CUTTER Laboratories Inc.

MEMORANDUM

TO: Ken Hamlin, Victor Cabasso, Duane Schroeder

FROM: Milt Mozen

DATE WRITTEN: August 28, 1975

SUBJECT: Visit to Scottish National Blood Transfusion Service (SNBTS) Protein Fractionation Centre, Edinburgh, Scotland, Aug. 4-5, 1975

COPIES TO: Karl Fischer/J. Mink/J. Lundblad/G. Mitra/B. M. Coan/D. Tankersley/M. Bertolini

August 4, 1975

The protein fractionation function of the SNBTS has been moved from the Royal Infirmary to their brand new research and production facility in the outskirts of Edinburgh. The new plant which is designed for fractionation using the Watt continuous small volume mixing (CSVM) system is very impressive. Implementation of total CSVM has not yet been achieved but is in the shake down stage. Three trolleys are in service but still mostly experimental. Processing is under computer control which gives rise to a process control room reminiscent of mission central during a launch; what with lights and numbers flashing, computer tapes spewing forth, typewriters chattering out data, and television monitors displaying the processing in live action.

John Watt mentioned that present production is at about 1500 l/week. However, when I calculate his production from other figures he gave me, namely, 3 units albumin/1000 population per year, or 22,000 AHF units per hemophiliac/year I come out with a figure of around 300 liter per week. (Scotland population total: 5,210,000, male: 2,515,140. Incidence of hemophilia A: 5-6/100,000 male. 1 unit albumin is equivalent to 400 ml of 4.3% solution).

My first day's visit turned out to be a holiday and only a skeleton staff (including John Watt) were on hand. Besides Watt I met with Allan Dickson, the production manager and Peter Foster. Also visiting were 3 Japanese from the Japanese Red Cross. There was a definite language barrier here and we were not able to communicate too well. Nevertheless, John gave us a general bird's eye view of the whole facility and it was a very quick look. The Japanese visitors indicated that the Japan Red Cross is planning to expand their transfusion service and to build a fractionation center in Japan. Some of the points that came up in the discussion are as follows: In discussing Konyne® type products John said he prefers a three factor concentrate and this is easier to make. We discussed the storage temperatures of plasma. This is stored commercially at -35°C, whereas the inventory at the center is maintained at -40°C. Transportation of frozen plasma is in a specially constructed and owned refrigerated truck, which operates at -35°C. John says the longer he is in this business the more he is convinced that these low temperatures are required. He believes that -40°can be obtained with a cascade system and that this is done routinely in Europe. He has plans to expand a development area with an appropriate lab to serve between research and production. This could be useful information for us in planning our development activity in the new research building. He indicated they are making a small amount of rabies ISG using the diploid vaccine of Merieux. He said when fully staffed, there will be about 180 people; 100 for QA and fractionation.

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In viewing the facility it was interesting to note that they had a plasma crusher to transfer the frozen plasma blocks into snow prior to thawing. The carrier which holds the product for freeze drying goes into the -40° with the product and then into the freeze drier which they have designed and has an 80 liter condenser capacity. He indicated they never dry anything higher than +10°C. The total area of the facility is about 4500 square meters, of which 3200 is for production.

Some tid-bits which he told me at dinner include that Abbott has apparently also taken out an option with the NRDC for the use of the Watt process. Dr. Noel had been there just prior to the Paris meetings and 2 more Abbott personnel are expected imminently. Also he mentioned that Parke-Davis has expressed an interest and that Sy Campbell through the NRDC requested a visit. He said that Armour is not out of the picture. John Watt has been retained by the Canadian Red Cross to help them revamp their whole transfusion service and presumably he will be spending some time on several occasions in Canada.

In the fractionation room, aside from the trolleys, they have 6 Westfalia centrifuges, Size KA2006. They also have 5 of the KO8006 models with 10 bowls and 1 KDD605. The bowls of the 1st two models are jacketed for temperature control. For changing bowls, that is removing the solids, they pull the insides quickly and replace with another unit so that the down time is minimized. This is possible by having multiple number of heads.

Regarding the metal mixing chamber, Peter thinks it might be too tight for fraction I or if we are trying to bring down I + II + III. He said the metal unit was designed for a very high surface area, particularly when very low temperatures are desired, and it was too tight in there for a precipitate of the nature of fraction I. He thinks ultimately they will have another mixing chamber designed for fraction I.

There was a lot of activity around the computer station where they were carrying out and monitoring a study on mixing alcohol and water, and temperature control, particularly as relates to the valve openings, that is the valve for the coolant.

August 5, 1975

Today, I again visited the protein fractionation centre in Edinburgh. The morning was spent in discussions with Jim Smith regarding the problems of KOnyne® thrombogenicity and hepatitis. The afternoon was mainly with Peter Foster and Allan Dickson trying to better understand the facility and what was going on with the computer control of the CSVM unit. Just before leaving at the end of the day, I came to speak with John Watt and he again mentioned about others interested in the system. He learned that Abbott has definitely signed with the NRDC for option rights to the Watt process. Apparently 2 Abbott people were at NRDC in London today to sign up for this. They are then going on to ACE to discuss the computer system and apparently five trolley units. They will then come to visit here in Edinburgh later in the week. One of the men from Abbott is Bill Thorn and the other was a name John didn't remember. (Probably Bogkes).

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He indicated that NRDC told him that Armour is still underway in negotiating towards signing as was Parke-Davis. NRDC was very happy about all this.

With respect to my discussions with Jim Smith several useful points emerged. He reiterated that extensive washing of adsorbed DEAE removes factor VII and possibly the HB_s antigen. This has been confirmed by two groups, the Dutch and presumably the Finns. We should try limiting the amount of DEAE we use in an effort to decrease the amount of antigen bound. A good study using hot plasma and tracing the fate of the antigen is certainly in order. I indicated that I would not be overly concerned about making a 3 factor concentrate, i.e. devoid in VII, if in doing so the process did not get inordinately complicated, and we would accomplish a reduction in the hepatitis risk as well as thrombogenicity. Jim agreed that possibly absorbing from cryo supernatant would be better although they use supernatant I. He said that in general he worries about what happens to proteins after the plasma has been treated with alcohol. I think we need to critically study the elution character of our adsorbed material. The antigen is presumably eluted somewhere along the point where factor VII comes off. We should know this elution character particularly through the range just before IX emerges. He said that if yield is not really a problem with us then he felt definitely that we should go Alan Johnson's way. He said that the protein concentration and ionic strength is important with PEG to remove virus. That has been the main problem with their work. Of course with our preparation we start with a salt free protein and. therefore. we can adjust the protein concentration and ionic strength to any value we design. Jim really feels that Johnson's method will reduce thrombogenicity as well as hepatitis B surface antigen. We must relook at this again and I will have to be in touch with Johnson to do this. Jim is not concerned that the lowering of pH increases thrombogenicity. We must check this via the Kingdon assay. I told Jim I would try to send him a compilation of information we have on pH measurements such as was developed last summer. I also told Jim I would send him some samples of Koāte™ for assay stability to compare with his, and some aluminum hydroxide. I should also send 3 or 4 vials of several lots of Konyne® for him to study regarding its antithrombin III content, both bound and unbound. He indicated that he will be leaving the transfusion centre here in Edinburgh in the middle of September to join the Biggs:Bidwell groups at Oxford. However, he indicated that the samples I send him could still be studied by John Cash to whom he would turn them over. Jim also promised to send me some samples of Edinburgh concentrates so we could look at it in our hands.

MMM/jt