MEMO

Discussions on May 20, 1986 and May 21, 1986

Present: Mr. Berry
Mr. Nicholson
Dr. Eibl (partly)
Dr. Habison (partly)
Dr. Schoppmann (partly)
Mrs. Kunschak (partly)
Dr. Jacobson (partly)
Dipl.Dolm. Diernhofer
Mag. Henninger

TISSEEL® KIT

As stated in the Section 21(3) letter of September 13, 1983 the DHSS was still not satisfied with the data submitted for our product license application. The 2 alternatives we have now are either to withdraw our product license application or to appeal to the Medicines Commission and ask for a hearing. (The Medicines Commission confines itself to the 3 main items of safety, efficacy, and quality.)

Since we have decided to go for an appeal we will have to provide the following data:

1. Clinical data to support our claim for the various indications (the authorities have not been willing to accept data on the deep-frozen sealant)

   We will now chose the indications on the basis of the following data:

   - Interim evaluation of US controlled clinical study covering 63 patients (on haemostasis)
   - Report by Mrs. Kunschak on marginal benefit and papers referred to in this report

- Papers available on lyophilised product

As a consequence a new draft pack insert will have to be prepared once a decision on the indications to be used will have been taken.

2. Data on bovine sensitisation

The following data have been collected so far:

- Statement by Prof. Schlag on 350 cases of repeated administrations of Tisseel® Kit with no anaphylactoid reactions observed
- Letter signed by Dr. Eibl on 400 cases of repeated administration of Tisseel® Kit with no allergic or anaphylactoid type reactions observed
- Letter signed by Dr. Eibl reporting on 3 occasions of allergic reactions following the application of more than 500,000 Kits
- Paper by Alter on "False positive tests for hepatitis-associated antigen in blood donors caused by antibodies to ruminant serum proteins"
- Paper by Cunningham-Rundles on "Dietary protein antigenemia in humoral immunodeficiency"

Based on the above data Immuno Ltd. will prepare a rationale which will be revised by Dr. Eibl.

In addition the preclinical data available on thrombin and aprotinin shall be submitted to the authorities.

3. Hepatitis / HTLV-III risk

A rationale should be prepared based on the following data and facts:

- Baumgarten study
- Scheele paper
- Panis paper
- Stark paper: Tisseel® Kit used selectively on 30 - 40 patients, no transmission of hepatitis despite theoretical possibility

- Case reports by Stark on each operation carried out, IMMUNO LTD. will ask for summary
- HTLV-III Ab, HBsAg, and ALT-screening on source material
- Heat treatment (including preclinical data on HTLV-III and model virus inactivation)
- Use of European plasma donations only
- Dose-related factors: very low doses, applied topically, not systemically

Due to all these measures and in particular the 3 studies which were carried out with the untreated product and in which still no case of hepatitis occurred, it seems to be justified to remove the restrictions originally requested for plasma donations (not more than 100 Austrian and/or German donors whose donations showed normal ALT values and proved to be free from HBsAg on 5 consecutive occcasions).

We should also state that although the transmission of hepatitis may be technically expected, it has never occured in x cases of application of Tisseel® Kit.

As to the pack insert we should include a warning like "Transmission of hepatitis has never been seen" (see statement in the B.P. under Albumin).

4. Animal data

The data included in the IND can be used. In addition, Mrs. Kunschak forwarded a number of recent publications to Mr. Berry and Mr. Nicholson.

A summary of all data available will have to be prepared.

The following additional items were discussed and clarified

1. Factor XIII

no inclusion of F XIII, leave everything as it is

2. HTLV-III testing on plasma pool

no

3. Medical devices

If the devices are contained in the packs containing the product it may perhaps not be necessary to have a DHSS number for the devices, but will be sufficient to provide some data. The situation has been checked but the above would in any case only apply to the Duploject, since neither the spray set nor the spray catheter are contained in the packs containing the product.

It would perhaps be worthwhile to find manufacturers who would be acceptable both to UK and US authorities, because the same problems may appear when a product license will be applied for in the USA.

ENDOBULIN

The questions posed in the letter dated July 11, 1986 were discussed as follows:

Question 1:

Data available:

- Statement by Prof. Eibl on clinical relevance
- Paper by Lefranc: "Familial Lack of IgG3 Subclasses"
- Comment on above paper by Dr. Bosch

Data required:

The comment prepared by Dr. Bosch on the Lefranc paper will have to be more comprehensive and must be discussed between Prof. Eibl and Dr. Bosch.

Lot specific data will have to be provided on the IgG subclasses.

Question 2:

Data available:

- Publication by Prof. Eibl: "PKA Contamination of Immunoglobulin G"

Data required:
Based on Prof. Eibl's paper we should prepare a rationale proving that pKA is of no clinical relevance.

Prof. Eibl's paper should be presented with a statement that the paper actually refers to Endobulin, definition of the BOB-standard used (probably No. 2) as well as an explanation of the pKA values mentioned in this paper (680 % = 6.8 % of BOB standard, etc.).

A number of recent batches (at least 10) shall be examined for their pKA-values. On the basis of these results Dr. Schwarz should decide whether the limit may be lowered. If not, a justification of the limit of ≤ 100 i.u./ml must be prepared in which we should also mention that pKA is a trace protein that might have considerable fluctuations from batch to batch. Another alternative would be to give an upper and lower limit.

The Quality Control will have to be adapted according to the limit(s) to be chosen.

Question 3:

Data available:
- US preclinical data on HTLV-III inactivation in Cohn Fraction II by treatment with immobilized trypsin gel in the process of manufacture of Endobulin

Data required:
The US data on HTLV-III inactivation in Cohn Fraction by treatment with immobilized trypsin in the manufacture of Endobulin should be submitted to the authorities. It will have to be discussed, however, whether or not we should include the data on fragmentation.

A rationale must be prepared to justify why immobilized trypsin is used, i.e.

a) to destroy and make anaphylactoid reactions causing substances removable
b) to inactivate HTLV-III

It should be stated that we detect a trypsin-like activity with chromogenic substrate which is equal to 150 - 250 ng/ml but that we think that the trypsin activity is practically nil.

The "Determination of Trypsin Content" will have to be included in our quality control and the lowest possible limit should be given (promotion against Sandoglobulin).

Test results of 4 batches or more (10, if possible, according to Mr. Berry) should be presented.

Question 4:

Data available:
- Compendium of various publications
- Papers referrred to in Endobulin folder

Data required:
The papers compiled by Dr. Linnau should be summarized.

Both the trade name and the generic name should be left as they were used in our original product license application. We should only add "aggregate-free and HTLV-III inactivated" on the packaging elements and give an explanation and in the pack insert.
Immuno Ltd. will, however, still comment on this proposal and inform us also on how the product could best be promoted in GB.

The composition has to be changed to 60 g protein/l and a rationale must be prepared for this change of the formula.

We claim that the product contains 5 % monomeric IgG. To achieve this we have to have a 6 % solution. 82 % of total protein are monomeric IgG (HPLC), the rest are split products with a molecular weight of below 160.000. We will have to explain why we leave in these split products (Although it would be possible to remove them, this is not done for economical reason.) We will have to prove that the split products are not harmful.

In the rationale we should also refer to the following 3 tests (quality control and preclinical) and explain their functions:

a) electrophoresis (≥ 96 % IgG)
b) protein-A sepharose test (≥ 90 % functionally intact IgG)
c) HPLC (~82 % monomeric IgG)

A paper by Van Furth should also be referred to.

As to the historical background we may use the data and arguments of our US application. (The starting material contains 100 fold increased anaphylactoid reaction causing potential in animals, which is reduced through manufacture so that the product is virtually free of anaphylactoid reaction causing substances.)

A revised "Composition" will have to be provided.

Question 5:

Data available:

- Confirmation that only HTLV-III antibody free plasma will be used
- No upper limit for transaminase values
- US preclinical studies
- US clinical studies (Rosen study and Polish study)
- Statement on the amount of Endobulin used from 1979 1985 with no evidence of transmission of hepatitis or AIDS

Data required:
The statement on the quantity of Endobulin used so far with no evidence of transmission of hepatitis or AIDS should be officially signed.

We should refer to Wells' paper which describes a 15 log step partition and inactivation during Cohn fractionation. Our own data will not be available until July, but preliminary results show compliance with the Wells paper.

A revised Method of Manufacture including freeze-drying must be prepared.

Question 6:

The indication of secondary antibody deficiency will be deleted.

Question 7:

The data presented by Dr. Bosch in a CPM circular will be used as a basis to answer this question.

The test for leucopenic activity should be withdrawn.

Pack insert

When all the data required will be available it will be decided whether we shall use the new "basic leaflet" presently being translated into English or stick to the leaflet already submitted which is based on the US circular and incorporate only the modifications of the Canadian circular.

New packaging elements will also have to be provided (inclusion of "aggregate-free, HTLV-III inactivated").

GAMMABULIN

The same data requested for Endobulin concerning virus inactivation during ethanol fractionation will have to be submitted for Gammabulin by October at the latest.

PROTHROMPLEX

A product license amendment shall be filed for Prothromplex TIM 4, since there are no clinical data available on Prothromplex, steam treated (Method S-2) (= TIM 3) for which we have already submitted a number of data.

As to Prothromplex TIM 4 6 cases by Brackmann and 9 further from Germany which will be evaluated by Mag. Fröhlich are available.

FEIBA IMMUNO, steam treated

Pack insert

- The individual chapters will be arranged as requested by IMMUNO LTD.
- A new version on the measures taken to decrease the potential risk of transmission of viral infections was discussed.
- Mr. Nicholson proposed to give a limit for ALT values (40 mU/ml) rather than to refer to values "within twice the normal range". According to Dr. Schoppmann we should perhaps refer to "non-pathological" values.
  This will have to be discussed again.

Clinical data

A "British" version of the evaluation of the US clinical study will be required. Dr. Schoppmann has asked Mrs. Kunschak to prepare such a "British" version from the evaluation of the 69 episodes once it will be ready.

KRYOBULIN

TIM 2: Mr. Berry was informed of the necessity to change our pack insert as far as our statements on HTLV-III are concerned.

2 papers, i.e. "HTLV-III seroconversion associated with heat-treated factor VIII concentrate" by White and "Seroconversion to HTLV-III in haemophiliac given

heat-treated factor VIII concentrate" by Van den Berg were handed over to Mr. Berry.

Dr. Eibl and Mrs. Kunschak will prepare a rationale to be passed on to Mr. Berry.

They will refer to the 2 papers and state that the inactivation rate of our steam treatment procedure is comparable to that of the heat treatment referred to in the papers.

If the authorities agree with our wording concerning HTLV-III we will leave it, otherwise we will revise it.

We might also seek the advice of Dr. Thomas and Shield.

Mr. Berry will check the wording used by our US competitors in Great Britain and inform us accordingly.

Mr. Berry mentioned that the Wellcome HTLV-III Test Kit is licensed in Great Britain and that we should perhaps also use this kit.

TIM 3: For the time being the product shall be sold on a doctor/named patient basis.

If we want to market both Kryobulin TIM 2 and TIM 3 we will have to submit a full product license application for Kryobulin TIM 3.

The question of price has not been resolved so far.

PPF 4.3 %

Although the haemoglobin values stated in the B.P. under Albumin do not comply with the limits required by the Austrian Plasmapheresis Law nor by the CFR nor with German requirements we will confirm that the selection criteria used for the source material of PPF 4.3 % is in accordance with the requirements of the B.P. under Albumin.

An average value provided by Dr. Kaeser gives 14.9 % w/v (B.P. ≤ 12.5 % w/v for females, ≤ 13.3 % w/v for males).

Dr. Jacobson will check the situation in our Austrian plasmapheresis stations and in the USA and initiate the necessary steps, if the Austrian and US values are actually too low. (In the meantime Dr. Jacobson has confirmed that we comply with B.P. requirements.)

GRO-C

1986-06-25/Hi/MB

Dipl.Dolm. I. Diernhofer

cc: Mr. Berry
Mr. Nicholson
Dr. Schwarz
Dr. Jacobson
Fr. Kunschak
Dr. Bosch

ITEMS TO BE DISCUSSED

TISSEEL® KIT

1. Indications

   specific indications <-> general indications
   (additional publications on
   lyophilised product required)

2. Source material

   no restrictions as to donor selection (see Ireland) → revised Method of Manufacture required

3. Manufacture

   inclusion of F XIII ?
   According to Dr. Schwarz: no — leave it as it is
   If yes, revision of Method of Manufacture

4. Quality Control

   inclusion of HTLV-III testing on plasma pool?
   If yes, revision of In-Process Quality Control. — no

5. Bovine sensitisation data

   The following data were provided so far:

   - Statement by Prof. Schlag:
     "At present 350 cases of repeated use of Tisseel in one and the same patient are known where no side-reactions (anaphylactoid reactions) have been observed.
     Besides, it should be taken into consideration that high doses of bovine thrombin have been used for many years under the name of "Topostasin" as an haemostatic agent for topical use (spray) to stop bleedings following tonsillectomies or gastric haemorrhages and that no side-reactions have been observed in these cases."

- Paper by H.S. Alter, H.F. Polesky and P.V. Holland on: "False positive tests for hepatitis-associated antigen in blood donors caused by antibodies to ruminant serum proteins"

Are these data sufficient ? How should they be presented ? Have any blood samples been tested in GB for antibodies to bovine material through the consumption of milk and beef as proposed by IMMUNO LTD ?

6. Hepatitis / HTLV-III risk

The following data were provided so far:

- 2 papers by Scheele and Panis which should not be used, however.
- interim evaluation of the Baumgarten Study
- preclinical study on HTLV-III inactivation

A final manuscript of the Baumgarten Study is now already available.
The preclinical study needs some minor changes.

Are these data sufficient ? How should they be summarized and presented ?

7. Medical Devices (Duploject, Spray Set, Spray Catheter)

None of the producers of these devices is registered with DHSS. It must be checked whether the manufacturers would be ready to apply for a DHSS number or whether IMMUNO AG may appear as the manufactuerer and apply for such a number.
If none of the above alternatives is possible we would have to think of the possibility of having to sell the product without any medical devices.

PPF

Dr. Schwarz agrees to confirm that only HTLV-III tested material will be used. As to the statement on compliance with the selection criteria of the B.P. for Albumin, different criteria are applied for the haemoglobin value.

In Austria:	haemoglobin value	≥ 12.0 % w/v
In the Federal Republic of Germany:	haemoglobin value	≥ 12.8 % w/v
In the USA:	haemoglobin value	≥ 12.5 % w/v
In B.P.:	haemoglobin value	≥ 12.5 % w/v (in females)
		≥ 13.3 % w/v (in males)

In Dr. Jacobson's opinion we could still confirm compliance with B.P., since normally the haemoglobin value will be above these limits anyway. Dr. Kaeser will examine the values of several donors and provide us with an average value.

KRYOBULIN, STEAM TREATED

Hepatitis and HTLV-III statements in pack insert.
Has a license already been granted in Ireland?

ENDOBULIN

Letter dated July 11, 1985

Question 1:

Data available:
- Statement by Prof. Eibl on clinical relevance
- Paper by Lefranc: "Familial Lack of IgG3 Subclasses"
- Comment on above paper by Dr. Bosch

Data missing:
- Lot specific data

Question 2:

Data available:
- Acceptance criterion for pKA: ≤ 100 I.U./ml (reference to the 1st International Standard)
- Publication by Prof. Eibl: "PKA Contamination of Immunoglobulin G"

Question 3:

must be revised, values too high

Data available:

- Determination of Trypsin Content in Endobulin (test description and lot specific results)
- US preclinical data on HTLV-III inactivation in Cohn Fraction II by treatment with immobilized trypsin gel in the process of manufacture of Endobulin

Data missing:

- Statement on philosophy by Dr. Eibl

Question 4:

Data available:

- Compendium of various publications
- Papers referred to in Endobulin folder

Data missing:

- Description of historical background as far as our manufacturing and analytical methods are concerned by Dr. Eibl
- Discussion of generic name of Endobulin required!
- Change of composition (60 g protein/l) →new Method of Manufacture and Composition required

Question 5:

Data available:

- Confirmation that only HTLV-III antibody free plasma will be used
- No upper limit for transaminase values
- US preclinical studies
- US clinical studies

Data missing:

- Revised Method of Manufacture including freeze-drying
- Statement on the amount of Endobulin used from 1979 - 1985 with no evidence of transmission of hepatitis or AIDS

Question 6:

Deletion of secondary antibody deficiency as an indication

Question 7:

Data available:

- Report by Dr. Bosch on animal tests for hypotensive and bronchospastic activity

Data missing:

- Justification of test for leucopenic substances
  According to Dr. Igel this test could be deleted because it has proved to be of no relevance

As a consequence of the above the following data will have to be revised:

pack insert

method of manufacture

manufacture

composition

quality control