Rorer

Health Care Limited

To: Mr G Thomas

From: Dr P Harris

Date: July 25, 1986

Subject: **FACTORATE HT**

Ref: PAH/LEW

cc Dr. J. Trotter
Dr. N. Hayes
Mr. H. McDo

Copies to:

Mr C Bishop
Mr R Christie
Mr K Fitch
Mr A Sheppard

Dr M Rodell

Mr L Lucas
Dr C Swartz

Dear Graham

Ken has asked me to send to you a status report on our product in the UK. As you now know, the American exchange programme of Armour product took everybody by surprise and has put us in a potentially very weak situation with regard to the DHSS and haemophilia unit directors. We have lost goodwill with both by not notifying them in advance of their coming across the American letter. The net result of this may, of course, have no effect on our forecast sales with existing Armour strongholds for this year, which I believe is the position that Chris Bishop proposes for the UK, but the impact on Scandinavian business is likely to be a deficit on forecast of $1,000,000+ depending on the introduction date of the new heat treatment process, currently predicted to be not before the year end.

However, there is the possibility that the DHSS, having put our product under the microscope, may start to ask us awkward questions concerning product safety. You will see from the document that there will be some difficulty in defending too hard our present product in the light of publicly announcing (Mike Rodell, New Scientist paper) our interest in developing a more stringent heat treatment process.

It is also worth noting that when I spoke with Dr Rotblat (DHSS) on Tuesday she noted that she had been summoned to the Chief Medical Officer of the DHSS to answer questions concerning our product recall and discussions held in March concerning potential problems with Armour Factorate HT. I do not believe that we have her goodwill any longer and she is no longer to be viewed as a sympathetic ally.

I would be most grateful if you would review our position in the light of the data presented here and indicate as soon as possible the potential for defending our product if and when we need to do so.

Thank you for your help.

Kind regards

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CENTRAL FILES

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Dr Peter Harris

REVIEW OF FACTOR VIII PRODUCTS WITH RESPECT TO POSSIBLE FREEDOM FROM VIRAL CONTAMINATION

1. FACTORATE HEAT TREATED - ARMOUR

Heat Treatment - 60°C for 30 hours

Also:
(a) Our own collection centres away from known high risk areas.
(b) Donor education.
(c) Pre-donation screen by questioning and physical examination. Unfortunately, experience has shown that prospective donors do not always tell the truth.
(d) HIV-antibody screening. Latent period reported within weeks up to 1 - 3 years before sero-conversion. Reduces but does not totally eliminate risk.
(e) ALT screening. Gives a dual extra protection for the following reasons:

(i) Can identify risk groups for AIDS since they often also have a higher risk of liver disease.

(ii) Eliminates those donors with active liver disease, particularly NANB at the time of sampling, but as incubation period is approx. 2 - 6 weeks and elevation can be short lived it is not an absolute guarantee that an infected donation will not be included in the pool. However, does reduce this risk.

(iii) Dr. Kernoff (London) has estimated that as the incidence of NANB in US paid donors is 28%, if the pool size is above 300 there is a 100% risk of NANB infection. Our pool size is in excess of this, but ALT testing could reduce the incidence of donors in the pool and hence the level of risk before heating. (Kernoff, P.B.A. Satellite Meeting, St. Thomas' Hospital. 17 March, 1986).

Non A, Non B Hepatitis

A multi-centre UK trial of Factorate Heat Treated I.P. was conducted in 1984. Two virgin patients were admitted in Sheffield and one in Glasgow. All three developed non-A, non-B hepatitis. Two had severe symptoms and the third exhibited markedly elevated ALT from 5½ weeks to 4 months following dosage, but remained clinically well. (Preston, F. E., Lancet, 1985; ii: 213). The trial was stopped.

Isolated reports have reached us since this date, indicating that virgin or minimally treated patients who have received Factorate Heat Treated have developed raised ALTs or jaundice, and have been diagnosed as having non-A, non-B hepatitis.

In France the High Purity Heat Treated product was tested, 7 batches on 10 patients. 2/10 developed non-A, non-B hepatitis over a 12 month period. (Personal communication. J. Gazengel, May 1985).

There is therefore some indication that the additional purification steps may assist in NANB viral reduction and this together with our heat treatment may reduce the NANB risk, i.e. - H.P. may be safer than I.P. Factorate.

HIV Infection

Culture of the virus from blood or product is very difficult and can only be undertaken in specialised research laboratories. Even there, culture is not entirely reliable or predictable. The only practical method of assessing HIV Infection is by HIV antibody test.

Test systems rely on RIA test kits, enzyme immuno assay systems and results are then usually confirmed by Western Blot immuno diffusion assays.

False negative RIA tests are rare, but false positive results are more common.

There is debate concerning the time between infection and sero-conversion, the level of inoculation needed to effect sero-conversion and the relationship of infection levels and time to sero-convert. No one knowns whether dead virus can provoke sero-conversion - i.e. a vaccine-like effect.

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Estimates vary from 2 - 3 weeks to 3 - 5 years for sero-conversion from time of infection. Development of symptoms, should they occur, may take a similar period. Paradoxically, in active AIDS, antibody levels can be very low, or absent.

All of these factors make interpretation of the significance of sero-conversion to HIV antibody positive difficult. It is not certain how long sero-conversion may have taken, whether it is due to live virus or a vaccine-like effect and whether the subject will merely remain in an immune state or proceed eventually to develop active AIDS.

A number of publications have confirmed that wet and dry heat are effective in inactivating HIV. McDougal showed that 60°C for 32 minutes will result in a 10-fold (1 log) reduction in HIV in a lyophilised Factor VIII. Levy, using model lipid enveloped retroviruses, demonstrated that 72 h at 68°C or 10 h at 66°C will reduce the incubation by at least 10^6 in the dry state. (McDougal, S. J. Clin. Invest., 1985; 76: 875 - 877. Levy, J. H. et al, Lancet, 1985; ii: 1457).

Evatt, at the International Congress of Haematology, 1986 stated that "30 hours at 60°C heating of lyophilised Factor VIII concentrate effectively inactivates HTLV-III/LAV without significantly altering its half-life."

Unpublished data from Meloy showed that our manufacturing and heating process for Factorate Heat Treated resulted in a reduction in HIV of at least 5.5 logs, 3.2 log reduction being achieved by the heat process alone. Similar results were reported by the Paul Ehrlich Institute but their methodology has since been discredited.

Three previously untreated patients involved in the Multicentre Factorate Heat Treated Non-A, Non-B study, were HIV antibody negative before treatment with our Factorate Heat Treated and have remained negative. This was not donor screened product. Similarly, using the High Potency material, the experience in Sweden is that in 46 patients no HIV negative patient sero-converted when totally treated with Heat Treated High Potency Factorate. (Felding, P. et al. Lancet, 1985; ii: 833).

Dr. Smit Sbinga has reported that no sero-conversion to HIV antibody positive has occurred in 15 patients treated exclusively with Armour H.T. Factorate for over a year. (Smit Sbinga, C. Personal communication 1985).

Dr. Kernoff has confirmed that a clean virgin patient who was sero-negative after treatment with the Alpha product has not sero-converted following 12 months' treatment with Factorate H.T. (Kernoff, P.B.A. Personal communication, 1986).

However, recent reports of unexplained HIV antibody sero-conversions have given rise to concern.

Van den Berg reported the experience of the Academic Medical Centre in Amsterdam where a patient sero-converted after approximately 2 years' treatment with Factorate Heat Treated. This patient had received cryoprecipitate prior to switching to Factorate. He had also received a batch which contained a known AIDS donor in the plasma pool about a month before becoming positive. (Van den Berg, et al. Lancet, 1986; i: 803-804). However, there have been no other reported cases of sero-conversion in sero-negative patients treated with the contaminated batch.

White (North Carolina) has also reported a sero-conversion following treatment of a minimally treated patient with Factorate Heat Treated. However, this patient was a known drug addict. (White, G. L. Lancet. 1986; ii: 611-612).

Whitmore (Lewisham Hospital) reported to us a sero-conversion in a patient who received a lot (Y69402) of Factorate known to contain a donation from an AIDS sufferer. The patient had received multiple treatment previously with concentrate but none for the previous 5 years.

Nevertheless, a further 6 patients who were sero-negative received the same batch. One died of liver disease (not product related) and the other 5 have remained HIV antibody negative. Follow up of other batches from the infected plasma pool in Germany have not revealed a batch-related sero-conversion but extent, completeness and timing of follow up is not known.

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Recently, a London centre has reported a patient who sero-converted after a year's treatment with Factorate Heat Treated, but who had been given NHS Heat Treated a fortnight previously. The latter was unlikely to have been implicated and this is now being investigated by the D.H.S.S.

2. OTHER MANUFACTURERS

Other manufacturers have adopted widely differing methods aimed at eliminating virus contamination. The following is a list of known/reported heat treatments.

Travenol		60°C 72 hours dry
Cutter		68°C 72 hours dry
NHS Factor VIIIY		80°C 72 hours dry
Immuno TIM II	(i)	60°C 10 hours dry
TIM III	(ii)	Gellis principle (steam)
Biotest		Cold -β-propiolactone + UV irradiation
Alpha		60°C 20 hours 'wet' heptane
Behring		60°C 10 hours in solution

Behring Werke have published convincing evidence of virus inactivation by their process. Some loss of potency is experienced but neo-antigens are not produced. No sero-conversion to HIV positive in patients have been seen. (Mossler, et al. Lancet, 1985; i: 1111. Hilfenhaus, J. & Weidmann, F. Arzneim. Forsh/Drug Res., 1986; 36(1): 621-625).

Travenol product has been reported to have been studied in 18 virgin patients -none sero-converted to HIV antibody positive (Montagnier, L. et al. Haemostasis, 1985; 15: 18). In a further 17 patients in Holland, none sero-converted. (Van der Meer, J. BMJ, 1985; 292: 1049).

Kernoff reported that Travenol (Hemofil T) had exhibited 11/13 Non-A, Non-B Hepatitis (84%) and Immuno 1/1 in virgin patient studies. (Kernoff, P.B.A. Satellite Meeting, St. Thomas' Hospital, 17 March 1986).

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Alpha's Profilate was studied by Kernoff, et al. 18 patients were followed for up to 42 weeks with 9 different batches. No Hepatitis A, B, Epstein Barr, CMV or HIV infection was observed. Acute Non-A, Non-B Hepatitis developed in 4 patients.

37 patients were followed up for up to 13 weeks - none had developed raised ALTs. Alpha have shown a 5.2 log reduction in HIV by their production and heat processes. (Detection limit was 2 logs). (Alpha Brochure).

Finally, reports at open meetings on the new NHS Factorate Y have shown that no patient followed up in their so-called 'virgin' patient study has developed NANB Hepatitis. The study is subject to criticism due to gaps in follow up and the inclusion of minimally treated patients who have received concentrate on one or two occasions previously, but essentially the product looks safe so far.

It should be noted that neither the SNBTS or Elstree donors are currently screened for ALT. Furthermore, both establishments have, until June 1986, been distributing non-HIV screened product.

CONCLUSIONS

1. Factorate Heat Treated is the only Heat Treated which has been positively associated in the literature with HIV antibody conversion.

2. With the exception of the known "contaminated" batches, Armour Factorate Heat Treated is likely to be as safe as other products with reference to HIV.

3. Armour Factorate Heat Treated has the least rigorous dry heat treatment schedule.

4. NANB Hepatitis is a recognised risk from all these products with the exception of the Behring and (possibly) the NHS product.

5. NANB Hepatitis may be more likely with Factorate H.T. I.P. than the H.P. product.

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6. Factorate H.T. I.P. may be less safe viz-a-viz NANB than at least 2 of our U.K. competitors (NHS and Alpha) and definitely less safe than the Behring product.

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EXPOSURES

1. Outstanding data has been requested by Dr Van den Berg via Eastbourne to Dr. Charles Swartz (February 19, 1986). No answer yet received is causing loss of favourable interaction with this Dutch centre.

2. Lack of confidence by Sweden in our heat treatment is compounded by the attempt to initiate a clinical study of a revised treatment process (Dr. Butler) the latter being referred to in the New Scientist article. The result in Sweden could be delays to registration of our product, prevention of even named patient approvals and also threaten the Monoclate study.

3. The decision to by Armour to change to a more intense heat treatment process combined with the recall of unscreened material is seen as an admission that the current process is not fully effective. It will make defence of the present product virtually impossible, both to customers and D.H.S.S. alike.

4. American exchange programme took our DHSS by surprise, who knew about it even before we in Eastbourne. This has jeopardised goodwill both with DHSS and some of our Haemophilia Centre Directors.

5. Natural concern has been generated in both patients and Haemophilia Directors by the "bad" press of the recent product exchange.

6. As a result of No. 3, Factorate H.T. will regrettably be under the DHSS "microscope" and safety questions may arise on both HIV and NANB safety. What would be our response to questions in this area? Would a defence be mounted by Armour if D.H.S.S. raised the question of NANB safety in the context of our studying a revised and more rigorous heat treatment process?

OPTIONS

There are therefore two scenarios possible:-

1. Current Factorate H.T. remains on U.K. market until new heat treatment Product Licence variation. (? timing of the latter data becoming available). Product is defended if attacked.

2. Current Factorate H.T. is forced off the market until revised.

All defence/attack data is presented above and it appears that defence of current product would be difficult, particularly without the defence document originally discussed with Dr. Rodell.