IN CONFIDENCE

NOTES FOR SCOTTISH HEALTH SERVICE HAEMOPHILIA CENTRE/

TRANSFUSION SERVICE DIRECTORS' MEETING: MARCH 1986

February 1986

JDC/SHHD/2/86/1

These notes have been produced to facilitate discussion with regard to future SNBTS planning for the production of blood products required for the management of patients with haemostatic or thrombotic disorders, within the Scottish Health Service. All annual figures contained in these notes refer to years ending 31st March and do not include Northern Ireland.

I am indebted to SNBTS Director colleagues who have been responsible for providing, through the national statistical returns, much valuable information, and in particular to Dr Perry for information on PFC's activities (Appendix VI).

FACTOR VIII CONCENTRATES

FRESH PLASMA PROCUREMENT FOR FACTOR VIII

The progress made in previous years has been maintained (see Appendix 1). The total annual SNBTS figures (kg) can be summarised as follows:-

1981	1982	1983	1984	1985
28,474	35,748	40,739	51,017	52,480

ISSUES OF FACTOR VIII CONCENTRATES

The figures below provide a summary position of trends since 1981 (details in appendices II and III), and one derived from issues from PFC to RTC and cryoprecipitate from RTCs to wards or Haematology Departments:-

	1981	1982	1983	1984	1985
Cryoppt. (donations)	26,045	17,855	12,953	11,646	12,693
Intermediate VIII (m.i.u.)	3.58	4.70	4.86	9.26	7.40

Note

(i) The intermediate VIII figures are somewhat suspect because of the intense activity in 1985 surrounding the establishment of batch dedication and the introduction of heat treated products.

(ii) It is probable that a substantial quantity of the issued cryoppt. was not used in the management of haemophilia A patients.

COMMERCIAL FACTOR VIII CONCENTRATES

The information obtained by the SNBTS is summarised below (m.i.u.) (details in Appendix IV):-

1981	1982	1983	1984	1985
1.37	1.40	1.04	0.11	0.03

SUMMARY (Details in Appendix V)

	1981	1982	1983	1984	1985
Cryoppt.	2.60	1.78	1.27	1.16	1.27
PFC	3.58	4.70	4.86	9.26	7.4
Commercial	1.37	1.40	1.04	0.11	0.03
Total	7.55	7.88	7.17	10.53	8.7

COMMENTS

(1) Production Target Figures

The past 12 months have proved to be an operationally turbulent period for the SNBTS, and in particular PFC and clinical units. Current clinical uptake of factor VIII would appear to be in the region of 1.7 m.i.u./m. pop./year. It is now becoming increasingly clear that the impact of existing heat treatment regimes is considerable in fractionation yield terms (see Dr Perry's report: Appendix VI) and recent calculations have indicated that the yield penalty using the existing product, is of such a magnitude that the plasma supply current demand is in a steady state. Put simply, we do not realistically anticipate being

able to respond to a significant increase in demand without increasing the fresh plasma supply. There is no problem with regard to fractionation capacity.

Colleagues are reminded that over the last 4 years both sets of Directors have repeatedly agreed that the SNBTS should target its factor VIII production at 2.75 m.i.u./m. pop./year (our current figure is say 1.7 and we have almost exhausted our facility to collect fresh plasma from routine donations). Colleagues are also reminded that at the last joint Directors' meeting (March 1985) one Haemophilia Director expressed the view that if there was a high purity, guaranteed "virus safe" product available then the clinical demand might reach 7.0 m.i.u./m. pop./year.

The SNBTS Directors have anticipated the emergence of fresh plasma supply difficulties and are incorporating into their development programmes a bid for additional central funds which, if received, will enable them to implement a variety of options designed to secure a production target of 2.75 m.i.u./m. pop./year over the next 3-4 years. These plans have not yet been submitted to central authorities but it would be of value to once again ask the question, "Is it the professional opinion of the SHS Haemophilia/Transfusion Centre Directors that the SNBTS' target for factor VIII production should remain at 2.75 m.i.u./m. pop./year"?

(2) HTLV-III

(i) Donation Screening Programme

All colleagues will be aware that routine HTLV-III antibody testing of all donations was commenced throughout the UK on October 14th 1985. All SNBTS Centres are using the Wellcome Diagnostics Ltd test. Confirmation (reference) testing is primarily based upon the Western Blot which is done by colleagues in the University Departments of Bacteriology in Edinburgh and Glasgow. Efforts have been made throughout Scotland to establish self-referral centres (for HTLV-III antibody testing and counselling) which it is hoped will divert high risk individuals away from donor sessions.

(ii) Retrospective Checking

Facilities have been developed which enable checks to be made of previous donations which may still be in process at PFC. If found to be HTLV-III antibody positive, notwithstanding the heat treatment programme, a "contaminated" batch will be discarded (not released for clinical use). If a batch has been released for issue prior to the discovery of "contamination" then it will be recalled.

(iii) Heat Treatments

Evidence emerged in mid 1985 that some heat treatment regimes are not effective with regards to non-A/non-B hepatitis viruses. We have assumed that whilst there is evidence to suggest that HTLV-III is more sensitive to heat, similar principles may apply and recent data from Montagnier's laboratories indicate this is a correct working assumption. These considerations have added weight to plans, which have been in preparation for over 12 months, to validate our heat treatment process with respect to HTLV-III. This work will begin in the Spring of 1986.

(iv) Batch dedication

All colleagues are to be congratulated for their considerable efforts to establish this system. It is suggested that this system should be retained for at least a further 12 months and used to target the phased introduction of the next generation of factor VIII concentrates (see below).

(v) High purity product

Reference should be made for details on this topic to Dr Perry's report (Appendix VI). Colleagues would wish to know that difficulties have arisen with regards to the heat treatment of this high purity product. As a consequence it is anticipated that there will be some delay in it reaching pahse 1 (recovery and ½) studies. Accordingly, a decision has been taken to introduce an interim solution: a product which is only 2-3 times purer that the existing intermediate VIII but which can be dry heated at 80°C for 72 hours.

It is hoped that this product will be available for routine clinical issue within 3 months. However, consideration must be given as to the way it will be phased in at the clinical level, because it will take several months of production to ensure free access of product to all patients and, it is strongly suggested, we should make every effort to use up stocks of the intermediate product which is dry heated at 68°C for 24 hours.

It is therefore proposed that the interim (new) product is phased in through the existing batch dedication system and that Haemophilia Directors advise PFC via their RTD of their priority rating, if any, for access to the new (interim) product.

(vi) Oxford Returns

We are again indebted to Dr Rizza and Miss Spooner for providing us with the relevant data.

	1982			1983			1984		
	Total Use	Use/m. pop.	% Commer-cial	Total Use	Use/m. pop.	% Commer-cial	Total Use	Use/m. pop.	% Commer-cial
E/W/NI	67.5	1.4	66	77.1	1.5	51	72.7	1.4	47
Scotland	6.1	1.2	9	6.8	1.3	6	7.2	1.4	0.6

These data are sufficiently close to the SNBTS data and thus permit satisfactory SHS planning.

FACTOR IX CONCENTRATES

SUPPLY TRENDS

PFC issues to RTCs since 1981 are summarised below:-

	1981	1982	1983	1984	1985
DEFIX (m. i.u. of IX)	1.0	1.0	0.9	1.43	1.59
PPSB (10^3 i.u. of IX)	44	44	20	35	30

COMMENTS

(1) Directors will note the sustained and dramatic increase in the demand for DEFIX. This has arisen due to its use in the management of haemophilia A patients with inhibitors.

(2) A heat treated DEFIX product was introduced in 1985 (dry 80°C for 72 hours). Evidence from England and Wales would indicate this product will not transmit non A/non B viral hepatitis and thus presumably HTLV-III. As a consequence it is suggested that no further consideration will be given to batch dedication.

(3) The basic fractionation process for this product (DEFIX) is poor yielding and variable in end product quality. The current heat treatment regimes give rise to substantial further losses.. As a consequence of these factors and the escalating demand there are chronic supply problems which demand careful monitoring by PFC colleagues.

(4) It is conceivable that the heat-treatment process destroys the usefullness of DEFIX in the management of haemophilia A with inhibitors (communication with Dr Elizabeth Mayne, Belfast). This problem is currently under investigation and any information from clinical colleagues would be most welcome.

(5) Further supply difficulties are envisaged if the heat treated DEFIX is used extensively in the management of neonates, liver failure and the reversal of oral anticoagulants. Current SNBTS estimates indicate that if these practices became widespread then the demand would be doubled. It is our current view that the extension of the use of this product should not be encouraged until further animal toxicity studies, currently underway, are completed.

FACTOR VII CONCENTRATE

As indicated in Dr Perry's report (Appendix VI) PFC staff are currently developing a heat treated factor VII concentrate so that it could be introduced and thus permit the abandonment of PPSB. It is not envisaged that this product will be available within the next 12 months as it will first require extensive animal toxicity testing.

ANTI THROMBIN III CONCENTRATE

As indicated in Dr Perry's report (Appendix VI) there is now a requirement to develop this product. It is anticipated that Haematology colleagues will be required to assist, in due course, to assist us in the in vivo evaluation of this product.

VON WILLEBRAND FACTOR CONCENTRATE

It is hoped to include this heat treated product in our development programme in the near future (see Dr Perry's report).

CONCLUDING REMARKS

(1) In respect to that facet of the SHS's work to which this report refers, 1985-86 has been a year dominated by HTLV-III. 1986-87 is likely to be dominated by planning for increased plasma procurement and further concentrate production developments. SNBTS Directors remain concerned that notwithstanding the quite excellent co-operation between Haemophilia Directors and the SNBTS we have not yet succeeded in achieving an entirely satisfactory SHS system for the ongoing study and reporting of patients, looking for seroconversion and evidence of antibody formation to neoantigens. It is proposed that this matter receives the attention of a small working Group made up of members and/or representatives of the Haemophilia/BTS Directors' Meeting as it represents a matter of major operational importance to the manufacturer (PFC) of these concentrates.

(2) I am aware of 3 published papers in which the authors have reported on their investigations of Danazol (an attenuated androgenic steroid) to increase factor VIII and IX levels in haemophilia A and B patients, respectively. Another paper suggests that Danazol may increase factor VIII and IX bypassing activity. Comments are invited by Haemophilia Directors and, in particular, SNBTS Directors would wish to know whether this work is being explored in Scotland.