INTER-OFFICE CORRESPONDENCE

TO	FROM: W. A. Thill
See Distribution	CO: Armour Pharmaceutical
	CITY: Kankakee
THIS IS IN REPLY TO YOUR LETTER DATED	DATE: July 20, 1982
SUBJECT: HEPATITIS-SAFE A.H.F.	

Minutes of Meeting in Kankakee on July 15, 1982.

Present:

Mr. R. C. Johnson	Dr. P. Roberts
Mr. J. A. Sedor	Dr. R. Landaburu
Mr. D. D. Hill	Dr. D. Winship
Mr. D. W. Gaston	Dr. C. Rehm
Mr. J. J. Bona	Mr. C. Brown
Dr. F. Feldman	Mr. W. A. Thill

1. BACKGROUND

Every major plasma fractionator is presently working on hepatitis-safe A.H.F. preparations. Although some of these preparations are already under evaluation or marketed in Europe, no license has been obtained for a hepatitis-safe A.H.F. in the U.S. So far, the following methods have been used to obtain hepatitis safe products:

Behringwerke (Germany)	Dry Heat
Biotest (Germany)	UV + beta-propiolactone
Hyland-Travenol (U.S., Europe)	UV + dry heat (?)
R.H.C.G.	Hep. B hyperimmune globulin + dry heat

Travenol seems to have progressed further in this field than the other U.S. manufacturers. It has completed a study on chimpanzees, clinical studies are well underway and the available data are now being presented to the German government and to German clinicians in Bonn. A hepatitis-safe product could increase Travenol's market share in Bonn from approximately 25 Mio U/yr. to 60 Mio U/yr. Furthermore, such a preparation would command a premium price (In Germany: 0.73 DM/U or approx. $0.31/U). Since Travenol does not hold an export license for such a product, it probably originates from Travenol's fractionation facility in Belgium. The German government may or may not require a clinical study in Germany prior to issuing a product license to Travenol.

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2. B.O.B.'s VIEW ON A HEPATITIS-SAFE A.H.F.

The B.O.B. is very interested in such a preparation. It has proposed repeatedly that the U.S. plasma fractionators concentrate their efforts on hepatitis-safe products. The B.O.B. has also proposed a P.M.A. group meeting in which the efforts of all manufacturers could be pooled. This would accelerate the development work and could eliminate the redundancy in chimpanzee studies. However, in view of the highly competitive A.H.F. market, such a meeting is not likely to take place. The B.O.B. plans to organize a symposium on this subject in September. The B.O.B. is aware of the results of the first heating experiments by R & D Tuckahoe and probably has data on Hyland's dry heat experiments as well. Since a B.O.B. research group initially performed studies on neutralization of hepatitis B virus by HB-Ab, it may look favorable upon the use of HB hyperimmune globulin in the formulation of A.H.F. The question of the infectivity of the H.B. Ag-AB complex has not been cleared and many scientists, especially in Europe, consider the antigen-antibody complex still infective.

At the first meeting with the B.O.B. on this subject, Mr. R. C. Johnson and Dr. P. Roberts discussed a hepatitis safe preparatio in general terms. In a second meeting, the B.O.B. (Dr. Aronson) agreed to an amendment to our existing A.H.F. license covering t addition of hepatitis B hyperimmune globulin. The heating of th freeze dried product was not included at that time.

3. ANIMAL EXPERIMENTS

a. Effects of heating:

R & D Tuckahoe has performed three chimpanzee studies. Each study included 3 animals. The first study has been completed, the other two studies are ongoing.

1 animal (control): A.H.F. Gen. II + Hep. B virus, unheated.
2 animals : A.H.F. Gen. II + Hep. B virus, heated (dry, 30 hrs., 60°C.)

Results: The control animal showed signs of hep. B, followed by non A - non B hepatitis (hep. NANB). The other two animals showed symptoms of hep. B but stayed free of hep. NANB. This seems to indicate that NANB virus can be inactivated by heating of the dry product while hep. B virus is less susceptible to heat inactivation.

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3. ANIMAL EXPERIMENTS - continued

b. Effects of hep. B antibody:

1 animal (control): AHF Gen. II + Hep. B virus, unheated.
2 animals : AHF Gen. II + Hep. B virus + Hep. B hyper-immune globulin, unheated.

Results: The control animal showed signs of hep. B, the other two animals are still healthy. This experiment was begun in March 1982 and will be concluded by October, 1982.

c. Effects of heating and hep. B antibody:

1 animal (control): AHF Gen. II + Hep. NANB virus + HB hyper-immune globulin, unheated.
2 animals : AHF Gen. II + Hep. NANB virus + HB hyper-immune globulin, heated (dry, 30 hrs, 60°C.)

Results: So far, all three animals remained healthy, which could indicate a natural immunity of the control animal. After three more weeks all animals will be challenged with NANB virus. This should result in a healthy control (natural immunity) and symptoms of hep. NANB in both remaining animals.

The data of experiments b and c will be submitted to the B.O.B. sequentially.

4. PROPOSED PROCESS FOR HEPATITIS-SAFE A.H.F.

A non-sterile bulk solution of A.H.F. Gen. I or Gen. II is prepared according to present manufacturing procedures. FR II poweder, previously obtained from hep. B hyperimmune plasma by the cold ethanol process is reconstituted to a solution containing approx. 1% protein and added to the non-sterile A.H.F. bulk solution (ratio: 1:30). The addition of 1 ml. HB hyperimmune globulin solution (= 10 mg FR. II) to 30 ml. A.H.F. bulk solution should result in a HB Ab titer of 1:2000. This requires a titer of at least 1:60,000 for the 1% hyperimmune globulin solution. The obtained mixture is then incubated for 60 minutes, followed by sterile filtration, fillir freezing and freeze drying as specified in the standard manufacturing procedures for A.H.F. Thereafter, the sealed vials are heated in a water bath at 60°C. ± 0.5°C. for 30 hours.

The proposed HB Ab titer of 1:2000 in the finished product is twice as high as the titer used in the above chimpanzee studies (1:1000). The heating process has so far been tried only with A.H.F. Gen. II. After the heating a loss in A.H.F. potency of approx. 5% was found. The properties characteristic for the unheated A.H.F. product remained unchanged after the heating (e.g. activation by thrombin, immuno-electrophoresis profile, in vivo half life in patients and hemophilic dogs).

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4. PROPOSED PROCESS FOR HEPATITIS-SAFE A.H.F. - continued

At temperatures around 70°C. or higher, the loss in activity increases rapidly.

Presently, there are 3 months stability data (refrigerated, R.T. and accelerated) from three heat treated A.H.F. Gen. II lots available.

Dry heating does not seem to affect the HB hyperimmune globulin since the HB Ab titer remains unchanged before and after heating.

5. MANUFACTURE OF HB HYPERIMMUNE GLOBULIN

A recently licensed HB vaccine was tested by Merck under its IND on Plasma Alliance donors. Approximately 140 L plasma collected from these donors is presently stored at Plasma Alliance. This plasma could be easily fractionated into HB hyperimmune globulin. However, the ownership of the plasma has to be determined first by Revlon Health Care Group's legal department. The HB Ab titer of this plasma is unknown. 6L plasma of this type were fractionated by R & D Tuckahoe resulting in the HB hyperimmune globulin used in the above described experiments. Approximately 20 g of this material are still left. Since the titer of the starting plasma was not determined, no data on antibody recovery is available.

Only small amounts of HB FR II would be required for initial conformance lots. 5L plasma resulting 15-20 g FR II would be sufficient for 1500-2000 vials A.H.F.

At the present time, there are no plans for marketing HB hyperimmune globulin per se, therefore, a B.O.B. license for this product is not required. HB hyperimmune globulin is manufacture and licensed by several U.S. companies including Alpha Therapeutics. This would make it possible to include other commercially available HB hyperimmune globulins in our license application for a hepatitis-safe A.H.F. For the conformance lots, however, this product should be manufactured by Armour.

The small scale fractionation of the HB hyperimmune plasma could be performed in Kankakee's Plasma Protein Pilot Lab.

6. MANUFACTURE OF CONFORMANCE LOTS

Only 2 conformance lots are planned initially, 1 lot A.H.F. Gen. I and 1 lot A.H.F. Gen. II. The Gen. I lot would consist of vials with 500 or 1000 U, the Gen. II lot would be made up of 1000 U vials.

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6. MANUFACTURE OF CONFORMANCE LOTS - continued

The following number of vials will be required for each conformance lot:

1.	Initial release testing	35 vials
2.	Stability study - A.H.F. Potency	50 vials
3.	Stability study - HB Ab	5 vials
4.	Clinical study, in vivo half life	10 vials
5.	Reserve samples	50 vials
	Total:	150 vials (Minimum)

(1000 L plasma yield approx. 250 vials at 1000U Gen. II)

These 150 vials could be prepared from aliquots of larger regular production lots of Gen. I and Gen. II. The manufacture of these lots would, of course, be done at Kankakee. The release specifications would be identical to the specifications for normal A.H.F. with addition of a test for the HB Ab. This test could either be a RIA assay performed by Electro Nucleonics (B.O.B. approved) or a hemagglutination assay by Quality Control

Product name, label claims and information on inserts will have to be discussed with A.P.C.'s management, marketing, R.H.C.G.'s legal group (liability questions) and B.O.B.

Furthermore, R.H.C.G.'s patent lawyers have to check if this process infringes on other patents covering the heating of plasma proteins in dry form. The specifications for the FR II (HB hyperimmune globulin) will be written by W. Thill, F. Feldma R. Landaburu.

R. Vukovich will be responsible for the clinical study. A draft of this study will be discussed at the next B.O.B. meeting A clinical study prior to the approval of the A.H.F. license amendment would require an IND. The rationale for the B.O.B. will be written by D. Winship.

7. T & E SCHEDULE

ACTION	DATE OF COMPLETION
Manufacturing procedures & specs. written	7/31
HB Plasma released from Plasma Alliance storage	8/1
HB Hyperimmune globulin manufactured	8/15
HB Hyperimmune globulin released	9/7
A.H.F. lots started/finished	9/15-9/22
A.H.F. lots released	10/15
Start of clinical study, stability studies	11/1

The above dates are contingent on a positive B.O.B. response. This project may require priority changes for Kankakee's Operation Services.

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