VISIT TO VIENNA - 15-18 JUNE 1989

The following is a summary of the comments made:

1. VIRAL INACTIVATION

Dr. Noel Barrett put forward the clearest explanation I have yet heard and Dr. Thomas was greatly impressed and felt that this was precisely the information we should have submitted.

Dr. Thomas pointed out that our vapour heating method is unique, not being dry heat and not being wet heat and not being heat with a solvent detergent. He further added that 5 log steps in one step is a recommendation not a requirement.

The claim that one manufacturer had claimed a 10 log step reduction was queried by Dr. Barrett because of the impracticability of producing a concentration of this strength, as a starting volume of several thousand litres would be necessary.

Dr. Barrett said that the original idea of 5 log steps probably arose from U.S. workers who said that 10^5 was probably the worst example of infected plasma hence it was suggested that a one step lowering of 10^5 should be attempted.

Dr. Barrett uses an initial stength of 10^7 or even 10^8 which on dilution is lowered to 10^6 which is further reduced by lyophilisation to 10^3. It is impossible to re-infect material after the lyophilisation stage because a homogenous mixture cannot be prepared. He can however provide information on inactivation kinetics which makes it clear that there is no live virus after 5 hours. The remaining 5 hours of heating are carried out as an additional safety measure. He recommended that we should present this information, at the same time stressing that the moisture level of 7% to 8% is thoroughly controlled and also make as much use of the current Mannucci study on non A, non B hepatitis which uses STIM 3 Kryobulin.

Should we be asked why Prothromplex and Feiba are heated for a further period at a higher temperature there is a perfectly straight forward explanation.

Prior to the availability of HIV virus these products were spiked with model viruses and were, as an added safety measure, heated to such extent as the product would stand.

Licences in many countries were obtained on this basis and to avoid re-licensing the company preferred to continue with these methods, despite the fact that 60°C for 10 hours is adequate.

Dr. Thomas stressed the need for applications to be made as soon as possible whilst the door is still ajar from the Plasminogen Licence which represents a breakthrough as far as vapour heated products are concerned.

The question of inactivation of Parvo virus arose. This virus is heat stable but it is not known as to what clinical significance it has.

We are testing for HIV II but not for HTLV I because this virus is cell related hence whole blood or cells must be tested. Plasma products would not be contaminated with HTVL I.

2. PROBLEMS CONCERNING USE OF BOVINE MATERIALS

a) Human Thrombin

As far as BSE is concerned, it is the intention to overcome this by converting to human from bovine thrombin. This will, of course, in turn require adequate proof of the inactivation of human viruses, but will remove the problem of bovine sensitisation.

b) Aprotinin

It is believed unlikely that any question of bovine sensitisation will arise concerning the use of this product. As far as BSE is concerned we will either ensure that our present suppliers fully meet the guidelines or, alternatively, seek material from Bayer of an equivalent standard to Trasylol.

3. PROTEIN C

a) It appears that Dr. Eibl has over-ridden the intention for the Addenbrooke Trial to be the first. This was on the grounds that our material should be used in adults before being used in sick children. Progress is being made in treating a homozygote lady in Germany using 500 u twice weekly (half life 8 hours). The patient is making progress having previously been unsuccessfully treated with Heparin and Coumarin.

The time may come when prior to surgery all patients will be tested for levels of ATIII, Protein C and Protein S.

Both Dr. Thomas and Professor Preston believe that a market exists for all products and documentation for a full licence should be completed at the earliest.

I have already informed Addenbrooke's of the delay expressing the hope that we might have the documentation and material ready for an August start.

b) Maximum effort is being made to produce ATIII. It is already licensed in Germany and Austria and the licence is pending in Italy.

Its use is favoured in Europe but not at this stage in US or UK.

It is used for control of severe septicaemia.

c) Low Molecular Weight Heparin

Dr. Thomas made it clear that this is the Heparin of the future, and expressed the hope that we would extend our interest in the product

Dr. Schwarz promised to attempt re-negotiation of our agreement so that Immuno Ltd. could sell the product in this country.

d) Vaccines

Dr. Barrett detailed the products which we hope to have available in the future in the vaccine field. These being Hepatitis B and AIDS.

4. Dr. Thomas had a discussion with Dr. Lang concerning our Factor VIII standards. This was carried out whilst I was escorting Professor Preston around the Fractionation Unit.

Dr. Thomas explained that 2 years ago the Immuno view was that plasma from 100 donors could be regarded as a normal standard. However, as the plasma is being rapidly withdrawn from the same donors, this premise is not reliable. More recently, however, Dr. Lang has calibrated our material in accordance with international standard. Dr. Lang has, in fact, been instrumental in persuading other European manufacturers to do likewise.

We may be presented with a problem in that Yvonne Stirling at Northwick Park Hospital has been carrying out a large study using our material. Dr. Lang is checking back and will inform us of the numbers of batches which are in accordance with international standard thus indicating those which are not. We must then check as to which batches Yvonne Stirling has had whereon the matter should be discussed with her.

5. Recombinant Factor VIII

a) Opinions were divided on whether clinicians would accept this new product regardless of price.

One reason for doubt was that recombinant material itself might contain viruses of some kind.

Plasma derived material is now very much safer than hitherto and it is believed that both will be used for many years during which time recombinant material will be offered at reduced prices whereon more will be used.

b) Inhibitor formation is not thought to be a serious problem.

It is interesting to note that Immuno is increasing the number of plasmapheresis stations it owns in US and in Europe. It is necessary for us to sell plasma derived Factor VIII to keep a balance as many other plasma derived products cannot be made by recombinant methods.

GRO-C: Norman Berry