TMC

BLOOD PRODUCTS MANUFACTURE: PARTICIPATION BY INDUSTRY
TECHNICAL AND POLICY BRIEF FOR SUPPLY DIVISION

Meeting to be held, 10.30 am, 3 March 1980 in room 87, Hannibal House.

The papers for this meeting are attached.

Policy matters for discussion	- paper 1
Initial staffing considerations	- paper 1(i)
Technical information	
List of products manufactured by BPL and forecast production requirements	- paper 2
Specifications of major BPL products	- paper 3
Current plasma supply to BPL and forecast plasma requirements	- paper 4
Additional points in relation to plasma supply	- paper 5

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February 1980

Mr Harley
Mr Smart
Dr Dunnill
Dr Prydie
Dr Tovey
Dr Gunson
Dr Lane ✓
Mr Flint
Dr Wills
Dr Wintersgill
Mr Dutton
Dr Oliver - for information
Mr Hart - for information

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BLOOD FRACTIONATION: INDUSTRIAL PARTICIPATION

POLICY

The following points of policy, not necessarily in order of priority, are put forward for discussion. The asterisks mark statements which would seem to require particular scrutiny. There are probably many other points which should be added to the list.

PLANT
- a new plant should be of sufficient fractionation capacity to meet forecast demands for UK self-sufficiency* ie 400 tonnes of plasma total capacity with 60% (250 tonnes) plant occupancy.
- adequate fall-back arrangements are needed both within the plant and externally (eg second factory; PFC Liberton etc).
- "the formal licensing and other requirements of the Medicines Act will have to be satisfied both in relation to the safety, quality and efficacy of each product and to the operations, premises, equipment and other arrangements relating to its manufacture."

SITE
- desirable for new plant to be built on Elstree site.

PRODUCTS
- industry must be prepared to manufacture the whole range of products currently manufactured by BPL* in the quantities required by the UK market even if it means that certain products are produced uneconomically.
- all products must meet BP or EP specifications where these apply. Where there are no pharmacopoeial monographs, products should meet current BPL product specifications.

TECHNOLOGY
- should be based on cold-ethanol precipitation. Batch processing is to be preferred*. Alternative technologies must have been 'proved' at full production scale.
- manufacturer should be prepared to make all possible efforts to improve the yields of FVIII (including the manufacture of lower purity products such as small-pool freeze-dried cryoprecipitate, should this be required).
- new technology acquired from BPL remains the property of the State eg polyelectrolyte fractionation.

RESEARCH AND DEVELOPMENT
- desirable for manufacturer to carry out an agreed amount of R and D*.

SOURCE PLASMA
- central coordination for the supply of plasma will be essential*. The manufacturer's requirements with regard to the quantity and quality of the source plasma would have to be agreed with the central coordinating body. This body would be responsible for ensuring that, as far as possible these requirements were met by the Regions. The manufacturer would not deal with individual Regions directly on matters of plasma supply.

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- procedure must be agreed in the event that there is a deficiency in either the quality or the quantity of plasma.

- manufacturer must undertake not to remunerate UK donors* by any means whether directly or by purchase of UK plasma from another agency.

- manufacturer must undertake not to set up plasmapheresis or other donor centres (even for non-remunerated donors) without specific authorisation from the DHSS.

- procedures must be adopted which ensure that UK plasma and any 'foreign' plasma are kept separate throughout the manufacturing process and that all possible steps are taken to prevent contamination of UK products by the imported material.

SALES

- the price of blood products in the UK must reflect appropriately the free plasma supply.

- a procedure must be worked out for agreeing initial prices and proposed price increases with the appropriate Government authority.

- there must be no sale of UK-derived products outside the UK without specific authorisation.

- there may be a requirement to confine any overseas sale of UK products to other voluntary transfusion services, the Red Cross etc.

STAFFING - see paper 1(i).

COMMERCIAL - Nature of collaboration with industry: Supply Division will be dealing with these aspects but questions which have been raised by members of this group include what safeguards would be necessary to deal with the following situations: changed ownership of parent company, bankruptcy, international hostilities, major fire or other damage to the plant, industrial action etc?

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Dr Walford

BLOOD FRACTIONATION: PARTICIPATION BY INDUSTRY
TECHNICAL AND POLICY BRIEF FOR SUPPLY DECISION

I am replying to your minute of 11 February.

I do not think that, in the early stages of discussions with industry, we need go too deeply into staffing issues. We should however sound firms on:

- the number of staff of different kinds they might employ
- their views on continuity of employment for existing staff
- who would meet the cost of any redundancy payments (the firm or the NHS)
- their personnel and industrial relations policies and experience (these could have implications for the continuity of supplies of products)
- what part they would expect to play vis à vis the trade unions in arranging to take over the BPL
- meeting staff expenses if the BPL should be moved and staff are asked to move with it
- recruitment and training of new staff.

12 February 1980

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cc

Mr Dutton

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LIST OF PRODUCTS MANUFACTURED BY BLOOD PRODUCTS LABORATORY

PRODUCTS	NOTES	QUANTITIES PRODUCED: 1979	FORECAST: 1985
Coagulation Factors			
Factor VIII concentrate 250 i.u	1	15m i.u	90m i.u
Factor IX concentrate (Oxford) 680 i.u	2	9m i.u	No major increase
Fibrinogen 2g	2	3kg	No major increase
Fibrinogen for isotopic labelling	2	)	
Thrombin 1000 i.u	2	)	
500 i.u		)limited quantities	No major increase
100 i.u		)produced	
Fibrin foam	2	)	
Fibrinogen 100 mg		)	
10 mg		)	
Factor VII concentrate (Oxford)	2	)	
Albumin Products			
Plasma protein fraction	3		
400ml (18g)		2376 kg)	
100ml (4.5g)		24 kg) 2,533 kg	6,900 kg
Salt-poor albumin 100ml (20g)		133 kg)	
Albumin solutions		)	
10g		)	
1g		)limited quantities	No major increase
0.25g		)produced	
Albumin for isotopic labelling		)	
		)	
Normal Immunoglobulin	2		
250 mg		16.7 kg) 43 kg	22.5) 49 kg
750 mg		26.7 kg)	26.7)
Intravenous immuno-globulin	4	Nil	(110 kg)

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BLOOD PRODUCTS LABORATORY (CONTINUED)

PRODUCTS	NOTES	QUANTITIES PRODUCED: 1979	FORECAST: 1985
Specific Immunoglobulins			
Anti-D 50 µg 100 µg 500 µg	2, 5	))11m µg)	18m (22m; 41m)µg
Anti-tetanus 250 i.u	2	10m i.u	Not known
Anti-chicken pox 250 mg 50 mg	2	0.9 kg	No major increase
Anti-hepatitis B 500 mg	2, 6	0.8 kg	1.6 kg - - → 28 kg
Anti-rabies 500 i.u	2, 7	0.5m i.u	No major increase
Anti-smallpox	2	)	
Anti-mumps	2	)	
Anti-herpes simplex	2	)limited quantities	No major increase
Anti-rubella	2	)produced	
Anti-kell	2	)	
Anti-bee venom	2	)	

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FOOTNOTES

1. Factor VIII used in 1979, 46m i.u.
   Factor VIII type: BPL 15m i.u
   cryoprecipitate 17m i.u
   commercial 14m i.u
Forecast of 90m i.u would need 5 x present supply of FFP

2. Self-sufficiency achieved for 1979; current production rates adequate to achieve 1985 forecast levels for self-sufficiency.

3. Albumin: actual production rate = 55g/1000 population. Fraction V (precursor of albumin products) production rate = 83g/1000 population. Forecast albumin requirement by 1985 = 150g/1000 population. Approximately 2 x present plasma supply needed.

4. Intravenous immunoglobulin: there is a big commercial sales drive for i.v immunoglobulin. This could result in a significant change in clinical practice, quadrupling the dosage of immunoglobulin given to patients with hypogamma globulinaemia. Raw material supply adequate for maximum predicted increase.

5. Anti-D: self-sufficiency achieved for 1979; raw material supply and production capacity adequate for self-sufficiency (18m µg) in 1985. Possible changes in recommended schedule of administration could increase usage from 22-41m µg - more raw material would be needed.

6. Anti-hepatitis B: self-sufficiency achieved for 1979. Forecast need for 1980 is based on administering 2 doses where known HBsAg-positive material has been introduced into an anti-HBs-negative individual (1.6kg). This level can be achieved with present raw material supply. Hypothetical forecast of 28 kg refers to a situation where 2 doses are given without testing either the inoculum or the recipient! Raw material supply would be inadequate.

7. Anti-rabies. Raw material supply gives potential for significant stockpile.

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PRODUCTS DISTRIBUTED BY BPL FOR RESEARCH

DATE	REQUESTED BY	PRODUCT	AMOUNT
17.1.78	Brian T. Nobbs, Senior Biochemist, St. Luke's Hospital, Guildford.	Human P.P.F.	10 x 400 ml
29.3.78	Dr. G.M. Mead, Research Fellow, C.R.C. Medical Oncology Unit, Southampton General Hospital.	Freeze-dried Albumin	1 x 25 gm.
6.4.78	Dr. M.W. Rampling, St. Mary's Hospital Medical School, Paddington, London W2 1PG.	Human Fibrinogen	3 x CPS.
30.6.78	Dr. B.J. Boucher, The London Hospital (Whitechapel)	Albumin, 10g%.	10 x 2.5 ml.
7.8.78	Dr. D. Schulster, The University of Sussex, Falmer, Brighton, Sussex.	PPF (unsuitable for clinical use)	10 x 400 ml.
11.8.78.	Dr. S. Van Schaick, The Radcliffe Informary, Oxford.	Albumin, 10g%.	10 x 250 mg.
10.10.78	Mr. J.G.W. Feggetter,F.R.C.S. St. Paul's Hospital, Endell Street, London, W.C.2.	Fibrinogen Thrombin	6 x 200 i.u. 10 x 100 i.u.
20.11.78	Dr. T. Wallington, R.T.C. Bristol.	Immunoglobulin (Not for Human Use)	8 x 250 mgm.
17.11.78	Dr. V.S. Chadwick, Royal Postgraduate Medical School, Hammersmith Hospital, London, W.12.	PPF (4.5g) Albumin (10g%)	30 x 100 ml 30 x 250 mgm.
8.8.78	Dr. T. Hawkins, Regional Medical Physics Dept., Newcastle General Hospital, Newcastle upon Tyne NE4 6BE.	Human Fibrinogen Human Fibrinogen	6 vials 6 vials
17.1.79	Dr. T.H. Thomas, University of Bradford, Bradford, Yorks.	Human Albumin (non-clinical use)	12 vials
23.1.79	Miss Y. Stirling, Coag. Lab., Northwick Park Hospital, Watford Road, Harrow, Middx.	Cryoprecipitate Supernatant	500 ml
25.1.79	Dr. P.M. Horrocks, Dept. of Med., Queen Elizabeth Hospital, Edgbaston, Birmingham B15 2TH.	Human Serum Albumin 20g%	2 x 100 ml
26.1.79	Mr. J.Ll. Williams, Royal West Sussex Hospital, St. Richard's, Spitalfield Lane, Chichester, West Sussex PO19 4SE.	Human Fibrin Foam	
11.1.79	Dr. S. Van Schaick, The Radcliffe Infirmary, Oxford.	Albumin, 10g%	20 x 250 mg
9.2.79	Dr. R.D. Leach, Dept. of Surgery, St. Thomas' Hospital Med. School, London, S.E.1.	Thrombin	100 units/ml per vial

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DATE	REQUESTED BY	PRODUCT	AMOUNT
21.2.79	Dr. A.J. Barnes, Royal Postgraduate Medical School, Hammersmith Hos., Ducane Road, London, W12 OHS.	Human Fibrinogen (time expired)	10 x 10gms.
26.2.79	Dr. D.L. Bloxam, St. Thomas's Hosp., Med. School, London, SE1 7EH.	Human PPF	2 or 3 bttls.
28.3.79	Dr. D.M. Lawrence, Obstetric Hosp., Huntley Street, London, WC1E 6DH.	Human Albumin, 10%	
24.6.77	Dr. M.W. Rampling, St. Mary's	Human Fibrinogen	3 x 2g
6.4.79	Hospital Medical School. Paddington.	Human Fibrinogen	6 g
23.4.79	Dr. R.N. Poston, Dept. of Pathology, Guy's Hospital Medical School, London Bridge, SE1 9RT.	Human Serum Albumin 10%	10 vials
11.4.79	Dr. V.S. Chadwick, Royal Postgraduate Medical School, Hammersmith Hospital, London, W12.	Albumin	50 x 2.5 ml.
4.5.79	Dr. Ferruccio Fazio, Snr. Lecturer in Med. and Radiology, Royal Post-graduate Medical School, Hammersmith Hospital, Ducane Road, London W12.	Human Serum Albumin 10%	10 x 2.5 ml.
8.6.79	Dr. P. Dandona, Director Metabolic Unit, The Royal Free Hospital, Pond Street, Hampstead, London NW3	Salt poor Human Albumin	5 x 100 ml.
23.7.79	Dr. G.L. Mills, The Middlesex Hospital Medical School, Mortimer Street, London W1P 7PN.	Fraction IV	approx. 30 grams
16.7.79	Dr. K.E. Kilbourn, Unit for Metabolic Medicine, Hunt's House, Guy's Hosp., London, S.E.1.	Dried Human Albumin	4 vials 2.5 ml 10% soln.
19.11.79	Ian Abbott, Chief MLSO, Haematology Dept., Royal Infirmary, Lauriston Place, Edinburgh, EH3 9YW.	Human Thrombin	10 x 100 iu.
9.11.79	Dr. T.H. Thomas, Lecturer in Chemical Pathology, Bradford West Yorkshire.	Human Serum Albumin 10%.	12 x 2.5 ml
8.2.80	Dr. Charles Turner, Dept. of Paediatrics, Guy's Hospital, London, SE1 9RT.	Normal Human Plasma	5L pack.

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Anti-HBs immunoglobulin supplied other than PHLS

Prof. Zuckerman	10 doses	26.2.79
Dr. Flewett	30 doses	13.2.79
	20	4.4.79
Dr. Dane	20 x 5 ml	5.4.79
Dr. Flewett	20 doses	3.7.79.
Dr. Flewett	20 doses	7.1.80.
Dr. Flewett	20 doses	12.2.80.

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PRODUCT SPECIFICATIONS

COAGULATION FACTORS

Factor VIII Concentrate

PROPERTY:-	BP LIMIT	RANGE	MEAN	± 2 SD
Factor VIII, iu/bottle	-	215-285	248	± 35
Reconst. vol., ml	-	15	-	-
Solubility, min				
at 20°C	<30	3-18	-	-
at 30°C	-	3-18	-	-
pH	6.8-7.4	7.07-7.23	7.14	± 0.08
conductivity, mS	-	11.6-14.9	12.4	± 0.1
protein, g/l	-	32.7-59.2	41.3	± 10.8
fibrinogen, % of total	≥80	46-61	53	± 6
factor VIII, iu/ml	≤3	11.7-18.7	16.0	± 2.6
specific activity, iu/mg	≤1	0.20-0.50	0.39	± 0.10
sodium, m mol/l	≥200	162-211	181	± 16
potassium, m mol/l	-	<5	-	-
chloride, m mol/l	-	46-157	109	± 20
citrate, m mol/l	≥55	23.2-37.2	31.2	± 6.8

Factor IX Concentrate

PROPERTY:-	BP LIMIT (9D ONLY)	RANGE	MEAN	± 2 SD
Factor IX, iu/bottle	-	530-740	656	± 118
Reconst. vol., ml	-	20	-	-
pH	6.7-8.0	7.01-7.37	7.18	± 0.20
conductivity, mS	-	15.1-17.9	16.3	± 1.3
protein, g/l	-	8.1-14.8	11.3	± 3.4
factor IX/VII, iu/ml	≤20	26.1-36.4	32.3	± 5.8
specific activity, iu/mg	≤0.2	2.3-3.6	2.9	± 0.7
sodium, m mol/l	≥300	230-286	262	± 25
potassium, m mol/l	-	<1	-	-
chloride, m mol/l	-	113-142	127	± 15
citrate, m mol/l	≥60	18.9-36.2	28.1	± 8.2
phosphate, m mol/l	≥50	13.2-18.1	10.2	± 2.2

PRODUCT SPECIFICATIONS

ALBUMIN PRODUCTS

a. PPF(BP) /will become Albumin in Saline EP when EP monograph is finalised/

	mean protein	= 4.5g/100 ml (4.3-4.7g/100ml) range
	albumin	= 98%
	albumin monomer	= 90% of total albumin
	diluent	= isotonic saline
	400 ml container	= 18g protein
PAEDIATRIC	100 ml container	= 4.5g protein

b. Salt-poor albumin (BP)

mean protein	= 20g/100ml (19.0-21.0g/100ml)
albumin	= 98%
albumin monomer	= 90% of total albumin
diluent	= ion-free water
NaCl concentration	< 15mg/g protein
100 ml container	= 20g protein; <300 mg NaCl

c. Special albumin preparations

i. for radioactive labelling

mean protein/container	= 10g; 1g; 0.25g
diluent	= 0.15M saline

ii. reprecipitated ultra pure albumin (customer service)

mean protein	= 10g/100ml
albumin	> 98%
IgG-free	
intermediate fraction	< 5%

IMMUNOGLOBULINS

1. Human Normal Immunoglobulin (EP)

mean protein	= 15g/100ml (14.5-15.5g/100ml)
IgG	> 90%
aggregates	< 8%
diluent	= isotonic saline
chloride conc	= 150m M
1.9 ml vol.	= 250mg
5.2 ml vol.	= 750mg

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CURRENT PLASMA SUPPLY TO BPL AND FORECAST REQUIREMENTS

Types of plasma sent to BPL by RTCs

1. Fresh frozen plasma (FFP): removed from red cells, pooled in 5 litre packs and frozen within 24 hours of donation.

2. Time-expired plasma ('TEP'): removed from red cells, after expiry date for donation, pooled in 5 litre packs and sent in liquid form to BPL.

Processing of different types of plasma

FFP can be used to produce the whole range of blood products. It is essential for the production of coagulation factors. TEP can be used for fractionation to albumin products and normal immunoglobulins.

Quantities of different types of plasma sent to BPL

Total whole blood donations pa	= 1.9 million
No of donations used for FFP	= 0.37 million (20%)
No of donations used for TEP	= 0.37 million (20%)
No of donations used for FFP+TEP + other plasma eg specific immune	= 0.78 million (41%)
∴ Total plasma in-put into BPL	= 160,000 litres
Total plasma available for FVIII	= 75,000 litres
Total plasma available for albumin	= 160,000 litres

Quantities of products manufactured in relation to plasma supply

Further details are given in tables 1, 2 and 3.

FVIII : maximum FVIII obtainable from 75,000 litres FFP at gross yield of 250 iu/l = 19 million i.u

forecast requirements for FVIII = 90 million i.u

Albumin: maximum albumin obtainable from 160,000 litres plasma at yield of 26g/l = 4160 kg = 83g/1000 population.

(The technology is available at BPL to increase yields from 72% to nearly 100% ie 36g/l = 5760 kg = 115g/1000 population)

forecast requirement for albumin = 150g/1000 population

Immunoglobulin: the current plasma supply is adequate to meet present and forecast requirements.

CONCLUSION: The present FFP supply is totally inadequate to meet the current FVIII usage (46 million i.u) let alone the forecast requirements.

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If BPL received all its plasma as FFP, the maximum FVIII obtainable with current yields would be 38 million i.u. Albumin production would remain at 83g/1000 population.

To obtain 90 million i.u FVIII with current yields would require an FFP input of 360,000 litres (ie 5 x the current FFP supply). However, if FVIII yields could be increased, the FFP requirement would fall proportionately.

Improving FVIII yields

Improvements to yields could be obtained as follows:-

a. with existing technology: yields could be increased by say 10% with better plasma handling eg single pack FFP

b. with new technology: yields should be significantly increased (say by 50%) with the successful development and the polyelectrolyte method of fractionation. Purity should also be increased whilst the hepatitis risk should be decreased. Companies will be avid for this technology.

c. with a reduction in purity: freeze-dried small-pool cryoprecipitate could have a gross yield of 1000 iu/l. Net yield could be substantially less because of QC losses. Theoretically the hepatitis exposure for the multi-transfused haemophiliac should be reduced but this will depend on the net yield per small-pool. Freeze-dried croyprecipitate will contain more protein 'impurities' than intermediate purity concentrates and would be likely to cause more patient reactions. Nordisk is currently manufacturing a freeze-dried cryoprecipitate.

Increasing plasma supply to BPL

Methods of obtaining FFP		FVIII production levels
a.	FFP from 60% of current donations	= 60 million iu pa
b.	Increase donors from 35 - 50/1000 pa FFP from 60% of increased donations	= 80 million iu pa
c.	Plasmapheresis	
i.	$1\frac{1}{2}$ x plasmapheresis 1 unit RBC, 2 units plasma x 3 per annum	
ii.	2 x plasmapheresis 0 unit RBC, 2 units plasma x ? per annum	

Note: commercial fractionators in USA and elsewhere generally use double plasmapheresis (0.4l) at rates of up to twice weekly: maximum plasma per donor per annum = 401!

Cost of plasma collection

	Approximate costs
Cost of collection 1 unit whole blood	= £13
Cost of collecting 1 litre of FFP	= £30
Cost of 1 litre FFP if donor numbers increased by 40%	= £42??
Cost of 1 litre FFP by plasmapheresis	= £45

Potential plasma supply problems in relation to industrial fractionation

To provide for self-sufficiency in blood products, the plasma supply will have to increase whether NHS or commercial fractionation is involved. However, there may be special problems of plasma supply to industrial fractionators.

a. Donor objections to industrial participation: possible adverse effect on donation rate.

b. Plasma in quantities adequate for self-sufficiency of FVIII would yield surpluses of many other products: ethics of overseas sale of surpluses.

c. Importing of overseas plasma to take up spare fractionation capacity: mechanics of keeping UK and foreign plasma separate.

d. Plasma collection: could cost of collection of plasma plus cost of purchase of the processed products prove more expensive to Regions than the cost of buying imported products (assuming even 100% increase in cost of imported products if BPL ceased to function)?

e. Product licences will contain precise specifications for quality of source plasma: possible penalties for Regions (or DHSS) for non-compliance resulting in loss of sales.

f. Plasma collection specifications: possible major additional expenditure for RTDs - who pays?

g. Plasma ownership: who 'owns' the plasma after collection and where does ownership start and stop?

h. Other problems: likely to emerge during talks!

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Table 1

RELATIONSHIP OF PLASMA SUPPLY AND YIELDS TO CURRENT PRODUCTION RATES AND FORECAST PRODUCTION REQUIREMENTS

ALBUMIN

QUANTITY PLASMA(l)	DONATION EQUIVALENTS	TYPE PLASMA	YIELD PER UNIT PLASMA	PRODUCT NAME	FILLED VOLUME	NUMBER OF CONTAINERS	ANNUAL PRODUCTION	QUANTITY PER 1000 POPULN	COMMENT
76,000	373,000	Time-expired Cryo-supernats.	72%	PPF	400ml	132,000	2376 kg		
75,000	367,000			PPF	100ml	5,000	24 kg		
				Salt-poor Albumin	100ml	6,630	133 kg		
				Fraction V*	400ml	90,000	1620 kg		
				Paste equiv to: Specials**		5,100	6		
TOTAL 161,000	782,000	Mixed	72%	As Above	-	148,730	2539 kg	55g/1000	ACTUAL 1978/9
161,000	782,000	Mixed	72%	As Above	-	238,730	4159 kg	83g/1000	Plus fraction V stockholding
282,209	1,380,000	Mixed	72%	As Above	-	(500,000)	6900 kg	150g/1000	PROJECTIONS 1985 yield constant
225,768	1,104,000	Mixed	90%	As Above	-	(500,000)	6900 kg	150g/1000	yield increased

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Fraction V paste is the fraction from which the albumin products are made. BPL has a stockholding of fraction V paste equivalent to 90,000 (x 400ml) containers of PPF. Fraction V paste is manufactured at 83g/1000 populn. BPL distributes albumin at 55g/1000 populn.

**Specials: see specifications

Table 2

RELATIONSHIP OF PLASMA SUPPLY AND YIELDS TO CURRENT PRODUCTION RATES AND FORECAST PRODUCTION REQUIREMENTS

FACTOR VIII

QUANTITY PLASMA(1)	DONATION EQUIVALENTS	TYPE OF PLASMA	YIELD PER UNIT PLASMA	PRODUCT NAME	QUANTITY PER CONTAINER	ANNUAL PRODUCTION	
75,051	367,000	FFP	220 i.u/kg plasma; net yield to patient	FVIII	250 i.u	15* million i.u	ACTUAL 1978/9
360,0001	1,760,000	FFP	220 i.u/kg (250 i.u gross)	FVIII	250 i.u	90 million i.u	PROJECTED 1985 requirements at current yields
327,300	1,600,400	FFP	275 i.u gross	FVIII	250 i.u	90 million i.u	assuming 10% ↑ yield because of better plasma quality etc
163,600	800,000	FFP	500 + i.u	FVIII	250 i.u	90 million i.u	assuming 100% ↑ yield (eg small pool freeze-dried cryo)

At current yields, 90 million i.u FVIII would necessitate increasing the rate of donation from 35/1000 to 56/1000 (3,000,000 donations pa) and the removal of plasma (as FFP) from 60% of the red cells. This would give BPL approximately 360,000 litres FFP equivalent to 1,800,000 donations. The present rate of donation is 1.9 million pa of which only 19% are used for FFP production.

At 100% increase in yields, 90 million i.u FVIII could be accomplished within the present donation rate provided plasma (as FFP) were removed from 60% of the red cells.

At present or increased yields, plasmapheresis (1½ x or double) could be used in addition to, or in substitution for, increased rates of whole blood donation.

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* Includes FVIII manufactured by PFL Oxford.

Table 3

RELATIONSHIP OF PLASMA SUPPLY AND YIELDS TO CURRENT PRODUCTION RATES AND FORECAST PRODUCTION REQUIREMENTS

IMMUNOGLOBULIN

QUANTITY PLASMA(l)	DONATION EQUIVALENTS	TYPE PLASMA	YIELD PER UNIT PLASMA	PRODUCT NAME	QUANTITY PER CONTAINER	NUMBER OF CONTAINERS	ANNUAL PRODUCTION	
160,000	763,000	Mixed	350 mg/l (to patient)	HNIG (EP)	250 mg	66,884	16.7 kg	
					750 mg	35,597	26.7 kg	
				(FRACTION II* (for diluting (specific immuno (globulin preps (			25.0 kg)))))	
				(FRACTION II SURPLUS			79.6 kg)	
TOTAL								
160,000	763,000	Mixed	350 mg/l	HNIG	-	102,481	43.4 kg	ACTUAL 1978/9
							123.0 kg	plus fraction II not bottled as HNIG
282,209	1,380,00	Mixed	350 mg/l	HNIG	250 mg	90,000	22.5 kg	PROJECTIONS
					750 mg**	35,597	26.7 kg	
							49.2 kg	projected growth rate 1985 assuming no change in pattern of use
				(FRACTION II	-	-	89.8 kg)	
					250 mg	90,000	22.5 kg	
					300 mg**	35,597	108.0 kg	
							130.5 kg	projected growth rate in 1985 assuming widespread use of i.v. immunoglob

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* Fraction II is the fraction from which immunoglobulin is derived.

**No growth for i.m dose of 750 mg HNIG which is for constant numbers of hypogammaglobulinaemic patients. Pressure for use of i.v immunoglobulin may lead to quadrupling of dose for all such patients

JJ

Dr Walford

I undertook to let you have quickly a list of the "technical" and "policy" points which the Department must consider, either prior to or in the cause of discussions with industry, about the possibility of their participating in the fractionation of NHS plasma.

It is useful to look at the problems which would arise under any such arrangement under the following headings.

A. Ensuring an adequate supply of plasma

I am assuming for the time being that NHS plasma would continue to be obtained by voluntary unpaid donation although there is certainly a case for examining alternative approaches, eg paid plasmapheresis, if the sole criterion is an economic one. I suspect, however, that tradition, the trend of world opinion against paid donations, our subscription to WHO resolutions on this subject and pressure from blood donors generally rules out any possibility of paying for donations in any form. Questions to which we must apply ourselves are:-

1. What materials would industry require of the RTCs; all fresh frozen plasma or would they accept some time-expired plasma?

2. Would industry accept "source materials" from all centres or only some?

3. If the latter, on what basis would these centres be selected and how would their plasma harvesting operations be financed?

4. To what extent would centres use plasmapheresis?

5. Who would prepare the specifications for starting plasma and how would these be enforced? What particularly would be the Department's role in defining and enforcing standards and deciding which products to make?

6. What sanctions would be available to the Department, or to the industrial fractionator if a centre failed to meet its commitments regarding quality and quantity?

7. Would the Regions required to supply raw materials be a party to any contract with industry?

B. Safeguarding raw materials

1. If a commercial fractionator intended to do more than fractionate for the NHS how would he segregate NHS from other plasmas?

2. What control would the Department exercise over commercial fractionation processes, storage etc, to ensure that NHS material was not misappropriated? A system of bonding and resident inspectors might be unavoidable if the fears of donors were to be allayed.

3. Where would the fractionator's responsibilities begin and end, eg who would be responsible for transporting plasma to the centres? Means of transport would have to be carefully controlled, especially where labile materials are concerned.

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4. Factory quality control staff outstationed at the RTCs and RTC staff at the factory might be unavoidable if disputes are not to ensue. A referee assay system may have to be devised.

5. What provisions would the Department build in to any contract to ensure that the fractionator used the most effective method of fractionation and kept plant and technology up to date?

6. Is industry likely to require assurances about the circumstances in which plasma is collected, assuming Medicines Division make no stipulations or recommendations?

7. What safeguards are industry likely to require to avoid the introduction of "pathological" plasma into their plant?

8. What safeguards would the Department require from industry to ensure that the plasma was not contaminated?

C. Is the Department prepared to undertake the management of a contract of this complexity with industry

1. A contract such as would be necessary will not manage itself; nor would industry be prepared to wait while matters are referred to countless committees. There will be questions arising almost daily to which they will look for speedy answers and the contract will doubtless include substantial penalties if raw materials are not delivered to time and to the required specification.

2. Is the Department sufficiently experienced to manage a contract with industry such as this or are there other Departments, eg MOD, better equipped to do so?

3. Is the Department willing to find the staff and meet the cost of managing a contract, renegotiating it periodically and to monitor it with the close attention which will be required? A small branch with technical and professional support would almost certainly quickly become a requirement. Alternatively, is there some other body to whom this responsibility could be devolved?

There are many other detailed questions but these are best left until we have a clearer idea of the main terms of any contract with industry.

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