MEETING BETWEEN IMMUNO LTD/IMMUNO AG AND MCA HELD ON 8th OCTOBER 1991

Present:	Immuno Ltd.	P.J. Coombes R. Nicholson
	Immuno AG	Mrs. I. Diernhofer
	MCA:	Dr. J. Purves Mr. J. Sloggem Mrs. M. Dow

As agreed with Immuno AG a meeting was arranged with the MCA to discuss the problems experienced with our vapour treated licence applications.

We took the core points from the following letters received from the MCA as the basis for an Agenda for our discussion.

19th July 1991 - Application for variation of PL 02165/0021-22 - FEIBA

22nd July 1991 - Application for variation of PL 0215/0006-7 - PROTHROMPLEX

7th July 1991 - Application for a Product Licence - KRYOBULIN

The last meeting with the MCA on this subject was held on 12th August 1987 (Minutes attached) when similar topics were discussed.

It was stated at the beginning of the meeting that the MCA (Medicines Control Agency) were not happy with the vapour treatment method of inactivation, principally because they were not assured of the consistency of the process and that it was sufficiently controlled or characterised. They regarded 'Dry Heat' as one end of the spectrum and 'Pasteurisation' as the other. They felt 'Vapour Heating' was somewhere between these two extremes but they were not sure of its relative position. It was up to the company to convince the MCA that the method was closer to pasteurisation than dry heat.

viral inactivation

FEIBA

There were no concerns given by the MCA in their letter relating to the Clinical Section of the licence variation or any adverse comments concerning the risk/benefit ratio.

Point 2

They were informed that the vapour heat cycle was monitored continuously by Dew Point measurement through each batch run. The MCA felt that this was not made clear in the data submitted. Our method of manufacture states that the Dew Point is only measured in the last 15 minutes. They felt it should be measured throughout the cycle and appropriate in process control values set.

At the last meeting in 1987 they had asked for Relative Humidity recorders to be fitted to the pressure vessel and they recommended a manufacturer. For whatever reason, Immuno decided to use Dew Point measurement and not Reltive Humidity. However, the MCA felt that Dew Point measurement should be acceptable but they would like the equivalent values given in Relative Humidity again throughout the cycle.

They are very interested in the 1½ hours build up to the 80°C cycle after the initial 8½ hours at 60°C. They would like to be assured that this build up phase is well controlled and the measurements of Dew Pointc are reproducible. We give a temperature range for the Dew Point of 39°C ± 3°. They would like to know what this variability means in relation to Relative Humidity.

How reproducible is this stage?

We need to reconsider Dew Point specification. Can it be tighter than 36° - 42°C and also tighter for the 80°C phase.

Point 4

A) There was great concern that the variability of the composition of different batches of product could have an effect on the inactivation ~~data~~. For example this is the declared tolerances on composition of bulk powder:

capacity.

590 - 810 mg/g protein
40 - 110 mg/g sodium citrate
80 - 220 mg/g sodium chloride
70 - 80 mg/g water

The vapour heating process needs to be more closely defined and controlled as the formulation variation affects the water content of the product which in turn affects the water exposure to viruses.

It would be a major advantage if we could tighten the specification. They would feel more comfortable with the situation if such variations were not permissible. They want to be assured that virus is inactivated at extremes of composition. They appreciate the problem in obtaining inactivation data for batches at both extremes of the specification. However, they feel that each major parameter should be validated. In pasteurisation they feel that the problem of variable composition is not so important.

Not nec. if test extreme values

A significant number of consecutive batches should be examined and composition recorded. The QC specifications can then be reviewed and tightened if possible. The associated reduction in variability should help our case in proving consistency.

Model virus studies must be carried out for different compositions. They showed interest in the data Mrs. Diernhofer presented on the experimental pressure vessel and felt we were working on the right lines. However, the Dew Point of some batches was around 41°C which was at the highest limit. They felt that any work of this type should also be carried out at the lowest Dew Point to make it more of a challenge.

What happens to the Sindbis inactivation at 36°C Dew Point?

Look for worst case scenario.

Inactivation data generally should be carried out at the lowest water content i.e. 7% or below. You must look at the set of conditions for your inactivation which are least favourable.

It was suggested that we look closely at the composition of the batches given to the 4 Mannucci patients to determine whether the various parameters in the process were at the extremes, particularly for water content - Dew Point measurement. Were those early batches controlled properly?

B) It is not expected that viral inactivation studies be repeated because of the EC guidance. The existing data should merely be re presented, taking the guidelines into consideration and filling any 'holes' as necessary (which may entail some additional work).

As far as the EEC Guidelines are concerned they felt that although they only came into effect on 15th August 1991 the main points of concern had been detailed to us in our meeting in 1987 and we should have provided the information. The EC guidance mainly reflected UK input and could not be regarded as new.

C) It was suggested by Dr. Purves that it was up to each company to closely follow the new EEC Guidelines. If the company were concerned about the interpretation of the Guidelines then they should prepare a comprehensive paper and submit it to the CPMP Biotechnology Working Party in Brussels, of which Dr. Purves is a member. The company may then be invited to discuss the report with the Working Party. He felt that this may be preferable to seeking the views of each member state. However, Dr. Purves did say that if we wish to present a similar paper to him he would discuss it with Mr. Sloggem and a representative of NIBSC. (I expect it would be Dr. Minor, Head of Microbiology) and after consideration they would be prepared to arrange a meeting with the company to discuss the paper.

One assumes that we would have to give consideration to the points they have made in Part 1 of our Agenda.

D) Mrs. Diernhofer showed the MCA some initial data on the parallel control assays to demonstrate the integrity of the virus titre in the presence of product - they raised no objection to this data but stated it should be present for all batches used in viral inactivation studies to discount toxicity of the product.

Dilution 1:20 why

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A general discussion was held on the wealth of Clinical data available on our coagulation concentrates. As expected, they felt that this did not compensate for an inactivation method which may not be controlled.

The Clinical data may hold up for some considerable time but if a set of circumstances occur as a result of the poor control of the method then you may see a breakthrough, ie viral transmission. They feel that good Clinical data should be based on sound Pharmaceutical practice. If you start to see 'cracks' in the production process then the Clinical data will collapse.

They made the point that they refused to licence a specific factor concentrate in recent years which had very good Clinical data and where they were not convinced about the inactivation process. The product subsequently caused HIV conversion and they were proven correct. (Would this have been one of the Biotest product?).

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Point 5

They would not give a total figure for the number of log steps inactivation which they felt was suitable. It is no longer as simple as adding the inactivation of various stages together. The total data has to be looked at as a package. The kinetics of the virus inactivation is very important. They indicated that extrapolation of inactivation data was not valid as presented by Mrs. Diernhofer.

Not really.

A) HIV was not the most hardy virus - you should use as high a titre as possible. They agree that this is difficult to achieve but it appeared as though they may have seen data with a higher titre. If we cannot achieve a titre $> 10^7$ then we should provide justification for this level.

B) Why do we dilute virus 1:20 - we should explain. Why not 1:10 we may be able to see an extra log step of inactivation.

C) Freeze drying is identified as a separate inactivation step. How reproducible is this stage? Our submitted data would indicate variable inactivation rates during freeze drying. Is the inactivation data valid at different compositions?

D) They suggested we consider using a hardy virus - perhaps Vaccinia to see what inactivation occurs throughout the whole cycle with the expectation that some virus will remain at the end of the process.

E) With Kryobulin at 180 minutes the HIV titre is 10^1 at, 300 minutes it is below detection limit - what happens between these points? How do we interpret this information?

F) The kinetics of the virus inactivation must be looked at very carefully.

G) Why do we use Sindbis? Inactivation for Kryobulin after 2 hours is below the level of detection. What happens in the second half of the inactivation at 60°C. Presumably any hardy virus will be killed by the 1 hour at 80°C. Can we offer evidence for this. What is happening at the transition phase, particularly in relation to Relative Humidity.

H) How does the second half of the inactivation graph alter with the variability of the process.

They drew our attention to the following points which I recorded in the Minutes of our previous meeting with the MCA. (Ref. point 5, page 2, MCA meeting 12.8.87).

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 USA 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 Acquired Immunodeficiency Virus with Specific Reference to Anti Haemophilic Factor). We should give D and Z values.

We had not given any attention to their comments on this subject. They felt that we should consider D and Z values as per this paper.

Point 8 - (Not included in agenda)

Copies of all product literature should be provided. This refers to pack inserts, labels, packaging - not promotional material.

Point 9

A) This point was resolved - they require details of the kits used by Immuno to test for HIV and HBsAg. This includes methodology, evaluation of results, use of controls. This is already a requirement of all our licences and we have forwarded details of each new kit to NIBSC since 1987.

B) However, a further suggestion was that as we were required to test final product for anti HIV and the current tests were only licensed for plasma, we should perhaps validate our tests for final product to ensure there is no product interference in the assay.

PROTHROMPLEX

1) We explained the situation concerning the new Immunine and as I suspected it was made very clear that they would not accept a Licence Variation for this new product. We will require an Abridged Licence Application.

2) There are no definite rules governing whether you apply for a Variation or Abridge Licence. However, major production changes producing a different product as with Immunine could not be regarded as a Variation.

3) Any application for Immunine would have to take note of all the points made at the meeting concerning the vapour process.

4) They were not happy with the name Immunine and suggested that consideration should be given to a new name. It was felt that it gave the impression of an antibody absorbed concentrate. They also did not feel we could continue to call the product Prothromplex if it was a single IX concentrate.

5) If columns were used in the process attention should be given to usual problems of contamination, adequate sterilisation, viral dumping and fate of removed virus.

6) If the product could be shown to comply with the BP monograph and suitable in vivo recovery and half life data provided, then there would be no requirement for formal efficacy trials or data. If it does not comply with all the BP specifications then we should discuss points of variance.

7) We may also wish to discuss with BPC the formulation of a new monograph.

KRYOBULIN

Point 1

The Mannucci cases were still of concern, but they felt that we could have made a better presentation of all the data surrounding the Mannucci cases and relate them to the success of the International Safety Study.

If the Pharmaceutical data relating to the inactivation had been satisfactory, they may have been willing to look more favourably at the Clinical. As stated earlier for Feiba, good Clinical data and evidence of extensive use will not override concerns on the process.

Point 2

The Committee simply felt that after considering all the benefits of the product against the risks, the risk/benefit ratio was not favourable enough to grant a licence. This was a unanimous decision. There is no formula for the calculation of this ratio.

Point 4.2 BSE

We should clearly state that we cannot comply with the DHSS Guidelines with our reasons. We should state, however, that we have taken certain steps to reduce risks and itemise these. I mentioned that the EEC Guidelines simply state that the source material should be from a non infected country. They asked us to quote this Guideline in our data.

It is important that the cattle are not fed ruminant feed. Can we source material for aprotinin from Australia or New Zealand? They also asked if we obtained aprotinin from Bayer. This has recently been licensed in the UK for blood saving during major surgery and so they are obviously familiar and satisfied with this product.

It was thought that ruminent feed was not used in USA. However, evidence shows that this is not the case. We will probably see cases in the US in time.

Point 4.6

All significant and unusual ingredients used in the manufacturing process should have limits in the product specification, eg ATIII Heparin complex, Polyanion SP54.

Point 5.2

It was stated that they would expect to see a significant difference in viral inactivation between dry heat and vapour heat. 6 log steps would not be considered as they have experience of a product passing on HIV with this level of data.

REVIEW OF EEC PRODUCT LICENCES FOR BLOOD PRODUCTS - UK IMPLICATIONS

The EEC Guidelines state that the Extension Directives have to be made law in the individual states by 1st January 1992 and that all licences will have to be reviewed and new licences granted by 31st December 1992. The policy in UK will be to submit all the additional data by 31st March 1992. They feel that licences obtained from 1988/89 onwards should not cause any real problems. It is essential to have Expert Reports of very high quality. This will significantly reduce problems with the applications.

a) Data requirements likely to be similar to Abridged, ie full Part II with preclinical and clinical expert reports. Changes to Product Licences could be dealt with at the review. Any significant changes should, however, be highlighted. The data presented should obviously be updated and in compliance with the Notice to Applicants plus any other EC guidance which is relevant (eg viral inactivation).

b) HCV-Testing
European position: from 1993 onwards products released to the