REVLON HEALTH CARE (UK) LIMITED

Armour Pharmaceutical Company Limited

BERK Pharmaceuticals Ltd.

INTER OFFICE MEMORANDUM

TO : Those Listed

DATE: 10.3.86

FROM : Dr P Harris

REF: PAH/LEW

SUBJECT : **NOTES ON MEETING WITH DHSS - 3.3.86 - FACTORATE**

COPIES TO :

Mr J Michelmore
Mr C Bishop
Dr M Rodell
Mr L Lucas

Please find attached for your information copy of the notes of our meeting with the DHSS on March 3, 1986.

GRO-C

PP **Dr Peter Harris**

REV 48

ARMOUR002834

ARMO0000507_0001

REVLON HEALTH CARE (UK) LIMITED

Armour Pharmaceutical Company Limited

BERK Pharmaceuticals Ltd.

INTER OFFICE MEMORANDUM

TO : Dr P A Harris

DATE: March 5, 1986

FROM : Mr R B Christie

REF: RBC/EB/10187

SUBJECT : MEETING WITH DHSS ON FACTORATE HEAT TREATED, 3 MARCH 1986

COPIES TO :

Present:-

Dr Rotblat	)	
Dr Isaacs	)	DHSS
Dr Betts	)	
Dr P Harris	)	
Dr M Rodell	)	Revlon Health Care
Mr R B Christie	)	

This meeting had been requested to clarify certain specific areas of information that had been requested by Dr Rotblat.

1. Manufacturing Process - HTLV-III Virus Kill

Dr Rodell presented the summary virus kill data on Generation I Factorate from both Paul Erlich Institute and Meloy Laboratories. The Meloy data was accepted by the DHSS but there was some reticence regarding the Paul Erlich data since at no time or temperature did they recover live virus.

We were asked the size of our donor pool wich was defined as between 5000 and 20,000 donors. Before screening 0.25 - 0.3% of donations were HTLV-III positive by the ELISA technique. If one accepts that the maximum virus contamination from a symptomatic AIDS case is likely to be 10^8 virus/ml, then at 0.25 - 0.3% infected donors per pool, the maximum virus challenge will be 10^5.

Our lyophilisation and heating process, which was defined as 60°C for 30 hours, will inactivate $10^{5.5}$.

Since we have started screening donors, the risk of potential positive donations to a pool is reduced to less than 0.05%. This means a substantial reduction in potential virus challenge in the final product.

there may be some variability in risk across the U.S., but all of our plasmaphaeresis centres are in areas of low risk for AIDS. All these centres are our own, we do not purchase blood to manufacture Factorate from any outside source.

Cont'd. ...

REV 48

Most donors are regular, with continuous follow up and all are regularly screened for HTLV-III antibody.

We have attempted to grow virus from final Factorate product, one batch of heat treated being heated and a batch from the same pool being unheated. No virus could be cultured from either batch.

Neither pooled plasma nor final product is routinely tested for HTLV-III antibody. The test kit used (Abbott) has not been qualified for other than individual samples of plasma.

We were asked how much material was in the market originating from unscreened donors. We estimated approximately 5 million units or about 3 months' stock. We were not asked to withdraw this material.

Dr Betts requested detailed experimental methods for the virus inactivation studies - information on the virus culture, buffer systems, incubation conditions, etc. An outline summary is not sufficient. Dr Rodell agreed to provide this data. We also agreed to provide a translation of the Paul Erlich Institute paper.

Dr Betts confirmed that a similar request was being made to all manufacturers of blood products.

During conversation, it emerged that Dr Rotblat had spoken to Dr Aronson of the FDA and that our position was consistent with that appreciated by the FDA.

It was clear that detailed HTLV-III virus inactivation data will be required for all blood products in the future which will include IVGG, Pseudomonas IVGG and Factorate C Monoclonal.

2. Dr Ten Cate

We gave Dr Rotblat a confidential transcript of my trip report to De Ten Cate's unit. It was pointed out that it had not yet been agreed formally by Dr Ten Cate and should be viewed in this light.

I highlighted a few important areas.

Dr Rotblat had already spoken to Dr Ten Cate and appeared satisfied with the record as written.

Cont'd. ...

3. Follow up on Factorate Y69402

I summarised our criteria on the follow up to patients who had received Factorate HT Y69402, which originated from a pool of plasma which contained a donation from an individual who subsequently developed AIDS.

Most of the batch was recalled but 12 patients had been identified as having received the batch.

Of these, 5 were seropositive before treatment with Y69402 and 1 died of massive liver necrosis unrelated to specific treatment. Of the remaining 6 patients, 5 were still negative, although a second follow up is due for a number of these, and 1 (Dr Whitmore's patient at Lewisham Hospital) had sero-converted approximately 3 months after treatment with Y69402. This patient had not been treated for 5 years prior to Y69402 and was not in any known risk category.

Dr Rotblat had discussed this case with Dr Whitmore. She requested that we continue to keep her advised of results of our continuing follow up of patients who have received this batch.

It was agreed that one could speculate for both Dr Ten Cate's and Dr Whitmore's cases that it was an antibody response to dead virus, as both patients were at present physically well. Dr Rodell elaborated on this theory from his experience.

4. U.S. Cases Quoted by Dr Jones

Dr Rodell said that only one case associated with heat treated Factorate was known in the U.S. and this case had received other products. Dr Rotblat had spoken to both Dr Jones and Dr Aronson of the FDA about this aspect. We agreed to advise her of any information that came from our follow up of these reported cases.

5. Further Developments

We were asked if we had any plans for further product improvements to reduce risk of virus infection in our Factor VIII products.

Dr Rodell described the development of a monoclonal antibody purified/ heat treated product as our major hope for the future, although some changes to our heating cycle were also planned in the shorter term.

Dr Rodell also stated that ALT screening would be introduced for all donors by the summer of 1986 following a decision made by our Plasma Executive Committee. This was seen as a move in the right direction and should be officially confirmed to the DHSS.

Cont'd. ...

6. New Scientist Article

Dr Harris asked if the DHSS members present had seen the recent article in the New Scientist in which the DHSS Factor VIII Y was described as the best available and the Armour process shown in a poor light. The DHSS did not heavily support this viewpoint and they appeared to take the view that there was not yet sufficient evidence to support this contention.

Dr Harris also tactfully tried to draw the DHSS members to compare our product's relative safety with that of competitors. It was not perceived as less safe by any comment made by Dr Rotblat or her colleagues.

In summary, the meeting went well in a frank, open and helpful atmosphere. There was no evidence that the DHSS regard our current heat treatment method as unsatisfactory, but are looking for evidence that we are steadily moving towards improved procedures of screening and processing that will provide extra guarantees of safety.

They also wish us to continue with our follow up on patients exposed to known possible risks.

No indication was given that they wish us to withdraw batches of product from unscreened donor pools.

GRO-C

R B Christie

LAV/HTLV-111 INACTIVATION STUDIES
(MELOY)

PRODUCT	TREATMENT	EXPERIMENTAL REDUCTION LYOPHIL	HEAT	TOTAL	MAX. POTENTIAL REDUCTION
AHF-Gen 1	60° - 30 hr.	>2.3	<3.2	5.5	6.3
AHF-Gen 1	68° - 30 hr.	1.0	4.0	5.0	7.0
	72° - 30 hr.	1.0	4.0	5.0	
	68° - 70 hr.	1.0	5.0	6.0	

LAV/HTLV-111 INACTIVATION STUDIES
(PAUL EHRLICH INSTITUTE)

PRODUCT	TREATMENT	EXPERIMENTAL REDUCTION LYOPHIL	HEAT	TOTAL	MAX. POTENTIAL REDUCTION
AHF-Gen 1	60°- 10 hr.	2.0-3.0	3.0-4.0	6.0	6.0
	60°- 20 hr.	2.0-3.0	3.0-4.0	6.0	
	60°- 30 hr.	2.0-3.0	3.0-4.0	6.0	