

0003

IN CONFIDENCE

NOTES FOR SCOTTISH HEALTH SERVICE HAEMOPHILIA CENTRE/  
TRANSFUSION SERVICE DIRECTORS' MEETING: MARCH 1985

February 1985

JDC/SHHD/2/85/1



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 CONCENTRATESFRESH PLASMA PROCUREMENT

Further progress has been made which is summarised below (details in Appendix I). Discussions held some 6 months ago, (at the time when surplus of factor VIII was being shipped to BPL (Elstree)), centred on the possibility that the SNBTS was producing FFP in excess of its needs, have been suspended pending examination of more recent trends in the use of factor VIII and the effect of heat treatment programmes.

Total Fresh Plasma Processed for Factor VIII Concentrate (Kg)

<u>1980</u>	<u>1981</u>	<u>1982</u>	<u>1983</u>	<u>1984</u>
15,059	28,474	35,748	40,739	51,017

ISSUES OF FACTOR VIII CONCENTRATES

The figures below include the issues of products from PFC to RTCs and the issue of cryoppt. from RTCs to Wards or Haematology Departments. The trends since 1980 are summarised below (details in Appendices II and III).

	<u>1980</u>	<u>1981</u>	<u>1982</u>	<u>1983</u>	<u>1984</u>
Cryoppt. (donations)	30,273	26,045	17,855	12,953	11,646
Intermediate VIII (million i.u)	1.99	3.58	4.70	4.86	9.26

COMMERCIAL FACTOR VIII CONCENTRATES

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

<u>1980</u>	<u>1981</u>	<u>1982</u>	<u>1983</u>	<u>1984</u>
0.98	1.37	1.40	1.04	0.11

SUMMARY (Details in Appendix V)

	1980	1981	1982	1983	1984
Cryoppt.*	3.02	2.60	1.78	1.27	1.16
P F C	1.99	3.58	4.70	4.86	9.26
Commercial	1.00	1.37	1.40	1.04	0.11
TOTAL	6.01	7.55	7.88	7.17	10.53

\* Each donation is assumed to yield 100 i.u. of factor VIII

COMMENTS(a) Production Target Figures

Colleagues will appreciate that the SNBTS is currently being subjected to considerable degrees of pressure both with regard to the supply and quality of factor VIII concentrates. Whilst we believe the 1984 figures are somewhat distorted (because of known high RTC stocks) we would conclude that the target calculated by the SNBTS for the late 1980s, and supported by SHS Haemophilia Directors, appears to have been a useful one. However, colleagues may wish to reflect on the likely impact on the eventual target of a freely available heat treated product. The author believes there may well be new additional pressures for supplies and that as a consequence the currently agreed targets may prove to be too low. The worst scenario that can be conceived at the present time is the data obtained from West Germany some years ago. At that time the average annual requirement of factor VIII for the comprehensive care of a severe haemophiliac was 200,000 i.u. If these figures were translated to the SHS (with the advent of a safe heat treated product) and to severe patients alone then I would calculate our requirements would rise from 2.75 m. i.u./m.pop./year to approximately 11.00 m. i.u./m.pop./year. The impact on the SNBTS of a move in this direction would be considerable.

Comments from clinical colleagues would be welcome. In the meantime the SNBTS is preparing the ground for an examination of its options should further demands arise for, in addition to the potential problems suggested above, we require to ascertain the effects of current PFC activities (see below) on plasma supply. Notwithstanding these difficulties the immediate future PFC interim production plans have been issued by Dr Perry and are included in Appendix VI.

(b) AIDS

(i) Donor Leaflet

SHS Haemophilia Directors will be pleased to learn that the SNBTS Directors moved in August 1984 to implement further improvements in the text of the leaflet provided to donors, designed to eliminate the bleeding of high risk donors (Appendix VII). In November 1984 the Directors took further action in order to ensure that all donors had read and understood the new leaflet and were not in the high risk group (example in Appendix VIII).

(ii) HTLV-III Antibody Testing of all Donations

The introduction of these tests for all donations is inevitable. The timing of this development is uncertain at this time. Haemophilia Directors will wish to know that aside from very substantial revenue costs (it may be in excess of £500,000 p.a. for the SNBTS) there are significant potential problems with regard to the effects the introduction of these tests might have on our donor population which in turn may affect blood supplies. These matters are currently being examined, on a UK basis with SNBTS involvement.

(iii) Heat Treated Factor VIII Concentrates

The period since November 1984 has been one of considerable difficulty for SNBTS Directors but in particular the senior staff of PFC. It has been a period in which disaster struck in Australia and in which both UK Transfusion Services were implicated in the transmission of HTLV-III viruses.

There have been some understandable criticisms of the way we

moved to make available unlimited quantities of heat treated factor VIII concentrate in late December 1984. These criticisms are justified (and supported by the letter of Dr A R Bird et al in the 19th January Lancet) and as National Medical Director I must accept responsibility. Nonetheless, I take the view that with the information we had, and in the circumstances we found ourselves, we acted responsibly and in the best interests of both the patients and the SHS. In all these difficult decisions I wish to put on record the considerable and continued practical support I received from PFC staff and Dr Charles Forbes and Dr Christopher Ludlam. It may be of interest to Haemophilia Directors that the efforts made by the SNBTS to cope with the problems appear to be no less than our commercial competitors.

The present position is as follows:-

(a) Dry (Intermediate) HT (68<sup>o</sup> for 2 hours)

The heat treatment programme has been based on preliminary information received from the USA (in November 1984) specifically with regard to HTLV-III. It involves the dry heat treatment of the existing intermediate product without the addition of stabilisers. The heat treatment regime of this product may be less than satisfactory, although there are no data to support this. However, it has been noted that several commercial companies have more aggressive heat treatment protocols - introduced primarily towards killing hepatitis viruses. This product has been tested (% recovery and  $\frac{1}{2}$  life) by Drs Forbes and Ludlam and has been shown to be satisfactory. It is anticipated that this HT product will remain the standard routine SNBTS issue until the autumn of 1985.

(b) Dry (Intermediate) HT (68<sup>o</sup> for 24 hours)

The heat treatment protocol of this preparation (routine intermediate product) requires the addition of stabilisers prior to heat treatment. PFC have already determined optimal conditions and it is anticipated that preliminary clinical evaluations (% recovery and  $\frac{1}{2}$  life) will be completed by the end of May 1985. Thereafter, the introduction of this product into routine use will be the subject of discussions with the

Haemophilia Directors. However, the author would like to see this product evaluated within the context of the "virgin" haemophiliacs/LFTs. Directors would wish to note that the overall yield losses with this product are in the region of 15-20%.

(c) High Purity (HT) Product

Work on this product is proceeding satisfactorily at PFC. Decisions have not yet been made with regard to the heat treatment regime but at the present time wet heat treatment is favoured. It is hoped that limited quantities will be available for preliminary clinical studies by late Autumn 1985. Efforts will be directed with this product to achieve AIDS and viral hepatitis "safety".

Haemophilia Directors will be interested to know that virus inactivation model studies performed at PFC would indicate that the traditional heating programme (applied to albuminoid products) at 60°C for 10 hours appears to be inadequate for factor VIII concentrates, to which stabilisers must be added.

(d) Batch Dedication

Although Haemophilia Centre and BTS Directors agreed to this approach in principle at their last annual meeting little progress was made until November/December 1984. Preliminary studies, carried out in the last 3 months at SEBTS and WBTS, have indicated that this approach, whilst posing significant new operational problems, is a feasible proposition for the SHS. Pilot studies will be established in Edinburgh and Glasgow with a view to extending this facility as soon as possible (see Appendix VI).

It is the opinion of the author that this represents a major and important development but will require a new approach to the liaison between RTCs and PFC.

(e) Restriction of Donation Exposure by Plasma Pool Selection

There is some (unpublished) evidence to suggest this approach may be of additive value, particularly with respect to viral hepatitis transmission. It is the view of the author that at the present time efforts directed towards this goal should await data obtained from heat treatment programmes,



primarily because in the present circumstances this approach would be operationally difficult and extremely expensive.

(f) Commercial Purchase of Human Factor VIII

Once again the SNBTS has had considerable difficulty in obtaining data on this topic from hospital pharmacists. Assistance has been requested from the Chief Pharmacist (SHHD). So far no response has been received.

From the data available it would appear that commercial product purchases are confined to Edinburgh. Dr Ludlam indicated at the meeting last year that he had one patient who required a high purity (low fibrinogen) product - a product currently not available from the SNBTS.

(g) Oxford Returns

We are again indebted to Dr Charles Rizza and Miss Rosemary Spooner who have provided data from which the following have been extracted:-

Factor VIII Use (m. i.u.): Oxford Data

	1981			1982			1983		
	Total use	Use/m.pop.	% Commercial	Total use	Use/m.pop.	% Commercial	Total Use	Use/m.pop.	% Commercial
<u>E/W/NI</u>	60.1	1.2	54	67.5	1.4	66	77.1	1.29	51
Scotland	5.7	1.0	22	6.1	1.2	9	6.8	1.3	6

These data are sufficiently close to SNBTS data to permit satisfactory SHS planning. That said their interpretation is self-evident.

(h) Filter Needles

PFC staff have ascertained that all companies selling heat treated factor VIII concentrates recommend that the 'dissolved' product is withdrawn from the vial using a filter needle. We have reason to believe that this is because of intrinsic solubility problems.

We take the view that provided sufficient time is given to

achieve full solubility of the current SNBTS product this development is not necessary. Nonetheless we would welcome views of the Haemophilia Centre Directors who have now had 2 months experience of the SNBTS product.

(i) Factor VIII (Vial) Content

Dr Ludlam has kindly liaised with his Haemophilia Director colleagues and drawn our attention to a general desire to see the factor VIII vial content increased (Appendix IX). It is the view of Dr Perry and myself that it would be inappropriate at a time when so many other changes are taking place (heat treatment and batch dedication) to make any changes in vial content, but that this topic should be examined in detail by the Joint Working Party with a view to making changes in the future. Colleagues would wish to note that changes in vial content could make significant savings but unless there were closely associated changes in clinical practice the reverse might apply.

(ii) PFC Factor VIII Licence

Due to some central difficulties the PFC factor VIII product licence inadvertently lapsed. Dr Perry took this matter up with the licensing authority and this anomaly has been corrected. It seems certain that we will request a product licence variation - for the dry HT (68°C-24 hours) product. More substantial data will be required for the High Purity (HT) product. In all these matters we will have to continue to rely on the excellent co-operation of our Haemophilia Director colleagues in providing in vivo recovery and  $\frac{1}{2}$  life and clinical efficacy data. These studies will be co-ordinated by the Joint Working Party chaired by Dr McDonald (see Appendix X).

CONCLUSIONS

Comments on any aspect of the narrative above would be most welcome. Specific topics on which comments are required are as follows:-

1. Production Targets

In the light of the data to hand (in particular consumption trends in the first 3 quarters of 1984/85), should the SNBTS continue to

plan for an annual total factor VIII concentrate use of 2.75 m. i.u./m.pop.?

2. Cryoprecipitate

The decision last year to reduce substantially the use of cryoprecipitate for the management of haemophilia A does not appear to have been implemented (see Appendix II). Comments from clinical colleagues would be most welcome. It is assumed the major usage may have been related to AIDS in the paediatric setting. If so then the question arises: will colleagues adopt the UK Haemophilia Directors' recommendations and opt for the current heat treated product in favour of cryoprecipitate? If so, will this also apply to VWD patients?

3. Vial (Factor VIII) Content

Would colleagues agree to refer this matter to the Joint Working Party?

4. Filter Needles

Would clinical colleagues agree to no further SNBTS action on this matter and that the use and therefore acquisition of filter needles would be a local matter?

5. Clinical evaluation studies

- (a) Do colleagues approve in principle of the protocols appended (Appendix X)?
- (b) Would colleagues agree to retain aliquots of serum for long term follow-up of patients outside the clinical studies referred to in 5(a) above?
- (c) If 5(b) is acceptable then is there a requirement for the central storing of such aliquots?

6. Batch Dedication

Would colleagues agree to the implementation of this programme as soon as possible?

FACTOR IX CONCENTRATESSUPPLY TRENDS

PFC issues to Regional Transfusion Centres since 1980 are summarised below:-

	1980	1981	1982	1983	1984	1985 <sup>o</sup>
DEFIX (m.i.u. of IX)	1.0	1.0	0.9	1.0	1.43	2.17
PPSB (thousand i.u. of IX)	44	44	20	35	30	30

<sup>o</sup> Estimate based on data from 3 quarters

Comments:

- (1) The sustained downward trend in the use of PPSB is welcomed.
- (2) There has been a significant and inevitably uncontrolled increase in the use of DEFIX for the management of Haemophilia A patients with inhibitors. All evidence points to the fact that these patients are currently consuming approximately 50% of issued product.
- (3) The unplanned nature of (2) above and the unexpected loss of product following batch recall associated with HBs-Ag contamination has given rise in part to significant supply difficulties in the last 12 months. Efforts are being made by PFC staff to surmount these difficulties. Until this is achieved (thereby having substantial stocks) it will not be possible to introduce batch dedication for this product.

HEAT TREATED FACTOR IX

Despite considerable efforts over the last 2 years it has only very recently been possible to make arrangements for animal model (thrombogenicity) testing. These were recently begun and provided all goes well it is anticipated that a heat treated product will be available for preliminary clinical evaluation by late Spring of 1985. The product currently the candidate for heat treatment is DEFIX.

SUPERNINE

Events over the past 12 months have necessitated the shelving of a programme (see last report) designed to bring forward this product for clinical use, as the limited manpower resources have had to be directed to other products. Whilst this has been a disappointment we believe it may eventually be turned to advantage - SuperNine is a very low yielding product and consideration may now be given to alternative manufacturing procedures directed towards the production of a high purity product. Such developments are not likely to emerge until the problems associated with the production of high purity factor VIII are resolved.

FACTOR VII AND ANTITHROMBIN III CONCENTRATES

Colleagues will recall that at last year's meeting it was agreed that PFC would not move to introduce these products but would watch the 'market' trends carefully. In the meantime, clinical colleagues were advised that concentrates were available from Dr J K Smith (BPU, Oxford). This arrangement was attractive to Dr Smith as the clinical data will be required for BPL product licences.

We are indebted to Dr Smith for his assistance and the provision of data summarised below:-

Supply of BPU Factors VII and AT-III to SHS and NI  
(Year ending 31st December, 1984)

Factor VII (i.u.)	Nil
AT-III (i.u.)	168,000

We are maintaining close liaison with Dr Smith on this topic in order to ensure that long term supplies are secure. Haemophilia Directors would wish to note that the SNBTS Directors are given to believe that no commercial products (factor VII and AT-III) have been purchased in the year ending 31st December..