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Dear John

HEAT TREATMENT OF FACTOR VIII

As you are aware we have adopted an interim pilot-scale approach to preparation of a product which is known to have viral contamination reduced by inactivation using heat. Our aim has been to monitor the heating process to achieve a viral inactivation rate equivalent to that obtained for albumin by heating at 60° for 10 hours.

This is in course of study using several viral species with vaccinia as a convenient marker organism, SV40 as being hard to inactivate and herpes simplex as representative of a group of organisms of clinical importance. We are also being careful to study both DNA and RNA virus species with a view to being able to extrapolate our findings over a wider range of organisms.

These studies are not complete but are progressing well and showing the predicted effects. It has been found, however, that heating for a shorter time, now known to be less than 10 hours, at a higher temperature is much more effective. For example, a vaccinia test loading of 10^9 particles/ml is reduced to about 10^4 when heated at 60° for 10 hours both in Factor VIII solution and in Albumin. However, heating at 70° for <1 hour reduces the same viral burden to 10 particles/ml. This is the limit of sensitivity of our assay because of the dilutions necessary to reduce the sugar content before assay.

The heating process carries a penalty in that some Factor VIII is inactivated and this can be as great as 20% of the total present. We have found that this loss occurs early in the heating stage and thereafter remains about the same level.

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The loss incurred by heating at 70° is not appreciably greater than that incurred at the lower temperature.

It has been our programme for 1983 that we process between 4 and 6 pilot lots in this fashion, involving makeshift pasteurising, and to design a system which would allow up to 30% of our total Factor VIII production to be heated treated in 1984.

The first pilot lot has been prepared as a small quantity of material taken from a larger pool so that comparison of heated and non-heated material could be made at all stages of manufacture and so that clinical comparison could be made. Unfortunately the non-heated material, lot No NY 760, has proven to fail laboratory release criteria on ground of pyrogenicity and should not be issued for clinical use. The associated lot, No NY 761, of heated product consists of 57 vials each containing 145 IU of Factor VIII. Normally we try to issue Factor VIII Concentrate so that it is isotonic (292 mOsmols) but, being in an early phase of the production programme, we did not get this right for lot No NY 761. Our desire for such bland conditions is not shared by all manufacturers for all products and it would be permissible to use a volume of 25 ml giving 5.2 IU/ml at 500 mOsmols. Later pilot lots will be of more acceptable concentration and volume. We are planning for 10 ml at approximately 25 IU/ml for the final product and now have the experience from which we should getr this right at about 290-300 mOsmols in the next pilot run. In the meantime I believe it is sensible to get some clinical experience of lot No NY 761 as part of the overall process introduction.

As you are aware there are several steps in the preparation of the (H)F VIII type of product:

1. Cryoprecipitation.
2. Zinc Extraction.
3. Calcium Stabilisation.
4. Heat Treatment.

Of these steps 1 and 3 can be applied to the existing Factor VIII and we plan to process several lots in this way to make sure, against a well known background, of the significance of the calcium stabilisation stage which seems to provide close on 20% increase in yield.

At present we have two product lots, NY 771 and NY 772 which were prepared from one plasma lot of which NY 771 was processed as normally and NY 772 was processed with the addition of calcium arranged to maintain a constant level of ionised calcium. These lots have not cleared all control testing so far but appear very promising. The pertinent details are:

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	NY 771	NY 772	% Increase
Plasma Vol (l)	285	245	
Process Vol After Adsorption (l)	11.63	10.00	
Dispensed Vol (l)	11.68	10.88	
Vol Dispensed ml/litre Plasma	40.98	44.41	8.4
Solubility Time (mins)	6.0	6.5	
Factor VIII Potency IU/ml	14.85	16.45	10.8
Process Yield IU/litre Plasma	372.2	446.0	20.0

The yield of the control lot NY 771 is higher than normally expected (280-320 IU/μlplasma) and may be a reflection of better than usual plasma quality. This trial system is to be repeated to enable us to make sure that the yield advantage of the stabilised product is maintained. I would like to see these products also submitted to clinical evaluation where I hope we may see an improved in vivo recovery of F VIII. An improvement in half-life is not expected.

In view of tecent news exposure of (?) infectivity of Factor VIII concentrates we have made a re-assessment of heat-treated concentrate based on a careful step-by-step appraisal of a series of pilot-scale lots.

In most areas of the development I believe we now prossess sufficient data to allow, by adopting a few calcuated risks, this programme to be speeded up substantially. It would mean expansion of the make-shift process now in use and would involve expenditure now instead of 1984-85 as well as some additional expenditure which would not advance the longer-term production process. By doing this we could expand production of the (H)F VIII quickly to at least the level of present production, which is limited by the ability to process the resultant cryo-poor plasma. My colleagues are engaged in a costing for the expedited programme in case public opinion rather than science may dictate the best course of action.

With kind regards.

Yours sincerely

JOHN G WATT
Scientific Director

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