0004 1983/1

IN CONFIDENCE

NOTES FOR SCOTTISH HEALTH SERVICE HAEMOPHILIA CENTRE/ TRANSFUSION SERVICE DIRECTORS' MEETING

JANUARY 1983

These notes have been produced primarily to facilitate discussion with regard to future SNBTS planning for the production of blood products associated with the management of patients with haemostatic or thrombotic manifestations. The figures given in this document refer to years ending 31st March.

FACTOR VIII CONCENTRATES

FRESH PLASMA PROCUREMENT

Progress made in the last 5 years has been maintained and consolidated. A summary of the trends over the past 5 years is given below (details in Appendix I).

Total Fresh Plasma Processed for VIII Concentrates (Kg.)

1978	1979	1980	1981	1982
19,581	20,553	25,059	28,474	35,748

ISSUES OF FACTOR VIII CONCENTRATES

The total issues for factor VIII concentrates from the Regional Transfusion Centres (cryoppt.) fell but there has been a substantial increase in issues of PFC product which largely parallels the increases in plasma procurement. These can be summarised as follows (details in Appendices II and III).

Total Cryoppt. Issued from RTCs (Donations)

1978	1979	1980	1981	1982
31,151	35,199	30,273	26,045	17,855

Total PFC Issues of Intermediate VIII (i.u. x 10^6) to RTCs

1978	1979	1980	1981	1982
1.55	1.66	1.99	3.58	4.70

COMMERCIAL FACTOR VIII PURCHASES

Recent evidence would indicate that the figures available to the SNBTS for this item may be in error (too low). It is hoped that improved precision will evolve in the near future. The figures available can be summarised as follows (details in Appendix IV).

SHS Commercial Purchases of Factor VIII (i.u. x 10^6)

1978	1979	1980	1981	1982
NK	0.85	0.98	1.37	1.4

Summary/

Summary Position (i.u. x 10^6) (Details in Appendix V)

	1978	1979	1980	1981	1982
Cryoppt.*	3.15	3.52	3.02	2.60	1.78
PFC	1.55	1.66	1.99	3.58	4.70
Commercial	(0.50)	0.85	1.00	1.37	1.40
Total	(5.2)	6.03	6.01	7.55	7.88

* Each donation is assumed to yield 100 i.u. of factor VIII.
Figures in brackets are 'guesstimates'.

NEW DEVELOPMENTS

(i) Freeze Dried Cryoprecipitate

The SNBTS would wish to put on record its thanks to colleagues in the West who undertook the successful clinical trial of the product produced at Law. Notwithstanding this work it has been decided to cease this activity in the light of closing down of the freeze dried plasma plant, the cost of meeting the demands of the Medicines Inspectorate and the recent evidence of imminent availability of a low risk factor VIII concentrate from commercial sources.

(ii) SNBTS Factor VIII Study Group

This Study Group was established in 1982 and is chaired by the NMD. The Group's activities include examination of ways by which the quality of fresh plasma fractionated at PFC can be improved. Satisfactory progress is being made and it is hoped that within the next 3 years significant benefits will accrue.

(iii) Higher purity Factor VIII concentrate

Rapid progress has been made following the last meeting of the Haemophilia/Transfusion Centre Directors during which it was requested that efforts be made at PFC to explore the possibility of producing an VIII concentrate with a low fibrinogen content. A new method has been developed and is currently subject to patent application. It is anticipated that by late 1983/early 1984 small amounts of the product will be released for limited clinical trials.

(iv) Heat treated Factor VIII concentrate

It is common knowledge that this type of product, which should have a reduced risk of transmitting hepatitis, will be commercially available in 1983 throughout/

throughout the UK. Colleagues at PFC have been working on this problem for some time and it is hoped that in 1983/84, in close association with the work referred to above (iii), that limited supplies will be available for clinical trials. The progress of this work has been slow, primarily due to a desire to minimise the deleterious effects on yield. Efforts are now being made to offset what is regarded as an inevitable yield penalty by the introduction of an additive anticoagulant programme at the RTCs. This programme will, in the fullness of time, yield a 25% increase of fresh plasma from existing donation input.

FACTOR IX CONCENTRATES

SUPPLY

(a) DEFIX

The supply position, with regard to DEFIX remains strong and the issues from PFC to RTCs reasonably stable. The position over the last 5 years can be summarised as follows:-

DEFIX Issues from PFC to RTCs (i.u. of IX x 10^6)

1978	1979	1980	1981	1982
1.1	0.86	1.0	0.89	0.91

(b) PPSB

The demand for a factor VII containing factor IX concentrate remains, albeit low. The position over the last 5 years can be summarised as follows:-

PPSB Issues from PFC to RTCs (i.u. of IX)

1978	1979	1980	1981	1982
130,000	70,000	45,000	66,000	30,000

DEVELOPMENTS

(i) Supernine (SIX)

This product, a more purified form of DEFIX and believed to have a reduced hepatitis transmission risk, has now almost completed those clinical studies from which data will be generated for submission for a product licence. This work has been organised by Dr Frank Boulton, but thanks are due to colleagues in the Haemophilia Centres of Edinburgh and Glasgow. The results, to date, look excellent.

(ii)/

(ii) Future Status of DEFIX

It had been anticipated that the introduction of SIX to routine clinical practice would permit the withdrawal of DEFIX from PFC's product range. Recent exploration of the feasibility of producing an activated IX concentrate for the management of haemophilia A patients with inhibitors has led us to reconsider the desirability of abandoning DEFIX prematurely. This decision has been fortified by the recent information following contact with colleagues in the US who have intimated that the 'proplex'/'autoplex' clinical trial has revealed no significant difference. Accordingly, a more detailed analysis of the constituents of PPSB, DEFIX and SIX is currently underway, as are studies with colleagues in NIBSC in the general area of new products for the management of haemophilia A with inhibitors.

(iii) Heat treated Factor IX concentrate

Heat treatment studies, to reduce the hepatitis risk, are currently underway, using SIX. It is probable that the rate of progress with this product will be slower than factor VIII because it will be necessary to submit the heated IX concentrate to intensive animal studies prior to administration to patients, in order to confirm that the heat reatment has not resulted in the evolution of a thrombogenic product.

It should be noted that the forthcoming arrival of a hepatitis 'safe' factor IX concentrate will raise the clinical demand for a prothrombin complex concentrate. The current inhibition to its use in patients with liver disease and oral anti-coagulants will be removed. This increased demand might necessitate a production target (vials on shelf) as much as 50% of existing programme.

FACTOR VII CONCENTRATE

There is a view, strongly held by some (including the author) that a small number of patients with acquired severe forms of prothrombin complex deficiency require factor VII to arrest bleeding. At the present time the SNBTS makes PPSB available for this use. PPSB is an unsatisfactory product from a manufacturing point of view (requires EDTA plasma) and PFC has now made significant progress towards the production of a VII concentrate. This product should be animal tested (thrombogenicity) in 1983 and be available for clinical evaluation in 1983/84. Dr John Davidson has kindly agreed to collaborate with the NMD on this project.

ANTITHROMBIN III CONCENTRATE

It is hoped that by the end of 1983 PFC will have reduced to practice (into production) their successful development programme designed to make available a heat treated antithrombin III (AT-III) concentrate.

The demands for this product are now under serious review. There seems little doubt that it will be of benefit to those patients, which are increasingly being recognised, who have a congenital deficiency associated with recurrent thrombotic problems. The biggest potential demand may arise from acquired deficiencies. However, the data available at the present time leads the author to conclude that considerable caution is required and that the SNBTS should endeavour to promote clinical research in this area within the SHS and, at the same time, maintain contact with colleagues overseas.

It is hoped that preliminary clinical evaluation (in congenitally deficient patients) of the SNBTS product will be initiated in 1983/84. In preparation for this work the SNBTS gratefully acknowledge the efforts of clinical colleagues throughout Scotland who have already agreed to participate.

MISCELLANEOUS

ACQUIRED IMMUNE DEFICIENCY SYNDROME (AIDS)

The attention of the Haemophilia Directors is drawn to this problem (Appendix VI). It is noted that in the US the National Haemophilia Foundation and CDC are already conducting a survey and intend to establish a permanent surveillance programme. The information contained in Appendix VI has been sent to Professor A L Bloom, Chairman of the UK Haemophilia Centre Directors' meeting.

PFC REFIT

The PFC is currently in the throes of the initial stages of a major refit, in order to bring it up to the standards required by Medicines Division (DHSS). There can be no doubt that despite the efforts of PFC staff there will be periods over the next 3 years during which all or part of production will cease for short periods of time. This will inevitably have some consequences on supply of products and Haemophilia Directors are strongly advised to maintain close liaison with their Regional Transfusion Directors with regard to the availability of factor VIII concentrate, in particular. In the meantime, regional/

regional allocations of intermediate factor VIII are being somewhat restricted so that sufficient national stocks can be acquired to cover any 'close-down' periods.

OXFORD RETURNS

The SNBTS would wish to record its thanks and appreciation to Dr Charles Rizza and his staff at the Oxford Haemophilia Centre for providing a complete breakdown of the UK Haemophilia Centre Directors' Annual Returns, with respect to Scotland.

Dr Ludlam may wish to comment on certain matters of detail but the following information of interest to both Haemophilia and Transfusion Centre Directors has been extracted:-

Use of All factor VIII (i.u. x 10^6)

	1980*			1981		
	Total Use	Use/ 10^6 pop.	% Commercial	Total Use	Use/ 10^6 pop.	% Commercial
E/W & NI	52.29	1.05	67	60.05	1.20	54
Scotland	5.38	1.08	20	5.65	1.01	22

* Calendar years