SPECIFIC COMMENTS ON PRODUCT LICENCE VARIATIONS FOR KRYOBULIN, PROTHROMPLEX AND FEIBA

1. The pharmacist argued that the spiking studies carried out on a small scale needed to be validated to results on a production scale. Conditions may not be identical and inactivation may be affected. It was noted that the residual moisture in freeze drying produced in the laboratory tests and in production differed which may affect inactivation of the virus. It was accepted that a production batch could not be spiked. The exact conditions of the spiking including formulation of the powder should be detailed and validated against the production batch. Ranges for all variables should be given as a small change in composition, residual moisture content etc can have an effect on inactivation. The virus was in a buffer solution for the spiking experiments. Had we considered for example that this may have an effect on inactivation? The DHSS needed assurance that for a given set of variables inactivation was achieved when they were all at their limits.

2. Measurement of residual moisture content during the production process was a major factor which concerned Mr. Sloggem and unless we measure the relative humidity together with time, temperature and pressure throughout the vapour process he will not be satisfied that the production process is properly controlled. He says that probes are available from a number of companies and are used in ethylene oxide sterilisation. The equilibrium relative humidity can be measured in the vapour phase, it is not necessary to have the probe in the powder. It must be shown that the relative humidity stays the same throughout the procedure and we have not shown this. If it varies it will have to be established what effect this has on inactivation of the virus.

3. The conditioning of the powder should be monitored more closely. Relative humidity probes are available to go into bulk powders. As we have various limits on the composition of the powder, will the amount of water bound to the powder vary. 95% of the water in the production process is bound to the powder and 5% is in the atmosphere. Concern was expressed as to whether the 95% bound to the powder remains constant even if the powder composition changes with the stated limits. Specific activity varies between 1.25 and 2.5 (i.e. twofold). Is the albumin content included? Concern was expressed that large variations in specific activity could cause variations in inactivation. Moisture content of the powder can be 7-8% and he wants to know if this variance has any effect on inactivation. Variation in times but not temperature were given for the conditioning of the powder.

4. There was a lack of model virus data in the application. Data for suitable viruses should be submitted with the reasons why these were chosen.

5. Inactivation data - We should define the kinetics of the curve on various batches. If steam 3 inactivates 6 log steps in 3 hours, it can obviously not be assumed that the correlation is linear and this has now been shown to be true. McDougal in U.S.A. characterises the virus under different conditions. D and Z values are given in terms of temperature and relative humidity. (Ref. J.S. McDougal, L.S. Martin, S.P Cort, Vol. 76, Aug. 85 pp875-77 - Thermal Inactivation of the Aquired Immunodeficiency Virus with Specific Reference to Anti Haemophilic a Factor). We should give D and Z values.

Powder

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6. HBsAg cases - Mannucci study - Three cases from one batch indicates a clustering effect. Could there possibly be a concentration of the virus. This would indicate that the process is perhaps not in control. The chimpanzee data was considered but is regarded as not particularly reliable. We should at least have argued the case as to how the patients may have acquired the virus. No mention was given of the age of the patients or their location. It was stated that certain areas of Italy are high risk areas but they assumed the patients were from Milan.

7. Details of ancillary materials used in the production were not given at the time of variation with their specifications and limits, e.g. just specify Nacl B.P. 1980. There is a draft E.P. monograph for Aprotinin which is approved but not implemented. Is Aprotinin coming through in the final product? If substances do not comply with a monograph, say why.

8. On going stability data and fiducial limits for coagulation factors on storage should be given.

9. The antibody used to assess the molecular integrity of the STIM 3 product should also be tried on the dry heat treated product.

10. Data Sheet / Pack Insert / Labelling - need to be changed to conform to B.P. and E.P. - this needs checking to clarify what is required.

11. To say that the vapour treatment inactivates 6 log steps is not correct as part of the inactivation is due to the lyophilisation process - this should be clearly stated. How much is due to the lyophilisation and will this value alter with changing conditions.

12. Data required on the HIV testing kits - new regulations. (Copy attached).

13. The statement on Hepatitis and HIV risk in the pack insert is not acceptable.

14. Ethanol fractionation stage - this needs to be characterised. Will this contribute to reducing virus titre.

15. Excess pressure of 190 mbars is a misleading statement as pressure is made up of thermal expansion, nitrogen, water vapour.

16. The statement "Did not have detectable virus" was not acceptable.

17. Effect of freeze drying on particle size and following on from this, possible variation in uptake of water due to changes in particle size.

18. The DHSS were interested to hear that the Steam 3 process had been evolved after looking at other treatments. A discussion on how we arrived at this method and the treatment methods we looked at with the reasons for not selecting them would be very useful. Any data on work carried out in heating in solution with stabilisers would be interesting especially if we have data to show that the stabilisers protect virus.

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19. We should keep away from statements in data sheets and pack inserts which are regarded as promotional.

20. Expert reports will be required with an abridged application for Kryobulin. This should be prepared taking into account guidelines on expert reports together with MAL 2 and MAL 41. It should be informative, cross referenced to the data and give a good overall critical appraisal of the product, not merely a summary.

21. B.P. title - we cannot use B.P. title in combination with Kryobulin. This comment was simply made due to the fact that the names were typed close together - there was never any intention of doing this.

22. Adverse reactions - A low incidence of reactions is experienced. This is not an acceptable statement.

23. Reverse transcriptase is now regarded as less sensitive than immunoassay. Cell culture may miss infectivity if assay is not capable of picking up a particular strain - we should comment on this.

PROTHROMPLEX AND FEIBA

1. Why is 1 hour at 80°C felt necessary in addition to the 10 hours at 60°C. Why was this particular time and temperature chosen for this additional treatment. Is there a break between the two steam treatment procedures.

2. D and Z values required as for Kryobulin.

3. Heat up, hold and cool down conditions should be accurately detailed.

4. General comments similar to Kryobulin.

5. Different Product Licence numbers for Prothromplex indicate different formulations - state why this is so.

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PJC/BMC