MSBT, JANUARY 1996

REPORT FOR INFORMATION FROM THE BIOLOGICALS/BIOTECHNOLOGY UNIT OF THE MCA

INTRAMUSCULAR IMMUNOGLOBULINS

1. Introduction

The purpose of this paper is to summarise the events that have led to the current EU regulatory position on intramuscular immunoglobulins i.e. the objective to introduce validated, effective viral inactivation/removal steps into the manufacturing processes and the request for nucleic acid amplification tests for HCV RNA for intramuscular immunoglobulins that do not have such steps.

2. The Events Leading to the Current Regulatory Position

2.1. In late 1993 and in 1994 there were viral transmissions associated with certain plasma-derived products. (Hepatitis A with Factor VIII produced by a particular manufacturing procedure, hepatitis C with an intravenous immunoglobulin (Gammagard) and hepatitis B from a German-licensed partially purified factor IX fraction.) The UK had not licensed any of these products.

2.2 This led the European Committee on Proprietary Medicinal Products (CPMP) and its Biotechnology Working Party to review the factors important for the viral safety of plasma-derived products. (A separate sub-group was formed to discuss clinical aspects.)

2.3 In November 1994 at Langen, Germany, an open workshop and a closed meeting of the Biotechnology Working Party were held to specifically discuss viral inactivation/removal procedures for plasma-derived products and their validation. Prior to this meeting, the Biologicals Unit of the MCA had detailed consultations with experts from CSM and its Biologicals Sub-Committee and informal consultation with representatives of the manufacturers of plasma-derived products. This allowed the Biologicals Unit to present a sound, scientifically-based UK position to the meeting in Langen.

2.4 Appendix 1 is an extract from the UK position presented at the Langen meeting. Essentially, this stated that:

i) It would be premature to introduce genome amplification methods.

ii) It was desirable to introduce validated, effective steps for the inactivation/removal of viruses into the manufacturing procedures for intramuscular immunoglobulins. This had a lower priority than intravenous products, it was important to ensure that any additional step contributed to the net safety of the product and progress to this goal should not jeopardise supply of essential specific immunoglobulins.

2.5 The European plasma fractionator organisations (EPFA/EAPPI) presented a position paper to CPMP at the Langen meeting. This was consistent with the UK view on intramuscular immunoglobulins and stated:

"c) For Intramuscular IgGs, there is no record of transmission of virus - but then little follow-up data exists. Evidence of freedom from transmission would be of value (e.g. from look-back studies). The introduction of a defined VE step should be an objective for all manufacturers."

(NB. VE = virus elimination)

2.6 Following the Langen meeting, the CPMP Biotechnology Working Party revised the CPMP guideline on "Medicinal Products derived from Human Blood and Plasma". This revision includes the objective of introducing validated, effective steps for the inactivation/removal of viruses into the manufacturing procedures for intramuscular immunoglobulins. (Appendix 2 contains the relevant extracts from the draft guideline.) This document is now at the stage of final revision following the consultation phase. Following MSBT comments, the UK have requested that the guideline makes it clear that, in the case of intramuscular immunoglobulins, the addition of an effective viral inactivation/removal step should be made particularly cautiously ensuring that the net safety of the product is not adversely affected by the change.

2.7 The US FDA had licensed Gammagard, the intravenous immunoglobulin that transmitted hepatitis C in 1994. While acknowledging that the transmission was a result of a weak process that did not incorporate a validated, effective inactivation/removal step for enveloped viruses, they also postulated that the introduction of screening of donations for antibodies to hepatitis C by second generation tests had adversely affected viral safety. This view has been widely disseminated by the FDA at international meetings and they are now stating that they have experimental data to support this. Inevitably, by this emphasis, the FDA also threw doubts on the continued safety of intramuscular immunoglobulins. Consequently, the FDA introduced a requirement for both intravenous and intramuscular immunoglobulin products, without specific viral inactivation/removal steps, to be tested by a nucleic acid amplification method for HCV RNA.

2.8 The CPMP Biotechnology Working Party took a different view on the Gammagard incident. They emphasised the importance of validated, effective steps for the inactivation/removal of enveloped viruses in the manufacturing process for intravenous immunoglobulins. The role of screening of donations for antibodies to hepatitis C is to reduce the virus load presented to the process. Nevertheless, the widely known views and consequent action of the FDA meant that the CPMP had to consider whether to take similar action. The majority view was set out in the CPMP document "Intramuscular Immunoglobulins: nucleic acid amplification tests for HCV RNA detection." CPMP/117/95. (See Appendix 3.) One of the conclusions of this document was that "For products where valid removal/inactivation steps are absent, nucleic acid amplification tests for HCV RNA, preferably in plasma pools, are requested. IM immunoglobulins from a positive pool should not be made available unless warranted by supply requirements."

2.9 Following this CPMP decision, the Biologicals Unit of the MCA consulted the CSM and its Biologicals Sub-Committee on issues surrounding the decision. In the event of a HCV RNA positive pool being found and where a supply problem exists, there is a mechanism for the CSM to take a risk/benefit judgement and to decide on whether or not the product may be supplied. CSM made a positive decision not to prejudge such a situation. CSM did not wish to

tie its hands but wished to consider any such situation on a case-by-case basis. Informally, the Biologicals Unit have emphasised to manufacturers supplying the UK market that they should try to avoid, if practicable, the risk of getting a positive pool. (It should be noted in this context that one commercial manufacturer has already introduced testing by nucleic acid amplification methods for specific viruses as an in-process control.)

2.10 In parallel to discussions at CSM, the Biologicals Unit of MCA held informal discussions with affected manufacturers supplying IM immunoglobulins to the UK market and with NIBSC (the control laboratory). This identified the need for a working reagent to test sensitivity of assays. This view was presented jointly by MCA and NIBSC to the Biotechnology Working Party in July 1995. The resulting CPMP document (see Appendix 4) stated that the implementation date for the introduction of nucleic acid amplification tests for HCV RNA detection, in the case of IM immunoglobulins without a validated, effective inactivation/removal step for enveloped viruses, would be decided once exploratory work on the use of a potential working reagent was available. The results of this work will be reviewed by the CPMP Biotechnology Working Party in early 1996 with a view to setting an implementation date.

3. Summary and Conclusions

3.1 Intramuscular immunoglobulins have a good viral safety record although the reasons for this are not understood. Nevertheless, the addition of validated, effective steps for the inactivation/removal of viruses is a desirable objective which has been agreed by CPMP and is reflected in the guidance issued by them.

3.2 CPMP have decided that testing of plasma pools for HCV RNA by nucleic acid amplification methods will be required, from a date to be decided, for intramuscular immunoglobulins without validated, effective steps for the inactivation/removal of enveloped viruses. The implementation date will be set once the results of exploratory work with a potential working reagent to check the sensitivity of methods are reviewed and found satisfactory. Manufacturers have been informally advised by the Biologicals Unit of MCA to take any practicable steps to avoid a "positive" result for HCV RNA on a plasma pool. CSM have indicated that they would wish to consider any positive result on a case-by-case basis.