Interoffice correspondence

TRAVENOL

Travenol Laboratories Ltd.,
Caxton Way, Thetford,
Norfolk, IP24 3SE, Great Britain
Telephone: Thetford (0842) 4581

to: See Distribution date: 2nd October, 1986

from: G. Taylor copies: See Copy Distribution

subject: D.H.S.S. MEETING 30TH SEPTEMBER - MONOCLONAL PURIFIED FACTOR VIII AND GAMMAGARD PRODUCT LICENCE APPLICATIONS

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D.H.S.S. Representatives

Dr. Francis Rotblat
Dr. John Purves

Travenol Representatives

Dr. Mark Philip
Ms. Gillian Taylor

Monoclonal Purified Factor VIII

Mark Philip reviewed the manufacturing process.

Comments were raised by Dr. Rotblat and Dr. Purves.

1. Pretesting

It is essential that we summarise very clearly the Travenol Philosophy of methods used to ensure the safety of blood donations used for this blood product - and all other blood products. (Gammagard included)

This should include details of H.I.V. method used, its sensitivity and controls.

A clear explanation and list of plasma donor centres and rationale behind choice of areas is essential in both Monoclonal Purified Factor VIII and Gammagard Licence applications.

NB Dr. Rotblat has worked in California in the field of Monoclonal Systems for many years. She has a good understanding of the process and the sourcing of blood in the U.S.A.

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2. Viral Inactivation

It is imperative to demonstrate that the inactivation process is as good as (if not better than) the heat treatment process. The emphasis should be on validation studies relating to the manufacturing process. It will not be acceptable to use the reverse transcriptase HTLV III measurements alone as there are superior methods of measurement, i.e. culturing the virus.

It will be necessary to demonstrate viral inactivation of "spiked" raw material.

3. Monoclonal antibody

- o Details of the preparation are essential including purity, specific activity of efficacy. Confirmation that Celltech use the "Mass Culture Technique" as opposed to the Mouse Ascites technique is required. (ACTION M. GRIFFITHS)
- o Evidence required to demonstrate Monoclonal antibody inhibits Factor VIII activity in situ.
- o Presence in F.P.S. should be confirmed and related to effacacy of product.

4. Albumin

Specification for Albumin required including donor selection and viral safety testing of plasma. Cross references to existing licences will be adequate if current licences are updated to include this information. (ACTION G. TAYLOR)

5. Quality of Product

Comparison with Factor VIII heat treated product is required in terms of Finished Product specification. All possible contaminants should be measured and included in the specification where necessary - in particular Ethylene Glycol.

6. Animal Studies

It is not envisaged that the animal studies would form a key part of the application due to the clinical data available and the fact that the product is a human blood product. Acute toxicity should be submitted, chronic toxicity is not essential. It was not felt necessary to carry out Neoantigenicity studies as long as clinicals were followed closely for neoantigenic reactions.

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7. Clinicals

It is essential that the Half Life and Recovery and Pharmacokinetic Data be available. Six non bleeding haemophiliacs in a cross-over study using monoclonal purified Factor VIII and Hemofil HT will be acceptable. Further clinical data is also required to demonstrate efficacy and safety.

Dr. Rotblat would be willing to accept a study in 20-30 patients that demonstrates the product stops bleeding after a single dose (Efficacy Study).

Follow up for this for 6-8 weeks would be sufficient for safety (to ensure no development of NANB hepatitis).

This would fit on with the planned study of existing haemophiliacs and it would not be necessary to wait for the completion of the whole study currently planned. After 8 week safety data is available a product licence submission could be made.

Clinical trial plans including the follow-up on the 20 haemophiliac patients and the planned viral safety study in virgin patients should be clearly described. Follow up data should be submitted on a regular basis, and, any unexpected results reported immediately.

8. Brand Name

The D.H.S.S. would prefer that we use a brand name which does not use an abbreviation i.e. Hemofil T etc.

GAMMAGARD

Gillian Taylor reviewed:

1. The manufacturing process and Finished Product Specification
2. Non Clinical studies and development of the product
3. Toxicity and safety clinical studies
4. Clinical studies completed and still be finished

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Comments were raised:

1. Manufacture process

o Quality of Product. The full manufacturing process should be validated with a study showing recovery after "spiking" cryoprecipitate with H.I.V.

The D.H.S.S. will be particularly interested in the alcohol contact phases and final purification with the Sephadex A-50.

2. Finished Product Specification

Wish to have in specification tests for:

- o HBsAg (full methods and validation)
- o H.I.V. by Western Blot method. This must be fully validated with controls. The N.I.B.S.C. will carry out this test on all batches as routine, but Travenol must give details of this test on several batches in Licence Application.
- o IGA limits should be as tight as possible.

3. Development of Product

Dr. Purves expressed interest in receiving full details of rationale behind product development and a historical account of why limits are tightened (IgA) and why certain levels are not measured in F.P.S. (IGE and antibodies titres). The D.H.S.S. will be perfectly happy with a F.P.S. with certain criteria not measured each time provided batch analysis in Licence application shows levels are consistent and reasons for not being carried out at F.P.S. are given,
i.e. no accurate test,
no need for test etc.

4. Toxicity/Safety Data

Seven day follow up on mice, rates and guinea pigs is adequate toxicity data for a blood product fractioned from human plasma.

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Dog Study, Vascular Irritant Study, Japanese Clinical Study and German clinical study should be included as General Safety data with Expert Summaries explaining their relevance.

5. Pharmacokinetic Data

Must be included data we have so far is adequate.

6. Clinical Studies

Full explanations of studies, rationale behind their instigation should be submitted. Two studies of 16-20 patients for P.I.D. and I.T.P. patients will be adequate to gain licence for these indications. These should be followed for some time.

Details must be given of all other studies being undertaken CLL, Mycloma etc. They do not consider Intravenous Gammaglobulin a proven treatment for thermal burns patients or underweight neonates and will require a good deal of data to convince them of these indications for use.

7. N.A.N.B./H.I.V.

- Dr. Rotblat is pleased with Travenol's response to these problems and would like to be informed of patients H.I.V./A.L.T. levels in the Licence Application. They feel quarterly updates will be satisfactory unless any problems arise. If this occurs they should be notified immediately.

- A warning statement will be required in the Data Sheet to the effect of:

  "Non A Non B risk from this product cannot be excluded".

  In the Expert Report they feel an explanation of "Company Philosopy" regarding N.A.N.B./H.I.V. research, development of new and better process, would aid their understanding of the application and speed its approval.

8. Submission Date

To speed an approval we should aim for an application in January 1987 to ensure a hearing at the March Sub-Committee Meeting.

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Any data we do not have at the moment must be initiated immediately to meet this date.

Maggie, please can I have the details of the induction phase of the I.T.P. trial and full details of the "spiking" study that was carried out. In addition could you send me the stability data on the product.

We shall need to do some validated Western Blot H.I.V. tests on batches at F.P.S. with controls etc.

Best Regards.

GRO-C

Gillian Taylor