IMMUNO

Aktiengesellschaft für chemisch-medizinische Produkte
Produktionsbetrieb: Österreichisches Institut für Haemoderivate GmbH
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to: IMMUNO LTD.
(AN) Att. Mr. Coombes

from:
(VON) IMMUNO AG Vienna
Registration Department

Dear Mr. Coombes,

attached please find a copy of the memo of the discussion held in Vienna on January 11, 1990.

Kind regards!

Encl.

If You have further questions, please call: (0043-222)2300-2534

M E M O

Meeting between Beecham and Immuno on January 11, 1990

Participating:	Dr. Brightwell	Mr. Coombes
	Mr. Taylor	Dr. Schwarz
	Dr. Planterose	Dr. Eibl (part-time)
	Mr. Hasler	Dr. Linnau
	Mr. Overell	Dr. Hetzl
		Dr. Igel
		Dkfm. Aschbauer
		Mag. Henninger

Great Britain

Molecular Weight Distribution (HPLC)

Both BEECHAM and IMMUNO are having problems with the new test method in so far as it has not yet been possible to quantify unresolved impurities. IMMUNO shall therefore file their standard method with the DOH before February 17, 1990 (together with a description of isoelectric focussing), which is 1 year after license approval. Mr. Coombes will send the test descriptions directly to Dr. Gate. In addition to the HPLC test description we will provide the DOH also with the test results of a number of batches to show consistency of the product.

It was agreed that the acceptance criteria should refer to Fraction I, II, and III which should be defined in the test description. (The 3 fractions correspond to the monomer peak, the low molecular and the high molecular portion; the term "monomer" should, however, not be mentioned.)

The individual acceptance criteria should be specified as follows:

$\geq$ 85 % for the monomer fraction
$\leq$ 7.5 % each for the high and low molecular fractions

The actual values that were obtained over the years are ~~average~~ a minimum of 88 % for the monomer fraction and a maximum of 6 % each for the high and low molecular fractions.

Before filing the additional data required by the DOH, Beecham should be provided with a copy for comment.

In parallel to our submission of the additional data BEECHAM will update their specifications for the UK (3 tightened tests, i.e. plasmin, glu-plasminogen, and pH, + HPLC + isoelectric focussing).

Human Pituitary Growth Hormone

BEECHAM were requested by the DOH to ensure that recipients of human pituitary derived growth hormone were permanently excluded from donating blood or plasma used to manufacture licensed blood products. IMMUNO confirmed that this would be done.

France

Removal of Human DNA During Production of Plasminogen

Prof. Dorner gave a summary of his discussion with Prof. Horaud last autumn in Vienna on viral inactivation procedures and the removal of DNA during the production of PLASMINOGEN. It was agreed at that time that IMMUNO should draft a protocol for the investigation of the removal of DNA during manufacture. Prof. Horaud would review the protocol before we would actually start any investigations to see whether the protocol would be up to the expectations of the French authorities.

Concerning the meaningfulness of such an experiment it seems that Prof. Horaud wants to see the efficiency of the purification method per se and that he is not particularly interested in the removal of DNA as such.

During the discussion last autumn Prof. Horaud changed also his view on the resistency of SV_{40}, Parvovirus, etc., and is no longer asking for such inactivation studies.

Asked what type of DNA should be used, Prof. Horaud stated that human DNA should be used for the experiment.

So far no draft protocol has been prepared for submission to Prof. Horaud since it is still not clear in what capacity Prof. Horaud is going to review the protocol and this seems to be a problem to him. Prof. Dorner promised to contact Prof. Horaud to clarify this matter and confirmed that the draft protocol would be submitted to Prof. Horaud within this month.

Dr. Eibl argued that preliminary tests should be done before we hand over the protocol to be sure that the investigation will end up with positive results. There might be problems with respect to the impurity of the material and with radiolysis during production. Dr. Eibl therefore proposed to ask Prof. Horaud to

perform such preliminary tests himself, i.e. to develop an analytical method and spike the plasma with his material to see how much DNA can be precipitated (e.g. up to Cohn Fraction III). If Prof. Horaud runs into difficulties, he may be expected to try to convince the French authorities that their request is not reasonable.

Dr. Schwarz mentioned that we could perhaps also use the US HIV-inactivation data for submission to the French authorities. BEECHAM do, however, not like this idea for fear of bringing up the question of inactivation of heat resistant viruses once again.

It was finally agreed that Prof. Horaud should be contacted within the next days.

Follow-Up of Hepatitis Non-A/Non-B Studies

BEECHAM informed us that the results on further patients are now available and that they would be ready to send in an updated report. BEECHAM wanted to know whether an updated report of the International Factor Safety Study would be available on the part of IMMUNO for submission to the French authorities. This was confirmed and Mr. Taylor was promised to be provided with a copy of the interim evaluation of July 14, 1989.

Dr. Eibl asked whether BEECHAM had already included hepatitis C antibody testing in their study. If not, they should perform the test as quickly as possible if samples were available.

It was agreed that BEECHAM should wait with the submission of the follow-up data of their own and of IMMUNO's study until Prof. Horaud had been contacted on the investigation for the removal of human DNA. The updated reports of both companies should be filed by the end of February.

Virology Issues

Studies with Parvovirus

Although an official request for studies with Parvovirus does no longer exist, BEECHAM would be extremely interested in such studies to have data available just in case a competitor comes up with something. Dr. Eibl mentioned that the results of these studies were not satisfactory. It would be much better to use other viruses to prove the efficiency of the purification method, e.g. a small phage would be suitable and also polio virus which is very heat resistant.

It was therefore agreed to start experiments with X_{174} and polio virus within this month.

Hepatitis C Test Kits

Dr. Schwarz stated that so far the FDA advises not to use hepatitis C test kits for the screening of plasma or blood donations. On the one hand these kits would exclude only approximately 50 % of the infectious donors. Besides, by eliminating hepatitis C positive donors, hepatitis B positive donors would also be removed from the donor programme and the hepatitis B antibody titre in the plasma pool would therefore be decreased.

ABRA advised that for the production of immunoglobulins the plasma pool should consist 1 : 1 of hepatitis C antibody tested and unscreened plasma. Hepatitis C antibody testing should, however, not be included in the plasma donation screening scheme.

The UK authorities have already asked for hepatitis C antibody testing. We will have to see what decisions will be taken by the individual health authorities concerning hepatitis C antibody testing since there seem to be different views at the moment.

Hepatitis B Virus Removal During Production

Dr. Eibl stated that these investigations were not yet completed.

BGA Activities

In a decree of December 11, 1989/GV72-7251-01-21320/214d the BGA are requiring a number of safety measures concerning the manufacture of human protein-containing preparations. Due to BEECHAM's use of Plasminogen and Albumin in the manufacture of EMINASE they have also received the BGA's letter.

As to the exclusion of Western Africans from the donor programme it was confirmed that no Western Africans are included in IMMUNO's donor programmes.

Generally, the above and all other requirements of the BGA will, however, be discussed in detail by all manufacturers of blood products. There will be a meeting on Friday to decide on further actions to be taken.

Dr. Kaeser will be asked to contact BEECHAM and provide them with our reply that will eventually be made to the BGA. BEECHAM's answer should correspond to our information given to the BGA.

Concerning the BGA's requirement to file an amendment and wait for the BGA's approval in the case of any change in manufacture, IMMUNO should quickly review what was filed by BEECHAM in the FRG. In case these data are no longer fully up to date, the BGA should be notified as quickly as possible. Mr. Taylor is going to provide the registration department with a copy of the documents filed with the BGA. The registration department will then quickly check the documents. In the case of serious descrepancies to our UK and US registration data we should file an amendment, but should in any case wait for the outcome of the Friday meeting. (The same documents as filed in Germany were also filed in Holland and Spain.)

Concerning HIV-II it was mentioned that test kits are already available in the FRG but not yet in the United States.

The whole situation concerning plasma and blood testing is quite unclear at the moment.

A test kit for testing HTLV-I in blood and cell concentrates has been available in the United States for two years. Besides, a test kit for HIV antigen testing is available in the United States, but when for example CUTTER wanted to introduce testing for HIV antigen, the CBER insisted that this test should not be performed by CUTTER, otherwise there licenses would be revoked.

USA

Outstanding Actions

Only two actions are still outstanding in connection with our US license.

First we will have to provide the CBER with stability study results of the first three production lots. A stability study programme has already been submitted to the CBER and the data will be presented in due course of time.

Besides, the CBER were promised to be provided with a detailed description of temperature monitoring during the transport of plasminogen used for further processing into Eminase for the US market. A draft of our proposed measures to monitor the shipping conditions was sent to BEECHAM Gronau for approval. The draft was not passed on to the UK, but according to Mr. Taylor involvement of the UK plant is not necessary. IMMUNO will forward a detailed description to the CBER before February 22, 1990 as previously agreed with the CBER.

It was confirmed by BEECHAM that as far as the US is concerned only Gronau should be mentioned as a manufacturing site for Eminase. (The UK product will be manufactured only at Crawley.)

Product Specifications and Test Protocols, Labels

It was agreed that the US specifications and test protocols will be valid for the US as well as for all other countries where plaminogen is licensed except for the UK. In the UK we have partly tighter test specifications as well as two additional tests and therefore different test protocols.

In case any country where a product license application is still pending will require the tightening of any specification or will ask for additional tests, individual discussions will be necessary.

IMMUNO confirmed that the product shipped to BEECHAM for further manufacture will of course always meet the specifications laid down in the agreement between BEECHAM and IMMUNO which correspond to the UK specifications.

In future all shipments to Gronau should be labelled with US approved labels, all shipments to Crawley should bear UK approved labels.

Registration in Norway, Sweden and Denmark

Mr. Taylor informed us that the Norwegian and Swedish health authorities had requested the UK assessment report and that approval of Plasminogen/Eminase may be expected within soon in these countries.

BEECHAM were informed that we had just received some questions from the Danish authorities concerning our license application. Mr. Taylor was handed over a copy of the respective letter.

GRO-C

1990 01 22/Hi/MB

Mag. I. Henninger

cc: alle Besprechungsteilnehmer (IMMUNO)
Mr. Coombes
Dr. Kaeser
Dipl.Dolm. I. Diernhofer
Mag. Quendler