC, UK	**J. Saldanha** NIBSC, UK
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	I. Van Hoegen PPTA Europe	**C. Waller**
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ADDENDUM
London, 28 March 2001
CPMP/BWP/BPWG/93/01

Conclusions and recommendations of the Biotechnology Working Party (BWP) and Ad-Hoc Working Group on Blood Products (BPWG)

There is considerable progress in the development of virus inactivation/removal methods and in nucleic acid amplification technology (NAT) for blood-borne viruses. The current Note for Guidance on Plasma Derived Medicinal Products is still valid (CPMP/BWP/269/95, rev 3). However, the rapid progress in the field requires a regular review of regulatory guidance.

When new measures to improve viral safety are considered, their impact on efficacy, overall safety and supply should be evaluated.

The development of improved inactivation/removal steps for non-enveloped viruses remains an objective for all plasma-derived medicinal products.

Whenever NAT test methods are used, they should be validated with the appropriate International Standards. (International standards are available for HCV RNA, HIV RNA, HBV DNA and parvovirus B19 DNA.)

Information on the effectiveness of the process for the inactivation/removal of viruses should be included/updated in the SPC of all plasma derived medicinal products in line with the BPWG Core SPC recommendations. Descriptions of the viral inactivation/removal procedures and information about testing beyond the mandatory requirements should not be included in the SPC.

Taking into consideration the information presented at the EMEA Workshop on Viral Safety of Plasma-Derived Medicinal Products with Particular Focus on Non-Enveloped Viruses (13 September 2000), the BWP and BPWG reached the following specific conclusions and recommendations.

- Methods have been established for HAV inactivation/removal for albumin and some coagulation factor products. Effective inactivation/removal steps for HAV need to be implemented for all coagulation factor products. Where possible, these methods should be applied to other plasma-derived medicinal products.
- The current methods to inactivate/remove HAV are generally not suitable for immunoglobulins and solvent/detergent-treated plasma. Transmission of HAV has not been reported with these types of products, presumably due to the presence of protective antibodies. The contribution of antibodies to the viral safety of products with respect to HAV and parvovirus B19 needs to be further investigated.

  Nevertheless, the development of effective inactivation/removal steps is an objective.
- Parvovirus B19 is difficult to inactivate/remove by current methods. However, some approaches can achieve limited inactivation/removal of parvoviruses depending on the product and process conditions.
- NAT testing of minipools for parvovirus B19 can be used to reduce the viral load in manufacturing pools. It is considered as a complementary measure to inactivation/removal steps in the manufacturing process. The impact of these complementary measures on the overall viral safety of individual products has to be demonstrated.
- The introduction of inactivation/removal steps in the manufacturing process and/or complementary measures such as NAT to improve viral safety with respect to parvovirus B19 should be prioritised for the following products:
  - Coagulation factors and solvent/detergent-treated plasma since they have been reported to transmit parvovirus B19
  - Anti-D Immunoglobulin since it is used in a high risk patient group.

- HCV NAT testing of plasma pools is in place. The need for additional NAT tests is dependent on a number of considerations including the epidemiological situation among the blood/plasma donors, the length of the window phase and the viral load, as well as the ability of the manufacturing process to inactivate/remove viruses.

  From the regulatory viewpoint, the current approaches to viral safety of plasma-derived medicinal products with respect to HIV and HBV are considered adequate and HIV and HBV NAT testing of plasma pools are not a requirement at the present time. Nevertheless, it is recognised that in certain circumstances NAT testing for HIV and HBV could contribute to the selection of the donor population.

- Due to the very low levels of viraemia that may still result in transmission of infection, NAT testing of plasma pools for HAV RNA is currently considered to be of limited value in improving product safety.

ANNEX 7 to CPMP March 2001
Press Release
London, 28 March 2001
CPMP/BWP/450/01

EMEA EXPERT MEETING ON HUMAN TSEs AND MEDICINAL PRODUCTS DERIVED FROM HUMAN BLOOD AND PLASMA

1 December 2000

SUMMARY REPORT

1. Introduction

An EMEA Expert Workshop was held in May 2000 to provide an update on the latest information on human transmissible spongiform encephalopathies (TSEs) in relation to plasma-derived medicinal products[1]. A further EMEA Expert Meeting was held on 1 December 2000 to consider:

- The new information that had become available since the May expert Workshop and, in particular, the preliminary report of transmission of the BSE agent to a sheep by transfusion of blood from an experimentally infected sheep[2].
- Whether the new information affects the conclusions or the May Expert Workshop.
- Whether or not country-based exclusion of donors (e.g. time spent in UK) should be considered as a precautionary measure.

2. New information

Transmission of BSE by blood transfusion in a sheep

C. Bostock clarified aspects of the study that make it very likely that the reported transmission is a true transmission, most probably of BSE. Strain typing in mice will be used to confirm the result but this will take some time (1-2 years). No further transmissions had been seen. However, it was too early to reach conclusions since the incubation period in sheep challenged with BSE by the intravenous route is not known.

It is expected that further experiments will be set up to look at how infectivity partitions and the effect of leucodepletion. The design of such experiments was being considered including whether sheep blood will behave similarly to human blood on leucodepletion filters.

Update from R. Will

At the time of the meeting, there were 87 definite and probable cases of vCJD in the UK (45 male, 42 female), with a mean age of 29 (mean age at onset 28), and an age range of 14-74 years. The youngest case was aged 12 at onset. All cases genotyped so far are methionine homozygotes.

The case in a 74 year old is the first case found in this older age group. There is some concern that vCJD in the elderly may not be recognised. However in this case, the geriatrician recognised that the symptoms were very atypical with respect to other forms of dementia in this age group and deterioration was rapid.

Outside the UK, there are 3 cases in France and 1 case in Ireland. (The Irish case had spent time in the UK.)

There is still an upward trend in the number of UK cases.

There is no evidence of transmission of vCJD by blood or blood components or plasma-derived medicinal products. However, as it is an emerging disease, it is still too early to conclude on the absence of risk.

3. Does the new information affect the conclusions of the May Expert Workshop?

The European Commission's Scientific Steering Committee had concluded that the preliminary information from the sheep transfusion experiment reported in the Houston *et al* paper "does not change the basis of risk assessment" but "it does reinforce the substance of previous opinions by the scientific committees"[3]. In line with this opinion, the EMEA Expert Meeting considered that the conclusions of the May Expert Workshop were still valid and discussed further precautionary measures that might be considered.

It was suggested that further donor exclusion measures might be considered such as neurosurgery and permanent (rather than temporary) exclusion of donors who previously received transfusions. The percentage of donors lost by exclusion of donors who have received transfusions may be significant (approx. 5% loss in France when this measure was introduced). This suggestion would be drawn to the attention of the European Commission (Health and Consumer Protection Directorate-General) for its consideration.

The CPMP recommendation[4] to avoid using, as an excipient, albumin derived from plasma collected within countries where a number of cases of vCJD have occurred was endorsed. It was again clarified that this was an issue of supply rather than safety. A country that has had cases of vCJD has the potential to have further cases and this could involve a blood donor. 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. A recall could affect complete stocks of a product and create severe shortages.

Since this is a supply issue, care is needed that supply problems are not created when it becomes advisable to make a transition to an alternative source of albumin for use as an excipient (e.g. in the case of albumin derived from plasma collected in France).

The lymphoreticular involvement seen with vCJD and the finding that TSE infectivity, when present in blood of experimentally infected animals, has been found mainly in the buffy coat, leads to the consideration of leucodepletion as a precautionary measure. There is currently insufficient information to establish whether leucodepletion will be effective and further research is needed[1,5]. In the meantime, leucoreduction steps (filtration/centrifugation) as soon as possible after collection of blood/plasma could be considered as a precautionary measure to reduce the white blood cells contaminating the starting plasma.

4. Country-based donor exclusions

The meeting considered the following questions:

Whether or not exclusion of donors who have spent some time in the UK should be considered as a precautionary measure?

Information from donor surveys within Member States and written contributions from associations involved in blood collection and plasma fractionation were taken into account in the discussion.

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.

Germany and Italy have decided to follow the exclusion criterion used by the US and Canada (i.e. exclusion of donors who have stayed for a cumulative period of 6 months or more in the UK between 1980 and the end of 1996). Germany chose the 6 month period as it was considered impractical to set different criteria. This exclusion criterion can be implemented in Germany and Italy without too great a loss of donors. There will be some countries where this measure could not be sustained because of the loss of donors.

Member States considering such a measure need to make a benefit/risk analysis. The evaluation done in France on this issue indicates the factors that need to be taken into account[6]. These include the pattern of travel to the UK and the endogenous risk from BSE within the Member State and from meat imports. The viral risks introduced when moving to first-time donors also needs to be considered.

The benefit of such an exclusion measure is difficult to evaluate. Available information indicates that the pattern of travel to the UK is different in the EU compared to the USA. Also the risk of donors having been exposed to BSE risk in their country of origin has to be recognised.

The benefit of such a measure should be balanced against the risk of shortage in blood supply (transfusion as well as plasma-derived medicinal products).

It was noted that different decisions in different Member States have the potential to create difficulties with the movement of plasma-derived medicinal products between Member States.

Whether or not blood/plasma that is collected in countries that have cases of vCJD should continue to be used in the manufacture of medicinal products derived from human blood and plasma?

France indicated that a detailed evaluation is underway and the result would be presented to ministers very soon (see postscript to this report).

It was agreed that a similar evaluation should be undertaken in any country where cases of vCJD are found. (In this respect, it should be noted that CJD cases will be reported according to the country of residence at the time of disease onset.)

It has to be recognised that any precautionary measure based on population exclusion can be expected to have a large impact on the overall supply of plasma-derived medicinal products. Such measures could become progressively impracticable should the epidemiology of vCJD change.

Whether or not exclusion of donors who have spent some time in France should be considered as a precautionary measure?

The group decided that it should await the decision of France on whether it would continue fractionating from French plasma.

Whether or not blood/plasma that is collected in countries that have the potential for vCJD development should continue to be used in the manufacture of medicinal products derived from human blood and plasma?

The group considered that there was a difference between a potential risk and confirmation of that risk with the occurrence of cases.

Postscript

The latest recommendations from France on the analysis of risk of transmission of vCJD by blood and its derivatives was published in December[7]. France has decided that plasma collected in France can continue to be used for fractionation. Leucodepletion is recommended as a precautionary measure. Donors who have spent more than a cumulative period of 12 months in the UK between 1980 and end of 1996 will be excluded from donation.

References

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2. Houston F, Foster JD, Chong A, Hunter N, Bostock CJ. Transmission of BSE by blood transfusion in sheep. Lancet 2000; 356:999-1000.

3. 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 26-27 October 2000. http://europa.eu.int/comm/food/fs/sc/ssc/out143_en.pdf

4. CPMP Position Statement on "New variant CJD and plasma-derived medicinal products", February 1998, CPMP/201/98. http://www.emea.eu.int/pdfs/human/press/pos/020198en.pdf

5. "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, 16 February 2000.http://europa.eu.int/comm/food/fs/sc/scmp/out28_en.pdf

6. "Revision of measures to minimise the risk of TSE transmission via blood products", Report of expert group convened under the aegis of the Agence Française de Sécurité Sanitaire des Produits de Santé (AFSSaPS) and the Etablissement Français du Sang (EFS), February 2000. http://afssaps.sante.fr

7. "Analysis of the risk of transmission of new variant Creutzfeldt-Jakob disease by blood and its derivatives", Recommendations of expert group convened at the initiative of AFSSaPS, 11 December 2000. http://afssaps.sante.fr

DOCUMENTS PREPARED BY THE CPMP WORKING PARTIES AND AD-HOC GROUPS ADOPTED DURING THE March 2001 CPMP MEETING

QUALITY WORKING PARTY

Reference number	Document	Status
CPMP/QWP/2845/00	Note for guidance on Limitations to the use of ethylene oxide in the manufacture of medicinal products	Adopted in March 2001

AD HOC WORKING GROUP ON BLOOD PRODUCTS

Reference number	Document	Status
CPMP/BPWG/283/00	Note for guidance on the Clinical investigation of human normal immunoglobulin for subcutaneous and intramuscular use	Released in March 2001 for 6 months' consultation
CPMP/BPWG/282/00	Core SPC for Human normal immunoglobulin for subcutaneous and intramuscular use	Released in March 2001 for 6 months' consultation

AD HOC WORKING GROUP ON ANTI HIV MEDICINAL PRODUCTS

Reference number	Document	Status
CPMP/602/95 rev. 2	Points to consider on the Assessment of an anti HIV medicinal product	Adopted in March 2001

Report from the meeting held on 26 March 2001

General issues

Applications under Annex II of Regulation EC No 541/95 in Mutual Recognition Procedure

The MRFG reconfirmed that for situations where the marketing authorisation of the original product has been granted through independent national procedures, it is acceptable to follow the same procedure for a line extension of that medicinal product. See "Member States recommendations for applications under Annex II of Regulation (EC) No 541/95 in Mutual Recognition Procedures", September 1999.

Relevance of patents for refusing an application for a marketing authorisation

The MRFG discussed the issue of whether an existing patent protection could give grounds for refusal of granting a marketing authorisation for a medicinal product. The European Commission has confirmed, by referring to articles 21 and 5 of Directive 65/65/EEC that this issue is out of the scope of Community pharmaceutical legislation. Therefore, whether an applicant preparing or filing an application for a marketing authorisation for a medicinal product infringes on a relevant patent in force, is not to be considered when issuing a marketing authorisation.

Organisation of the Heads of Agencies website

The MRFG noted the comments received from the trade associations (AESGP, EFPIA, EGA) proposing improvements in the quality and content of information published on the Heads of Agencies Website. Based on these comments, Sweden is reviewing the Website.

Best Practice Guide on Breakout Sessions

The MRFG adopted an updated (and renamed) version of the *Best Practice Guide on Breakout Sessions*, which will be published on the Heads of Agencies website.

Member States Standard Operating Procedure on Urgent Safety Restrictions

The MRFG adopted an updated version of the *SOP on Urgent Safety Restrictions*, which will be published on the Heads of Agencies Website.

Communication between the MRFG and the interested parties in relation to preparation of MRFG guidance documents published on the Heads of Agencies website

The MRFG noted that the interested parties wish to be consulted before finalising guidance documents, such as SOPs and recommendations, prepared by the MRFG. The MRFG decided that, from now on, once final draft documents adopted by the MRFG are available, some would be released for a short consultation period to the interested parties. The decision on which documents that should follow this approach will be taken by the MRFG on a case by case basis.

Sub-group on harmonisation of SPCs

The third sub-group meeting on harmonisation of SPCs was held on 26 March 2001. The Group agreed on a list of medicinal products to be taken forward and adopted the following timetable for the project:

2 April 2001:	Request for information regarding SPCs (focusing on sections 4.1 to 4.4) to be sent to the concerned Marketing Authorisation Holders and trade associations
23 April 2001:	Selection of co-ordinating Member States
1 May 2001:	Response from the Marketing Authorisation Holders
21 May 2001:	Assessment of responses by co-ordinator Member States
28 May 2001:	Final selection of medicinal products for the first wave of harmonisation through article 11 procedures
12–13 June 2001:	Final list of medicinal products to the Heads of Agencies meeting for adoption

The above mentioned procedure will be co-ordinated by Sweden.

Meeting schedule

The next MRFG meeting will be held on 23 April 2001.

Mutual Recognition Monitoring

The MRFG noted that 35 new mutual recognition procedures were finalised during the month of February 2001, as well as 115 type I and 38 type II variations.

The status as of 28 February 2001 of procedures under mutual recognition is as follows:

Year	Procedures from New applications finalised	Procedures from New applications in process	Procedures from Type I variations finalised	Procedures from Type I variations pending	Procedures from Type II variations finalised	Procedures from Type II variations pending	Arbitrations referred to CPMP
2001	45	81	174	60	59	182	--

40 new procedures (regarding 73 products) started in February 2001. The categories of these procedures are as follows:

1 procedure was not classified by the RMS.

7 new active substances (first authorisation in the European Community after RMS approval).

4 known active substances (already authorised in at least one member state), including **1** repeat use and **1** multiple applications.

26 abridged applications including **7** multiple applications and **2** repeat use.

3 line extension applications.

The new procedures started this month relate to 7 full dossiers, 27 generics, 3 bibliographic applications and 2 for different use, route or dose.

The procedures consisted of 37 chemical substances and 2 biological vaccines[1].

36 of these procedures were prescription-only medicinal products in the reference Member State and 3 were Non-prescription (including OTC) medicinal product[2].

1. As considered by RMS.
2. In this category products are classified as prescription-only or Non-prescription (OTC) products when the RMS has approved them accordingly, although the legal status is not part of the Mutual Recognition Procedure.

Reference Member State (number of products involved in the procedure)	Number of CMSs involved in the procedure
DE (1)	12
DE (1)	11
DE (1)	8
DE (8)	9
DE (4)	1
DK (4)	1
DK (4)	11
DK (2)	5
DK (2)	7
DK (2)	1
DK (2)	1
DK (2)	1
DK (2)	6
DK (2)	1
DK (1)	4
DK (1)	14
DK (2)	2
DK (3)	2
FI (1)	1
FI (1)	9
FI (1)	10
FI (1)	10
FI (1)	5
FI (1)	5
FI (1)	4
FI (1)	7
FR (1)	4
FR (1)	10
NL (1)	1
NL (1)	16
NL (1)	8
SE (3)	1
UK (2)	1
UK (2)	13
UK (1)	3
UK (2)	16
UK (4)	5
UK (2)	1
UK (1)	2
UK (1)	16

All documents mentioned in this press release can be found at the MRFG website at the European Medicines Authorities Windows under the heading SOP.

Information on the above mentioned issues can be obtained by the presiding chair of the MRFG:

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Alternatively, you could visit the MRFG web site at the EUROPEAN NATIONAL MEDICINES AUTHORITIES WINDOW: **http://heads.medagencies.org/**