BLOOD PRODUCTS - SUPPLY AND DEMAND

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SUMMARY

Estimates based on the best information available at the time of writing indicate that substantial stocks of Albumin (approximately 1 year) and FVIII could be established within Scotland and Northern Ireland by mid-summer 1984. The latter is in excess supply and plans are presented to transfer excess material to the NBTS.

National stocks would be as follows:

FVIII 8.0×10^6 IU

SPPS 62,000 bottles

In addition to establishing this stockpile 72,000 units of SPPS and up to 20.3×10^6 IU FVIII will be available for issue in the forthcoming year. It is proposed that the existing pro rata distribution of products be superseded by a system based on minimum regional stock levels and issues calculated prospectively rather than retrospectively. The availability of a substantial national stock permits greater flexibility in the distribution of routine issues and proposals are presented for the regional allocation of SPPS based on both plasma input and regional demand. RTCs will be required to specify minimum stock levels and projected annual demand.

A similar system for the manufacture and issue of IgG products is proposed. It is anticipated that the new manufacturing chemistry for IgG will substantially reduce the plasma input requirements for all products. A detailed assessment of the plasma supply/product demand equation should be deferred until 6-9 months experience of the new process is available. Yield and stability data relating to this process is appended (Appendix VI) and it is proposed that approval be given to its routine implementation for all specific IM products.

PFC will implement plans to ensure that an annual demand of 1.25×10^6 IU DEFIX and 250,000 IU Supernine can be satisfied.

Proposals for stock control, minimum stock levels, and issue procedures for all products are presented for discussion.

BLOOD PRODUCTS - SUPPLY AND DEMAND

1. A REVIEW OF PLASMA SUPPLY, PRODUCT SUPPLY, CLINICAL DEMAND AND YIELDS (FVIII AND ALBUMIN)

Table I provides a review of trends in plasma input and product issues from PFC between 1979 and the present time. Substantial increases in plasma input and in particular fresh plasma, coupled with a progressive increase in yields have resulted in a comparable increase in product supplies leading to self sufficiency in FVIII within the current year and the generation of a large national stockpile.

Similarly the supply of albuminoid products has increased though process capacity restrictions at PFC has created a ceiling with regard to manufacturing capability which will not be overcome within the near future.

Current yields of FVIII and SPPS are as follows:

FVIII - 300 IU/kg

SPPS - 1.2 bottles (400 ml) per kg (gross)

It is clear that clinical demand for FVIII is comfortably satisfied at this level of plasma input and projections indicate that the target figure of 2.75×10^6 IU FVIII/10^6 population has now been achieved.

In contrast there remains a significant shortfall in the supply of albumin to RTCs particularly in the West of Scotland and Dundee when measured against demand. PFC is not able to respond to this demand at the present time despite plasma being available. Instead, outdated and cryosupernatant plasma is stored in an external cold store pending a solution to the problem of process capacity. At present rates of plasma input it can be estimated that the non-fresh stockpile is and will continue to grow at a rate of approximately 10,000 kg/annum. At present levels of supply the processing of fresh plasma is under control (through the use of extensive overtime) and fresh plasma stocks remain stable at approximately 4,000 kg (equivalent to approximately four weeks throughput).

In all calculations to date a conversion factor of 200 IU/kg plasma per vial has been used in assessing supply or stock levels of FVIII.

Increased and consistent yields substantially greater than 200 IU/kg plasma require that a more accurate approximation is used for future projections.

It is proposed that the following conversion factors are adopted:

1 kg Fresh Plasma = ~~300~~ 250 IU FVIII

1 vial FVIII = 230 IU FVIII

These factors will be used throughout this document.

2. REVIEW OF THE PRO RATA SYSTEM FOR DISTRIBUTION OF PRODUCTS

Following/

TABLE 1

REVIEW OF PLASMA SUPPLY AND PRODUCT ISSUE/DEMAND

Year	Plasma Supply			FVIII			SPPS			Plasma Stock (at 31 March)	
	Total	Fresh	Outdated and Cryo	Manufactured	Issued	National Stock	Manufactured	Issued	National Stock	Fresh	Outdated and Cryo
79/80	38485	18581	16731	10383	10053	596	34496 907(E)	37094	20128 13723(E)	1482	1973
80/81	41812	22976	16076	19721	18154	2163	41542	24215 12838(E)	37455 892(E)	1785	2509
81/82	46831	32047	15002	22256	23988	431	49349	52314	34968	3636	4261
82/83	61005	41658	16422	25411	25132	710	44628	62017	17579	7647	8859
83/84	72761	54516	14100	57518	51474	6754	78030	62877	32732	2727	18677

(E) = NBTS Stock

Following the initial introduction of a pro rata system for the distribution of FVIII and Albumin a number of modifications have taken place to the procedures used for calculating issues to individual RTCs. The system currently in operation, which reflects both plasma input levels and the volume of plasma actually entering process, is as follows:

Quarters 1	Quarter 2	Quarter 3
Total plasma received from all regions (x)	Plasma entering process (kg) (z)	Product Issued FVIII (Unit doses)
Total plasma received from individual RTC (kg) (y)		SPPS
Total fresh plasma received from all regions (a)		
Total fresh plasma received from individual RTC (b)		

Therefore product issued is:

$$\text{FVIII (vials)} = \frac{b}{a} \times z \times 1.0$$

$$\text{SPPS (bottles)} = \frac{y}{a} \times z \times 1.25 \times 0.85$$

At present time all fresh plasma is processed thereby enabling the issue of the full entitlement to RTC of FVIII. Little outdated or cryosupernatant plasma is currently being processed resulting in an issue level to RTCs of SPPS approximately 25% below the entitlement based on their total plasma input.

The demand for Human Albumin (20%) is currently met from immune plasma and is substantially less than the 15% allowed for in pro rata calculations. Finished product is issued in response to demand from individual RTCs and at the present rate of use equates closely to the volume of immune plasma received by PFC.

3. SNBTS STOCKS OF SPPS AND FVIII AND PRESENT DEMAND

3.1 SPPS Stocks

At the time of writing the PFC stock position is as follows:

TABLE 2

Finished Product For Issue (Bottles)	Finished Product Awaiting Release (Bottles)	Product Awaiting Rework (Bottles)	Product As Excess Intermediate Paste		Plasma Outdated and Cryo	
			Kg	Bottle Equivalent	Kg	Bottle Equivalent
28,219	13,200	Approx 8,000		11,500	22,000	30,800

With the exception of the plasma stock, intermediate rework, and paste material can be brought to the issue status within three months providing a total PFC stock of SPPS of approximately 61,000 bottles. This assumes plasma input to be balanced with product issue. RTC stocks are variable at the present time and are at less than a safe strategic level, particularly in the West of Scotland.

Current RTC stock levels are as follows:

TABLE 3

Aberdeen	Belfast	Dundee	Edinburgh	Glasgow	Inverness	Total
2090	421	740	777	500	630	5158

3.2 SPPS DEMAND

The present demand for SPPS based on 83/84 issues to RTCs is as follows:

Regional credit/deficit balances (since pro rata was initiated) are specified as cumulative deviations from the theoretical entitlement.

TABLE 4

Region	Aberdeen	Belfast	Dundee	Edinburgh	Glasgow	Inverness	Total
PFC Issue p.a. 83/84	5381	7032	6365	11554	30235	1830	62877
Credit (+) Cumulative Deficit (-) Over 3 yrs	+14	+1376	+405	+4630	-1886	+8846	-

3.3 Factor VIII Stocks (Including Northern Ireland)

At the time of writing the PFC stock position is as follows:

TABLE 5

Finished Product for Issue at PFC	RTC Stocks	Total National Stocks	Plasma Stock
4.0×10^6 IU	6.1×10^6 IU	10.1×10^6 IU	4,000 kg

3.4 FVIII Demand (Excluding Belfast)

TABLE 6

Region	Aberdeen	Dundee	Edinburgh	Glasgow	Inverness	Total Issued 83/84
PFC Issue 83/84	0.577×10^6	0.515×10^6	2.567×10^6	6.504×10^6	0.489×10^6	11.84×10^6

Demand for FVIII within the current year has been substantially below the PFC output of product. At the current estimated rate of usage, output exceeds demand by a factor of approximately 2. In Scotland, product derived from SNBTS plasma amounts to approximately 12.75×10^6 IU, whereas the estimated usage stands at approximately 5.83×10^6 IU. A detailed summary of the SNBTS plasma supply/product supply/demand equation is presented in Appendix IV.

4. PROJECTED PRODUCTION LEVELS IN 1984/85

4.1 SPPS

The anticipated plasma input to PFC in the forthcoming year from Scotland and Northern Ireland is estimated at 73,000 kg of which approximately 54,000 kg will be fresh frozen. With an extensive use of overtime a total of 60,000 kg plasma will be processed to FVIII and SPPS maintaining a stock of fresh plasma at between 2,000-4,000 kg. In addition, plans are in hand to reprocess a substantial backlog of intermediate SPPS pastes and reject batches by the end of May producing a total output of approximately 107,000 bottles in 1984/85. There remains for the foreseeable future little possibility of processing all outdated and cryosupernatant plasma and the plasma stockpile will continue to grow at a rate of approximately 10,000 kg/annum. On this basis the outdated plasma stockpile will be approximately 32,000 kg by April 1985 and equivalent to 39,000 unit doses of SPPS.

This can be summarised:

SPPS Stock at 31 March 84	Reduction of In-Process Stocks and Rejects 84/85	Product Derived from Total Plasma Input 84/85	Product Issues 84/85*	Total Nat Stock at 31 March 85	Non-Fresh Plasma Stock March 85
28,000	35,050	72,000	72,000 c/f ( ) 83/84	63,050	32,000 39,000 Bottles

*To be discussed

Following clearance of the backlog of intermediate material PFC will minimise and maintain intermediate paste and product stocks at a level consistent with continuity of production and supply at a rate of approximately 6,000 bottles per month.

Anticipated planned closure of PFC for execution of minor works and upgrading (Phase IIa) has been taken into account in the above projections. Substantial National stocks (62,000 bottles) should be available prior to any close down. Any unplanned reduction in production will require a comparable reduction of the National stockpile. This should not exceed 6,000 bottles in any event.

Increased process capacity reflected in these figures is largely the result of a substantial reduction in the level of fibre rejects (eliminating rework) and increased batch size following commissioning of the automated bottle washing/filling equipment. The latter will permit, in/

in particular, clearance of reject material.

4.2 Factor VIII

Projected fresh plasma input to PFC in 1984/85 is approximately 54,000 kg. Assuming maintenance of plasma quality and process yield approximately 16.2×10^6 IU FVIII will be available for issue during 1984/85. It is hoped that a small proportion of this will be in the heat treated form with the object of achieving total transition to the new product by April 1985. In addition to this routine level of manufacture, plans are in hand to rework substantial accumulations of reject material providing an additional output of 2.0×10^6 IU FVIII.

TABLE 8

Plasma Stock at 31 March 1984	FVIIII Stock at 31 March '84 IU x 10^6		Product Derived from Plasma Input 84/85	Rework of Reject Material	Product Issues 1984/85*	National Stock at 31 March 1985	Plasma Stock at 31 March 1985
	PFC	RTC					
4,000	4.0	6.1	16.2	2.0 (Estimate)	8.0×10^6*	20.3 (RTC and PFC)	4,000 kg

*Current SNBTS demand (excluding Northern Ireland) = 5.8×10^6

It should be noted that National Stocks at 1985 will exceed the nominal one years stock requirement by approximately 11×10^6 IU. Acceleration of the heat treated Factor VIII programme within 1984/85 may reduce this to 9-10 x 10^6 IU (25% Heat Treated Product). This level of FVIII manufacture is comparable to the output during 1983/84 and assuming no unplanned process failures or shutdowns (Phase IIa has been allowed for) the above figures represent a realistic target on which forward planning can be based. The figures presented take no account of domestic and hospital stocks which can be assumed to be high.

5. PROPOSALS FOR THE DISTRIBUTION OF SPPS AND FACTOR VIII

5.1 SPPS

The demand for albumin products within Scotland and Northern Ireland is variable between regions and to date limited process capacity has led to a shortfall in supply to some regions, in particular the West of Scotland. It should be noted however that this is in part due to the inability of PFC to process outdated plasma which accounts for approximately 25% of the total plasma input.

Plans to reduce the level of in-process and reject material at PFC will provide the dual benefit of increasing National stock levels of SPPS and simultaneously reduce existing acute and dangerous storage problems at PFC. Thus, with access to adequate levels of overtime working (present levels should be adequate) the following distribution of the National stock (see section 4.1) could be achieved by August 1984.

TABLE 9/

TABLE 9

ABN	BEL	DUN	EDI	GLA	INV	PFC (External Storage)	Total Nat Stock
1000	2000	1000	2000	6000	500	50000	62500

Stocks of in process material and intermediate pastes would be maintained at PFC at a level which would ensure continuity of production in the event of temporary failure of a discrete part of the production process (eg contamination of aseptic dispensing area). Such material would be distributed as follows:

TABLE 10

Production Stage	Plasma	Paste	Awaiting QC	Awaiting Release	Rejects
Wt/Unit of SPPS	4000 kg	4000 (bottle equivalents)	10600	4000	1000
Bottle Equivalents	5600	4000	10600	4000	1000

The distribution to RTC of SPPS in 1984 will consist therefore of two distinct phases.

Phase I

Distribution of product derived from reject and intermediate materials together with product derived from routine plasma input. This phase would also be used to build up the PFC stockpile of SPPS in external warehousing and should be complete by August 1984. Pending completion of this phase, the existing stockpile could be used to supplement RTC stocks which are at dangerously low levels.

Phase II

Distribution of product derived from routine plasma input. This has been estimated at 72,000 bottles per annum (6000 per month).

Having achieved the above stock levels (equivalent to 12 months supply) it becomes possible to simplify the existing pro rata system for distribution of product while at the same time maintaining structured and planned issues. Thus, if the plasma input from individual regions is maintained at present levels and demand remains fairly constant then monthly issues could be based on a prospective calculation of the yearly output (84/85). Each region would therefore receive 1/12 of its annual entitlement each month thereby eliminating complex pro rata calculations and fluctuations in supply caused by discontinuous output by PFC and seasonal plasma input by RTCs. Such a system would still reflect plasma input levels by individual RTCs based on projected plasma input levels for the coming year and the contributions of each region (based on 83/84 figures). Monthly issues to regions would be as follows (excluding additional material in Phase I):

TABLE 11

ABN	BEL	DUN	EDI	GLA	INV	Total
455 bottles	659 pro rata	370	1360	2823	329	5996

If RTC stocks exceed the specified levels then material will be decanted to the PFC stockpile or to the regions where demand exceeds the strict allocation. It is known that the West of Scotland has a demand in excess of the present supply. This could be offset by allocating issues to the West of Scotland on the basis of projected plasma input (fresh plus outdated) as a proportion of total plasma processed. This will maintain a structured distribution of product based on plasma input but an increased issue to the West will result in a deficit in other regions. The net result would be as follows:

TABLE 12

ABN	BEL	DUN	EDI	GLA	INV	Total
407	589	331	1217	3160	294	5998

Directors may wish to consider this proposal in detail since other variations may be possible.

In conclusion, with a substantial stockpile of SPPS within Scotland and a significant anticipated increase in routine output (62,017 in 82/83 to 72,000 in 84/85) it is possible to issue on the basis of need as well as plasma input without the need for cumbersome pro rata calculations which result in fluctuations in supply and relative inflexibility. Continuous review of output from PFC will facilitate adjustments to these figures.

5.2 FVIII

In contrast to SPPS, stocks of FVIII and anticipated issues in 84/85 exceed the present demand by an uncomfortable margin. It is proposed therefore that issue of FVIII be based on regional need exclusively with stocks and supply controlled by a system of minimum stock levels at RTCs and PFC as follows:

TABLE 13

PFC Stock	RTC Stock
6 months National Supply	6 months Regional Supply

The necessary RTC stock levels will be specified by individual regions. Stocks at peripheral hospitals and domestic stocks will not be included in the system since they cannot be easily controlled. It should be noted also that this product has a shelf life of two years and in a complex supply chain overall stocks in excess of 12 months may lead to product outdating.

It has been calculated (see section 4.2) that there will be a substantial over supply of FVIII in Scotland and Northern Ireland amounting to approximately 11.0×10^6 IU.

In the absence of an increase in demand of approximately 100% (which is unlikely) it has been proposed that excess stocks be decanted to England and Wales where in contrast to Scotland, such material could be used immediately. Thus any system for product distribution requires to (a) maximise stock turnover in Scotland so that material approaching its expiry date is/

is minimised and (b) ensure that excess material is efficiently despatched to centres in England and Wales where a rapid uptake and use is possible and can be guaranteed. Flexibility is a prerequisite in any such system so that the foreseeable (and unforeseeable) demand in Scotland and Northern Ireland can be met at any time.

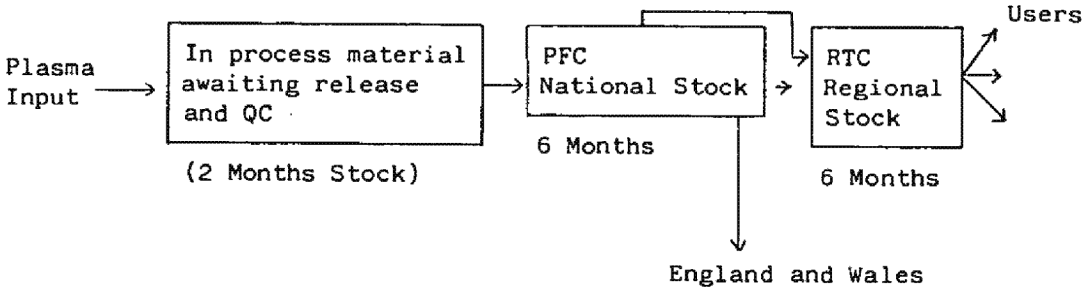
In the light of the above considerations the following outline system is proposed:

1. National stocks (RTC and PFC) are defined and established as above. An estimate of the potential demand is required for 84/85. Provisional (PFC) estimates are 8.0×10^6 IU based on present usage and a nominal increase consequential on increased availability.

2. RTC stocks will be maintained at the prescribed minimum stock level from the PFC stocks on a monthly basis.

3. PFC stocks will be reviewed on a monthly basis after issues to RTCs and material in excess of the prescribed National stock level will be "exported" to England and Wales on a monthly or quarterly basis (monthly preferred).

In this way the SNBTS will always hold 12 months supply and in practice material supplied to RTCs will be 3-6 months old (measured from date of manufacture). Such a system does not imply any quantitative commitment outside the SNBTS and is inherently flexible.



Estimates based on the best information available at the time of writing indicate that approximately 11.0×10^6 IU FVIII could be supplied to England and Wales in the forthcoming year.

6. FACTOR IX

6.1 DEFIX and Supernine

Two FIX products are currently manufactured at PFC.

1. DEFIX (Factors II, IX and X).

2. Supernine.

Issues of DEFIX have been relatively constant for some time and amount to approximately 1.25×10^6 IU per annum. It is possible that development such as the treatment of Haemophilia A patients with inhibitors will significantly increase demand in the near future.

Manufacturing/

Manufacturing processes for DEFIX and Supernine are labour intensive and have a long lead in time between plasma input and product issue (approximately 6-9 months). Supernine has a yield at present 30% that of DEFIX.

Plans have recently been implemented to establish stocks amounting to one years supply and thereafter to maintain this stock by manufacturing approximately 1.25×10^6 IU per annum. In addition a limited supply of Supernine will be available, on a named patient basis, amounting to approximately 0.25×10^6 IU per annum. It is not known at the present time when Supernine will be available for issue.

A stock level of 12 months supply will permit an expansion in the clinical use of both products while at the same time providing PFC with adequate time to respond to such an increase, bearing in mind the extended time scale for manufacture.

It is estimated that a stock level of 1.25×10^6 IU DEFIX will be established by mid-summer of this current year.

It is proposed that this stock be distributed as follows:

TABLE 14

PFC	RTC	
7 months = 0.75×10^6 DEFIX	5 months 0.5×10^6 DEFIX	
0.2×10^6 Supernine*	0.05×10^6 Supernine*	(As and when available)

*(Unlicensed product and therefore not available for routine issue).

Stock control and distribution of DEFIX will be based on a system of prescribed minimum stock levels at RTCs and PFC.

6.2 PPSB (Factors II, VII, IX and X)

Issues of this product, primarily as a source of FVII are low and constant at approximately 50-60,000 IU per annum. EDTA plasma is supplied exclusively by the West of Scotland. The current yield is approximately 200 IU/kg plasma.

It is proposed that stocks of this product be maintained and distributed as follows:

TABLE 15

PFC Plasma Stock (Min)	PFC Finished Product Stocks	RTC Finished Product Stocks
250 kg	25,000 IU	25,000 IU

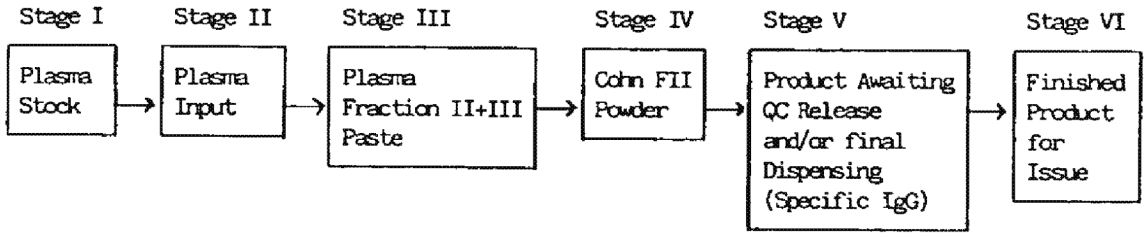
PPSB/

PPSB is manufactured infrequently and plasma stock levels are subject to large fluctuations. Hitherto, PFC has been supplied with EDTA plasma in anticipation of product manufacture. It is proposed that this ad-hoc system be replaced by a planned input of plasma on a quarterly basis of approximately 60 kg. Increased demand or batch failure could be notified to the West of Scotland who could respond accordingly.

7. IMMUNOGLOBULIN PRODUCTS (INTRAMUSCULAR)

7.1 General Considerations

The discontinuous nature of the IgG manufacturing methodology results in a misrepresentation of total stock levels as presented in PFC Quarterly and Annual Returns. The manufacturing process can be summarised as follows:



The present system of stock control and reporting is based on material available at Stage VI and Stage I (plasma stock). This tends to conceal sometimes large stocks of intermediate material at Stages III, IV and V. In theory it is possible to respond to a situation of plasma over-supply by storing intermediate material at Stage III, IV or V though in practice the majority of materials surplus to immediate need is stored as powder since in this form it is relatively stable and minimises storage implications. For Normal IgG material such a system is adequate for purposes of stock and manufacturing control since surplus material is destroyed. For specific IgG product however the option to destroy is not available with the result that substantial powder stocks have accumulated. The present position is as follows:

TABLE 16

Product Type	Plasma kg	Paste II + III kg	Powder g	Intermediate Finished Product Vials	Finished Product Vials (PFC)	Total Vial Equivalent
IgG(N)	N/A	N/A	1900	3100	4141	9780
IgG(D) 500	)			1253	4471	
250	)446	10.56	433		3395	
5000	)					
IgG(V)	69.5		822			
IgG(T) TP	)110.8	12.95	822.9		36	
250 IU	)			3617	3188	6805
IgG(H)*	157	5.8	618	250	528	
IgG(Z)*	486.3	1.7	1722	460	910	4814
IgG(R)*	61.3	2.16	800	600	4	1670
IgG(Ra)*	64.7		1173		14	2-3000
IgG(Mu)	98.0				67	
IgG(M)	49		217		107	
IgG(HA)	21.8		252			?
IgG(Simplex)*	375	5.9	722			

*Substantial Over-Supply

Table 16 is incomplete since it is not always possible to accurately predict the yield from in process material. However, it is clear that substantial stocks of powder exist in excess of any projected demand for the foreseeable future. By implication this means that there is an excess supply of specific plasma to PFC.

It is proposed therefore that a system of minimum stock levels be implemented for both RTC and PFC stocks and also that a system of minimum (and maximum) stock levels for intermediate materials operate in an attempt to define the required plasma input. The following levels would be defined:

TABLE 17

	Plasma Stock	Paste Stock	Powder	Intermediate FP	Product at Issue (PFC)	RTC Stock
Proposed Level (Months Supply	Product Dependent but sufficient for 2 batches	Product Dependent	Product Dependent	Product Dependent	6-12 months	6 months

Total ≯ 12 Months Supply

The above figures are estimates of a safe supply chain but in principle any analogous system should be able to define the required plasma input for any product type assuming implementation of existing plasma cut off titres for hyperimmune plasma. Thus at equilibrium RTCs would collect plasma against a known annual target which could be reviewed in the light of experience, on an annual basis. Such targets cannot be defined at this stage since imminent changes to IgG process chemistry will substantially increase yields of all products thereby reducing the plasma requirement. Estimates of specific plasma requirements could be made available within 6-9 months following operational experience of the new process. Similarly, implementation of the minimum stock levels specified above should be delayed pending an assessment of future yield/kg plasma.

7.2 Anti-D and Anti-Tetanus

Current plans to increase the yield of Anti-D IgG at PFC have already been discussed in some detail elsewhere. Such developments apply equally to Anti-Tetanus IgG. As indicated above, information will be available in due course which will permit reappraisal of plasma input requirements. In the meantime, adequate stocks exist at all stages of the manufacturing process to ensure continuity of supply at the present level.

7.3 Rubella IgG

Recent data suggests that the existing Anti-Rubella IgG is only marginally more potent than a comparable Normal IgG.

Mean potency of IgG(N) = 1438 IU/ml

Mean potency of IgG(R) = 3000-3500 IU/ml

In view of this it is proposed that the minimum acceptable titre of hyperimmune rubella plasma be reviewed with a view to producing a lower volume, higher specific activity product. Such a course of action will reduce the number of vials available but will still comfortably satisfy existing demand. Since 1981/82 a minimum plasma potency of 300 IU/ml has been adopted producing a rapid drop in plasma supply. To date this amounts to 145 kg which is currently being fractionated to high specific activity product. A detailed report will be made available in due course.

7.4 Over Supply of IgG(H), (Z), (Ra), (Simplex)

It is apparent from Table 16 that the potential capacity to supply the above products (powder and finished product) is substantially in excess of demand. RTC Directors may wish to review input levels of, in particular, Rabies, Zoster and Simplex plasma. A more modest reduction or an increase in usage in HB hyperimmune plasma is also possible.

Consideration should be given to the processing of intermediate material with a view to reducing stocks to a sensible level. Tentative data suggests that IgG powder is unstable (with respect to specific activity) when stored in the only available area at PFC (30° C). Finished product derived from these stocks, and in excess of SNBTS requirements could be decanted to the NBTS.

8. PROPOSALS FOR STOCK CONTROL OF ALL PRODUCTS AND DEFINITION OF NATIONAL STOCKS

8.1/

8.1 General Considerations

Following a substantial increase in plasma supply to PFC during the past 12 months and a concurrent increase in plasma processed, the SNBTS is now potentially self-sufficient in blood products. This being the case, it becomes necessary to construct systems of stock control within the total organisation such that the level of plasma input is carefully balanced with PFC output and most importantly clinical demand. Assuming plasma input continues to be synchronised with product issues and the National demand, the need for a pro rata system for distribution of product diminishes. In its place, however, is a need for a prospective method for stock control on a National basis on which both RTCs and PFC can plan and which eliminates fluctuations on supply caused by both seasonal fluctuations in plasma supply and PFC processing. For such a system to be totally secure, substantial reserve stocks of major products at PFC and RTCs are required in order to minimise th effects of supply fluctuations. Such stocks of approximately 12 months supply, are or can be made available within the near future thus permitting a uniform supply of product on a monthly basis, to all regions. Superimposed on this distribution pattern will be a definition of minimum stock levels (RTC and PFC) so that material in excess of minimum stocks at any one region will be decanted to regions where shortfall exists or alternatively to the National stockpile. In addition, a local PFC system of stock control will operate, which, in addition to finished products will take account of material held in process or held as a strategic reserve (eg IgG powder). Thus the shape and size of the "sausage machine" can be defined and controlled in such a way that a more predictable output of product is achieved.

8.2 Information Required

Certain information and policy decisions are required in order to successfully implement the above system.

(a) Projected regional demand for all products (to be reviewed formally on an annual basis or as required).

(b) Minimum regional stock levels.)
) Total National
(c) Minimum PFC stock levels (finished product.) Stock Levels

(d) Requirements for strategic stockpiles of specific immunoglobulin products.

(e) Plasma supply requirements for specific immunoglobulin products.

(f) RTC holding capacity for finished product stocks.

(g) Effect of new IgG process chemistry on product yields and stability.

(h) Existing RTC stocks of finished product.

(i) Proportion of albumin to be issued to each region taking account of both need and plasma input to PFC.

8.3 Procedure for Calculating Monthly Issues to RTCs

Each RTC will have defined stock levels for each product calculated on the basis of projected annual usage and stock holding capacity. PFC will/

will increase the supply of finished product (where necessary) until minimum stock levels have been reached. Thereafter RTCs will submit to PFC, on a monthly basis, actual stock figures from which the monthly issue will be calculated to bring stock to the minimum specified level. Assuming a National stock of 12 months supply can be realised in the near future, it is suggested that at this stage issues to specific regions of albumin in any quarter should not exceed 25% of their defined annual usage, except by formal review and consultation (eg Co-ordinating Group). It is anticipated that the supply of coagulation factors and IgG products will be on demand, subject to regular monitoring of National usage patterns.

A typical pro forma which could be used for the purpose of product issue is appended (Appendix I).

8.4 Proposals for SNBTS Product Stocks 1984/85

For the purpose of discussion, proposals are appended which define minimum stock levels. This table includes minimum stocks of in-process materials but does not identify specific distribution patterns among regions. The figures presented (PFC issues) assume processing and issue of accumulated intermediate and reject material.

Also appended are outline plans for stock control of intermediate materials to ensure continuity of supply. These figures are tentative only and are intended primarily for discussion within PFC in response to requirements for maintenance of finished product stocks (Appendix III).

Appendices II and III can be summarised and expressed as stocks in terms of the number of months supply (Appendix V).

9. IMPACT OF NEW DEVELOPMENTS

9.1 Heat Treated Factor VIII

This development is now well advanced and plans are in hand for the exclusive manufacture of this product by April 1985. At this stage in the development a significant reduction in yield from 300 IU to 225 IU/kg fresh plasma. At the projected scale of manufacture in 1984/85 this will not substantially affect FVIII issue levels. Any reduction will be reflected in reduced issues to England and Wales. Similarly for 1985/86 projected output will be 12.4×10^6 IU which is substantially in excess of the maximum demand of $2.75 \times 10^6/10^6$ population. More accurate yield figures will be available in due course since the PFC programme to manufacture small batches (250 kg) of heat treated material has now been initiated.

In view of a total transition to this product by April 1985, it is proposed that urgent consideration be given to the construction and implementation of a comprehensive clinical trial which will form part of a licence submission by PFC in due course.

9.2 Immunoglobulin Manufacturing Process

The proposed new manufacturing chemistry for IgG production will increase both process capacity and yield/kg plasma for all IgG products. Yield/

Yield and stability data for this modified process are presented in Appendix VI. This data is based on production batches of Normal IgG (Cohn II powders) and it is proposed that approval be given to the implementation of this chemistry for all intramuscular immunoglobulin products as previously agreed with a view to establishing yields of specific products (in particular Anti-D, Anti-Tetanus and Anti-Hepatitis B). This will provide a sound basis on which to calculate plasma requirements for specific intramuscular immunoglobulin manufacture.

9.3 Intravenous IgG

Pending evaluation of the effect of the chemistry on the downstream processing of IV IgG this product will continue to be manufactured using the existing process chemistry. An issue target of 12 kg for 1984/85 has implemented and safe reserve stocks for use in applications other than hypogammaglobulinaemia will be available by June/July 1984. In addition to Normal IgG (IV) a specific CMV IgG is also available. Directors may wish to note that substantial stocks of hyperimmune CMV plasma are accumulating (present level = 500 kg equivalent to 600 unit doses).

In view of substantial stocks of other hyperimmune plasmas it may be appropriate to give consideration to the supply of other specific intravenous products eg Zoster and Tetanus (5,000 IU) with a view to obtaining clinical experience and product licenses (as extension of the existing application) in due course.

The recent submission to the DHSS for a product licence was rejected on the grounds that insufficient clinical experience of the product in hypogammaglobulinaemic patients was available. It is proposed that to expedite the submission of additional data, more patients are required in both Scotland and England (Northwick Park). Such an extension of the trial can be carefully serviced with product within existing production targets (maximum requirements for clinical trial = 5 kg/pa) which at the same time maintaining the availability of product for other potential applications (approximately 7 kg).

10. PACKAGING

New packaging systems have been designed for both DEFIX and IV IgG with a view to reducing storage requirements at RTC and PFC. Examples will be presented at the meeting.

11. PHASE II(a)

Phase II(a) of the PFC programme for upgrading is planned in November/December 1984 (best estimate) and total downtime is expected to be approximately five weeks. Sufficient stocks should be available by this time thereby eliminating the need for a special period of product stockpiling. However, in order to accommodate plasma deliveries a slight increase in planned over-time may be required prior to this shutdown to provide -40° storage capacity.

12. MONTHLY, QUARTERLY AND ANNUAL RETURNS

The above reporting forms will be modified and extended to take account of specified minimum stock levels at PFC of both intermediate and finished products. Cumulative figures for plasma input, and product issues will be maintained to permit an on going assessment of the overall National stock position. Such information will be of particular value in determining require-ments for specific plasma supply and will provide a more comprehensive picture of/

(Appendix I)

ISSUE OF PLASMA FRACTIONS

Regional Transfusion Centre.....

PRODUCT		Specified Working Stock Level	Actual Stock Level at	Product Issued from PFC
Code	Name			

Notes

Signature.....

RTC will submit form at monthly intervals.
PFC will calculate issues required and return copy of this pro forma with delivery.

PROPOSALS FOR SNBTS PRODUCT STOCKS 1984/85 (INCLUDING BELFAST)

Appendix II

PRODUCT	Projected Issues* from PFC (or demand) †including in process material	Projected Plasma Required	Existing RTC Stock	Existing PFC Stock (includes in process)	Proposed RTC Stock	Proposed** PFC Stock (Finished Product)	Target Date for Achieving National Stocks
Factor VIII	†17.6 x 10^6 IU	To be calculated when new chemistry evaluated	To be defined	5.62 x 10^6 IU	4.0 x 10^6	4.0 x 10^6	Immediate
DEFIX	1.25 x 10^6 IU			683,000	400,000	850,000	July 84
PPSB	50,000 IU			45,600	25,000	25,000	May 84
Supernine	250,000 IU			0	50,000	200,000	August 84
SPPS	† 72,000			47,000	12,500	50,000	July/August 84
Human Albumin 20g	1,500			2,278	525	1,000	Immediate
Human Albumin 1g	750			200	250	525	May 84
Normal IgG (750mg)	5,500			>5,963	1,050	4,500	Immediate
Normal IgG (15mg)	200			649	105	150	Immediate
Normal IgG (3.0g) (Intravenous)	4,000			~400	300	1,000	Depending on Uptake
Anti-D (5,000 IU)	50			416	25	100	Immediate
Anti-D (500 IU)	9,000			7,724	3,000	6,000	June
Anti-D (250 IU)	3,200			>4,000	1,500	1,500	Immediate
Anti-Vaccinia	50			0	?	?	As required
Anti-Tetanus (5,000)	20			36	11	20	Immediate
Anti-Tetanus (250 IU)	4,000			>4,805	525	3,500	Immediate
Anti-Hepatitis B	600			1,730	200	400	Immediate
Anti-Zoster	400 (or greater ?)			4,310	200	600	Immediate
Anti-Rubella	300 (or greater ?)			1,000	125	175	May 84
Anti-Rabies	?			3-4,000	20	60(+powder)	Immediate/May 84
Anti-CMV (IV)	?			50	0	?	
Anti-Mumps	20			67	25	25	Immediate
Anti-Measles	50 (or greater ?)			107	25	50	Immediate

*Based on existing usage.

**May consist of Finished Product plus material awaiting release (Specific IgG)

PROPOSALS FOR PFC STOCK CONTROL (FINISHED PRODUCT AND INTERMEDIATES)

PRODUCT	MINIMUM STOCK LEVELS				
	Plasma	Paste Bottle/Vial Equivalent	Powder Vial Equivalent	Awaiting QC/ Release Vials/Bottles	Finished Product For Issue
F VIII	)	-	-	8,000	8,000
SPPS	)	4,000 ≡ 300 kg	-	14,000	50,000
Human Albumin 20g	) 4,000 kg fresh plasma	600) ≡ 50 kg	-	750	750
Human Albumin 1g	)	600) ≡ Fr V paste	-	750	500
PPSB	250 kg plasma	-	-	125	125
DEFIX	-	-	1,000 (as eluates)	1,000	3,000
Supernine (1,000 IU)	-	-	125 (as eluates)	60	200
Normal IgG	-	2,000) 110 kg	4,000	1,000	4,500
IV IgG (3.0g)		2.0 kg) II+III paste	-	600	600
Anti-D	400 kg plasma	2,000 ≡ 6 kg II+III paste	3,000	2,000	6,000
Anti-Tetanus	150 ± 50	1,000	1,000	1,000	3,000
Anti-HB	150 ± 50	0	400	200	400
Anti-Zoster	150 ± 50	0	200)	200	200
Anti-Rubella	150 ± 50	0	100)) or	100	200
Anti-Rabies	150 ± 50	0	?) equivalent	0	60
Anti-CMV (IV)	500 kg (Present level)	?	?) to 2 years) supply	?	?
Anti-Mumps	150 ± 50	0	100)	0	50
Anti-Measles	150 ± 50	0	100)	0	50

PFC F VIII PRODUCTION 1975-1985 (EXCLUDING NORTHERN IRELAND)

Year	Plasma Delivered tp PFC (kg)	Plasma into process (litres	Process Yield	F VIII Produced IU x 10^6	F VIII Issued to RTC IU x 10^6	PFC Finished Product Stock IU x 10^6	Plasma Stock (at 31 March) (kg)
1975/76	5 866	6 531	250.6 (1)	1.26	1.07	0.183	116
1976/77	10 824	9 496	229.7 (1)	1.84	1.64	0.374	1 060
1977/78	13 365	12 174	180.1	1.81	1.85	0.336	1 402
1978/79	15 001	13 673	197.2	2.25	2.11	0.419	4 650
1979/80	18 581	17 256	247.3	3.44	2.53	1.396	2 023
1980/81	22 976	20 773	260.1	4.64	4.48	1.558	2 476
1981/82	32 407	28 562	287.2	6.00 (5)	6.35	1.211	5 016
1982/83	38 307	34 163	275.2	8.16 (5)	6.22	3.152	7 647
Forecasts							
1983/84	48 000 (2)	47 191 (2)	300.3 (2)	12.74 (2)	11.35 (3)	4.54 (2)	4 000 (2)
1984/85		45 000	300	12.15	N/A	N/A	
1985/86 (4)		50 000 (4)	225 (4)	11.25 (4)	N/A	N/A	

(1) F VIII Assay calibrated with plasma standard. Concentrate standard introduced in December 1976.
(2) Estimates based on first 9 months of 1983/84.
(3) Assuming F VIII issued according to pro rata input of plasma (current procedure).
(4) Exclusive production of heat-treated F VIII.
(5) High batch rejection in these years. This material is awaiting rework and is equivalent to 1.2 x 10^6 IU F VIII.

Comments and Conclusions

1. The figures and estimates overleaf (1983 onwards) are based on 1 kg plasma ≡ 270 IU F VIII and one vial ≡ 238 IU. (Data presented on P2 is calculated on 200 IU per kg plasma or per vial).

2. Improvements since 1977 can be summarised:

   (i) Plasma into process has increased 3.7 fold.

   (ii) Process yield has improved by 67%.

   (iii) QA losses have been reduced from 17% to 8.7% per batch.

3. F VIII production levels in 1983/84 are likely to be artificially high as a result of a substantial reduction in the fresh plasma stockpile (7 647 kg — 4 000 kg). It is anticipated that the remaining stock of fresh plasma will be reduced by a further 2 000 kg before April 1984. This will provide an additional 0.5×10^6 IU F VIII.

4. At the current estimated demand of PFC F VIII in Scotland (5.83×10^6 IU) the projected output from PFC in 1984/85 will exceed demand by approximately 6.32×10^6 IU.

5. It can be calculated from the above figures that when added to the present PFC stock of F VIII, total stocks in 1985 will be approximately 10.9×10^6 IU which is equivalent to two years stock at present rates of usage. This forecast does not take account of substantial stocks of F VIII at Regional Transfusion Centres.

6. Work is in progress aimed at the exclusive production of heated treated F VIII by 1985/86. It is anticipated that this process will initially reduce the process yield to 225 IU F VIII/litre providing 11.25×10^6 from an estimated 50 000 kg plasma.

SNBTS STOCKS NUMBER OF MONTHS SUPPLY (INCLUDING BELFAST)

PRODUCT	ANNUAL DEMAND (84/5) (Estimates)	R.T.C. STOCK LEVEL MINIMUM	PFC IN PROCESS STOCK LEVEL (excluding Plasma)	PFC FINISHED PRODUCT STOCK LEVEL
FVIII	8.0 x 10	6 months	3 months	3 months
SPPS	> 2,800	2-3 months	3 months	8 months.
Human Albumin	32kg = 1600 bottles @ 20g.	4 months	4 months	8 months
Defix	4,200 vials	2-3 months	8 months	9-10 months
P.P.S.B.	250 vials	6 months	6 months	6 months
Supernine	250 vials (@ 1000iu)	2-3 months	9 months	9-10 months
Normal IgG	5,500 (750mg)	2-3 months	12 months	9-10 months
I.V. IgG	12 kg.	1 month	4 months	3 months
Anti D (500 iu)	9000	4 months	12 months	8 months
Anti D (250 iu)	3,200	6 months	12 months	6 months
Anti Tetanus	4,000	2 months	9 months	10 months
Anti HB	600	4 months	10 months	8 months
Anti Zoster	400 (or greater?)	8 months	18 months	18 months
Anti Rubella	300	6 months	12 months	6 months
Anti Rabies Anti CMV (IV) Anti Mumps Anti Measles	⩽ 50	⩽ 50	100	⩽ 50