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BIOTECHNOLOGY/PHARMACY WORKING PARTY

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GRO-C

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BWP

BLOOD PRODUCTS AND NON-ENVELOPED VIRUSES

INTRODUCTION

Plasma-derived coagulation factors are of particular concern in terms of viral transmission because there is no species barrier to human viruses. Historically methods of production have been designed to preserve biological activity rather than ensure viral safety of the products. Viruses which have been transmitted include HIV, HBV and HepCV, all of which are enveloped viruses.

Methods of production have been altered to cope with the possible presence of these enveloped viruses, e.g. by the addition of pasteurisation or solvent/detergent methods. However, it has always been recognised that the latter method is not effective against non-enveloped viruses, but was adopted because of its high yields, high potency of resulting coagulation factors and efficacy against enveloped viruses.

FACTOR VIII

Recently it has been recognised that hepatitis A (caused by a non-enveloped virus) has been transmitted by one Factor VIII product subject to a solvent/detergent process (Octavi). This brings into focus the problem of non-enveloped viruses being transmitted by blood products. Such viruses also include Parvo virus B19 which is pathogenic in certain groups of recipients. There may be other unknown viruses which may be found to be of importance in the future. Therefore, following the case of Octavi, the CPMP asked the Biotechnology/Pharmacy Working Party to examine other blood products with respect to hepatitis A virus and other non-enveloped viruses.

Most current production processes have a very limited capacity to remove and/or inactivate non-enveloped viruses.

However, for products subject to pasteurisation or other validated heat treatments, the results of inactivation studies suggest that these methods of treatment will kill not only enveloped but also non-enveloped viruses. These methods of virus inactivation result in a broad spectrum of virus safety.

Bearing in mind the problem of hepatitis A transmission, manufacturers should be asked to introduce a step which also inactivates non-enveloped viruses, which is capable of a greater than 4-5 log reduction factor for relevant and model viruses. The step should be validated.

In the interim, solvent/detergent-treated Factor VIII (without pasteurisation) should only be administered to patients who have been immunised against or shown to be otherwise immune to hepatitis A given the added protection of this category of patients against HAV transmission. The recommendation has already been made that patients receiving Factor VIII should be immunised with the vaccine. It should be noted that currently hepatitis A vaccine is not licensed for use in patients under 16 years of age in all Member States.

It should be stressed that recombinant Factor VIII products are free of these particular blood-borne viruses.

OTHER COAGULATION FACTORS (FACTOR VII, IX, XIII, AT-III, FIBA (Factor VIII inhibitor bypass activity))

These other plasma-derived coagulation factors present the same problems as the plasma-derived Factor VIII. For products which rely solely on a solvent/detergent step to inactivate viruses, manufacturers should introduce a further validated virus-inactivation step as for Factor VIII above.

Apart from Factor VIII, there are currently no other recombinant coagulation factors marketed.

INTRAVENOUS IMMUNOGLOBULINS

Sporadic cases of hepatitis B and C have been associated with the use of intravenous immunoglobulins. Production methods have been designed to prevent aggregation and complement activation. Some of the techniques used for these purposes have been shown to reduce viral titre to some degree. Certain products are additionally subject to a specific virus-inactivation step, e.g. solvent-detergent step or pasteurisation.

The production process should be validated to demonstrate the removal or inactivation of relevant and model viruses. One step should be shown to be capable of removing at least 4 logs of viral infectivity.

INTRAMUSCULAR IMMUNOGLOBULINS AND ALBUMIN

Intramuscular immunoglobulins and albumin have not been implicated in the transmission of viral infection. However, in accordance with directive 89/381/EEC and the CPMP guidelines, validation studies for virus removal/inactivation should be provided.