

IN CONFIDENCE 87/39

**BLOOD PRODUCTS LABORATORY and
PLASMA FRACTIONATION LABORATORY**

ANNUAL REPORT

**MANUFACTURING and
RESEARCH & DEVELOPMENT**

APRIL 1986 - MARCH 1987

2296

2/86

The Report covers Operations defined in the 1986 CBLA Accountability Review. Operations include production of therapeutic, technical grade and serological products, quality assurance and control, research and development.

The Operational budget for 1986/7 has been finalised in the CBLA Finance and Administration Report.

R. S. LANE,
Director, BPL
September 1987.

PRODUCTION: THERAPEUTIC PRODUCTS

Part I **1986/7 targets**

Part II **Plasma intake**

Plasma fractionated

Plasma stock at end March 1987

Part III **Products released to stock**

Products despatched

Products stock at end March 1987

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PART I

TARGETS: Therapeutic Products

The following targets were set for the financial year 1986/7:

Fresh frozen plasma (FFP)

Received into stock 320,000 kg

Fractionated 150,000 kg

Closing stock 360,000 kg

Factor VIII 250 iu 90,000 vials

Albumin solution

4.5% 400 ml 205,000 bottles

20% 100 ml 25,000 bottles

PART III

Plasma intakes, volumes fractionated and closing stock positions are shown below.

PLASMA April 1986 - March 1987 inclusive					
Plasma Type	Intake kg*	(85/86)	Into Fractionation kg	(85/86)	Stock End March 1987 kg*
Fresh Frozen					
(Oxford):	304665**	(253769)**	14705	(14661)	354045**
(Elstree):			129967	(126465)	
Hyperimmune	8914	(5892)	5941	(5195)	2701
Time Expired	32142	(36307)	46238	(45740)	141400
TOTAL	345721	(295968)	196851	(192061)	498146

* Plasma weights in stock estimated by multiplying numbers of containers by nominal contents.

** FFP intake and stock figures combined for Oxford and Elstree.

Included in these figures are 51750 kg FFP and 127100 kg TEP collected before screening donors for HIV antibodies was established.

Plasma intake from Regional Transfusion Centres is kept under constant review.

1986/7 intake of FFP was 15,335 Kg below target, generally interpreted as the response of regions to the 12-month delay in process commissioning of the new production unit. A closing stock of 354,045 Kg was considered a sufficient basis on which to plan process commissioning and work up of production in 1987/8, but leaves no room for complacency. In effect, input represents best endeavours from 10 of 14 regional centres. The remaining four retain major problems limiting supply capability now and in the foreseeable future when FFP demand will inevitably increase as BPL reaches full capacity. FFP supply therefore remains a regular review item on the CBLA agenda.

Supply of hyperimmune plasma was irregular. Problems with source material for tetanus and hepatitis B immunoglobulin experienced the previous year were resolved during 1986/7. Plasma for anti-D immunoglobulin remained short and the predicted breakdown in supply of finished product occurred in the third quarter, necessitating purchase of commercial anti-D from Cutter Biologicals Inc. This unfortunate precedent will occur repeatedly until anti-D plasma supply meets fractionation demand. Stock-out failure of anti-D was precipitated by stop orders on product release caused by late reporting of defects in donor plasma.

Time expired plasma (TEP) supply continued a predictable decline as the efficiency of FFP collection in regions increased.

BPL continued to stock 51,750 Kg of FFP and 127,000 Kg of TEP which had not been screened at source for HIV-antibody. A meeting of experts at DHSS early in 1987 failed to elicit a directive on the fate of this material. If fractionated to albumin alone, product with a shelf value in excess of £6m would be realised. A decision from DHSS is expected early in the financial year 1987/8.

Fractionation

FFP fractionated at BPL and PFL during the year totalled 144,672 Kg. BPL fell short of target by 20,033 Kg due to changes in the Factor VIII process schedule necessitated by the change to Factor 8Y production. The new process involves more stages prior to filtration, sterile filling and freeze drying - further extending the working day. Time economies were found in limiting centrifugation to a smaller batch size. Intermediate product cannot be stored frozen overnight without severe yield losses.

Additional problems were experienced in the coagulation factors production unit which resulted from failures in plant and services. Approximately 20 batches were lost from the production programme, representing approximately 14,500 vials of Factor 8Y (250 iu).

The shortfall in supernatant from the coagulation factors unit required that 46,238 Kg of TEP were used to make up cold ethanol fractionation volume. By the third quarter it became possible to predict a shortfall in HIV-tested TEP arising early in the following financial year with a consequent diminished output of albumin. Equally, during 1986/7 the stock of Fraction V albumin concentrate was scheduled to finish. This material, predating the completion of MARP-01 reconstruction in 1983/4, had significantly augmented output of 4.5% albumin. Its consumption in 1986/7 was planned to coincide with transfer of production into the new building. The overrun on completion of Building 27 will result in a cutback in 4.5% HAS supply of at least 60,000 containers issued during 1987/8.

Data on Plasma Distribution

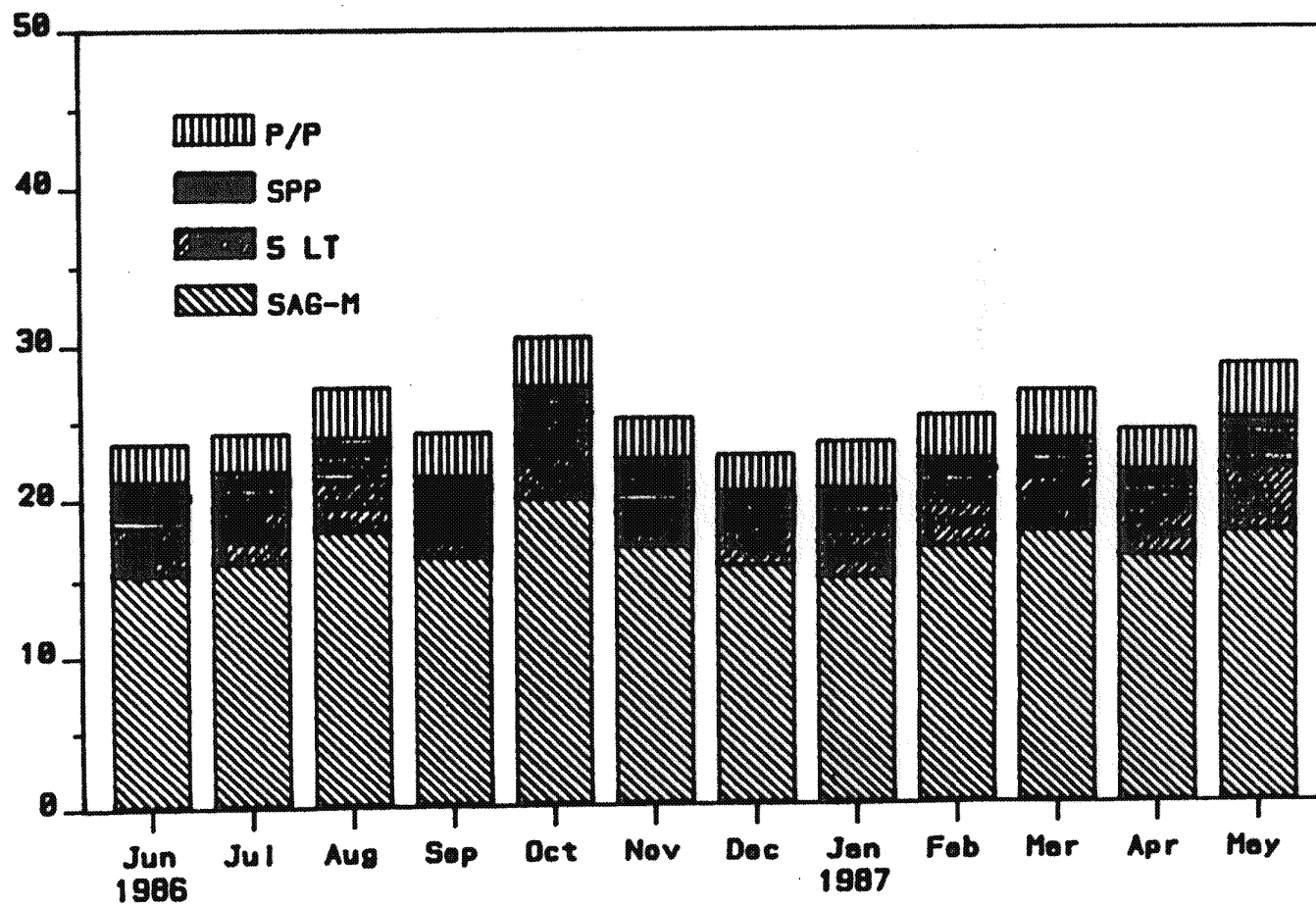
The following charts show:

1. The distribution of FFP received at BPL during the financial year. PP (Plasmapheresis plasma), SPP (Single plasma pack 200 ml), 5LT (5-litre pooled plasma), SAG-M (Plasma 300 ml, from blood collected into optimal additive solutions). The established practice of blood collection into SAG-M has resulted in a 30% increment in plasma supply to Elstree.
2. The chart shows the above FFP distribution in percentage form.
3. The plasma supply curve since 1984 shows the progress in introduction of SAG-M blood collection by regions. In certain regions, between 60% and 80% of blood collected into SAG-M is set aside for FFP separation. Applied to the BTS nationally, these rates would realise in excess of 430,000 Kg of FFP annually - i.e., self sufficiency without plasmapheresis.
4. Future requirements for FFP are shown by quarter commencing January 1987 and assume start up of production in Building 27 in the third quarter

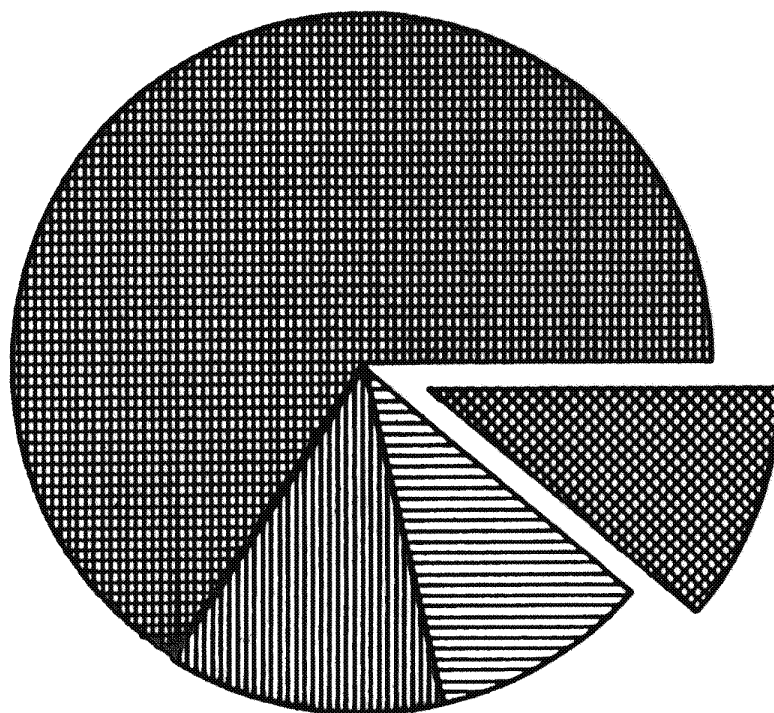
of 1987. Fractionation rates in the final quarter of 1986/7 are shown as 30,000 Kg. The corresponding outputs of containers of albumin and Factor VIII are indicated.





5. Intake during 1986/7 is shown for hyperimmune tetanus and Rh(D) plasma. A promotion within Regional Transfusion Centres in October 1986 failed to avert stock-out failure of anti-D plasma referred to above. Apart from October 1986, regional response to demand for more anti-D plasma remained poor, partly because collection is pursued actively by only half of the 14 regions.
6. The bar chart shows the rate of increase in supply of Source Plasma (Human) collected by plasmapheresis. By the year end, some 35,000 Kg was provided - theoretically, this corresponds to 35 separators working at optimal efficiency. It is believed that Regional Transfusion Centres possess collectively in excess of 100 separators, indicating the latent capacity for this type of source material.

PLASMA (TONNES) RECEIVED AT BPL JUNE 1986 - MAY 1987



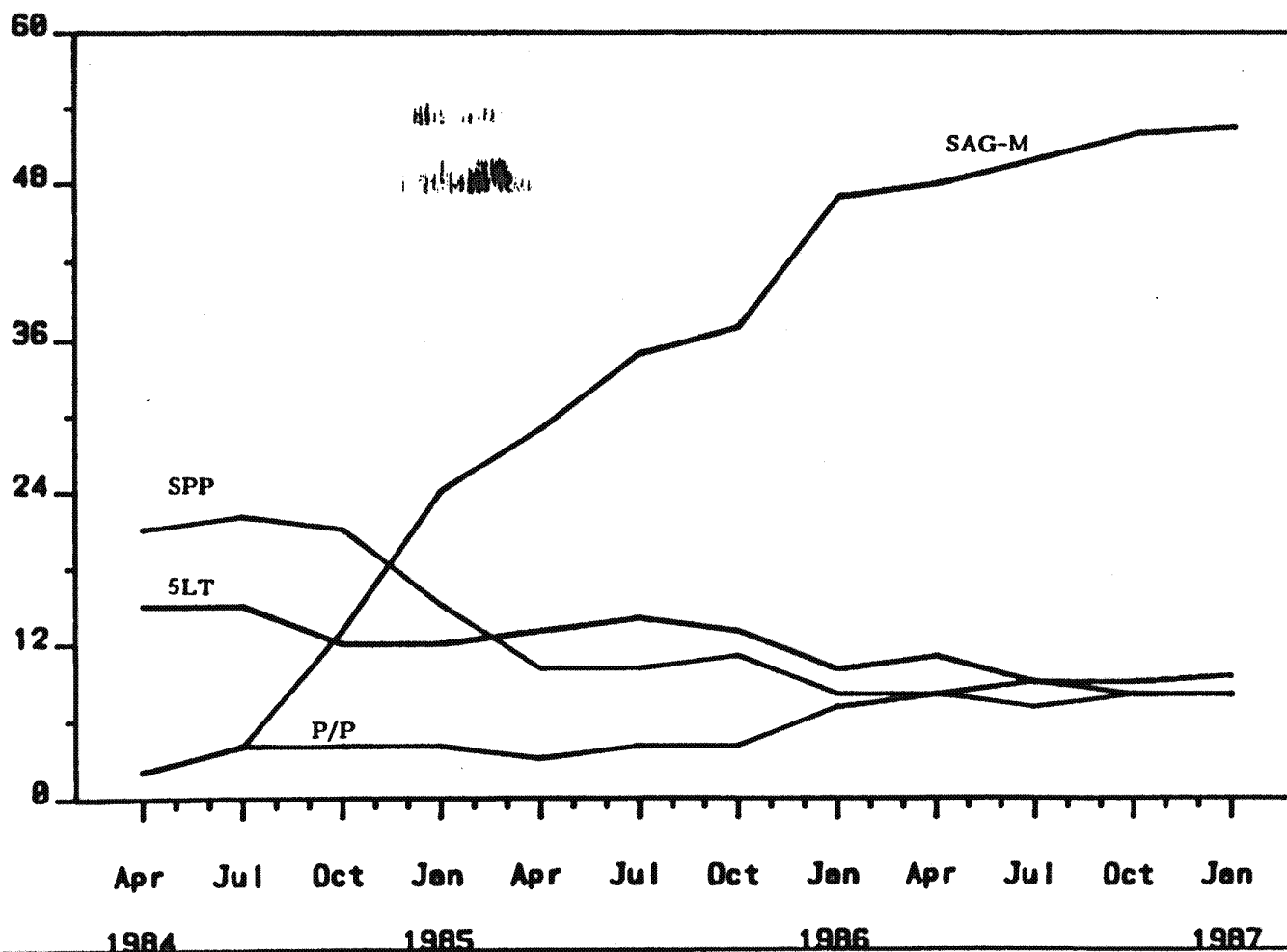
TYPES OF PLASMA APR 1986 – MAR 1987



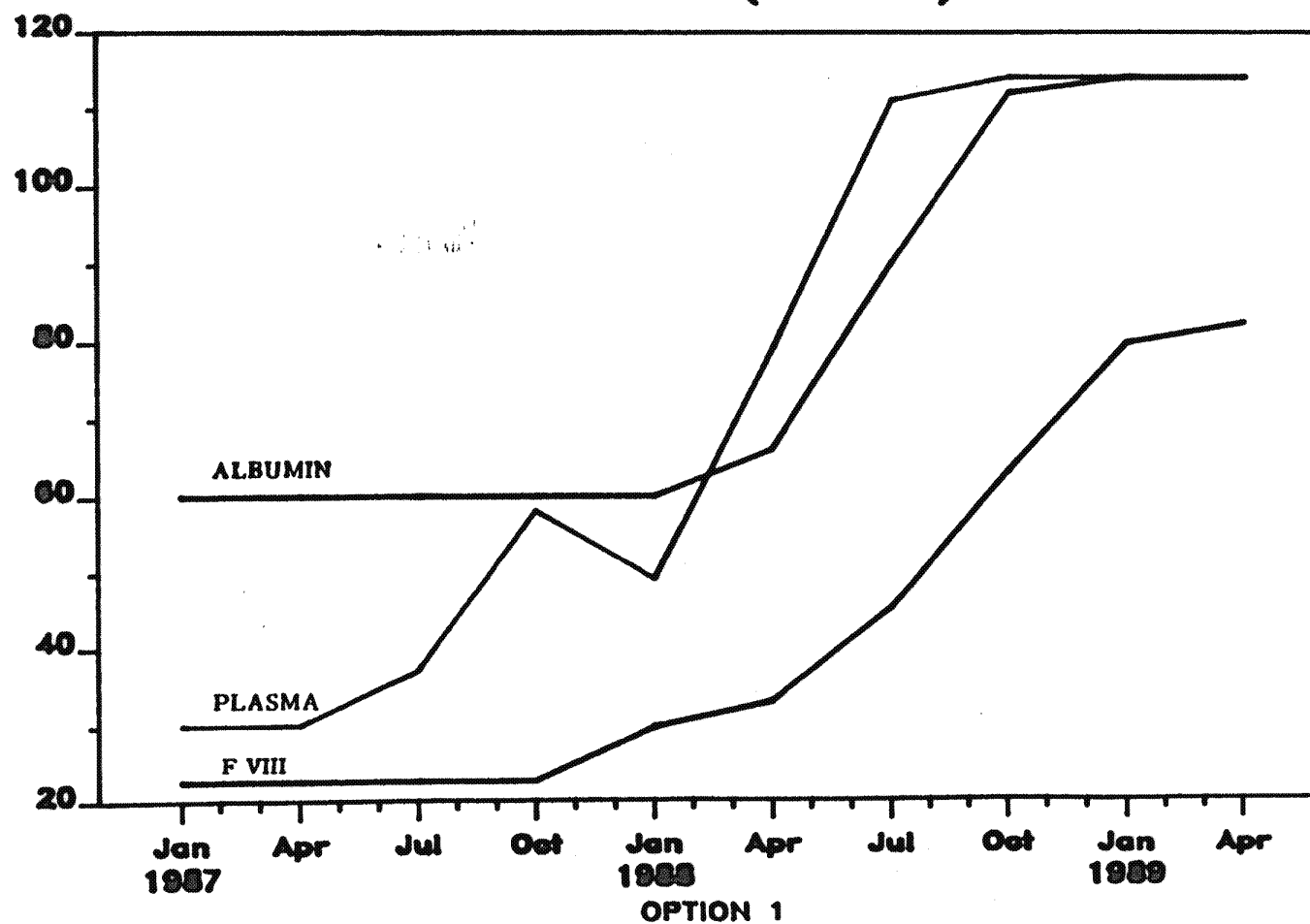
 SAG-M
 65.8 %
 S LT
 12.8 %
 SPP
 10.2 %
 P/P
 11.2 %

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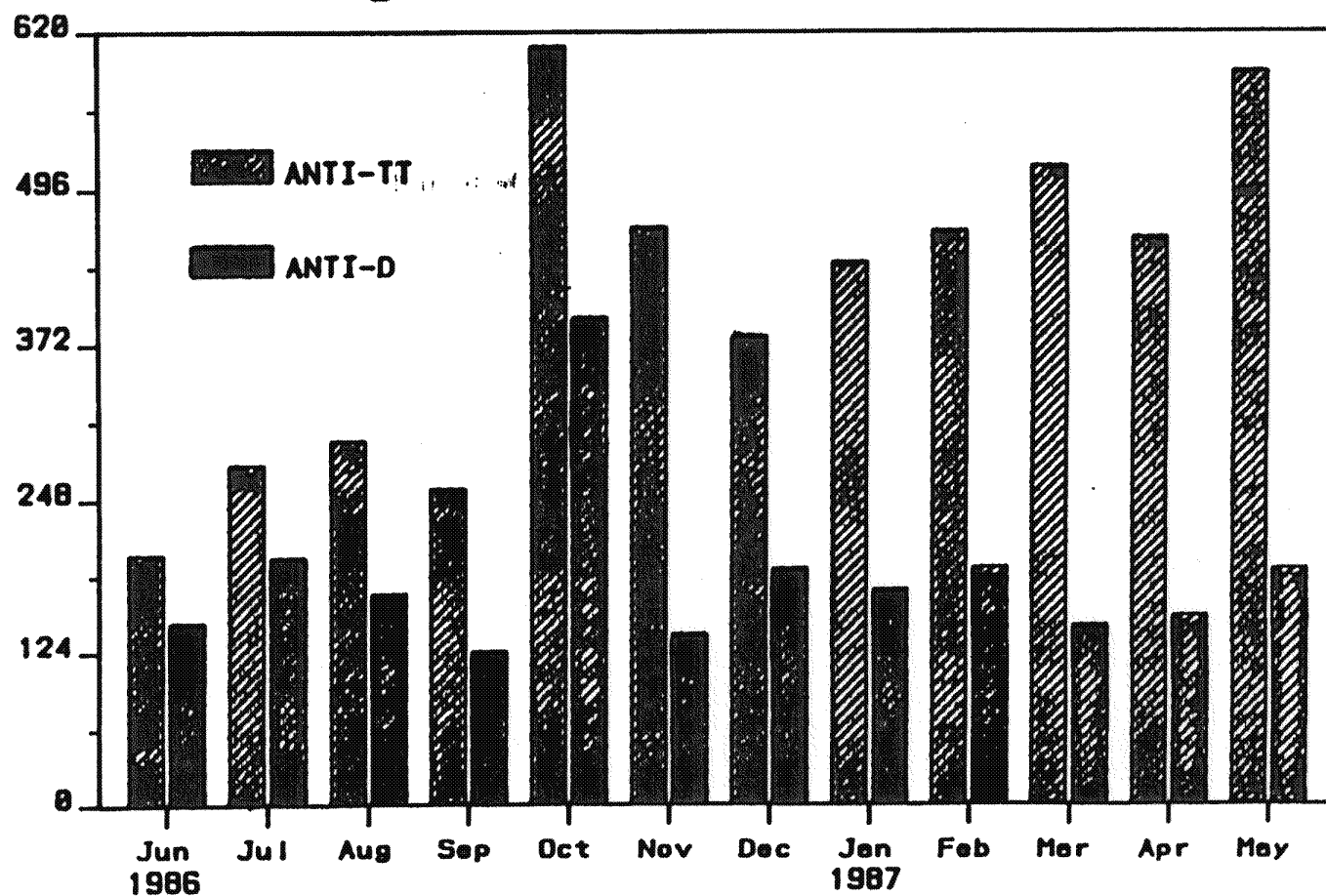
2.

PLASMA TYPES : QUARTERLY INPUT
(tonnes)

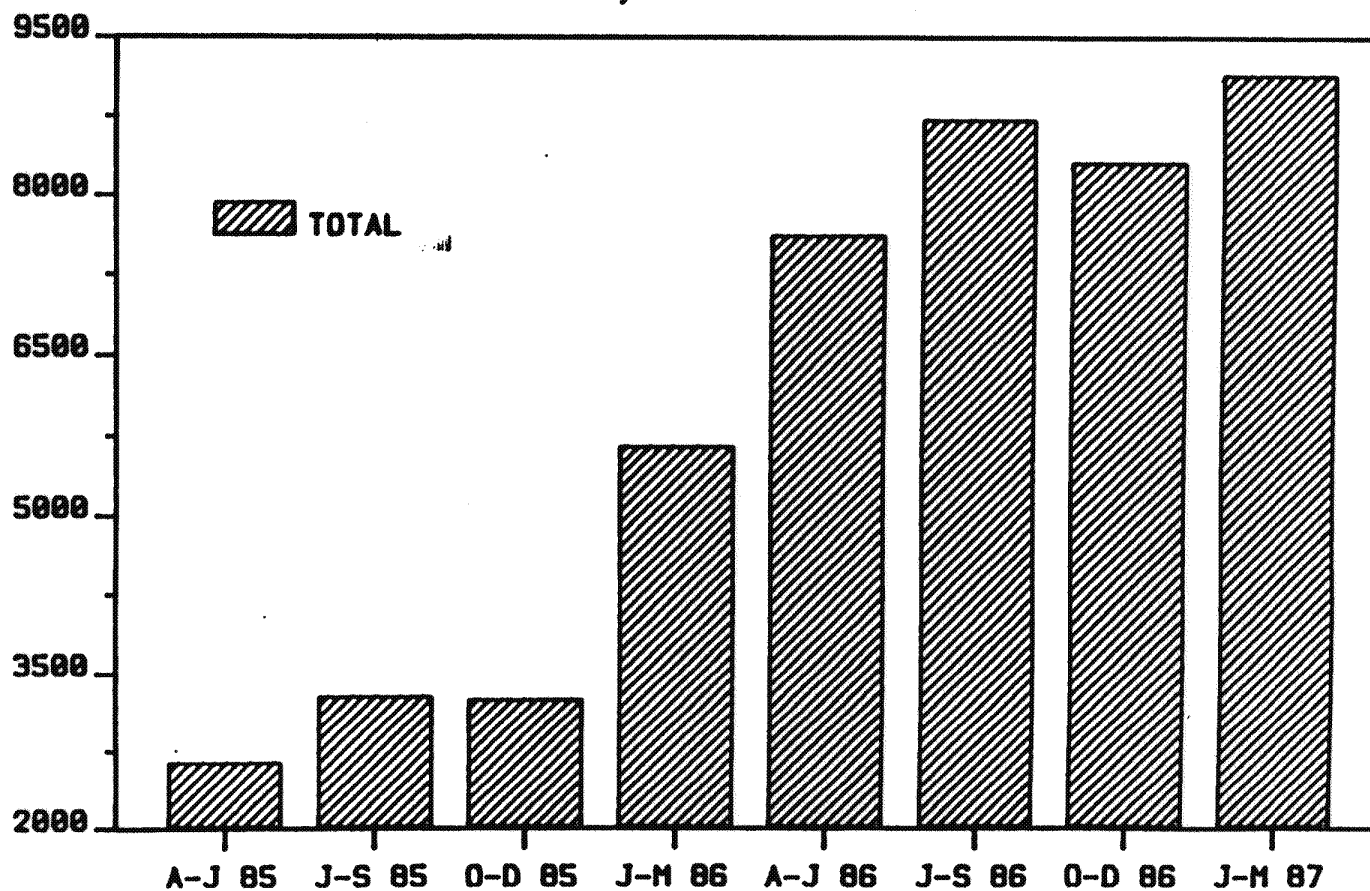
PLASMA PRODUCTION AND PRODUCT OUTPUT (000's)



TOTAL SPECIFIC PLASMA INTAKE (kgs) : Jun 86 - May 87



PLASMAPHERESIS INPUT(kgs) AT BPL 1/4 YEARS



15

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PRODUCT ISSUE FORECAST . 1988/89

450 tonnes FFP + any TEP

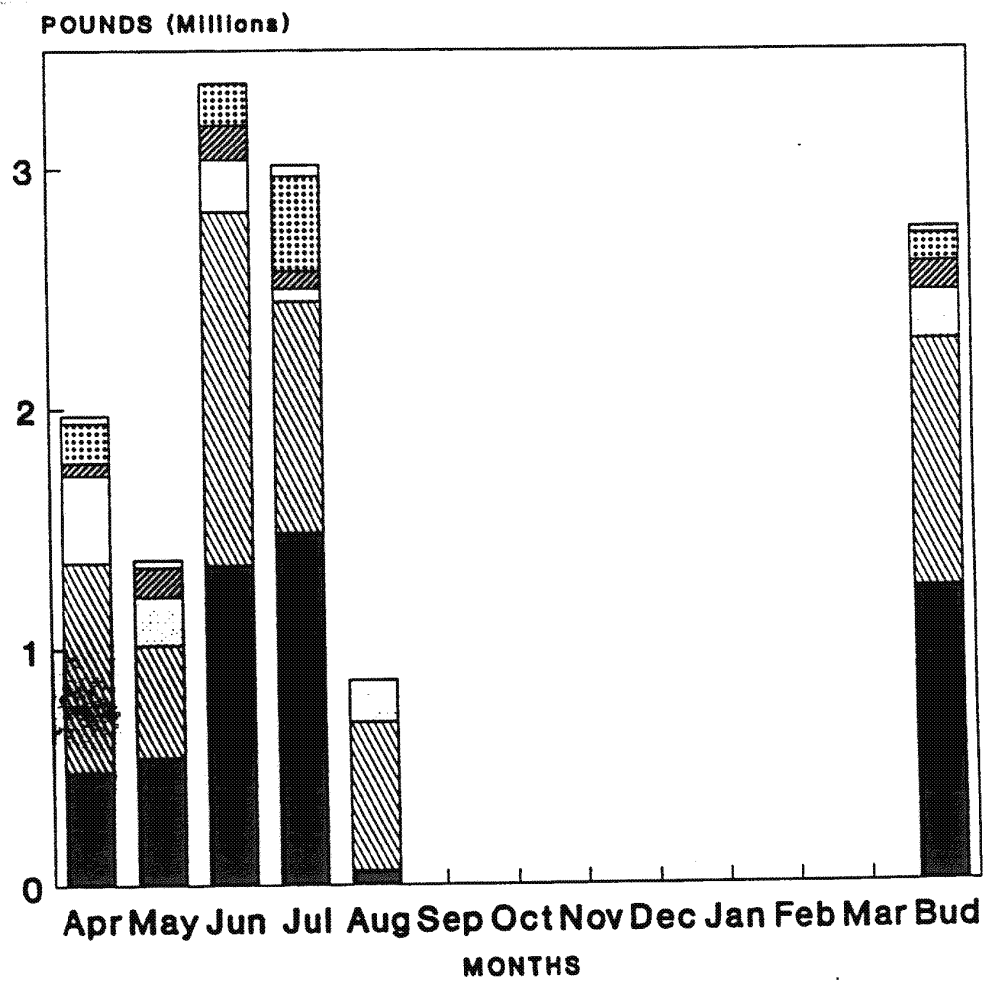
78 million iu Factor 8Y

Self-sufficiency in all other coagulation products

4.5% Albumin	100 ml	20,000
	250 ml	136,000
	500 ml	300,000
20% Albumin	100 ml	75,000 (if required)

Ig as necessary.

VALUE OF WORK IN PROGRESS BUDGET YEAR 1989 - 1990



Alb
Slg

F8
Nig

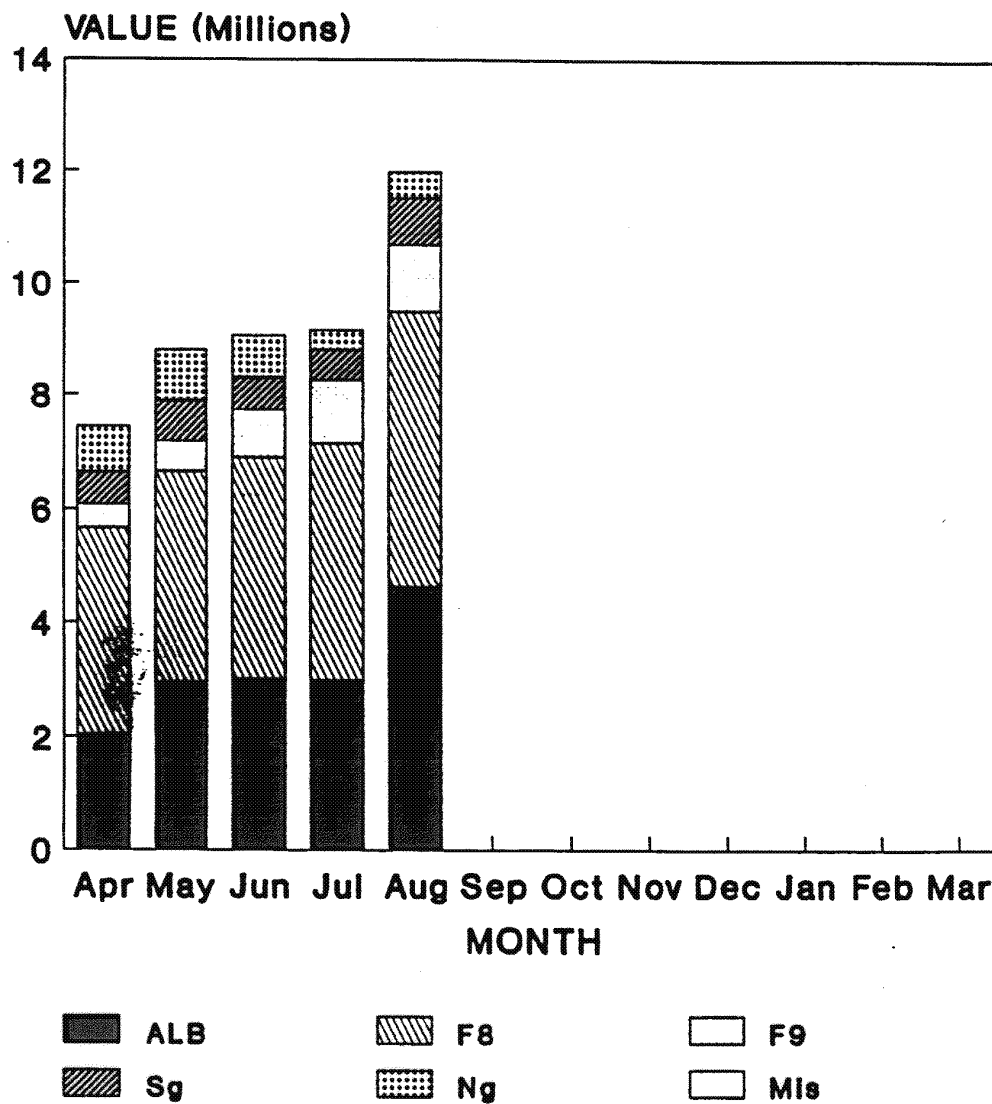
F9
Mis

VALUED AT COST PRICE

CD 01/09/89

2/100

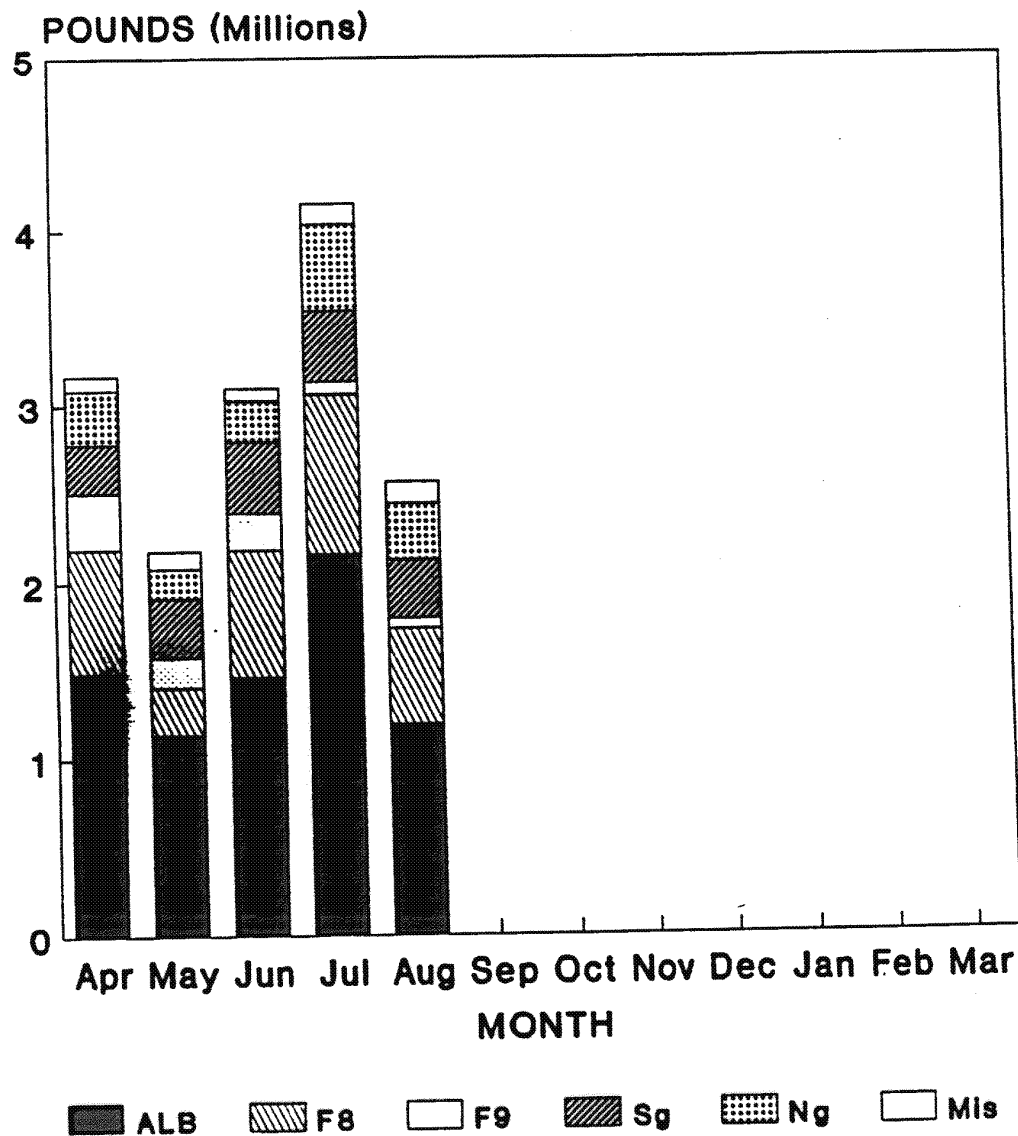
MONTHLY QUARANTINE STOCK VALUE BUDGET YEAR 1989 - 1990



VALUED AT COST PRICE

CD 06/09/89 2/101

VALUE OF FINISHED GOODS BUDGET YEAR 1989 - 1990

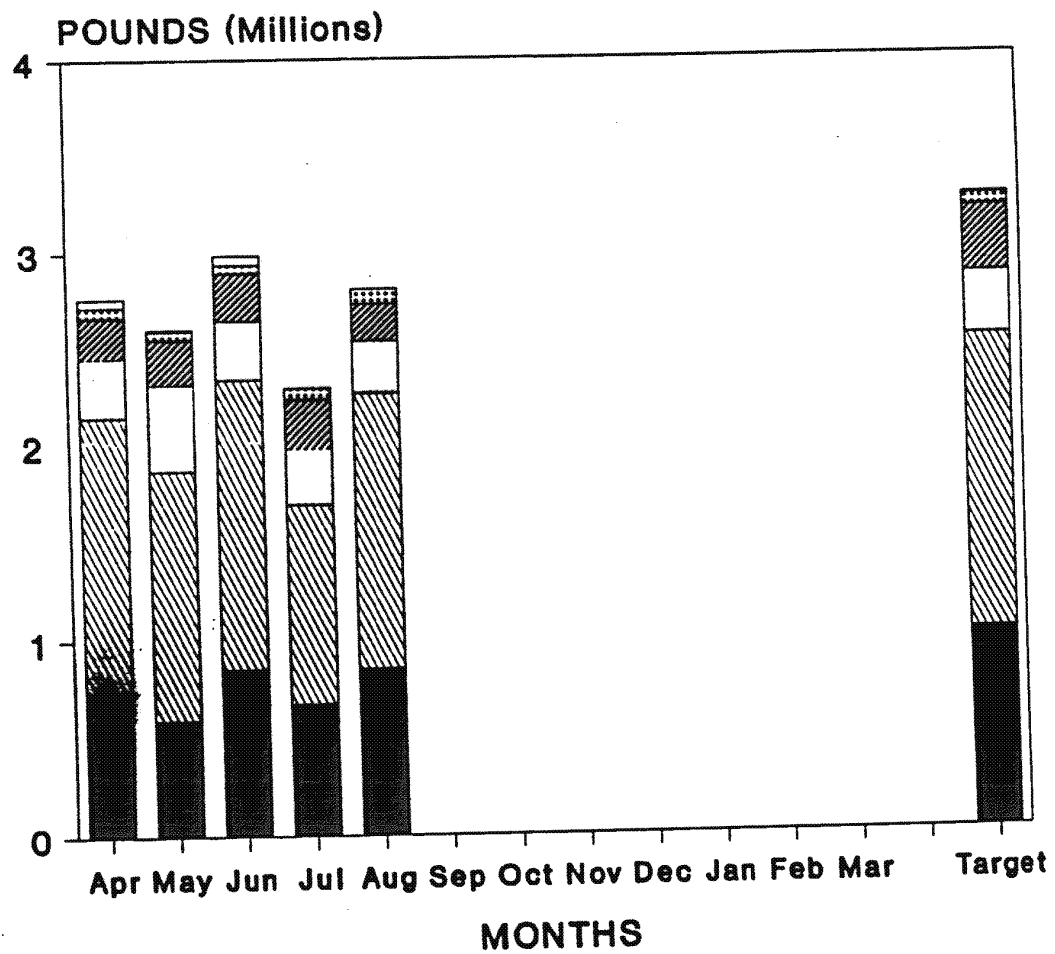


VALUED AT COST PRICE

CD 01/09/89

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MONTHLY VALUE OF SALES BUDGET YEAR 1989 - 1990



Alb
Sig

F8
Nig

F9
Mis

VALUED Incl 7.6%

CD 01/09/89

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PART III

Production of Therapeutic Materials

The Table below shows the opening stocks, production, issues and closing stocks of all current production lines.

1986/87 : Report on Product "Passed to Stock" and Issued

PRODUCT	OPENING STOCK	PASSED TO STOCK	ISSUED	WITHDRAWN	CLOSING STOCK
HAS 4.5% 100 ml	5853	12056	11608	1742 ³	4559
HAS 4.5% 400 ml	18042	211734	217176	130 ³	12470
Alb 20% 100 ml	3582	24991	24172	0	4401
Alb 20% 5 ml	1107	4230	3382	397	1558
Alb 10% 100 ml	185	59	152	29	0
Alb 10% 2.5 ml	8317	3681	1890	6953	3155
Reprecipitated Albumin	437	494	600	331	0
Factor VIII	9730	86199	87466 ²	0	8463
Factor IX	2204	28038	27167	1131	1944
Fibrinogen (FC)	0	339	339	0	0
Thrombin 1000 iu	430	0	141	289	0
Normal IgG 250 mg	160	161030	122293	9071	29827
Normal IgG 750 mg	6640	37748	37436	20	6932
IgG for use with measles vaccine	4954	21155	11371	4376	10362
Anti-D 250 iu	5500	38430	29297	0	14633
Anti-D 500 iu	9978	67802	76462	0	1318
Anti-D 2500 iu	1015	0	374	0	641
Anti-V-z 250 mg	0	3772	3680	0	92
Anti-Tetanus 250 iu	1934	29856	22967	0	8823
Anti-HBs 100 iu	700	682	1	0	1381
Anti-HBs 500 iu	40	4263	2083	0	2220
Anti-Rabies 500 iu	195	476	431	0	240
Anti-Mumps 250 mg	29	0	29	0	0
Anti-Vaccinia 500 mg	0	829 ¹	12	0	817

1 Reassayed during the year

2 Includes product sent to PFL

3 Includes rejected bottles

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The 1986/7 target for issue of HAS 4.5% 400 ml was exceeded by 12,176 containers, while issues of factor 8Y fell below target by 2,534 vials or some 3%. Reasons for the latter shortfall were stated earlier.

Using the price list for issued products, published with DHSS, the notional value of these was £19,491,000 compared with £14,989,000 in the previous year (inflation at 4% is included).

Proportional values were	Albumin	£8.234 M
	Factor 8Y	£4.464 M
	Factor 9A	£3.293 M
	Immunoglobulin	£3.5 M

Priced at £40,000/tonne, value of FFP processed was £5.5M.

The following charts show main product trends and market distribution in the NHS where BPL product has a share with imported commercial product.

7. In Building 25, albumin output peaked near 250,000 containers in 1985. Estimated output for 1986 shown on the bar chart coincided with actual issues. The fall in output was caused principally by feedstock shortage into ethanol fractionation.
8. This chart taken from the 1986 returns of the Haemophilia Services shows the growth in use of factor VIII of all kinds since records commenced. The fall in NHS factor VIII use in 1985 (which persisted in 1986/7) was caused by the introduction of NHS high purity heat treated 8Y: cutback in output resulted from lost yield (225 iu -> 180 iu/kg FFP) and reduced process volume.

The effect of AIDS on factor VIII use has interrupted the linearity of the curve, but 1986 figures may well show this to be merely temporary. 1986 estimated use of all factor VIII is above 80M iu.

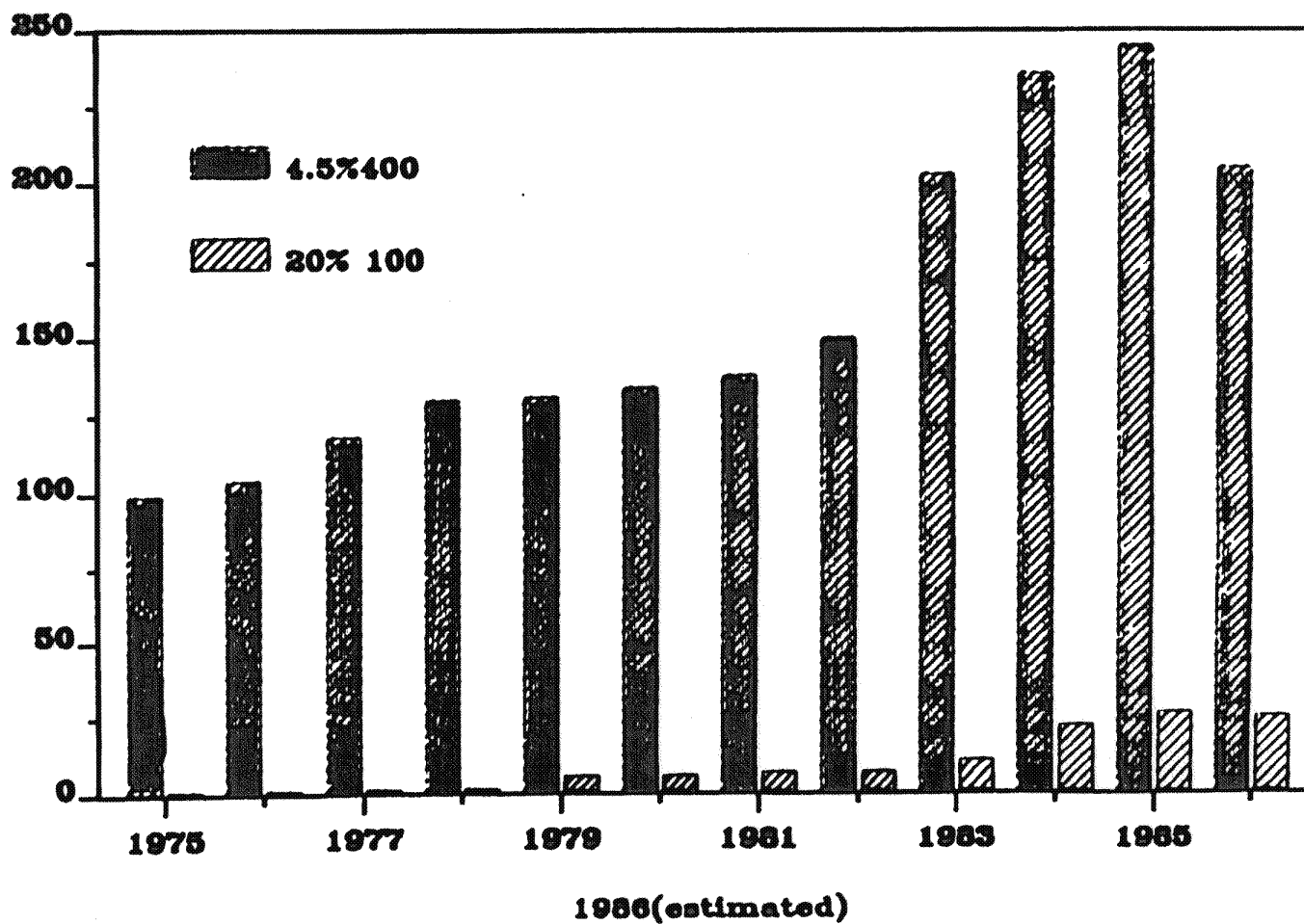
9. The bar chart highlights the above graphic data for 1984 and 1985. It should be noted that current total utilisation of factor VIII is equal to, or marginally above, current estimates of output of 8Y from the new production unit. Allowing for full production on-stream in 1988, use of factor VIII is likely to have risen above current programmed output from 450,000 kg of FFP/annum.
10. In 1985, commercial factor VIII occupied 65.8% of the NHS market: NHS had a 29.9% share.
11. Factor IX issues in 1985 showed an intrusion of commercial product into the, hitherto, totally NHS occupied market. This was due to an intentional delay in product issue by BPL to complete toxicity testing on heat-treated factor IX to exclude increased thrombogenicity. In 1986/7, 27,167 x 600 i.u vials were issued, equivalent to 16.3 million i.u. Haemophilia returns for 1985 show total use at approximately 13.2 million i.u. and it is anticipated that 1986/7 records will show that BPL factor 9A has recaptured the whole market and that the market trend is continuing to rise. Some BPL factor 9A is used to treat factor VIII deficient patients with immune inhibitors (~1.5M i.u.).
12. Normal Human Immunoglobulin (750 mg and 250 mg) issues are shown since 1975. The 750 mg vial is used mainly for replacement therapy in hereditary deficiencies and some severe acquired deficiencies in special patient treatment units. Numbers of patients are now fairly constant but use of the intramuscular product is expected to decline in favour of intravenous IgG.

250 mg IgG is used increasingly to achieve protection from hepatitis A infection in travellers abroad. The trend in use has increased since 1977, but may now be levelling off since many medical agencies including general practitioners now exact a charge.

13. Use of anti-D immunoglobulin remains relatively constant and will do so until the policy to treat Rh -ve mothers during pregnancy is generally applied. This application is currently inhibited by short supply although an upward trend in 250 i.u. anti-D is evident. If fully implemented, ante-natal prophylaxis would increase demand from 70 million i.u. to between 90 and 110 million i.u. per annum. The supply failure rests with feed stock plasma.

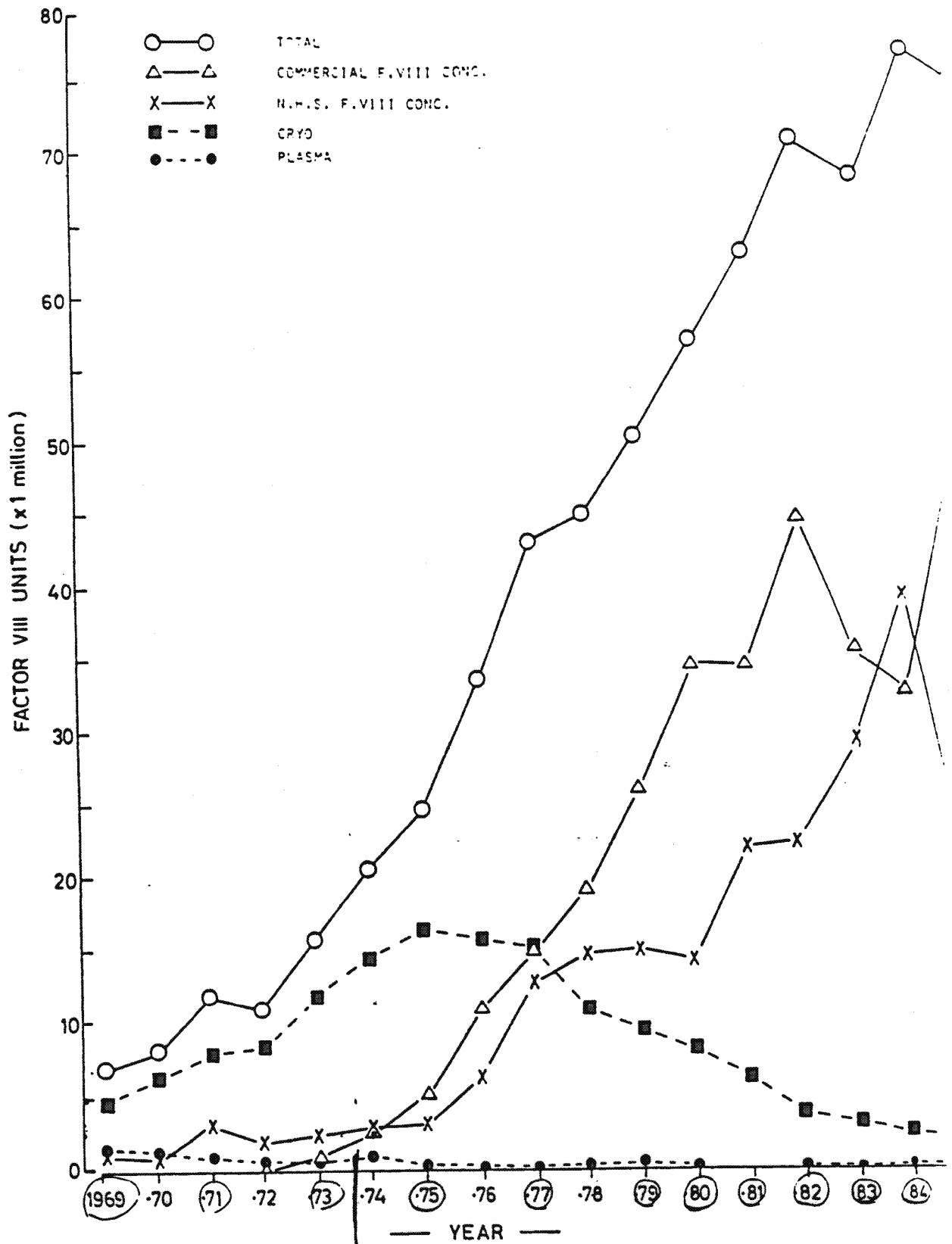
A significant rise in use of anti-tetanus immunoglobulin has taken place since its promotion in 1980/81.

ALBUMIN PRODUCTS (000's) FROM BPL 1975 - 1985.



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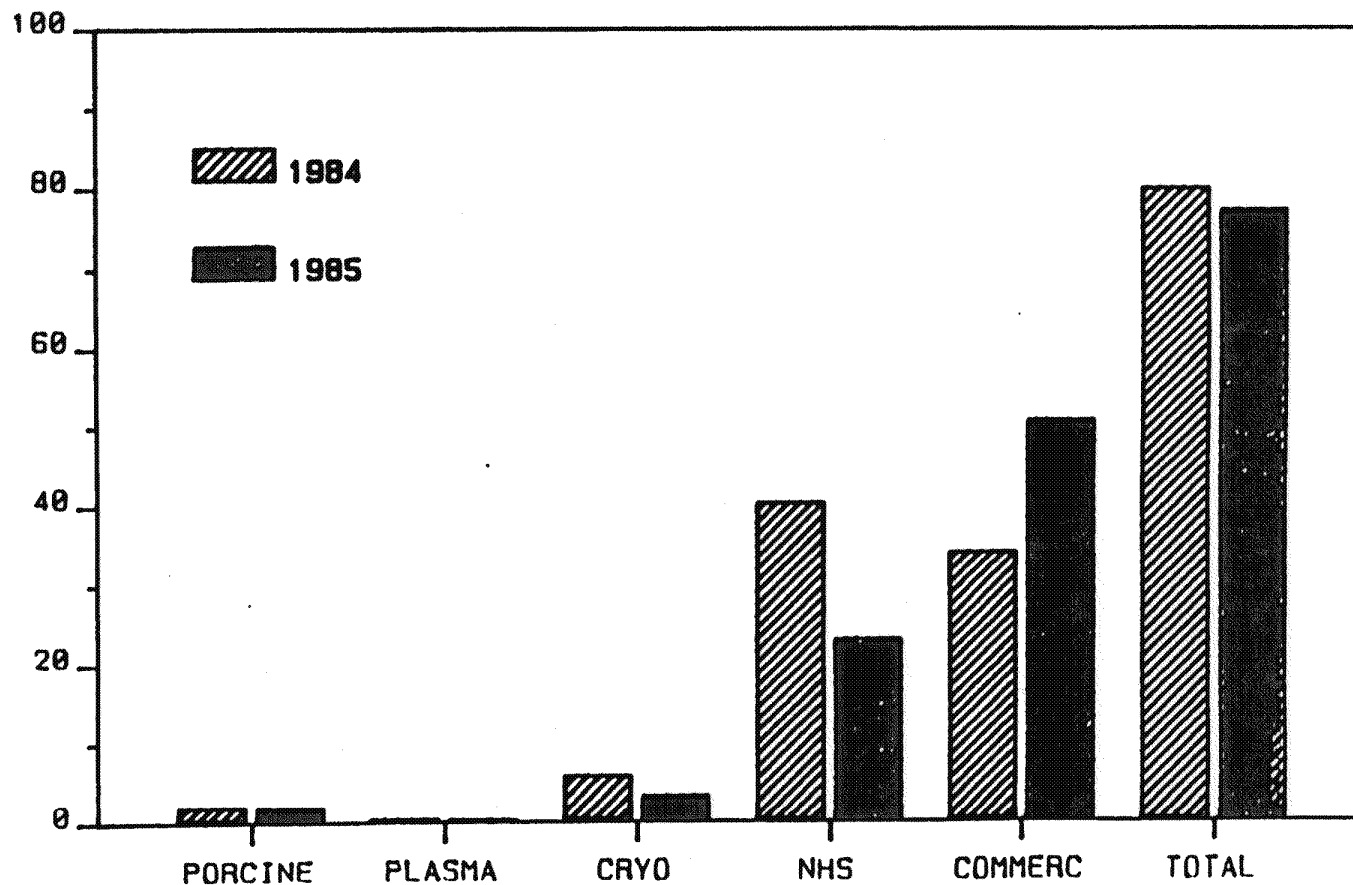
7.



AMOUNT OF BLOOD PRODUCTS (F.VIII UNITS) USED TO TREAT HAEMOPHILIA A PATIENTS IN THE U.K.

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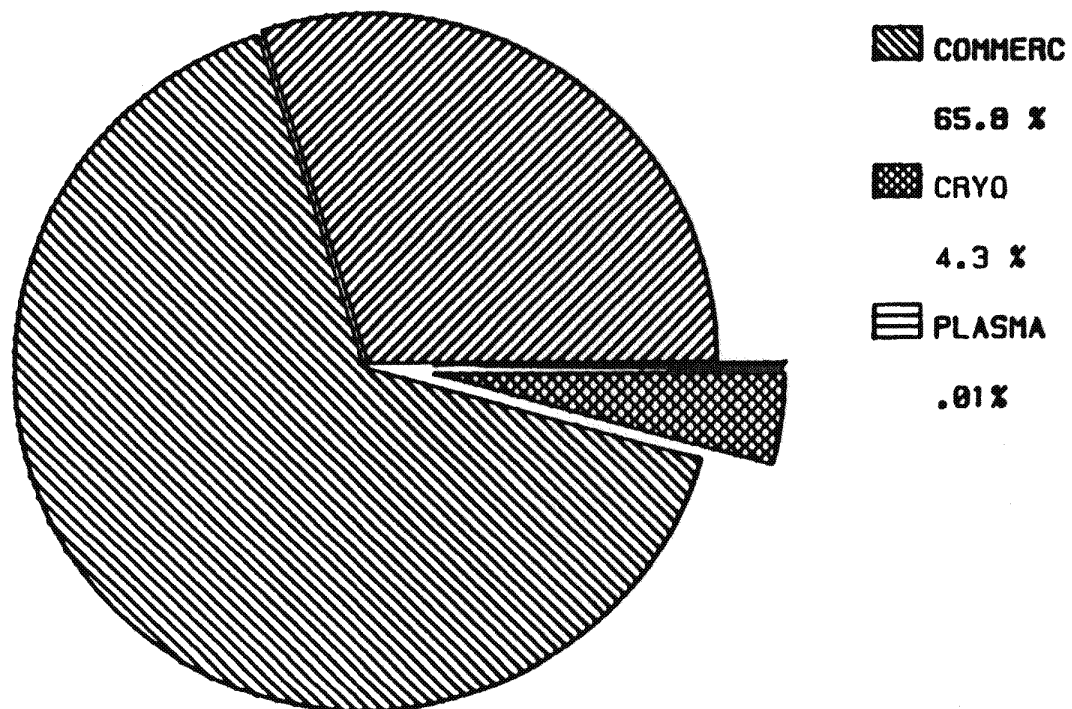
FACTOR VIII UNITS (Miu) USED IN UK 1984/1985



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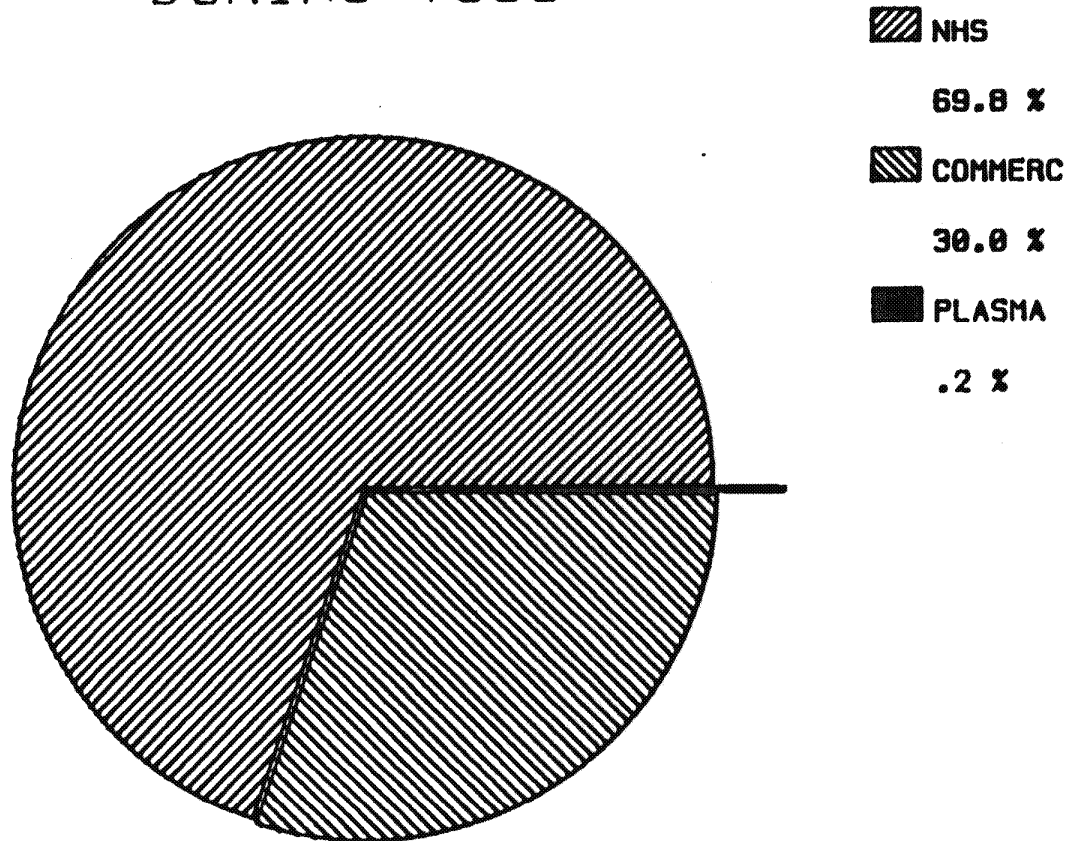
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FACTOR VIII UNITS USED IN UK DURING 1985



TOTAL=77.3 Miu

FACTOR IX UNITS USED IN UK DURING 1985

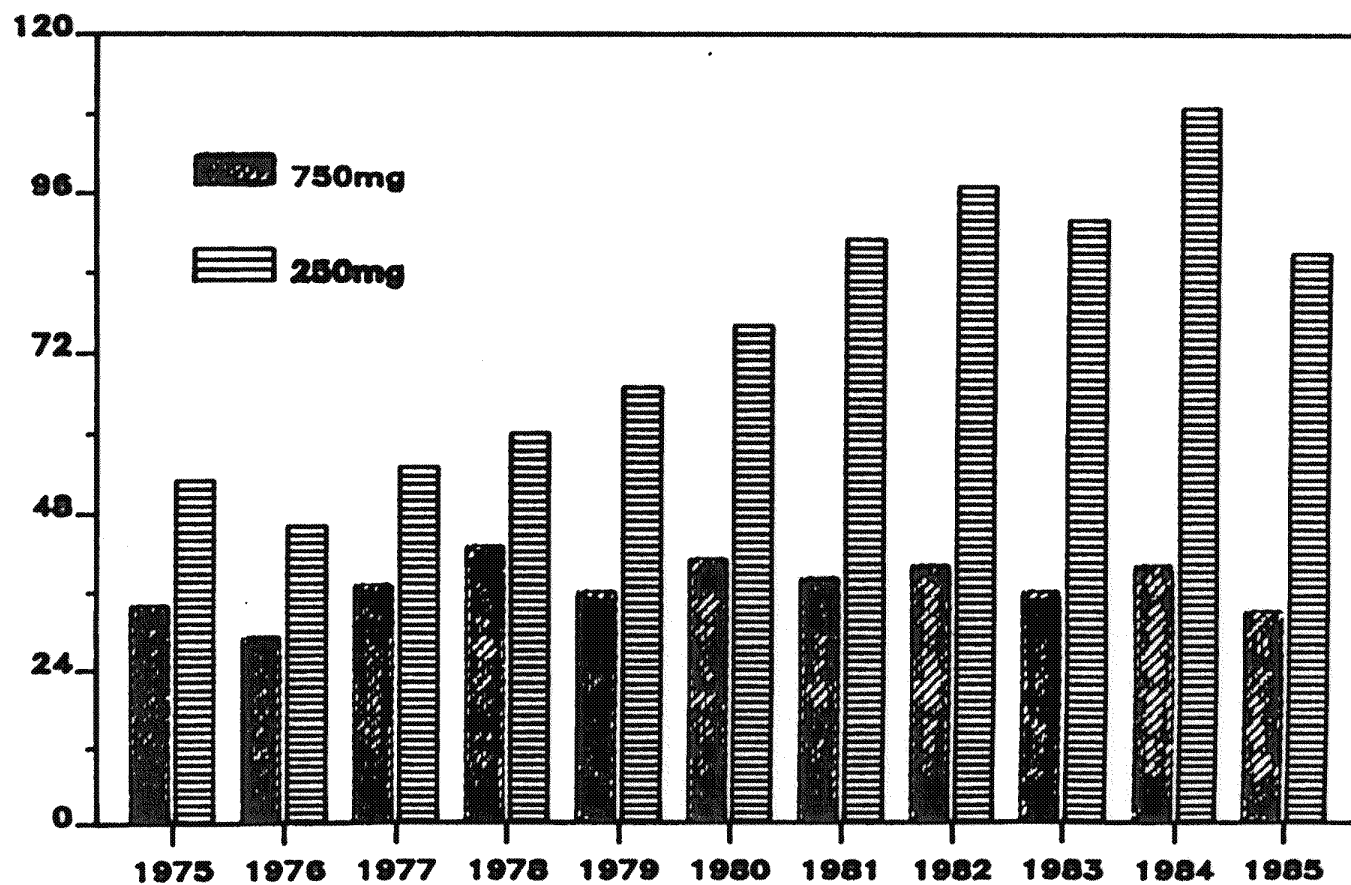


TOTAL=13.2 MIU

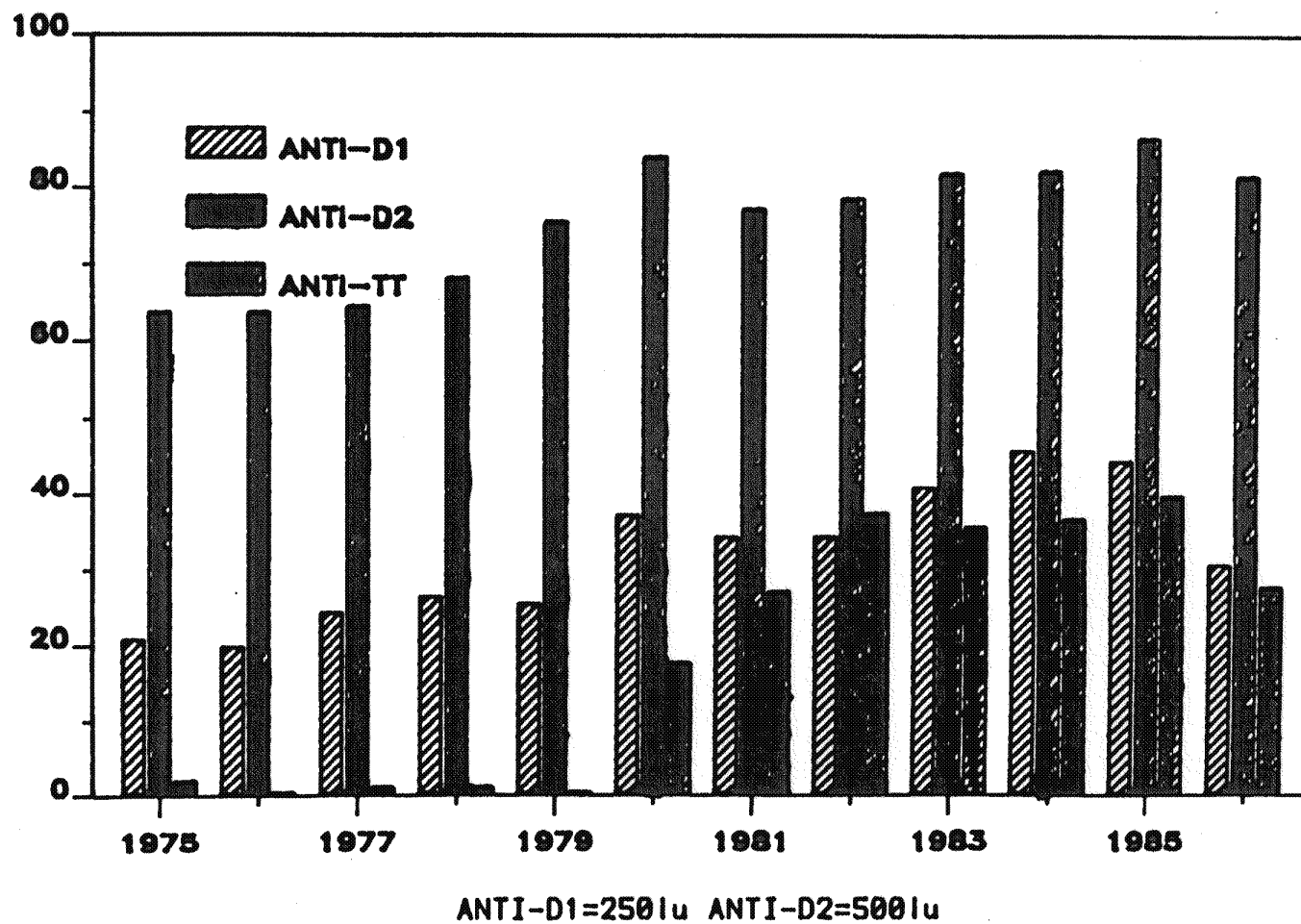
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11.

IMMUNOGLOBULINS (000's) FROM BPL 1975 - 1985.



ANTI-D AND ANTI-TETANUS (000's) FROM BPL 1975-1986



DIAGNOSTIC PRODUCTS
BLOOD PRODUCTS LABORATORY

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Diagnostic Reagents

Serological reagent production was placed under BPL operational management in April 1986. Following the departure of the Director with responsibility up to that time, there was extreme uncertainty among staff at the Harkness Laboratory, Oxford. This uncertainty was shared by the Blood Group Reference Laboratory and, most significantly by the NHS customers of BGRL both in Regional Blood Transfusion Centres and Transfusion Laboratories in NHS hospitals. A number of staff left the Harkness Laboratory.

The main tasks in 1986/7 were to consolidate the overall position of production and staffing of the new BPL:D.

Manufacturing procedures documentation and production staff structure were reviewed and corrective actions taken where necessary and when possible. The production processes were audited.

A Manager of Quality Control (Serology) was appointed, reporting directly to the BPL QC/QA Manager.

This appointment was followed by the appointment of Mr. P. Prince as Head of BPL Diagnostics, reporting to the Director, BPL Operations.

A review of production requirements led to accelerated introduction of monoclonal antibodies in replacement, wherever possible, of existing reagents based on human plasma antibodies collected by Transfusion Centres.

By collaboration with external units, increasing production at Oxford and purchase of some bulk monoclonal antibodies, BPL:D assembled a satisfactory portfolio of blood grouping reagents which were submitted to clinical trial and then offered for distribution.

A policy of charging for monoclonal antibodies put BPL:D in direct competition with commercial suppliers and drew attention to the poor profile presented by the Unit in the market in comparison with others. Steps are planned to rectify this shortcoming during financial year 1987/8.

Monoclonal Anti-D MAD-2

During the year, BPL:D launched the first full field trial of monoclonal 1 gm anti-D prepared in-house from the Cambridge cell line developed by Dr. Hughes-Jones and co-workers. General reaction to the reagent was good with results based on assessment of over 200,000 samples. The product will be formally released for sale in 1987.

Reagent Production 1986/7

Issues of products during the year are tabulated below with comparative figures for the previous year.

<u>Human Source</u>	86/7 Litres	85/86 Litres
Anti-A	54.75	244.2
Anti-B	99.4	250.53
Anti-A,B	136.68	240.13
Anti-D	256.62	333.97
AB-serum	129.65	152.68
<u>Animal Source</u>		
Anti-human globulin	849.65	923.31
Bovine serum albumin	589.32	738.2
<u>Monoclonal</u>		
Anti-A	225.46	214.64
Anti-B	215.28	213.53
<u>Reference and Quality Control Sets</u>		
NEQAS	3126	3135
SAQAS	0	1543
Screening cells	7056	10695
<u>Other Reagents</u>		
Reference Reagents	10.45	8.43

Comment

Human ABO issues dropped significantly, primarily due to shortage of quality source plasma from Regional Transfusion Centres who receive no payment for this material and have traditionally kept the best material for their own use.

Problems indicated by the above trends are accelerating the transfer to monoclonal antibodies.

D-Grouping reagents: issues fell during 1986/7 for the same reasons set out above but compounded by the shortage of anti-D immune plasma for therapeutic product fractionation (see earlier).

Anti-Globulin reagents prepared from hyperimmune sheep serum and augmented with anti-C3d monoclonal products from the Bristol cell line BRIC-8 have maintained their place. As with human-sourced reagents, no charge is made for anti-globulin reagents.

Monoclonal Anti-A and Anti-B. These products are charged for and their distribution has remained similar to the previous year. The bulk monoclonal antibodies are purchased from Celltech plc.

Bovine Serum Albumin. There is a drop in sales reflecting the fall in use of albumin-dependent techniques in transfusion practice. Extension of monoclonal antibody methods will increase this downward trend.

Standing Orders. Standing orders for monoclonal anti-A and anti-B to Regional Transfusion Centres in Sheffield, Bristol, Leeds and Newcastle were lost during the year because of the introduction of a charging policy for these reagents in spring 1986.

The above losses were compensated for by increased distribution to hospitals.

G.M.P. A long-term programme to achieve a completely new edition of batch documentation was commenced during the year. Detailed attention was given to microbiological surveillance in the laboratory. The August '86 Health Notice (re: source testing of plasma for diagnostic reagents to exclude HIV and Hepatitis B) was completed within due time: 750 Kg of source plasma is scheduled for sterilisation and write off.

PRODUCT SALES

I Therapeutic Products

Product Analysis

Customer Analysis

II Diagnostic Products

(a) BPL : Diagnostics, Oxford

Product Analysis

Customer Analysis

(b) BPL : Diagnostics, Elstree

BPL RIA test for Hepatitis Bs Antigen

L. BPL ANALYSIS OF PRODUCT INCOME
April 1986 - March 1987

<u>PRODUCT ANALYSIS</u>	£
Albumin Salt Poor	18,383
Albumin Solution 10% 2.5 ml & 100 ml	4,678
Albumin 100 ml & 400 ml	220,671
Reprecipitated Albumin	11,490
Reagent Grade Human Albumin 100 ml	60
Out-dated plasma for non-clinical use	89
Fraction IV Paste	40,423
Human Albumin Fraction IV	4,988
Fibrinogen	41
Fibrinogen for Isotopic labelling	104,662
Human Fibronectin	120
Plasminogen	6,000
Thrombin	320
PFL-Thrombin	500
Special Fractions	22,936
Normal Immunoglobulin	57,154
Discount on Normal Immunoglobulin	<u>4,997</u> -
TOTAL	£ <u>487,518</u>

CUSTOMER ANALYSIS

Biotest Pharma Dreieich, Germany	33,983
Amersham International	124,176
E. Moss Ltd	13,680
Thomas Cook	15,357
SAS Laboratory	1,288
Charter Medical	1,612
Anthony Rumsay International	218
Rothman's Exports	366
MOD	243,180
Committee of Public Health, Jersey	15,414
Civil Service Medical Advisory Service	2,685

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CUSTOMER ANALYSIS

Belfast City Hospital	58
Egyptian Embassy	225
BTSB Dublin	10,728
Public Health Department, Guernsey	648
St. Thomas Hospital	479
St. Bartholomew's Hospital & Medical College	763
Cambridge University	730
Devonshire Hospital	1,047
Government Medical Stores, Malta	101
Community Health Service, Jersey	855
University of Helsinki	100
Charing Cross Hospital	500
Beecham Pharmaceuticals	6,000
BUPA Hospital	304
Oxfam House	440
The Heart Disease & Diabetes Research Trust	60
Hanover House	458
Princess Elizabeth Hospital, Guernsey	555
Chaim Sheba Medical Centre, Israel	420
Royal Post Graduate Medical School	61
The Children's Hospital, Dublin	1,095
Dr. N C King	599
Reading University	104
Queen Elizabeth Military Hospital	1,041
John Bell and Croydon	219
Wellcome Laboratories	315
Northwick Park Hospital	320
Charles Kendall & Partners	75
Northern Regional HA	139
United Medical & Dental School	104
Medical Suppliers, New York	6,440
Others	<u>576</u>
TOTAL	£ <u>487,518</u>

II(a) BGRL ANALYSIS OF PRODUCT INCOME
April 1986 - March 1987

PRODUCT ANALYSIS

	£
Monoclonal Anti-A & Anti-B	106,585
Bovine Serum Albumin	<u>81,073</u>
TOTAL	£ <u>187,658</u>

CUSTOMER ANALYSIS

Princess Margaret Hospital	292
Manchester RTC	6,024
Lewisham Hospital	1,416
NBTS Sheffield	4,668
N E Thames RTC	10,290
Dundee BTS	746
Belfast RTC	1,440
Birmingham RBTC	15,687
North London BTC	17,173
South Western RTC	7,360
Wessex RTC	10,972
South London TC	29,257
Oxford RHA	7,766
Western Infirmary	676
Belvoir Park Hospital	216
Leeds Western Hospital	156
Nobles Hospital Administration Committee	215
Alexandra Hospital	150
RBTC Liverpool	14,476
Welsh RBTC	11,462
Greater Glasgow Health Board	180
NBTS Lancaster	2,211
Royal Devon & Exeter Hospital	540
Bon Secoures Hospital	56
Cambridge RTC	13,715

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CUSTOMER ANALYSIS

	£
NBTC Newcastle upon Tyne	10,816
BUPA Hospital	770
RTC Leeds	7,934
Pontefract General Hospital	416
Metropolitan Police	269
Staincliffe General Hospital	624
The General Infirmary, Leeds	1,248
London Hospital Medical School	52
Eastern Health & Social Services Board	3,480
Seacroft Hospital	624
Burton General Hospital	208
Royal Postgraduate Medical School	288
Phillip Harris Biologicals Ltd	200
Leicester Royal Infirmary	52
General Hospital, Lancs.	468
Macclesfield District General Hospital	104
Queens Medical Centre	260
The General Hospital, Hartleypool	52
London Chest Hospital	760
West Park Hospital	52
Wharfedale General Hospital	52
Friarage Hospital	104
H M Stanley Hospital	67
Harold Wood Hospital	112
Princess Alexandra Hospital, Essex	70
Broomfield Hospital	75
Chase Farm Hospital	30
Homeston Hospital	191
Victoria Hospital	60
North of Scotland RBTC	158
Aberdeen TC	78
City Hospital, Nottingham	260
Orgett Hospital	68
Others	<u>512</u>
TOTAL	£ <u>187,658</u>

II(b)

1986 - 1987

BPL - RIA

TOTAL SALES OF BPL- RIA KITS AT 23p/TEST

Month	English RTCs	Scotland & PHLS etc.	Total	Accumulative Total
April 1986	53433.60	7749.62	61183.22	61183.22
May	33605.76	9480.60	43086.36	104269.58
June	33142.08	7439.58	40581.66	144851.24
July	41554.56	9409.76	50964.32	195815.56
August	28836.48	7637.84	36474.32	232289.88
September	32832.96	8143.38	40976.34	273266.22

PRICE REDUCED TO 12p/TEST from October 1st

October	17913.60	4236.48	22150.08	295416.30
November	15229.44	3185.04	18414.48	313830.78
December	20471.04	3731.64	24202.68	338033.46
January 1987	15932.16	2973.36	18905.52	356938.98
February	14964.48	3099.84	18064.32	375003.30
March	16761.60	2907.84	19669.44	394672.74

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Cumulative product sales from all sources contributed £1,070 million towards the DHSS funding of the CBLA cash limit for 1986/7.

This sum was obtained without a formal commercial presence in the market and must benefit in future from establishment of a Commercial Affairs department.

The year's experience with diagnostic reagents is salutary, even though anticipated. The coordination of NBTS Serological policy within Regions varies from complete to non-existent: in the latter hospital transfusion laboratories operate freely to select blood grouping reagent suppliers from the commercial sector, regardless of a centrally funded operation within NBTS to provide standardised, quality products. Not more than half the Regional Transfusion Centres support central reagent production at present.

A legacy of poor, unreliable supply of reagents from BGRL has to be overcome, but there is a clear need now for BPL:D to establish a presence in the market and acquire a clearer information base on consumers' needs and reactions.

The decline in income from sale of the BPL RIA test is the direct outcome of DHSS policy not to invest in development of new reagents in this field and its associated field, HIV-antibody. Consequently the BPL RIA test for HBsAg, which was a market leader when introduced seven years ago, is now outmoded by the greater facility and security of enzyme-linked immune assay technology. The message must be clear for the future.

QUALITY CONTROL AND ASSURANCE

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QUALITY DEPARTMENT

Department Structure

The structure and staffing of the Department at the time of preparation of this report is presented as Figure 1. The extension of activities to cover quality assurance and control at BPL Diagnostics took place on August 1st 1986.

Review of product statistics (including rejected product)

The data for this review is presented in Table 1. The single most significant cause of rejection of factor VIII concentrate was instability of the reconstituted product in solution, 10733 vials from 10 batches being rejected for this reason. Of the 3827 vials of factor IX concentrate rejected, 2779 vials (2 batches) were rejected because the batches failed the BP (rabbit) pyrogen test. In the case of human albumin solution 4.5%, the presence of particulate matter in the solution, detectable at inspection, was the most common reason for rejection, 13077 bottles (400 ml) from six batches rejected on these grounds. In addition, two batches failed the rabbit pyrogen test and one batch failed the test for sterility.

Review of plasma incidents

There were 382 units of plasma implicated in reports from RTCs in this period, the data is presented in Table 2. Occasionally, one report may cover more than one pack/donation/product, thus the numbers given in Table 2 are for the number of packs/donations/products concerned and not the number of reports.

Of these 382 units, 100 were already fractionated. The increase in the number of units already used at the time of reporting (in 1985 only 18 units had been used) is due to the fact that the past donations of donors now anti-HIV positive have been treated as plasma incidents. Also included is a 'high risk for AIDS' category. This plasma could have been donated up to six years ago.

Review of product complaints

During 1986/7, 42 product complaints were received, including nine reports of adverse reactions. The adverse reactions reports are summarised in Table 3.

Of product complaints not associated with adverse reactions, the most common complaint concerned the quality of overseals on HAS 4.5% (400 ml). Numerous users reported that the overseals came away from the bottle when they attempted to remove the flip-off cap. So far, there have been complaints from 28 users concerning 30 batches. Although this particular complaint file is still open, no reports of this problem have been received since February 1987.

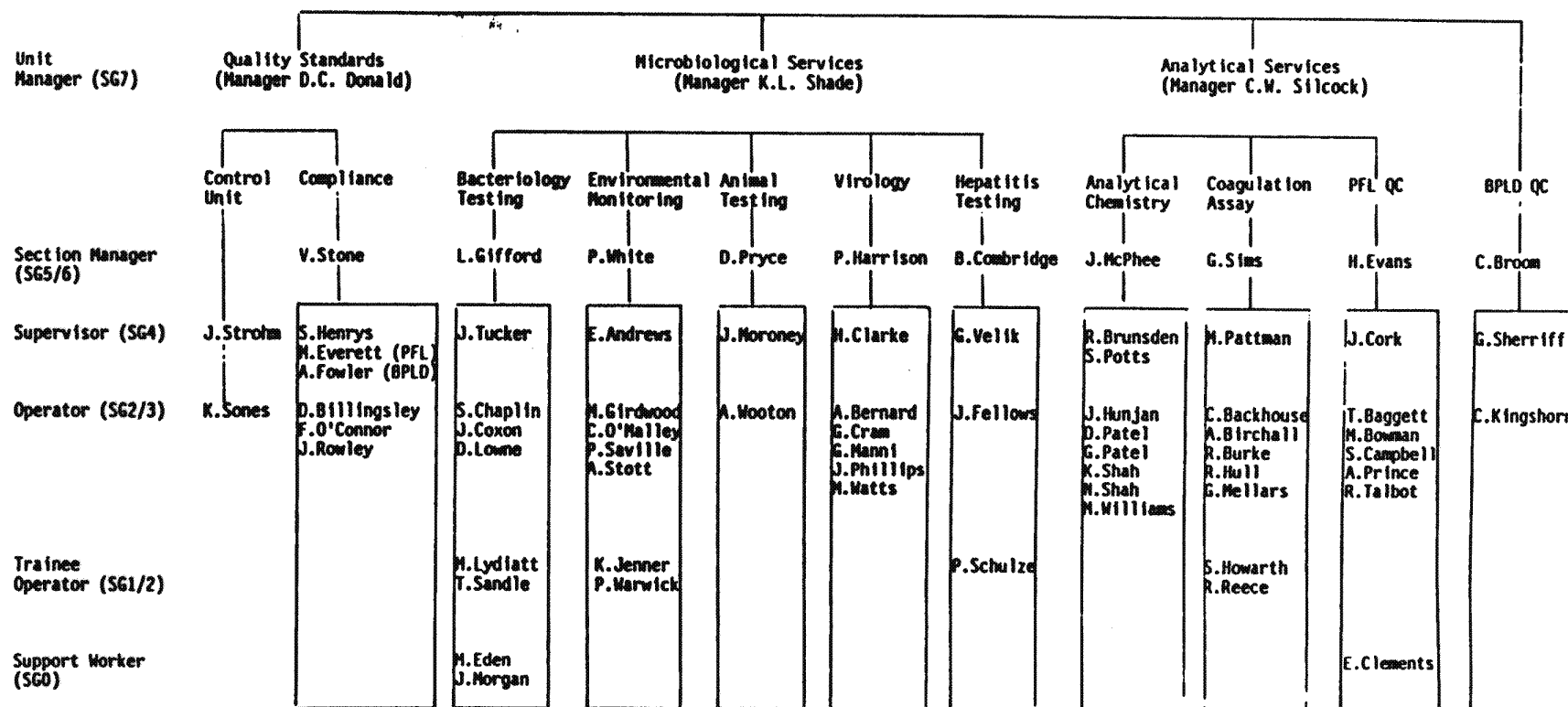
There were 16 other complaints about packaging, e.g. 400 ml bottles falling out of cartons, ill designed slings for HAS, etc. and two enquiries concerning the storage conditions of immunoglobulin.

FIG 1

QUALITY DEPT : JULY 1987

Department Manager (Dr. T.J. Snape) - (Secretary Mrs. A. Richards)

Report 1986/7



Clerical Staff: BPL - Miss S.L. Spreadbury, Miss S. Parlour

PFL - Mrs. J. Burrell (part time)

TABLE 1.

ANNUAL REVIEW OF CONTAINERISED PRODUCT APRIL 1986 - MARCH 1987 - ALL PRODUCTS

PRODUCT	CARRIED FORWARD	FILLED	ISSUED	REF	REWORK	QC	REJECT	MISCOUNT	REJECT BATCH	BATCH REWORK	REMAINING IN QUARANTINE
Factor VIII	23732	11687	85896 593*	237	4266	3977	2493	0	14929	0	24321
Factor IX	4402	31445	28038	88	0	989	434	0	3827	0	2471
Thrombin	1529	0	0	0	0	0	0	0	1529	0	0
Fibrinogen	50	571	339	0	0	51	1	0	0	0	230
HAS 4.5% (400ml)	61877	280110	211717	357	38875	4922	8420	-3825	13113	9076	59332
HAS 4.5% (100ml)	2186	19587	12506	20	1009	258	1807	-5	0	0	6628
HAS 20% (100ml)	5791	37233	24991	53	3523	594	470	1	2128	1811	9453
HAS 20% (5ml)	0	18067	4230	30	0	160	86	1146	0	0	12415
HAS 10% (100ml)	0	283	59	1	52	17	0	0	0	0	154
HAS 10% (2.5ml)	0	3914	3681	20	86	109	0	18	0	0	0
Rppt. HAS (5ml)	550	477	494	10	0	48	0	-2	0	0	477
Normal IgG (250mg)	92789	181852	161030	221	0	1909	7273	-3233	0	0	107441
Normal IgG (750mg)	17893	41724	37748	100	782	723	1272	100	6417	0	12475
Normal IgG for use with Measles vaccine	8259	13622	21155	20	0	210	485	11	0	0	0
Intravenous Normal IgG	772	0	0	0	0	0	0	0	0	0	772
Anti-D IgG (250iu)	9316	40097	38430	50	1207	402	5	3	0	9316	0
Anti-D IgG (500iu)	16408	70854	65333 2469*	260 10*	1286	518 4*	78 10*	-416	0	0	20203
Anti-HBs IgG (100iu)	0	1561	682	10	45	73	0	5	0	0	746
Anti-HBs IgG (500iu)	2702	1792	4263	20	143	79	0	-11	0	0	0
Anti-Rabies IgG	0	516	476	10	11	60	0	-41	0	0	0
Anti-Tetanus IgG	5896	35159	29856	40	435	507	50	-108	0	0	10275
Anti-Vaccinia IgG	0	0	829*	0	0	0	1*	0	0	0	0
Anti-VZ IgG	1619	3844	3772	30	85	182	0	-70	0	0	1464

* Re-assayed batches

TABLE 2.

PLASMA INCIDENT REPORTS																						
REGION	NBS	OF	AIDS	NIV	MRA	VD	NZ	RB	NP	NL	T/H	SP	RTC	C	S	UF	Doo	NT	NS	DAN	MISC.	TOT
BPL	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3	0	0	0	0	23	0	26
YORKSHIRE	1	1	0	1	0	1	3	0	0	0	0	0	0	0	0	0	0	0	0	0	1	8
TRENT	2	2	0	1	0	2	0	1	0	0	0	3	0	2	0	0	0	0	0	0	6	19
OXFORD	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
EAST ANGLIA	1	0	0	0	0	0	0	0	1	0	1	0	0	2	0	0	0	0	1	0	2	8
W. MIDLANDS	1	0	0	10	0	0	0	0	0	0	0	0	1	0	0	0	0	1	0	0	0	13
N.E. THAMES	3	1	0	18	0	0	2	2	0	0	3	1	0	6	0	0	1	2	0	0	8	33
MERSEY	0	2	0	2	1	1	0	0	0	1	1	18	2	0	0	0	0	3	0	0	2	30
LANCASHIRE	2	0	0	1	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	10	15
MANCHESTER	1	0	0	0	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	5
S. THAMES	0	1	0	3	1	3	3	0	0	1	0	2	2	1	3	0	1	0	0	0	5	26
ARMY	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
WESSEX	1	0	0	0	0	0	1	0	0	0	0	0	0	2	1	0	0	0	1	0	3	9
S. WESTERN	2	0	0	0	1	0	0	1	0	0	0	0	0	1	0	0	0	0	0	2	0	7
LEWISHAM	0	0	0	0	0	0	0	0	0	0	0	0	0	8	0	0	0	0	0	0	1	6
WALES	6	2	0	1	1	2	3	0	0	1	0	2	0	2	0	0	0	0	0	0	0	20
NORTHERN	26	1	0	4	6	0	0	0	0	0	0	0	1	0	0	0	0	2	0	0	0	10
N.W. THAMES	5	2	0	7	26	1	2	0	1	0	15	0	0	21	1	0	0	2	9	0	5	97
** Total **	81	12	0	48	42	19	14	4	2	3	20	23	6	42	8	0	2	10	11	26	43	382

TABLE 2 (KEY TO ABBREVIATION)

PLASMA INCIDENT SUMMARYKEY

HBs	Hepatitis
GF	Glandular Fevr
AIDS	Positive AIDS symptoms (inc. past donations)
HIV	Anti-HIV positive (incl. past donations)
HRA	High risk for AIDS.
VD	Venereal Disease.
HZ	Herpes Zoster.
RB	Rubella.
MP	Mumps.
ML	Measles.
T/M	Tropical Donor - Malaria.
SP	Specific Plasma sent to BPL as non-specific.
RTC	RTC request return of pack.
C	Cancer.
S	Failed on sterility test.
UF	Unspecified infection.
Doc	Incorrect documentation.
NT	Not Anti-HIV and/or HBs and/or VDRL tested.
NS	Plasma processed under Non-Sterile conditions at RTC.
DAM	Damaged packs.
Misc	Misc.

Please refer to current SOP on categories on plasma problems (QCCU23) for fuller explanations of the definitions of each problem.

TABLE 3

SUMMARY OF ADVERSE REACTIONS 1986-1987.

REF	REPORT DATE	REPORTED BY	PRODUCT	BATCH NO.	DATE OF MANUFACTURE	SUMMARY
PR 86/16	11/04/86	Kings College Hosp.	4.5% HAS	AD 1466A	03/12/85	Renal dialysis patient, nausea, vomiting and hypotension.
PR 86/27	09/07/86	Meanwood Park Hosp., Leeds.	Normal IgG	GG 279	25/11/85	4 patients collapsed, fall in blood pressure, irregular pulse and feeling unwell for 20 minutes.
PR 86/31	16/10/86	Newcastle RTC	Anti-D IgG	GD 114	02/06/86	Large tennis ball like swelling at site of injection.
PR 86/34	05/11/86	Q.E. Hospital, Birmingham	Factor IX	9A 3399	25/07/86	Pulmonary embolism after FIX therapy.
PR 86/36	11/11/86	Churchill Hospital, Oxford.	Factor IX	9A 3394	05/06/86	Thrombo-phlebitis in vein in right arm.
PR 86/37	19/12/86	Yorkshire RTC	4.5% HAS	AD 1538C AD 1535C	25/06/86 19/06/86	Plasma exchange, 2 patients showed pyrexia rigors, raised blood pressure, tachycardia to 2 different batches.
PR 87/1	14/01/87	Edware RTC	Anti-D IgG	GD 116	22/08/86	Anti-natal Anti-D patient showed malaise and chest pain.
PR 87/6	10/03/87	Newcastle RTC	Anti-D IgG	GD 111R	14/07/86	Widespread urticarial reaction
PR 87/7	10/03/87	Manchester RTC	4.5% HAS	AD 1249 onwards	02/02/84	Plasma exchange patients with tingling hands and mouth, tightness in chest or throat, nausea and vomiting.

**A SECTION OF THIS DOCUMENT HAS BEEN REMOVED
TO THE FILE CONTAINING TECHNICAL AND
SCIENTIFIC DOCUMENTS SUBJECT TO RESTRICTIONS
ON INSPECTION AND COPYING SET OUT IN THE
ORDER OF MR JUSTICE OGNALL ON 8TH MAY 1990**

IX.

OVERSEAS MEETINGS ATTENDED

1986		
April 8-9	L.Vallet	European Pharmacopoeia Commission, Group 6B (Blood Products), Strasbourg.
April 11	R.S. Lane	WHO Meeting to review data on safety of blood and blood products in relation to AIDS, Geneva.
April 14	R.S. Lane	Discussion with Organon Teknika on scientific results of plasmapheresis programme, Brussels.
May 3-8	J. More	EMBO Workshop "Fibronectin and related adhesive proteins", Genoa.
May 2-17	J.K. Smith T.J. Snape	International Association of Biological Standardisation conference on Blood Products, Melbourne: invited speakers and session chairman. Visit to Commonwealth Serum Laboratories. Int.Society of Blood Transfusion conference, Sydney: session co-chairman.
May 11-15	K. Kinnarney	Freeze Drying training course, Nuremburg.
May 11-16	J. More	Pharmacia conference "Recovery of Bioproducts", Stockholm.
June 1-6	P. Feldman G. Neal G. Sims	Int. Congress on Thrombosis and Haemostasis, Jerusalem. (Two presentations given)
June 8-13	G. Sims J.K. Smith	World Federation of Haemophilia Conference, Milan. (Presentation and paper). Discussion on proposed collaborative study of heated factor IX.
June 30- -July 2	C. Silcock	IAT Course "Pharmaceutical and Bulk Chemical Product Stability and Expiration Dating", Frankfurt.
Sept.8-10	J. Little	4th International Symposium on Bioluminescence & Chemiluminescence, Freiburg.
Sept. 29- -Oct. 2	R.S. Lane	European Society of Haemapheresis meeting, Interlaken.
Sept. 29- -Oct. 2	L. Vallet	European Pharmacopoeia Commission, Group 6B (Blood Products), Strasbourg.
Nov. 2-9	R.S. Lane	39th Annual Meeting of American Association of Blood Banks, San Francisco.
1987		
March 16-18	J. Williams R.S. Lane	ISBT Working Party on Automation and Data Processing, Turin.

COMMENT

A review of the actively pursued internal projects indicates that the main preoccupation still resides in areas of improved safety of existing products achieved through greater purity, more defined process control and virus inactivation and validation procedures.

With the exception of fibrinogen, all products can now be heat-sterilised, the marker of process efficacy being inactivation of viruses associated with non-A non-B sporadic hepatitis.

Factor 8Y: the success of the previous year has stood the first two years of clinical trial with a record that sets this product ahead of all competition. Even so, the start of 1987/8 will see the initiation of the second part of the formal clinical trial of 8Y and the extension of research into important areas of freeze drying, more potent chemical affinity systems for purification and a more detailed system of validation of virus inactivation during process stages.

A new Factor IX is under development seeking to overcome problems of purity, thrombogenicity and maintain virus inactivation potential.

An active area of work is the assessment of new forms of source plasma obtained by automated plasmapheresis. The scaled-down fractionation models have already yielded important data concerning improved quality of cryoprecipitate with reduced fibrinogen. The critical dependence on the plasma thaw cycle will have obvious application in improving quality and prospective yield of Factor VIII from fresh frozen plasma.

New product developments are all geared to areas of potential commercial advantage: e.g. an assay for Somatomedin C used in the control of treatment with growth hormone; transferrin with potential use in cell culture systems and lys-plasminogen, under development for distribution to Beecham Pharmaceuticals.

Significant areas of process development in cold ethanol fractionation and preparation of intravenous immunoglobulin make no progress until pilot-process facilities become available.

The limitation of internal R & D facilities has extended the programme of external collaborative work. These are set out in the text and the commercial potential of their work content is self-evident.

Where appropriate, commercial advantage is being protected through patents and by Crown Records. Scientific interest is being maintained through publication and active participation in a wide sphere of scientific meetings and symposia.

The R & D programme is kept under regular review and operates within the strictures of budget, capital facilities and available scientific staff.

All projects carry a budget allocation and expenditure is monitored and controlled - the figures are shown in the text; so is a breakdown of the R & D budget for 1986/7.

There is no doubt that additional financial control can be usefully exercised, as can the fuller demonstration of potential commercial value of projects serve to justify increased expenditure in new facilities and extended working commitment.

4th Annual Report

Chairmans
Statement.

April '86 - March '87

STATEMENT BY THE CHAIRMAN

During the year 1986/87 the Authority's main concern, and that of its officers, was again necessarily concentrated on the factory project at Elstree. Despite the best endeavours of those officers concerned, working closely with the consultants (BDP Project Management Ltd., appointed at the behest of D.H.S.S. in September 1985), the supervising contractors (Matthew Hall Engineering (Southern)) again failed to achieve their frequently revised target dates or cost estimates. However, the new fractionation facility was sufficiently close to completion by the end of the year to permit arrangements to be made for the official opening by HRH The Duchess of Gloucester at the end of April 1987.

Strenuous efforts by all members of the Blood Products Laboratory production staff made possible the continued manufacture of a full range of blood fractions in the old buildings. It cannot be emphasised too strongly that the achievement of production targets in facilities which increasingly fall far short of the standards expected of the pharmaceutical industry depends on exceptional exertions by the staff and on a high degree of good fortune. The problems of maintaining quality are formidable and at the end of the year it was becoming increasingly difficult to meet the protocols of albumin solutions on a consistent basis.

The year saw the introduction of an arrangement with NIBSC whereby, from 1st October 1986, the latter body has undertaken testing of samples from plasma pools to verify the absence of viral contamination and has also accepted protocols and samples of BPL products for approval prior to their release for therapeutic use. This arrangement is of a temporary nature since it remains firm Authority policy that the new factory should be licensed by the Licensing Authority and that all products manufactured in it should be the subject of Product Licences. It is felt very strongly that the new facility and its products should be beyond reproach and that operations under Crown Privilege are totally inappropriate to the manufacture of therapeutic products.

During the year under review the membership of CBLA was changed following the resignation of Mr. Michael Storey, for business reasons, and the retirement of the Vice-Chairman, Mr. Arthur Jerwood, after four years of highly valued service and much constructive advice. The Authority was glad to welcome Mr. R. Braithwaite and Dr. B.W. Cromie as Members and also that Mr. W.V.S. Seccombe was willing to accept his unanimous election as Vice-Chairman.

In December 1986 a Chief Executive was appointed. There were more than 70 applicants for the position, most of them very well qualified, and Mr. Bernard Crowley, who has had long and successful experience of senior management in the pharmaceutical industry, was the unanimous choice of the selection committee.

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In March 1987 Mr. W.P.N. Armour, the Secretary/Chief Finance Officer since the creation of CBLA in November, 1982, resigned to take up a hospital management appointment in Scotland; his contribution to the early development of the Authority and of its staff had been considerable. Mr. Leon Vallet, the Deputy Director of BPL retired in 1986 after 38 years of dedicated service to the Blood Products Laboratory and to the Lister Institute.

During the year plans were elaborated for submission to DHSS for approval of the construction of a Warehouse, Engineering Services, and Quality Control Laboratory complex. These vital ancilliary functions require expanded accommodation if the new factory is to function efficiently at its full capacity. Its location is catered for in the Master Plan for the development of the Elstree Site which was also formulated during the year 1986/87. The Authority plans to move reagent production from Oxford to Elstree when space becomes available in the old buildings after the commissioning of the new factory. Following the resignation of Dr. A.M. Holburn; The Director of BGRL, in March 1986, Dr. George Bird gave the Authority considerable help in supervising the activities of BGRL pending the appointment of a new director. The Director of BPL now has responsibility for reagent production.

The greatest threat to the realisation of the full potential of the new factory remains the continuing lack of proper pilot plant facilities and, in the longer term, Research and Development investment. With production plant which is large scale and fully occupied it is simply not feasible to embark on experimental process work in situ and process improvements cannot be validated under conditions which bear little relationship to current manufacturing practice.

No major pharmaceutical manufacturer can be kept competitively updated without the availability of appropriate pilot plant and the new factory at Elstree is no exception. Any continuing lack of such pilot plant will, at best, be extremely costly in that economies of process improvements will not be secured; at worst, the factory will be unable to introduce the new products which will undoubtedly be required over the next decade and the NHS will again turn to our better-equipped commercial competitors.

Similarly, no technologically based enterprise can survive and compete without a commensurate investment in Research and Development; any case study of the past fifty years of the pharmaceutical industry demonstrates that the companies which have fostered R & D have succeeded while those that have neglected them have gone to the wall. The success of BPL depends very heavily indeed on our ability to offer to the NHS the products which current therapeutic practice demands; the physician will not readily accept our products if they are demonstrably inferior to those offered by our foreign competitors and we shall only be able to preserve our competitive edge by the constant process of product innovation and product improvement which can only come from effective R & D.

Although many difficulties remain we confidently anticipate that 1987/88 will see the new factory approaching full production and making a substantial net contribution to the finance of the NHS. We also expect that income from licences covering our intellectual property will become significant and that our collaborative ventures with industry will start to provide a growing income. We are nearing the completion of the first phase of the Authority's existence and we look forward to making the contribution to the NHS which remains our primary objective.