BLOOD PRODUCTS LABORATORY and
PLASMA FRACTIONATION LABORATORY

ANNUAL REPORT

MANUFACTURING and
RESEARCH & DEVELOPMENT

JANUARY - DECEMBER 1984

ANNUAL REPORT 1984

The 1984 report is fully indexed overleaf for reference purposes.

In summary, there are introductory comments and an appraisal by the Director followed by the manufacturing report, which includes production, quality assurance and engineering; there is a standard presentation of budget expenditure and income, followed by a report from product services, and finally the report of research and development (already received by CBLA).

The report is from the Director of BPL/PFL to the CBLA and is confidential. Because the calendar and fiscal years do not coincide, certain information on current fiscal year activities is included, e.g. budget and production.

There are no direct comments on the building programme of the new factory.

Acknowledgement and thanks are made to staff who have assisted with compilation of this report.

R.S. LANE,
Director.
April 1985.

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ANNUAL REPORT SUMMARY

1984 was dominated by the management of the capital redevelopment of BPL. All senior staff and several juniors spent up to 60% of their time on project design in order to assist Matthew Hall Norcain Engineering advance their programme in line with schedules. This input from BPL has been necessarily more sustained than was anticipated considering MHNE's original statement of their intrinsic capability and flexibility to meet client's needs.

The impact of the capital redevelopment programme on maintenance of routine functions at BPL has taken several forms all exacerbated by the poor condition of the existing buildings, problems with staff recruitment and training and the lack of certain key decisions in areas of financial planning which have complicated management of resources.

It would be an omission to exclude AIDS, since production has been disorganised in the short term. It is unwise to consider AIDS as a mixed blessing with regard to the overall programme at BPL. Some political pressure may have accrued and been beneficial but it is far outweighed by the problems that management of AIDS in the NBTS will engender and the general loss of confidence in the safety of traditionally accepted blood products like human normal immunoglobulin. Coping with HTLV-III has heightened the level of awareness in clinicians of the danger of transmission of <u>all</u> viruses by blood and blood products and the fractionator will have to respond in full measure.

<u>Production</u>

The Interim Programme (MARP-01) reconstruction and re-equipping in the old building has failed to give production a trouble-free run for the 2-3 years envisaged necessary before commissioning the new factory. The main report details numerous examples of failure in fabric and machinery resulting in lost production. These difficulties are not likely to lessen in 1985 and the very limited resources of maintenance and engineering will be fully committed to their resolution instead of dealing with essential preventive maintenance and preparation for entry into the new BPL during the summer of 1985.

In general, production of fractions valued at £12.8M has reached established targets but this performance has been maintained with diminished reliability.

> Plasma sources for anti-D immunoglobulin and hepatitis B immunoglobulin are both perilously low because of contamination by potential oncogenic virus or virus altering T-cell otogeny.
>
> Intravenous normal human immunoglobulin caused elevation of transaminase levels in patients with hypogammaglobulinaemia and induced liver histology indicative of hepatitis. This is necessarily of non-A non-B type by definition although the aetiological basis is not established. Other commercial equivalent preparations have been similarly implicated. The BPL product was withdrawn and a new intravenous preparation is now under trial in chimpanzees using an established FDA protocol.
>
> Factor IX demonstrated instability on reconstitution and was frequently pyrogenic. Some batches were thrombogenic. Re-evaluation of the chromatographic method in relation to increased plasma pool size and re-programming of the freeze-drying cycle in new MARP-01 plant has resolved all the difficulties for the time being. On immuno-pharmacological grounds, it is likely the damage to protein on freeze drying and the pyrogenicity could be associated.

Terminal filtration of albumin showed bacterial contamination in some batches prior to heat treatment: final product always appeared sterile. A change in process procedure has corrected this problem.

Several batches of product were lost because late hepatitis reports and, more recently, reports of AIDS-implicated donations, reached BPL after the plasma entered fractionation. Product was not released with the exception of one batch of factor VIII contaminated by plasma from a donor with AIDS. Partial product recall was efficiently expedited, but some product had already been used. The event is fully documented. In general these problems highlight the need to consider the financial implications and additional process efficacy of a quarantine plasma stock at least three months ahead of production needs.

Heat-treatment of factor VIII has been achieved and implemented on schedule. The programme has coincided with development of a new, high purity product, designated VIII-Y, which is capable of maintaining satisfactory yield from fresh frozen plasma. The product is undergoing satisfactory clinical trial and production has been scaled-up successfully at BPL. No intermediate concentrate is now being made.

Anti-thrombin III (HT) has met with regular demand and persistent satisfactory reports from clinicians.

A trial batch of lys-plasminogen is in preparation for despatch to Beecham Research Division for assessment. Pasteurisation of this product will now be necessary.

Quality Assurance

The department has further consolidated its staff structure and is now offering a substantially better service to production and R & D than at any previous time.

There is an increasing need for a select committee with regional BTS officers to analyse and resolve problems with quality control and assurance which develop round plasma supply and blood product management.

The department faces the commissioning task in the new BPL with inadequate capital facilities, much improved manpower and good technical ability; however, an extended programme of product licensing cannot be met from existing resources.

Engineering

The affairs of this section remain critical. Recruitment and retention of competent staff are difficult. In 1984, nine staff were recruited and five left: there were further leavers in the period January to March 1985.

Maintenance of manufacturing in BPL is demanding, yet there is an imminent need to become familiar with equipment and systems in the new BPL. Future operations rely far more than at present on efficient electronic, electrical, instrument and mechanical maintenance but, at present, there is no capability in two disciplines and substandard potential in the others.

The problems reside entirely with establishment of competitive terms and conditions of service which recognise the pharmaceutical GMP requirements of engineers and fitters at BPL.

Staff

Proposals for a linear pay scale, with associated terms and conditions commensurate

with the functional needs of the new BPL have been under negotiation with DHSS for three years without success. Faced with the choice, maintaining Whitley Council practices appears to have preference over assuring the manpower resources to guarantee the new BPL effective manufacturing capability. The arguments are exhausted but the facts on recruitment at BPL in 1984 set the future course unless BPL is given justifiable special treatment.

Some 65 extra established positions were identified for 1984 and budget restrictions reduced this to approximately 50. In the period, BPL recruited 78 new staff but lost 49 - a net increase of 29.

Established production units with higher-paid staff or staff receiving considerable overtime benefits, and in quality assurance, recruitment of staff was possible and staff turnover was low.

In Administration, of thirteen starters, there were ten leavers and in Technical Services supporting production, in the lower grades, seven of fifteen staff were lost with eleven recruited in the year: for two positions, three staff left and three joined during twelve months. In February 1985, through illness added to reduced establishment, Technical Services failed to meet production targets.

Full details of staff turnover are shown in the report.

Commensurate with the building programme of the new BPL, projected requirements for staff revenue and budget allocations have been defined for over two years. Satisfactory progress with increasing staff numbers is not taking place; this threatens the security of operations in the new factory and makes annual revenue budget allocations for staffing a nonsense. The deficiencies and defects of each year become enshrined in the succeeding one and proper budgetary management becomes impossible within budget procedures.

The impracticalities of the present staffing situation are ironic in that early recruitment ahead of commissioning the new plant was to allow training and improve the basis of experience in operations. In practice, the high turnover of staff is having the opposite effect. During the next three years in particular, BPL needs a stable, trained, operational staff to effect transfer of manufacturing to the new factory.

Budget

Details are shown in the report. Problems with recruitment and late information on salary adjustments to certain staff groups resulted in the characteristic increased rate of expenditure in the second half-year. Advantage has been taken of cash allocations not used on recruitment to purchase systems and equipment which will improve safety and reliability of production within MARP-01 modified buildings. Most production equipment in the old building will transfer to the new building in due course.

Income of ~£825,000 was realised in the financial year 1984/5. The move to charge for technical-grade protein fractions in 1985/6 should increase this income.

Product Services

During 1984 the value of increasing market surveillance was evident and its role in determining production inventory, presentation and distribution of products throughout the NBTS and NHS became a more valued necessity at BPL.

A campaign is now well advanced to bring information about BPL and its products and services to key sections of health services staff and to record their response to

developments at Elstree. Clinicians in the NHS hospitals are used to obtaining significant amounts of their information on pharmaceuticals direct from industry: to compete in the relevant sectors, BPL will need to adopt a more energetic and questioning approach.

Research and Development

From the background of an active programme of research, 1984 saw the new high purity factor VIII product develop rapidly through to production and clinical trial. Other promising lines of process and product development should give results in 1985.

The R & D department at BPL and PFL has great strength in the areas of blood coagulation factors and in basic separation technology. Thus anti-thrombin III, fibronectin, a new fibrinogen preparation, factors XI and XIII and thrombin have all been realised recently. A means to separate lys-plasminogen has also been fully evaluated at BPL. The expertise extends to albumin and Cohn fraction IV proteins.

There are imbalances which need early correction. Immunoglobulins have for years presented little challenge but now the scene has changed with rapid development of clonotypic antibodies against conventional plasma proteins but also protein subunits and cell surface receptor proteins. Immunoglobulin from normal plasma is now not without considerable potential problems from the aspect of its associated immune pharmacology: the time when immunisation of volunteer donors will become unacceptable must be anticipated and alternative means of production and separation will need to be available.

BPL must redress this imbalance in its R & D capability both by internal augmentation and by association with external units in areas of immune protein chemistry, immune pharmacology and hybridoma technology. BPL has a limited virology capability which needs expanding and co-ordinating with the microbiological resources of the laboratory.

The future management of R & D needs urgent decisions which are integrally linked with activities at PFL. A limited feasibility study of buildings at Elstree has been undertaken to determine their suitability to rehouse an expanded R & D department and pilot/process development unit. The alternative is a purpose-built new building. To support a £35M production building, there seems no alternative but to remain at the forefront in relevant areas of R & D and plans for such facilities to house this work are not getting necessary priority.

PFL

In 1984, Oxford was operated mainly as a pilot process development laboratory, responsible to R & D at BPL.

The laboratory functioned both as a development unit and production unit. The three principal work streams were development of VIII-Y, heat treatment of factors VIII and IX and examination of plasma from new automated plasmapheresis systems operating in six Regional Transfusion Centres.

13.3 tonnes of plasma were fractionated in 1984 and PFL took over finishing factor IX while problems existed at BPL.

Improvements in buildings, plant and GMP have been sustained and the plant was inspected by Medicines Division Inspectors late in the year. No complaints have been received.

Plasma Supply

For three-quarters of the year, plasma supply remained at 1983 levels. In the last quarter and carried through into 1985, plasma input at BPL rose due to increasing collection of blood into optimal additive solutions (SAG-M).

Current supply levels are at an annual rate of 220 tonnes which is sufficient for short-term commissioning of the new plant. There is cause for real concern, however, that in 1984 the introduction of plasmapheresis equipment into the transfusion centres did not receive adequate support. Without parallel supply by plasmapheresis, plasma procurement will plateau at 250 tonnes per annum by the end of 1985 and plasma stocks will fall below production requirements by the end of 1986.

MANUFACTURING:

ADMINISTRATION BPL/PFL

PRODUCTION REPORT

Mr. E.D. Wesley (Head of Department)

Production during 1984 has been influenced by a mixture of factors. Benefits have resulted from the MARP 01 Interim Redevelopment, the last phase of which was completed during the year. These include:

i) Increased freeze-drying capacity for factors VIII and IX.
ii) Improvements to general manufacturing environment within Coagulation Factors Section.
iii) Increased incubation and storage space for PPF and albumin.
iv) Increased -40°C storage capacity for fresh frozen plasma.
v) Step-over and change facilities for entry into the Large Fractionation and the Final Solutions sections.

Conversely, production was affected because of breakdown in services and maintenance of satisfactory working environment, malfunction of equipment and the general deterioration of the fabric of the building. Additionally, the pressure to maintain production at levels beyond those originally anticipated when plant and equipment was installed, prevents essential preventive maintenance of ageing equipment. Of particular note were:

i) Cracks and the lifting of tiles in the LF -5°C manufacturing area.
ii) Relagging of glycol coolant pipes.
iii) Centritherm thin layer vacuum equipment.
iv) Finn Acqua still.
v) High temperatures in the filling rooms.

Routine production was also hampered by lack of consumable items, e.g. 400 ml bottles and satisfactory 13 ml vials and overseals.

Microbiological contamination affected production of several batches of PPF during the year.

During the second half of the year, production of factor IX was inhibited by the failure of batches, because of instability of the product after reconstitution. Finishing of this material was transferrred to Oxford. Investigation indicated that the freeze-drying cycle adopted at Elstree is too harsh.

The efficient management of the Department was frequently placed under strain during the year because of demands made on the Senior Management by the new production facility project (e.g. the Head of Production during the year spent 65% of his time on the new project and 35% attempting to manage production). It is to the credit of the junior staff that production during the year was maintained. The situation also had its advantages in that the more junior staff were exposed to additional responsibilities.

The staff structure remained stable during the year with only the Technical Services section operating with staffing levels significantly below normal. Few members of the production staff left BPL employment although there was some movement from Production to Q.C. It was detrimental to management that the key position of Pharmaceutical Services Manager was not filled during the year.

Production development continued during the year, alongside routine production. Projects include:

i) Introduction of BKA 45 Westfalia centrifuge into routine use. Assessment of capabilities.
ii) Ultrafiltration for the removal of water from factor IX Supernatant.
iii) Non-asbestos filter media for various investigations.
iv) Intravenous immunoglobulin, development of a suitable method for clinical product.
v) Teardown machine for plasma pack opening, in particular development of a fixed blade system.
vi) Increase in batch size and use of SS 304 column for factor IX production.
vii) Use of BKA 28 Westfalia centrifuge for cryoprecipitate separation.
viii) Use of Broadbent centrifuge for separation of loaded DEAE cellulose.

Production of material for clinical use was at times made difficult because of the problems listed previously. However, in spite of many difficulties, production and release of albumin and PPF increased and the commercial sale of these products in England and Wales was reduced. The total quantities of these materials available for clinical use was in excess of the MARP 01 target (i.e. 240,000 containers). Normal and specific immunoglobulin production met the clinical demands for these products by NHS, with the exception of intravenous normal human immunoglobulin.

Production of factor VIII and IX consolidated increased production achieved during the previous year. Problems encountered with the stability of factor IX (after reconstitution prior to clinical use) necessitated finishing (filling and freeze-drying) at Oxford, towards the end of the year.

Individual reports by managers of production units follow.

SPECIFIC FRACTIONATION: Dr. M. Kavanagh

Production

Production of specific immunoglobulin was sufficient to meet the needs of the NHS, the two main products being anti-D (Rh_o) immunoglobulin and anti-tetanus immunoglobulin. Plans to extend the use of anti-D immunoglobulin by giving it antenatally had to be postponed when 8.7 kg dried Fraction II (equivalent to approximately 120,000 x 500 iu vials) was found to contain material derived from a donor who developed a soft tissue sarcoma. An appeal was made to Regional Transfusion Centres in July for an increase in the supply of anti-D plasma to make good the loss and to facilitate increased production. An initial increase in supply occurred but was not sustained.

The anti-HBs immunoglobulin supply problem was overcome in the short term by the implementation of an accurate and reliable quantitative antibody assay, enabling the immunoglobulin to be presented as 500 iu antibody, not 500 mg protein. This increased the effective yield two to threefold.

All other plasma supplies were adequate for the required production targets.

Human normal immunoglobulin for intravenous use (HNIiv)

During the clinical trial of HNIiv, type IV, in hypogammaglobulinaemic patients at Northwick Park Hospital, all the patients developed elevation of alanine transferase levels and liver histology compatible with a diagnosis of hepatitis. By definition, this is non-A non-B in type but the basis of its aetiology remains unproven and is under active investigation. The product was withdrawn from use. A new product, HNIiv, type GGV, has been developed using a method similar to that used successfully by the Protein Fractionation Centre, Edinburgh. This method, based on the method of the Swiss Red Cross, involves incubating Fraction II with pepsin at pH4 for twenty hours at 35°C, and it yields a product which has low levels of both anticomplementary activity and pre-kallikrein activator; it also does not appear to transmit NANBH, on the evidence gained from the use of the Swiss and Scottish products. Three batches were produced at BPL in 1984 and these satisfied the in vitro criteria for intravenous use. In 1985, a study is being undertaken in chimpanzees at the Laboratory for Experimental Medicine and Surgery in Primates (LEMSIP) in New York to test BPL HNIiv, type GGV, for freedom from transmission of NANBH. (The HNIiv, type IV, is to be used as a positive control.)

Further Developments

Assuming HNIiv, type GGV, is shown by the LEMSIP chimpanzee trial not to transmit NANBH, then a clinical trial in hypogammaglobulinaemics will be instigated. Other immunoglobulins, most notably anti-CMV, will also be prepared for intravenous use by the same method.

COAGULATION FACTORS: Mr. P.J. Prince

Plasma Receipt

C.F. took over responsibility for receipt/quarantine/issue of plasma.
162,137 kg FFP were received as follows:

	Wt. plasma received kg	% increase of 1st ¼	% SPP	% 5L	% SAG-M
1st quarter	37,811	-	57.5	41.2	1.3
2nd quarter	37,634	-0.5	54.5	40.3	5.2
3rd quarter	39,393	+4	52.8	38.6	8.5
4th quarter	47,299	+25	43.4	26.2	30.4
TOTAL	162,137 kg				

The significant change during the year was the increase in the quantity of SAG-M received. Single plasma donations remained virtually the same, whereas 5 litre plasma pack receipts dropped by 20%.

A main cold room, CR10, was out of commission for approximately two months during Autumn. Plasma had to be stored with Christian Salvesen at -25°C.

Factor VIII

145,488 kg plasma were processed to factor VIII. The total of 140,631 vials produced included two batches finished from Oxford intermediate and one batch of reprocessed factor VIII.

The main problems encountered during the year were in two periods where significant numbers of vial caps failed during freeze-drying.

Six planned batches had to be cancelled during the year, but all production targets were achieved.

Factor IX

Heparin was excluded from all batches produced during the year.
1200 kg plasma batches became routine.
Several Broadbent centrifuged batches were satisfactorily produced. Of the 63 batches filled at Elstree, over 50% failed Q.C. testing:

i) Initial problems were associated with pyrogenicity, with intermediate results indicating thrombogenicity. Many areas for improvement were identified, including better chromatographic management on ion-exchange columns of larger pool-size batches.

ii) From June to October, virtually every finished batch of factor IX failed primarily stability tests with pyrogenicity in a significant number of batches. Detailed investigation by BPL and PFL personnel showed that the freeze-drying cycle used on the new plant for factor IX at Elstree was implicated. A modified, gentler cycle was used from December onwards; of the ten batches filled since then, eight have passed both pyrogen and stability tests.

iii) During November and December, ten intermediate batches were filled and freeze dried at Oxford. Nine batches passed QC, one failing on stability. Whilst BPL managed to meet all demands for factor IX during the year, CF relied on PFL filling and freeze-drying for two months and on the release of nearly 2,000 vials produced from Haemonetics plasma at Oxford.

Room 14 (Sterile Suite)

Two major problems occurred during the year:

i) High levels of aerobic spore-bearing contamination in particular areas of the room. The source of this contamination was finally traced to the breakdown of wall surface coating. Re-tretoplasting and filling of the cracks eliminated the problem.

ii) The sterile area had to be closed and formalinised following a water leak through the ceiling.

Personnel

Towards the end of the year, a greater emphasis was placed on more senior supervision of batch processing, by the introduction of the Production Supervisor role. This role is direct involvement in and supervision of the batch processing. This was made possible by the appointment of a full-time CF clerk, who has taken on many of the routine operations previously carried out by the Duty Supervisor.

LARGE FRACTIONATION: Mr. A. Butcher

In the current year there has again been only one new trainee in the section and the work has continued to benefit from the loyalty, competence and efficiency of all the staff. However, the commitment to planning for the new building has become time consuming and has highlighted the shortage, in the section, of people with sufficient seniority and available time to accept the responsible tasks of maintaining and improving standards and efficiency.

Two members of staff were quarantined for three weeks and a further two for four weeks until they could be shown to be clear of a Salmonella outbreak (started at a wedding breakfast).

For much of the year there has been Saturday working twice a month which has made possible a 30% increase in Fraction II production and a slight increase in fraction V production. In the second quarter there was a ten-day shutdown to remedy cracks and lifting of tiles in the main fractionation cold laboratory: the opportunity was taken to relag pipes in the re-solution cold room, to introduce a step-over into the section, provide staff with particle-free suits and designate nearly all of the Large Fractionation and Specific Fractionation sections as a clean working area.

The centritherms have continued to show unreliability and much overtime has been worked to catch up on lost production in this area. Production has also been lost due to the failure of the following items of equipment:

Plasma thawing rack calorifier
Fractionation vessel stirrer
Fractionation vessel Honeywell control.

Poor temperature control has continued to cause concern in the main fractionation cold laboratory and in the +2°C re-solution room.

Secondary fractionation records are now stored on disc.

Large-scale trials have been carried out using non-asbestos AMF Cuno 50 CP filter sheets in place of Carlson 3/1250 BK9 sheets.

FINAL SOLUTIONS: Mr. B. Kennedy

Staffing

The unit was incompletely staffed during the year. Mr. M. Francis transferred to Physical Chemistry in March and was replaced by a new recruit, Mr. J. Gomez (JLT). Mr. A. Fowler transferred to Q.C. in October and it is planned to fill the process worker vacancy on the establishment and leave the JLT vacancy unfilled, with a view to the longer term need for a shift in the balance towards more process workers and fewer technical staff. The process vacancy was not filled before the end of 1984 because of shortage of suitable applicants.

Human Albumin Solution 4.5%

121 batches were filled in the year. A disturbing aspect was the number of production opportunities lost for reasons outside the direct control of Final Solutions staff. These are summarised as follows:

Batches lost to:	Pyrogen-free water shortage (Finn Acqua still failures)	8
	Insufficient bungs (Stores failure to maintain stocks)	8
	Sterile Suite closures for gassing	5
	Shortages of bungs/overseals from Technical Services	3
	Construction of L.F. Change Area	2
	High temperatures in Sterile Suite	2
	Accidental opening of both sterilising oven doors together	2
		30

In Final Solutions considerable difficulty was experienced in filtering Fraction V solutions, although it has not been possible to predict in advance which batches would cause problems. Filtration costs have risen considerably as a result.

There has been microbiological contamination of albumin solutions before heat treatment. Following the introduction of a new sampling regime and an appraisal of the final filtration assembly, it was agreed at the end of the year that the final filter assembly would be simplified by dispensing with the pre-flush and recirculation of product. The changes were instituted at the end of December in collaboration with Q.A. staff. The system remains under study.

Normal Immunoglobulin

Twenty-one batches were prepared as follows:

11 x 750 mg
8 x 250 mg
2 x immunoglobulin for use with measles vaccine.

Work has been carried out to investigate and eradicate an apparent increase in microbiological contamination during clarification and sampling of the final solution.

20g% Salt Poor Albumin

Nine batches were prepared this year.

FREEZE DRYING: Mr. K. Kinnarney

There were no major problems with the equipment until late 1984. Maintenance of the equipment was fully co-ordinated with the production programme. Late in the year, the hydraulic stoppering rams on two units required rebuilding.

Fraction II and factor VIII drying continued unabated and without any major difficulties. Factor IX drying was started in early 1984. There appeared no problems to begin with but, by the end of the year, few batches were passing control testing. Factor IX seems sensitive to heat during drying. By modifying the drying cycle to run at a lower temperature, the problem appears to have been overcome, but this adds twenty-four hours to the drying cycle.

HNIiv was reintroduced in its Mark II form. The first batches appeared to dry satisfactorily although problems may yet occur due to the very high maltose concentration.

TECHNICAL SERVICES: Mr. P.S. Leavens

Most equipment performed in a consistent manner. The Pickstone oven has a tendency to develop leaking door and fascia seals and is kept under close surveillance.

The contract cleaning of site continues to be good; the Technical Services Users Committee (TSUC) provides a forum for discussion between BPL and the contractor. The TSUC has also agreed on a standard for BPL Class 1 and Class 2 particle-free clothing. Following appropriate tender action, garments will be laundered by one company, commencing 1st April 1985.

The biggest problem confronting Technical Services during the period reviewed has been the loss of several key persons and the continued difficulty in finding a suitable Supervisor for Building 11. Considerable dislocation of services has occurred, particularly in the Primary Support area, since the loss of Mr. J. Ruegg. The secondment from CF department of a technical staff member served to keep the section operating at reduced efficiency and, since then, absence of the new TS Supervisor, loss of the Clerical Assistant and sickness of the female Chargehand in the wash/assembly area for five weeks, has accentuated the lack of continuity.

Staff sickness reported in the previous twelve months period is still a concern. The following illustrates this point:

Certified sickness	168 days
Uncertified sickness	100 days
Compassionate leave	13 days.

INSPECTION, PACKING AND DISPATCH: Mr. G. Sharman

The new cartonning machine for albumin has been running satisfactorily for several months. Attachments have been ordered for final casing of cartons.

Distribution of albumin from IPD continues to cause difficulties due to lack of warehouse space for sorting and stacking allocations, and is further aggravated by the inability of some RTCs to provide adequate transport to uplift their albumin and factor VIII. Changes in factor VIII production which have created large numbers of small batches have caused some slowing down in labelling and packing.

Factor IX packing and distribution has run quite well and given no problems other than very low stock levels on several occasions. These caused some rationing to occur for larger demands; however, all requests were met within a few days. Throughout the year, there has been a steadily growing demand for IgG for use with measles vaccine, peaking at just over 1,000 per month. This has now dropped back to about 600.

Quarantine cold room space +4°C is a continuous problem and shows no sign of easing. On occasions there is no option but to overflow into other cold rooms; this action is contrary to the GMP documentation for the area.

PLASMA FRACTIONATION LABORATORY, OXFORD (PFL): Mr. D. Evans

Plasma into Process

The total weight of plasma processed at PFL during 1984 was 13,338 kg - a 4% increase over 1983. The most notable change was the steadily increasing proportion of plasma derived from the Haemonetics automated pheresis system, as the Liverpool, Cardiff, Bristol and Lewisham centres joined Leeds and Tooting in delivering Haemonetics plasma to PFL.

Products

The most important changes concerned factor VIII. The Pickstone oven was commissioned and on 10 February 1984 the first batch of conventional 8CRV material was treated. A further five batches were heated at 60°C for seventy-two hours, then the conditions were changed to 70°C for twenty-four hours and a further fourteen batches were heated.

A number of 8P pools were processed combining two of the conventional steps. The results were inconclusive and the work has been overtaken by events.

The first production batch of the new factor VIII concentrate 8Y was made on 9 November 1984, followed by four more batches during the remainder of the year.

The unusual occurrence of particles in sterile filtrate during April and May was ascribed to magnetically stirring the filtrate and this was discontinued.

Factor IX processing was remarkably uneventful in contrast to the rash of short NAPTT pools which was a feature of the last half of 1983: only 4 of 53 pools were associated with NAPTT <150 seconds (i.e. thrombogenic) during 1984. Ten batches of factor IX processed at CF were finished at PFL to counter a suspected freeze-drying problem at BPL.

Production of anti-thrombin III continued at the 1983 level, but production of factor XI (essentially unheated AT III) was increased.

Factor VII, factor XIII and fibrinogen were produced on an occasional basis, as were various technical grade products and standards.

Facilities

During the first and final quarters of the year, considerable effort was made to upgrade GMP-related aspects of fabric and facilities.

The fabric and surfaces of the Class I rooms were significantly improved. Air filtration systems were made more reliable and a better system of monitoring pressure differentials was introduced. Much of the furniture and fixtures were replaced by easily cleanable and non-shedding items. All services were cleaned up by simplification and filtration. A modern LAF unit was installed in the dispensing room.

The limits of the main processing area were defined and more controlled, and entry procedures were improved. The first stage of a major redesign of the layout of the fractionation area was executed. The fabric and surfaces of the tank wash facility were considerably improved. The functions of the shared cold room were specified to improve management and a dehumidifier introduced into the area.

An Edwards 'Minifast' freeze-drier was commissioned to permit technical or unsterile product to be dried without intrusion into the Class I rooms.

Quality Assurance

In addition to the changes made to the structure and fabric, a much more comprehensive system of environmental monitoring and testing was introduced. The QC department assumed many more QA-related functions.

Staff

A new scientific post was created within the production section, and a part-time laboratory assistant/driver post was made full-time.

QUALITY CONTROL
Dr. T.J. Snape (Head of Department)

Department Structure and Function

With the appointment of Mr. Kevin Shade as Microbiological Services Manager (October 1984) and of Mr. David Donald as Quality Standards Manager (January 1985), the department is assuming a structure and weight consistent with its role in the organisation: an organogram for the department at January 1985 is shown as an appendix to this section. Analytical and microbiological service functions are at a strength appropriate for present demands, and the additional staffing requested for 1985/6 will allow for the increased commitment required to commission and service the new manufacturing unit.

Quality Standards

The addition of two technical staff, Karen Sones (recruited externally) and Andrew Fowler (transferred from BPL Final Solutions Section), and a senior scientist, David Donald, to head up the group and contribute substantial experience of quality assurance methods, reflects the commitment to a shift towards product quality assurance rather than quality control.

Close liaison with Plasma Receipt Section, involving establishment of a defined quarantine period for incoming plasma (currently eight weeks) and the development of a more secure system for processing late reports of suspect plasma donations, an increasingly frequent occurrence during 1984, will be further improved by the introduction of a microprocessor based system utilising the QC computer network and a database shared with Plasma Receipt. During 1984 in excess of 150 such reports were processed, two of them leading to the recall of factor VIII and factor IX concentrates. In both cases the subsequent recall procedure was aided by prompt action from the Regional Transfusion Centres and Haemophilia Centres involved, leading to incomplete but fully accountable recovery of issued concentrates.

The section has made (and continues to make) a significant contribution to the effort to convert unheated factor VIII concentrate to a dry-heated form acceptable to UK haemophilia centre directors, and provides the essential interface with PFL allowing secure documented transfer of product between the two laboratories.

Analytical Services

The three sections of this department continue to report direct to the Head of Quality Control; the possible requirement for an Analytical Services Manager is under continuous review but is not presently considered critical.

Analytical Chemistry

Three new members of staff were appointed to the section during 1984 (David Cooke, Michael Francis and Miss Gita Patel), two as staff replacements, giving a net increase in establishment of one technician. The section continues to offer an analytical service to all operations in the laboratory.

Coagulation Assays

Two new members of staff were appointed during 1984 (Miss Anne Hulse and Richard Reece) bringing the technical staff establishment for the section to four technicians. Not surprisingly, given the comparative inexperience of the technical staff in post, training operations and many routine commitments are still supported from the PFL QC section. Whilst this deficiency in numbers and experience would be most

satisfactorily remedied by transfer of appropriate staff from PFL QC section, the reluctance of PFL staff to commit themselves to a transfer, and the need in any case to maintain the PFL QC section at strength in order to service the product development operation at PFL, make external recruitment inevitable.

A number of significant changes and events during the year may be recorded:

March - the section provided, and continues to provide, to the R & D department, an on-demand service for factor VIII assays.
September - all coagulation testing/assays on factor VIII finished product transferred to the section (from PFL QC).
October - all coagulation testing/assays on in-process factor IX samples undertaken.
November - Geoff Sims attended ICTH meeting in Miami, presenting a joint paper with Dr. G. Mariani (Rome), outlining the results of the European collaborative study of factor IX concentrates undertaken jointly by BPL/PFL and Dr. Mariani's group.

PFL QC Section

Mrs. E. Clements joined the section in June as laboratory assistant.
The section has operated under extreme pressure of work throughout the year, providing support for extended product development activities at PFL as well as support for training operations at BPL (Mike Haddon and Helen Evans spending, on average, one day per fortnight at BPL). In addition the section has greatly extended its quality assurance activities, introducing a comprehensive system of utilities monitoring (including autoclaves, PFW system and cold-rooms) and extending the system of environmental monitoring (previously the responsibility of the production section).

Microbiological Services

The five sections of this department now report to the newly appointed Microbiological Services Manager, Kevin Shade (previously Microbiologist at May & Baker).

Environmental Testing: Mrs. Jasmine Winkworth joined the section in October as a staff replacement; there has been no change in the staffing establishment for the section. Difficulties in recruitment led to a situation in which the section had only one experienced technican (in addition to the section manager) for over three months.

Sampling programmes throughout the manufacturing area have been subjected to continuous review, completely revised programmes being introduced in the Final Solutions and Terminal Processing area. Monthly 'performance' charts, related to individual filling operations, are now issued in respect of both aseptic filling areas.

The cleaning/disinfection schedules undertaken by contract cleaning staff have been the subject of detailed monitoring. The results of this work have led to major reviews ot the cleaning practices in three manufacturing areas.

The section has provided guidance to staff in PFL QC section on a complete review of environmental monitoring procedures in the PFL manufacturing area.

Bacteriology: Three new members of staff have joined the section in 1984, David Lowne and Michael Winson (Technicians, one as a staff replacement) and Mrs. June Morgan as process worker in the newly established media unit. The increased level of staffing has allowed time for more investigative microbiology in support of the manufacturing operation.

The production of media in the new media unit was slow to gain impetus but is now performing an extremely valuable function. When the autoclave is fully operational in 1985, it is intended to expand the service currently available to Bacteriology and Environmental Testing. In particular the facility for in-house manufacture of small quantities of special media should greatly enhance the section's capacity for investigative microbiology.

Virology: There have been no significant changes in the amount of routine QC work done by the section. Work has continued on the modification and development of new assays but no new assays have been brought into routine use during the year.

An increased amount of work has been done for the R & D department during the year. This work included preliminary virus spiking/inactivation of coagulation factor studies, an assessment of a commercial β_2-microglobulin assay kit, the preliminary co-ordination of reverse transcriptase assays as a possible marker for non-A non-B hepatitis and a preliminary assessment of the feasibility of screening for antibodies to bacterial endotoxins.

Hepatitis Testing Laboratory: A Junior Technician (Helen Cleary) was added to the staff in June 1984. Junior Technicians, Mark Watts and James Klatt were upgraded to Technicians on March 1st and July 1st 1984 respectively. The present level of staff in the laboratory stands at five.

BPL-RIA Test for HBsAg: Test kits are prepared at BPL for the purpose of screening for the presence of hepatitis B surface antigen in blood donations at Regional Transfusion Centres, Public Health Laboratories, University Medical Schools and Regional Virus Laboratories.

Reagents prepared and issued to these laboratories during 1984 amounted to 2,802,360 tests. The price per test was set at 21p (January - March) and 22p (April - December), the total income for the year being £609,258.

Three additional laboratories became regular users of the BPL-RIA: Edinburgh Regional Virus Laboratory, Sheffield Public Health Laboratory and the Isle of Man Transfusion Centre.

BPL-RIA System for Screening at BPL: A total of approximately 52,000 tests were performed during the year, of which 22,000 were concerned with the quality control testing of BPL-RIA test reagents. The remaining 30,000 were used for the screening of all incoming 5L plasma pools designated for fractionation within the BPL and for the testing of all final products and some intermediate fractions. Testing is also carried out on samples from PFL and BGRL (Oxford).

It should be noted that for the first year since hepatitis testing has been carried out at BPL (i.e. since November 1970) no positive 5L plasma pools have been detected. This must reflect higher efficiency of testing programmes at the Regional Transfusion Centres and the involvement of these Centres using the BPL-RIA test kit.

Other Tests: All normal and specific immunoglobulin preparations are tested to find the level of hepatitis A and hepatitis B antibodies in these products.

During the year other tests e.g. β-thromboglobulin assays and fibrinopeptide-A assays have been carried out in collaboration with the R & D department (a) to assess the level of these proteins in plasma collected in the presence of varying amounts of different anticoagulants and (b) as a prelude to experiments being planned at some Centres on various filtration techniques.

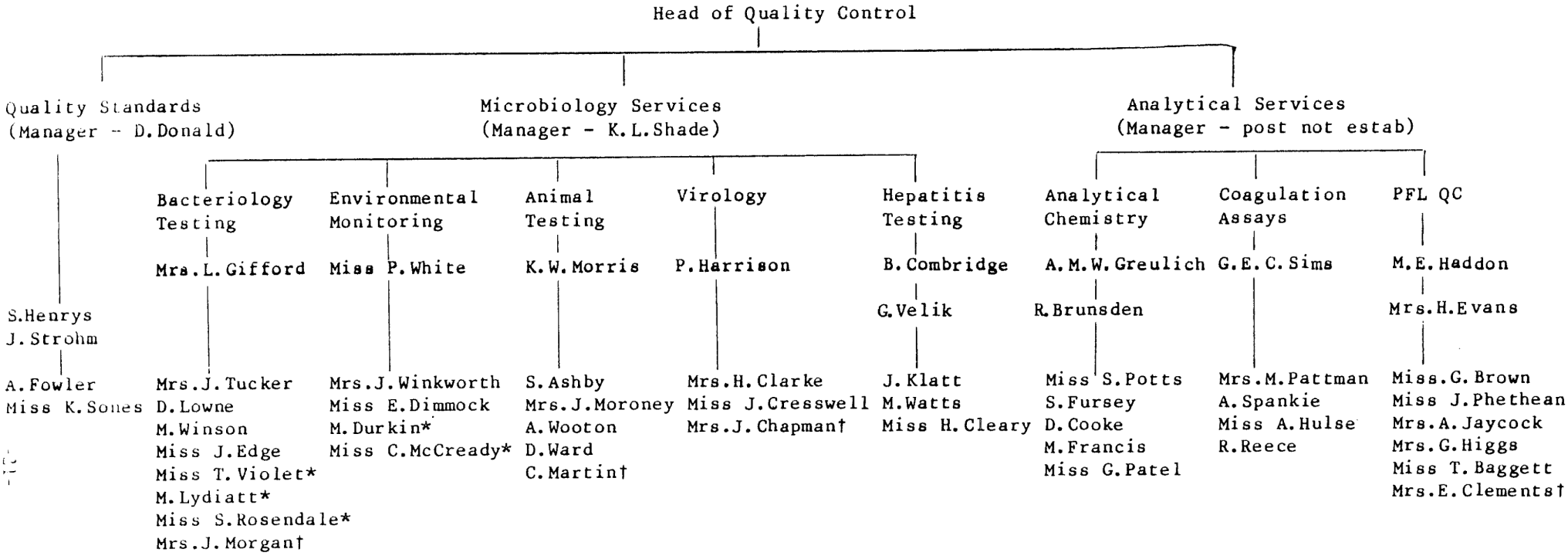
Quality Control and Assurance of BPL-RIA Testing at Centres: In order to assess the performance of screening at RTCs for hepatitis B surface antigen, a questionnaire was designed which was distributed with each batch of radio-labelled antibody used in the BPL-RIA test. Each centre returns the questionnaire giving important information from test data which is used to monitor the technical precision and equipment performance for the test. This is a means of giving BPL quality assurance of the hepatitis B status of incoming plasma to be used for fractionation.

P.S. The newsletter 'Transfusion Microbiology' No.5 was issued in August 1985, edited by B.S. Combridge (BPL) and J.A. Barbara (N.London RTC). Approximately 150 copies were distributed.

Animal Testing: A programme of complete refurbishment for all animal and service buildings was begun. By December construction work and the purchase of new equipment was nearly complete on two of the animal houses.

This work, together with the increase in staffing, will allow the section to deal with a continued expansion of its work load.

Quality Control Dept. : January, 1985



* Junior Technician operating in Bacteriology and Environmental Monitoring on a 'rota' basis but reporting structure as shown.
† Process worker.

Clerical Staff :- BPL, Mrs.J.Giffin + 1 post vacant
PFL, Mrs.J.Burrell (part time)

ENGINEERING
Mr. W.I.T. Ling (Head of Department)

Staffing

Recruitment of technicians, fitters and electricians of adequate calibre continues to be a problem. This is unlikely to be completely resolved until satisfactory structure and salary conditions, relevant to modern pharmaceutical manufacturing enterprises with consideration of locality, are established.

Personnel Changes

Draughtswoman resigned	-	Draughtsman engaged
Two Project Engineers recruited		
Instrument Technician recruited	-	Resigned
Two Fitters recruited		
Electrician recruited	-	Resigned
Refrigeration Fitter recruited	-	Resigned
Fitter resigned		
Electrician resigned		
Services Operator recruited.		

Projects

Media building procured and fitted out.
Incinerator replaced with unit capable of consuming all waste including plasma bags.
Refurbishment of Animal House carried out with own labour.
Refurbishment of Animal House (disused) in hand with own labour.
Proposals for Warehouse and QC/Engineering block commissioned and completed.
Feasibility studies for Warehouse and QC/Engineering block commissioned and completed.
Feasibility study for re-use of building 25 commissioned and completed.

The employment of a draughtsman has enabled studies to be commenced and also the design and drawing up of various trolleys, fabrications etc., to be carried out for tender enquiries. Progression of this activity will ensure correct design in conjunction with users and smooth the procurement path.

Services' records are also being brought up to date.

The addition of Project Engineers ready for the commissioning and start-up phase of the new Production building will also enable in-house projects to be properly planned and managed.

General Maintenance

Additions of personnel (not always retained for long!) are being made in order to prepare for the new building requirements and put the current maintenance on a more organised basis. The system of job requests is leading to improved response to problems.

Routine autoclave testing/validating is proving difficult to contain due to inability to recruit suitable additional fitters. The situation is under review with QC and user departments.

ADMINISTRATION: Mr. G.M. Bailey

During the year the Administration Department's reporting route was transferred from the Deputy Director Manufacturing and Control (formerly Manufacturing and Administration) to the Secretary/Chief Finance Officer of the Central Blood Laboratories Authority. A similar transfer has occurred with the Accountancy in 1983-4 and from early 1984 both Administrator and Accountant reported separately to the Secretary/Chief Finance Officer. Both retained a responsibility towards the BPL Director. The Administrator continued his joint responsibility for administration at the Plasma Fractionation Laboratory, Oxford, where day-to-day management is part of the remit of Dr. J.K. Smith.

The act of changing the reporting route was not formally conveyed to senior managers in BPL and occurred without consultation with the Director of BPL. The resultant division of activities and the potential inconsistencies between lines of reporting and responsibilities in manufacturing have been commented on by staff at recent Industrial Management Training seminars and elucidation demanded.

Since management of BPL and the new building project has stretched the total manpower resources at Elstree to the limit, any attempt to optimise management functions is to be encouraged. However, the structure of management and established responsibilities must remain clear to all staff.

A large part of administration activities at BPL relate to manufacturing, e.g. manpower, stock control, inventory and purchasing, and there must be no loss of cohesion between these activities and the Head of Manufacturing at BPL. Similarly, nothing must obscure or invalidate matters which influence determination of product safety and the Director's responsibility therein.

Staff and Equipment

Staffing levels increased during the year in preparation for meeting the demands for the new manufacturing unit with the creation of Personnel and Purchasing Sections, the numbers increasing from 24½ to 27½, including secretarial, storekeepers, drivers, purchasing and estate staff.

During the year all administrative secretarial staff equipment was upgraded to electronic word processing standard. Telex was introduced but attempts to interface it with the word processing system have been unsuccessful. This represents a move towards office automation but further progress awaits a report from a computer consultancy in an initial survey of the laboratory.

During the year contract security patrols were upgraded to full cover during dark hours, weekends and public holidays.

The transport fleet remains static at eight cars and three vans (including PFL). Five of the cars are allocated, the other three being fleet vehicles. In addition, the estate operates two electric floats and an agricultural tractor. Two cars were changed routinely during the year.

Personnel

In July the Personnel Section was formed as a separate function within Administration with the appointment of a Personnel Officer. This section became well established during the year, operating a manual recording system. It concentrated on recruiting in preparation for commissioning the new manufacturing facility. Procedures for recruiting and advertising were produced and approved by the CBLA.

Stores and Purchasing

Introduction of a stores computer for the first time produced an improved stock control system. Difficulties remain with stores personnel as the NHS storekeeper/clerk pay scale does not attract a satisfactory employee for the stores task.

Recruitment in October 1984 of trained staff allowed establishment of a Purchasing Section within Administration to improve the purchasing function. Following this, a complete inventory/asset register check was started and should be completed in 1985.

External storage of 8,200 sq. ft. continued in use during the year for both albumin and bulk stores and items for the new manufacturing unit; the cost was £45,000 per annum.

External -40°C cold storage was also acquired during the year on a two-year negotiable contract at a first year cost of £72,500.

Works and Buildings

During the course of the year, the final accounts for both the C.F. Laboratory upgrading and MARP 01 upgrading were agreed by N.W. Thames RHA although the final certificates with a small cash requirement remain to be paid in 1985. The final consultants' fees also were approved by N.W. Thames.

In September 1984 building 13, the Lister Institute anaerobic laboratory was demolished and the ground reinstated.

Accommodation in Queensberry Lodge was upgraded and adjusted to accept the changes in Administrative organisation.

Site fencing of the new manufacturing unit and remaining site was 80% completed by the end of the year.

Cottages

The cottage occupancy by BPL staff remained at 93% for much of the year, but achieved 100% in March 1985. During the year, gas fired central heating was installed in all the cottages and cottages numbers 1-4 were given treatment for worm and damp in the timbers. New fencing was erected around the cottage gardens.

MANUFACTURING:

PRODUCTION DATA SHEETS

PLASMA INTAKE (January - December 1984)

	kg
Fresh frozen plasm (Oxford)	14,151
Fresh frozen plasma (Elstree)	162,137
Special fractions (Elstree)	4,690
Time-expired plasma (Elstree)	52,915
TOTAL	233,893

PLASMA PROCESSED

	kg
Fresh frozen plasma (Elstree)	145,488
Fresh frozen plasma (Oxford)	13,338
Fresh frozen plasma TOTAL	158,826
Specific fraction plasma	4,593
Time-expired plasma	34,510
Plasma processed TOTAL	193,336

PLASMA STOCKS (28 December 1984)

	kg
Fresh frozen plasma (Oxford)	2,066
Fresh frozen plasma (Elstree)	45,119
Fresh frozen plasma TOTAL	47,185
Time-expired plasma	180,985
Special fractions (total)	985

PRODUCTS DESPATCHED FOR CLINICAL USE (January - December 1984)

PRODUCT	DOSE	UNITS ISSUED	UNIT VALUE £	NOTIONAL TOTAL £ VALUE
Albumin solution 4.5%	100 ml	14,000	11.00	154,000
Albumin solution 4.5%	400 ml	236,000	23.10	5,451,600
Albumin 20% solution	100 ml	22,000	26.25	577,500
Albumin 10% solution	100 ml	105	17.85	1,874
Albumin 10% solution	2.5 ml	4,574	4.75	21,727
Reprecipitated albumin	5 ml	460	17.45	8,027
Dried factor VIII fraction	250 iu	111,782	19.45	2,174,160
Dried factor IX fraction	600 iu	22,379	63.00	1,409,877
Fibrinogen	1 gram	0	5.00	-
Fibrinogen for isotopic labelling	35 ml	93	345.70	32,150
Normal IgG PHLS	250 mg		3.15	
Normal IgG Hypo	250 mg		"	
Normal IgG PHLS	750 mg		6.30	
Normal IgG Hypo	750 mg		"	
IgG for use with measles vaccine	18 iu	6,129	1.60	9,806
Anti-D IgG	250 iu	45,748	9.45	432,319
Anti-D IgG	500 iu	82,537	16.80	1,386,622
Anti-D IgG	2500 iu	590	63.00	37,170
Anti-varicella-zoster IgG	50 mg	624	24.15	15,070
Anti-varicella zoster IgG	250 mg	4,410	99.75	439,898
Anti-tetanus IgG	250 iu	36,612	11.00	402,732
Anti-HBs IgG	500 mg	3,140	65.25	214,305
Anti-rabies IgG	500 iu	601	92.90	55,833
Anti-mumps IgG	250 mg	81	52.50	4,253
TOTALS		457,704		£12,828,923

PRODUCTION VOLUMES AND YEAR END STOCKS 1984

PRODUCT		RELEASED TO STOCK 2.1.84 -31.12.84	RELATIVE TO 1982/3 +/- %	YEAR-END STOCK 28.12.84
Albumin solution 4.5%	100 ml	17,000	+471	10497
Albumin solution 4.5%	400 ml	197,000	+ 46	42824
Albumin 20% solution	100 ml	16,000	+ 91	5595
Albumin 10% solution	100 ml	0	-	331
Albumin 10% solution	2.5 ml	0	-	1224
Reprecipitated albumin	5 ml	835		375
Dried factor VIII fraction	vials	118,400	+ 33	8297
Dried factor IX fraction	vials	21,823	+ 18	583
Fibrinogen	35 ml	689		738
Fibrinogen for isotopic labelling		85		0
Normal IgG PHLS	250 mg	102,005		12680
Normal IgG Hypo-gamma	250 mg	14,600		0
Normal IgG PHLS	750 mg	19,150		3360
Normal IgG Hypo-gamma	750 mg	24,600		7170
Ig for use with measles vaccine		6,350	+373	2430
Intravenous IgG	1 g	0	-	0
Intravenous IgG	5 g	0	-	0
Anti-CMV intravenous IgG	1 g	0	-	0
Anti-D IgG	250 iu	38,871	+ 13	5503
Anti-D IgG	500 iu	85,977	+ 24	10938
Anti-D IgG	2500 iu	1,500	+ 56	1235
Anti-varicella-zoster IgG	50 mg	670	+ 52	266
Anti-varicella-zoster IgG	250 mg	1,990	- 40	628
Anti-tetanus IgG	250 mg	39,677	+ 20	6058
Anti-HBs IgG	500 mg	3,370	+193	240
Anti-rabies IgG	500 mg	0	-	1024
Anti-mumps IgG	250 mg	0	-	4

PRODUCTS ISSUED AND IN-STOCK
NOTIONAL AND ACTUAL INCOME
Fiscal Year: April 1984 - March 1985

PRODUCTS ISSUED	Jan	Feb	Mar	Apr.84/Mar.85	Apr.83/Mar.84
	£k	£k	£k	£k	£k
Albumin 400 ml	383	401	603	5780	5301
Factor VIII	111	116	140	1934	2340
Factor IX	59	97	131	1417	1278
Immunoglobulin	63	27	64	607	592
Anti-D	267	123	162	1886	1795
Other products	200	156	144	1697	1050
	1083	920	1244	13321	12356
INCOME FROM SALES					
RIA Test	55	49	55	616	604
Other Sales (12 months)				218	140
PRODUCTS IN STOCK (March 29th)				2306	3451
PLASMA VOLUME PROCESSED					
FFP	215	218	305	3703	3991
TEP	85	91	114	702	331
				4405	4322

Plasma price levels 1984: Recovered FFP/kg £26.25
Time-expired 1 kg £15.00

MANUFACTURING TARGETS

Fiscal Year: 1984/5

FFP receipts	175,000 kgs (150,000 fractionated) (25,000 stored)
Factor VIII	30×10^6 iu
Albumin	225,000 units

PERFORMANCE April - March 1985 12 months:

	Performance	Target
FFP receipts	189,545 kg	175,000 kg
FFP fractionated	141,137 kg	150,000 kg
FFP in store	77,472 kg *	25,000 kg
Factor VIII (250 iu)	24.2×10^6 iu **	30×10^6 iu
Albumin issued (400 ml)	235,972	225,000

N.B. * FFP stock April 1st 1984: 25,554 kg.

** Does not include 1.5×10^6 iu held by PFL for clinical trial.

REJECT BATCHES

FACTOR VIII

Batch No.	No. of Vials	Reason
HLA 3163	52	Post transfusion hepatitis RTC report
HLA 3232	499	Hepatitis B: late report RTC
HLB 3232	455	Hepatitis B: late report RTC
HLB 3163	304	Post transfusion hepatitis RTC report
HL 3186	115	AIDS suspect RTC report
HL 3186	338	AIDS suspect RTC report
HLB 3233	214	Glandular fever RTC report
HLB 3221	575	Pyrogens
HLB 3200	385	Potency
HLA 3217	575	Post transfusion hepatitis RTC report
HL 3233	434	Post transfusion hepatitis RTC report
HL 3223	1,027	Sterility
HLA 3149	560	Stability
TOTAL	5,533	

% of throughput: 4.46%

ALBUMIN

Batch No.	No. of Vials	Reason
AD 1315	2,284	AIDS suspect as above
AD 1305	2,150	AIDS suspect as above
AD 1308 R	2,310	Pyrogens
AD 1309 R	2,310	Pyrogens
AD 1328	2,277	Sterility
AD 1332	2,267	Sterility
AD 1339	2,248	Sterility
AD 1338	2,266	Sterility
AD 1350	970	Sterility
AD 1348	2,065	Sterility
TOTAL	16,527	

% of throughput: 6.7%

FACTOR IX

Batch No.	No. of vials	Reason
9D 3147	355	Pyrogens
9D 3138	368	Stability
9D 3150	389	Pyrogens
9D 3143	367	Stability
9D 3188	295	Stability
9D 3200	473	Stability
9D 3194	543	Stability
9D 3206	441	Stability
9D 3205	374	Stability
9D 3209	668	Stability
9D 3183	338	Stability
9D 3199	403	Stability
9D 3204	323	Stability
9D 3211	529	Stability
9D 3214	234	Stability
9D 3215	455	Stability
9D 3134	373	Pyrogens
9D 3218	262	Stability
9D 3163	200	Post transfusion hepatitis
9D 3173	305	Pyrogens
9D 3179	362	Pyrogens
9D 3185	264	Pyrogens
9D 3170	205	Pyrogens
9D 3169	321	Glass contamination
9DA 3221	416	Stability
9DA 3223	294	Stability
9DB 3221	44	Stability
9D 3229	493	Stability
9D 3230	381	Stability
9D 3163	81	Post transfusion hepatitis
9D 3236	266	Stability
9D 3222	319	Stability
9D 3174	166	Stability
9D 3228	492	Stability
9D 3231	302	Stability
9D 3233	97	Pyrogens
9D 3234	497	Stability
9D 3218	1,103	Sterility
9DB 3223	44	Stability
9DA 3249	126	Pyrogens
9DA 3249	271	Pyrogens
9D 3249 A	138	Pyrogens
9D 3249 B	287	Pyrogens
9D 3142	46	Time-expired
TOTAL	14,710	

% of throughput: 40.26%

PERSONNEL MANNING

DEPARTMENT/UNIT	31st December 1984			Variations from 31.12.83		
	Scient. Staff	Tech. Staff	Others	Scient. Staff	Tech. Staff	Others
Director	1	-	1			
Deputy Directors	2	-	-			
Product Services	1	-	-			
Production Manager	1	-	-			-.5
Large Fractions	-	8	7		+1	
Final Solutions	-	5	3		-1	
Specific Fractions	1	3	-		-1	
Coagulation Factors	1	14	8		-1	+1
Insp. Packing & Desp.	-	2	8			
Technical Services	-	3	16			+4.5
Freeze Drying	-	3	2			
Terminal Processing	-	2	5			-1
QC Unit (inc. Assay)	2	8	2		+4	+1
Bacteriology	1	7	1	+1	+1	
Environmental Control	-	4	-			
Pyrogen Testing	-	5	1		+1	
Hepatitis	1	4			-1	
Control Chemistry	1	6	-			
Virology Laboratory	1	2	-			
Research & Development	6	9	2	+2	+4	+2
Engineering	1	2	20		+2	+2
Administration						
Personnel			3	)		
Accounts	1		7	)		
Purchasing			3	)		+3
Admin.	2		10	)		
Estate			3	)		
Stores			3	)		
Sub-total for Admin.	3	-	29			+3
PFL	4	19	8		+2	-2
TOTALS	27	106	113	+3	-12	+14

STARTERS AND LEAVERS FROM 1st JANUARY TO 31st DECEMBER 1984

DEPARTMENT/UNIT	STARTERS			LEAVERS		
	Scient. Staff	Tech. Staff	Other	Scient. Staff	Tech. Staff	Other
Director	-	-	-	-	-	-
Deputy Directors	-	-	1	-	-	1
Production Manager	-	-	-	-	-	.5
Large Fractions	-	1	-	-	-	-
Final Soslutions	-	-	-	-	1	-
Specific Fractions	-	-	-	-	1	-
Coagulation Factors	-	-	1	-	1	-
Insp. Packing & Desp.	-	-	2	-	-	2
Technical Services	-	3	11	-	3	6.5
Freeze Drying	-	-	-	-	-	-
Terminal Processing	-	1	1	-	1	2
QC Unit (incl. Assay)	-	4	1	-	-	-
Bacteriology	1	2	1	-	1	1
Environmental Control	-	1	-	-	1	-
Pyrogen Testing	-	3	-	-	2	-
Hepatitis	-	1	-	-	1	-
Control Chemistry	-	1	-	-	1	-
Virology Laboratory	-	-	-	-	-	-
Research and Development	4	5	2	3	1	-
Engineering	-	3	6	-	1	4
Administration	-	-	13	-	-	10
PFL	1	5	3	-	3	1
TOTALS	6	30	42	3	18	28

PRODUCT SERVICES

PRODUCT SERVICES
Mr. N. Pettet (Head of Department)

Strategy

The marketing strategy for the new department can be summarised as follows:

1) To develop within the UK formal lines of communication with users of products.

2) To identify and satisfy user requirements for blood products in matters of presentation, acceptability and distribution.

3) To determine current and future demand levels of clinical and technical-grade products by expanding market research.

4) To promote the supply of information within health care services and other organisations relating to the availability of blood products and services from BPL.

5) To develop and maintain data communication between BPL and the NBTS.

6) To expand the marketing activities in those areas that will influence product design, product development and cost effective manufacture.

7) To promote those public relations activities that will present the best corporate image of BPL to a wider public sector and to users, by exhibitions, seminars, press and media coverage.

Report on Activities

During 1984 progress was made in each of these areas. Most Transfusion Centres were visited during the year and, where requested, seminars were given to the technical and scientific staff. The visits also included the Army Blood Supply Depot at Aldershot and the Lord Mayor Treloar College at Alton.

Through 1984 a decision was made to improve our corporate identity. A new logo has been designed and approved and will subsequently be applied to product labels, packaging and stationery.

In the public relations field, contact with press and media was continued. A poster demonstration was held at the ISBT meeting in Munich; a joint stand (with the Metropolitan Transfusion Centres) was manned at the Barbican "Health Exhibition"; a stand was held at the British Blood Transfusion Society meeting in Manchester, and BPL participated in a "Biology in Action" meeting at Hatfield Polytechnic. Exhibition stands were also held at local "careers" meetings.

Many visits to BPL were arranged. These included staff from several Transfusion Centres; local schools and colleges; the Haemophilia Society; Independent and BBC Television. Transfusion Centre Registrars visited as part of their training.

Overall, an improvement in the level of contact was made, both personally and by supply of information. The marketing activities will be extended through 1985/6 with a redesign of the product range to include presentation and extension of product lines to meet requirements of users in the Health Service.

Staff

Internally, there has been some progress with acceptance that BPL should become more appreciative of the benefits of market research. This increased awareness has resulted in the development of better communication and information systems between Product Services and the other departments. To maintain and expand the marketing activities, an assistant post was advertised in January/February 1985. Interviews have been held and an appointment made. Miss Jacinta Collins took up her post in April 1985.

The Department Head, N. Pettet, added to the Diploma in Management Studies gained in 1983, the Diploma of Marketing. This award has led to application for full Membership of the Institute of Marketing.

BUDGET 1984/5

BPL/PFL FINANCIAL OUTTURN: Mr. A.G.W. Bailey

Payments on revenue account amounted to £5,132,764 compared with a cash limit including retained receipts of £5,277,000. By November it became clear that the progress of recruiting new staff was well behind schedule, due in some degree to our NHS pay structure failing to attract and retain the calibre of staff required. Therefore, to avoid a consequent underspend against the cash limit, it was decided to use the funds to purchase equipment which was both necessary to ensure maximum production in the existing Laboratory which was threatened by MARP 01 contract shortcomings, and could also be moved to the new Laboratory in due course.

Receipts at £825,078 were 16% of the revenue outturn.

On normal capital account BPL exceeded its cash limit by £76,000, but substantial purchases of factor VIII heat treatment and production equipment were included in the expenditure. Work on Canteen and Staff facilities was postponed and funds have been included in 1985/6 for this essential project.

The overspending on capital was funded by BGRL capital and BPL/PFL revenue underspending.

The balance of BPL/PFL revenue underspending was utilised to fund BGRL revenue overspend (£73,000) and £21,000 was carried forward to 1985/6.

The outturn on the New Laboratory Project is the subject of a separate report.

BPL/PFL CASH LIMIT OUTTURN

	BPL £'000	PFL £'000	TOTAL £'000
REVENUE			
Gross cash limit	4,767	456	5223
Add income in excess of original estate which may be retained for 1984/5	54	-	54
Funds available	4821	456	5277
Payments	4689	444	5133
Underspending	132	12	144
CAPITAL (excluding New Laboratory)			
Gross cash limit	223	-	223
Payments	299	-	299
Overspending	76		76

SUMMARY	
BPL/PFL revenue underspend	144
Reduced by BGRL overspend	73
	71
Virement to Capital a/c (£76 less BGRL underspend £26)	50
Underspend c/f to 1985/6	21

N.B. BGRL due to repay BPL/PFL net £47, being net overspending on BGRL revenue and capital accounts.

BPL/PFL PAYMENTS & RECEIPTS

FOR 12 MONTHS APRIL 1984 TO MARCH 1985

	BPL £	PFL £	TOTAL £
Revenue			
Salaries etc.	1,913,519	259,429	2,172,948
Staff expenses	124,669	11,467	136,136
Lab supplies	1,126,236	84,024	1,210,260
Overheads	587,871	31,715	619,586
External Grants and Research	36,719	-	36,719
Equipment	608,109	26,376	634,485
Buildings and Estate	53,334	12,745	66,079
VAT	258,882	17,840	276,722
Customs duty	-	525	525
Supplementary Pensions	4,604	-	4,604
Central Services	(25,300)	-	(25,300)
Revenue Payments 12 months	4,688,643	444,121	5,132,764
Cash Limit and retained income for 12 months	4,821,000	456,000	5,277,000
Capital			
New Lab Project	16,647,685	-	16,647,685
Cash Limit 12 months (incl. requested increase)	16,835,000	-	16,835,000
Other Capital Expenditure	298,432	414	298,846
Cash Limit 12 months	223,000		223,000
Receipts			
Loan repayments	789	-	789
Rents	11,733	-	11,733
Sales of products	217,528	-	217,528
Sales of RIA tests	585,394	-	585,394
Miscellaneous sales	2,063	60	2,123
WHO Grant	-	-	-
Sale of Services	-	-	-
Grants R & D	7,511	-	7,511
Receipts 12 months	825,018	60	825,078

BPL/PFL CAPITAL EXPENDITURE
12 MONTHS PERIOD 1 APRIL 1984 TO 31 MARCH 1985

Project/Scheme		Payments to 31.3.85 £	Budget Provision for year £
Telecom Monarch System		42,939	
Car replacement		6,930	
F.VIII production equipment		13,997	
F.VIII heat treatment		62,337	
Bottle filling machine		224	
Consultancy: Viability old BPL	(Lawn & Smith)	-	
MARP 01	Retentions etc.	27,558	
CF Lab reconstruction	"	56,062	
Site heating phases 3 & 4	"	164	
New incinerator	"	864	
Glycol cooling	"	4,136	
Animal House restructuring	"	15,677	
Vic Hallam building conversion	"	2,913	
Rabies House restructure	"	13,021	
Media Preparation Unit	"	3,905	
Carmichael cartoning machine	"	1,084	
Vial driers (PFL)	"	414	
Cottages central heating		19,354	15,000
Canteen and staff accommodation		-	105,000
Coolspin and rotor		-	10,000
Cage washer		27,267	35,000
Immunofluorescence plate reader		-	16,000
Room 2.11 cooling		-	15,000
VAT		included above	20,000
Professional Fees		included above	7,000
		£298,846	£223,000

BPL ANALYSIS OF PRODUCT SALES RECEIPTS
APRIL 1984 - MARCH 1985

Product Analysis	£
PPF 100 ml and 400 ml	9,425
Salt poor albumin	2,328
10% albumin solution 100 ml	1,428
Reprecipitated albumin	12,729
Fibrinogen for isotopic labelling	32,150
Normal immunoglobulin	29,470
Special fractions	112,158
Factor IX	14,038
Factor VII	2,020
Whole plasma	1,750
Dried fibrinogen	32
	£217,528

Customer Analysis	£
M.O.D.	59,649
Amersham International	48,057
Belfast Royal Victoria Hospital	5,040
Belfast City Hospital	7,836
Jersey P.H.A.	9,900
Guernsey P.H.A.	774
Northern Ireland B.T.S.	27,870
Dublin B.T.S.	1,995
Eastern Health and S.S. Board	43,479
E. Moss Ltd. (British Airways)	4,410
The Children's Hospital, Dublin	2,993
J.S. & Mrs. M.M. Oakey	2,020
Other	3,505
	£217,528

(NEW LABORATORY PROJECT ONLY)

	Total to 31.3.84	Year 1984/5 from 1.4.84 to 31.3.85	Grand Total to 31.3.85
	£	£	£
Salaries and wages	33,242	47,850	81,092
Overtime	-	-	-
Superannuation, Employer's	2,493	3,589	6,082
National Insurance	1,814	2,889	4,703
Agency	6,476	4,177	10,653
Travelling and subsistence	11,533	15,833	27,366
Other staff expenses	316	563	879
Crown Cars - fuel	689	819	1,508
Crown Cars - other expenses	92	66	158
Main Building contractors	2,217,774	5,843,059	8,060,833
Other support contractors	274,303	998,551	1,272,854
Central Establishment apport.	6,500	-	6,500
Capital equipment	525,725	5,542,039	6,067,764
Professional fees	2,016,679	3,985,640	6,002,319
Special Audit fees	-	104,214	104,214
Other capital expenditure	131,006	80,888	211,894
VAT	24,627	18,142	42,769
	5,253,269	16,648,319	21,901,588
Less private mileage recovery	445	634	1,079
TOTALS	£5,252,824	£16,647,685	£21,900,509
Cash Limit		£16,835,000	

RESEARCH & DEVELOPMENT REPORT

RESEARCH AND DEVELOPMENT REPORT

Dr. M.J. Harvey (Head of Department)

Introduction

This report contains general details of the Research and Development programme which has taken place during the year January to December 1984 and follows on from the previous report.

The year has maintained the continuous process of selection and reselection of projects to meet the ever-changing demands made on the organisation through requirements for new products or modifications to existing products to improve safety and efficacy.

The outstanding example this year has been the concurrence of requirements for improved product safety due to the presence of viruses causing non-A non-B hepatitis and the Acquired Immune Deficiency Syndrome. The widely-based group of projects aimed at purifying factor VIII to enable it to be satisfactorily heat-treated to inactivate non-A non-B hepatitis viruses has provided the means to inactivate HTLV III. The new factor VIII product, VIII-Y, materialised during the summer 1984 and is now successfully in clinical trial. Patent applications on the process will be submitted by the end of March 1985. VIII-Y has increased purity by more than one order of magnitude and tolerates more heat than is being applied to any other commercial factor VIII at present on the market, i.e. 80°C for 72 hours: yields are satisfactory and will not threaten existing plans for plasma procurement by NBTS.

The VIII-Y story underlines the importance of having a widely-based active research programme from which major advances can be made with all possible speed as demand arises.

One outstanding problem now remains in repeating the success with factor VIII in the more complex area of factor IX, and a major allocation of resources to meet this end is now established. This year BPL requires factor IX which is non-thrombogenic and free from transmission of HTLV III and other viruses causing hepatitis. The current requirement is for 15M international units per annum, which at current market rates would cost the NHS between £2M and £3M per annum.

The general report follows, then there are papers, which show the estimates of expenditure for 1985/86 and the way in which it is distributed. There is finally the project index to the main report of projects. The main report of projects is confidential and is available to the Authority and its members on request. In this way its circulation will be reduced and detailed discussion on projects can be had with the Director and the Head of Research and Development.

Research and Development Programme

The continuous review of project status throughout the year has resulted in six projects being merged into three revised projects; fifteen new projects have been started in response to internal and external demands; six projects have been completed and a further ten projects have been held, or shelved, pending further information or changes in emphasis. Details of all projects are given in the annual R & D project report.

The major thrust of this year's programme has been in developing methods for virus inactivation, especially non-A non-B hepatitis viruses (NANBH). Fortuitously the recognition that the clinical condition AIDS is initiated by infection with the retrovirus HTLV III, and the implications this had for blood products, was covered within this research remit. It is well established that almost all previously untreated patients with no prior immunity to hepatitis viruses acquire NANBH after their first one or two infusions of either factor VIII or factor IX. The infection is often apparently

trivial or sub-clinical but it is feared that more serious chronic liver damage may develop in later life. Heating coagulation factor concentrates in either the lyophilised state or in protective solutions is thought to be an effective action against NANBH viruses, HTLV III and other retroviruses. Routine batches of intermediate potency factor VIII have survived heating with acceptable factor VIII yields but some loss of solubility, this parameter has been resolved by the addition of sucrose to the factor VIII concentrate. The results from three batches which have been infused into factor VIII-deficient patients are encouraging. Each subject has been followed up for one year, six months and two months respectively; recovery, half-life and clinical effect have been normal without any adverse effects. No clinical attacks of hepatitis have been recorded and to date there has been no serological evidence of hepatitis A or B, CMV or HTLV III infection, and no evidence of NANBH from liver function tests. Similar dry-heat pasteurisation regimes have been successfully applied to routine factor IX concentrates. Clinical infusions of heated factor IX are scheduled for late 1985 on the satisfactory outcome of the current dog infusion studies with respect to potential thrombogenicity. Contingency programmes are in hand for both factor VIII and factor IX should process modifications be required, these include treating the concentrates with detergents designed to disrupt retroviruses and methods of heating in solution. The clinical trial of pasteurised antithrombin III has been extended with consistent clinical efficacy and no evidence of hepatitis transmission. The first pasteurised therapeutic concentrate of factor XIII, developed at PFL, has been successfully infused into a patient.

Undoubtedly one of the most significant advances in the past year has been the development of the new 'high purity' factor VIII concentrate. The method selectively precipitates 90% of the fibrinogen and 70% of the fibronectin present in a cryoprecipitate extract, while factor VIII remains virtually quantitatively in solution. Precipitation of the factor VIII yields a product with an eightfold increase in specific activity when compared with the intermediate potency concentrate. Furthermore, the product can be subjected to very severe heating, 70 or 80°C for 72 hours without significant loss of factor VIII activity and very little loss of solubility. This process has been rapidly transferred through pilot scale studies to successful 900 kg production runs. Product characteristics have remained consistent and it is expected that the new 'high purity' concentrate (VIII-Y) will become the national product during 1985. The first batches for clinical trial were released at the end of February with a protocol designed to assess safety and efficacy together with monitoring of possible transmission of HTLV III and viral hepatitis. Further processing of VIII-Y on chromatographic adsorbents results in a five- to tenfold increase in specific activity. The adsorbent has a high capacity for factor VIII and with recoveries in the 80-90% region offers a clear potential application for large-scale processing.

Considerable effort has been centred on the separation and concentration of vitamin K-dependent proteins. This reflects a BPL production requirement for a method of preparing factor IX concentrate which does not involve dilution of cryosupernatant, and recognises the planned increase in production in the new manufacturing unit. The single step preparation of factors IX, II and X from undiluted cryosupernatant has been achieved using DEAE-Sepharose at the 50 kg pilot plant scale. A diluted factor VII concentrate is recovered from the same chromatographic process. The process is being refined, scaled-up and its effect on other processes assessed while awaiting results from the on-going thrombogenicity trials in dogs.

Plasma quality and its effect on plasma proteins, particularly factor VIII, has been investigated. Problems associated with the operation of filtration pheresis machines have prevented a detailed assessment of filtered plasma. Preliminary results indicate a lower level of β-thromboglobulin and fibrinopeptide A than in centrifuged plasma suggesting that platelet disruption and thrombin activation are reduced during filtration pheresis. Two new machines have been installed at the Leeds and Sheffield transfusion centres and collection of samples for detailed analysis and pilot-scale factor VIII production has started. The effect of anticoagulant volume and concentration on plasma quality has been investigated in collaboration with Cambridge

RTC. At low volumes of anticoagulant there was no evidence of poor mixing, factor VIII activity and total protein were not detectably different, and there was no apparent increase in protein degradation. The level of β-thromboglobulin was observed to increase with decreasing anticoagulant volumes suggesting greater platelet lysis; this effect, together with an increase in fibrinopeptide A, was more apparent in sodium citrate plasma than CPD plasma. Cryoprecipitate produced from these experimental plasmas showed no difference in factor VIII activity or fibrinogen concentration; fibronectin levels appear to be a function of the anticoagulant volume. These results, if substantiated, would reduce the volume of 5,000 donations by 240 litres, thereby allowing an increase in the plasma content of each production batch with a concomitant decrease in the amount of water, buffer and ethanol used in the manufacturing process.

Clinicians continue to express interest in the availability of fibronectin and α_1-antitrypsin. The introduction of a new process for the preparation of factor VIII-Y necessitates a re-evaluation of the methods established for fibronectin preparation. Notwithstanding, the principle barrier to the release of fibronectin for clinical assessment remains the lack of an acceptable reliable assay for in vivo function. This deficiency severely limits our capacity to investigate the pasteurisation procedures required before product release. Assay development and assessment are proceeding; a candidate for the measurement of relevant biological activity, developed at Birmingham University, has been incorporated into a work programme directed ultimately to the clinical use of fibronectin concentrates following thermal injury. The British Thoracic Association continue to maintain a keen interest in the availability of α_1-antitrypsin for replacement therapy in emphysema. More recently we have been approached for a supply of α_1-antitrypsin for use in heart/lung transplant patients. The preparation of 'pure' α_1-antitrypsin has been achieved using Cohn fraction IV as a source material, however, for a variety of reasons the process cannot be transferred to either pilot or full-scale production. Recognising the limitations imposed by the use of fraction IV as an alternative source material has been sought with the initial objective of deriving an α_1-antitrypsin enriched concentrate without detriment to the existing manufacturing process.

Following a commercial approach we have investigated the possibility of preparing lys-plasminogen for use as an acylated complex in thrombolytic therapy. Source materials have been defined and the appropriate assays established. The affinity adsorbent lysineSepharose has been prepared at BPL and elution conditions selected to yield glu-plasminogen at greater than 90% purity. Conversion to lys-plasminogen has been achieved by plasmin digestion and interim analysis suggest that the product will meet specifications. The first test sample 750 mg is now undergoing assessment.

The production of reagent grade albumin from waste Cohn fraction IV has been successfully scaled-up to a level which can accommodate all the available fraction IV from production. The in-house preparation of the 40L blue-Sepharose column provides a system yielding 1.4 kg albumin/10h cycle. The full potential of the automated system has been achieved through the introduction of a fraction IV clarification procedure based on graded sand bed filtration. Downstream processing has been improved by modifications to existing diafiltration and ultrafiltration systems; sterile filtration and dispensing are now routinely employed. There has been a positive reaction to the use of the basic product in automated serology and in some instances this reaction has been extended to manual serology. The level of false positives experienced in manual serology with earlier batches has been reduced and results with a whole range of blood group antibodies have been more than equivalent to the results obtained using two commercial products. Various albumin treatments have been examined with a view to improving the performance of the product in manual serology. Gluteraldehyde cross-linking to increase the level of polymeric albumin has resulted in an improved reagent according to the recent trial undertaken by the ISBT/ISH working party. In this comparative study against commercial products, the BPL reagent gained top ranking in two of the three tests. However,

two trial participants experienced false positive agglutinations with the displacement technique. A quality control programme involving 'in-house' characterisation and serological assessment by the Manchester RTC has been introduced to monitor reagent consistency. The occasional sub-standard preparation prevents the launch of a reagent for manual serology, however, the basic product for automated serology will be launched, after extensive field trials, later this year.

Apart from albumin there are other reagent grade proteins derived from waste fractions of the manufacturing process, which appear to have market potential. Preparations of transferrin and fibronectin have been assessed as tissue culture supplements with positive user reaction, however, the use of Cohn fraction IV as a direct replacement of foetal calf serum has not been successful and further work is required to advance this product. There is an increasing demand for plasminogen in the assay of tissue plasminogen activators and a product, prepared from the waste fraction B+1, is currently under assessment at CAMR, Porton. Other proteins requested as reagent-grade products include fibrinogen, thrombin, immunoglobulins and modified albumins. The requirement for these products, excluding serological albumin, is largely unknown; a market survey will be initiated early this year to evaluate their potential prior to deriving a costing programme.

Personnel

Two new scientific appointments were made at the beginning of the year; Dr. Neal was employed to investigate the chromatographic fractionation of factor VIII and Dr. More was assigned responsibility for reagent grade products. The continuity of the plasma filterpheresis programmes was maintained by appointing Miss Brady as a project scientist to replace Mrs. Harvey GRO-A Dr. Ross completed her MRC project grant in October and the department also lost the services of Dr. Brown and Mrs. Cotton during the course of the year. The position of senior scientist has been filled by Dr. Young who comes to us with experience of both academic and industrial environments. Five new technicians have been appointed at BPL, and two replacement technicians have been taken on at PFL. Miss Kingsland has been promoted to a trainee management position at PFL, whilst Mrs. Winkelman (PFL) and Mrs. Rott (BPL) have been promoted to Senior Project Leader and Chief Technician respectively.

Building

The conversion of Building 9 to give three new laboratories was completed in late summer. The area was commissioned in September and is operating at 40% occupancy. Further staffing is, in part, dependent upon the completion of an animal house facility for the department. Additional space has been released for laboratory work by acquiring a Portacabin to serve as office space for the Head of Department and the Department Secretary: Mrs. Thompson was appointed to the latter position in October.

The scheduling of the new manufacturing unit to come on stream during early 1986 has considerable implications for the R & D department especially in relation to the life time of the pilot production facility (coagulation factors) at PFL. A facility appraisal report commissioned last year examined the options available for integrating the Oxford unit onto the Elstree site. The consultants, after considering the feasibility and associated costs of re-using the existing production facility, recommended the alternative approach of providing a purpose-built new facility. They stressed the need for a medium-term stop-gap plan which recognised the problems of accommodating the functions of the Department efficiently and acknowledged the necessary expansion of the Department's activities. It must be stressed that currently the Department is unable to offer the necessary technical and scientific support essential to the production units and that this situation is likely to continue throughout the commissioning and early years of the new manufacturing unit.

RESEARCH AND DEVELOPMENT

ESTIMATED EXPENDITURE 1985/6

All estimates, derived from the individual project reports, are for the year starting January 1985.

BPL Quality Control Department	12,000	(a)
BPL Production Units	301,200	(b)
BPL Research & Development Department	566,842	(c)
Plasma Fractionation Laboratory	94,400	(d)
	974,542	

Notes :

(a) Costs met from the Quality Control Department Budget.

(b) Costs attributed to R & D projects are accommodated within the Production Department Budget; they include the purchase of developmental equipment for future use in routine production together with the estimated cost of the chimpanzee study on the new intravenous immunoglobulin preparation for freedom from transmission of non-A non-B hepatitis.

Tear-down machine development (CF/04)	70,000
Haemonetics plasma pack opening machine (CF/06)	50,000
Heat-treatment ovens (CF/07)	35,000
Chimpanzee study (IgG/01)	100,000
Sub-total	255,000
Project expenditure (see R & D project report)	46,000
Total	301,200

(c) A breakdown of the Research & Development Department budget is given on page 48.

(d) PFL estimates have been adjusted for GMP requirements and proportioned according according to the efforts of Research & Development, Fractionation and Quality Control in each project, taking into account the expenses incurred in the Administration and Technical Support Groups.

RESEARCH AND DEVELOPMENT

DISTRIBUTION OF BUDGET COSTS

PROCESS			£295,312
(a)	Improvement of existing process	£87,850	
(b)	New process development	£207,462	
PRODUCT			£288,250
(a)	Improvement of existing products	£71,400	
(b)	Investigations on potential products		
	(i) Clinical	£152,000	
	(ii) Reagent	£64,850	
RESEARCH			£143,050
(a)	Analytical developments	£56,250	
(b)	Basic	£86,800	
		Sub-total	£726,612

Research & Development Department Expenses

Administration overheads	106,598		
Equipment	37,332		
External research contracts	104,000		
	247,930		£247,930
		Total	£974,542

RESEARCH AND DEVELOPMENT

1985/86 BUDGET

Forecast Expenditure:

Projects (see R & D project report)	318,912	
Equipment	37,332	
	356,244	 356,244
Department administration/New staff	76,478	
Staff expenses	11,810	
V.A.T.	18,310	
	106,598	 106,598
External research	104,000	 104,000
Total submission		£566,842

PROJECT INDEX

(New projects are denoted by an asterisk)

Topic : Coagulation Factor VIII

Project Code — Estimated Budget : £105,562

	8/01	Simultaneous removal of alhydrogel adsorbent and cold precipitate
	8/02	Improved recovery with heparin as primary anticoagulant
	8/03	Inactivation of hepatitis viruses in concentrate
	8/04	Precipitation behaviour and discrimination from fibrinogen
	8/05	Molecular exclusion chromatography
	8/06	Ion-exchange and hydrophobic interaction chromatography
	8/07	Susceptibility to proteolytic activation
*	8/10	Chromatography on anion-exchange media
*	8/11	Anticoagulant volume: effect on factor VIII and plasma quality
	FT/01	Filterpheresis trials

Topic : Vitamin K dependent coagulation factors

Project Code — Estimated Budget : £55,000

	9/01	Inactivation of hepatitis viruses in concentrates of factor IX (II and X) and factor VII
	9/02	Improved ion-exchange and affinity chromatography of vitamin K dependent factors
	9/03	Improved concentrate of thrombin for clinical and laboratory use

Topic : Fibrinogen

Project Code — Estimated Budget : £13,600

	FG/01	Preparation for clinical and laboratory use
	FG/02	Quantitative analysis
	FG/04	Fibrinopeptide analysis
	FG/05	Fibrinolytic potential of factor VIII concentrate

Topic : Fibronectin

Project Code — Estimated Budget : £23,200

	FN/01	A potential clinical product
	FN/02	Reagent grade product
	FN/04	Fibronectin and Factor VIII
	FN/06	Degradation products - isolation, identification and quantitation
*	FN/35	Fibronectin: opsonic activity and functional assay development

Topic : Factor XIII

Project Code — Estimated Budget : £ Nil

	13/01	A concentrate for clinical use

Topic : Antithrombin III/Factor XI

Project Code — Estimated Budget : £10,000

AT3/01 Concentrates for clinical use

Topic : Albumin

Project Code — Estimated Budget : £44,250

ALB/01 Large scale production of reagent grade material from Cohn Fraction IV
ALB/02 Automation of large scale affinity chromatography process
ALB/05 Recovery from pathological plasmas
* ALB/34 Albumin: traditional and polymer-enhanced serological reagents

Topic : Immunoglobulin Production

Project Code — Estimated Budget : £124,400

IgG/01 Development of a preparation for intravenous use
IgG/02 Clinical trial of intravenous preparation
IgG/03 Trial of prophylactic immunoglobulin to prevent CMV infections in CMV seronegative bone marrow transplant recipients
* IgG/08 Anti-D immunoglobulin: acid/pepsin treated for intramuscular preparation
* IgG/09 Immunoglobulins: evaluation of virucidal treatments

Topic : Ethanol Fractionation

Project Code — Estimated Budget : £1,000

EF/02 Filtration of cold-ethanol supernatants using non-asbestos filter media
* EF/05 Filtration of normal immunoglobulin using non-asbestos filter media

Topic : Coagulation Factors Production

Project Code — Estimated Budget : £175,800

CF/01 Computer technology for plasma receipt/quarantine/batching
CF/02 Schubert filling machine: development of a filling pump/needle assembly
CF/03 Factor VIII production: commissioning of plasma crusher/thawing vessel
CF/04 Teardown Machine: development and evaluation
CF/05 Factor IX production: recycling and centrifugation of DE52
* CF/06 Haemonetics pack-opening machine
* CF/07 Coagulation factors: provision of ovens for heat treatment

Topic : Potential Products

Project Code — Estimated Budget : £56,650

AT/01 α_1-Antitrypsin: distribution and purification by selective precipitation
* AT/23 α_1-Antitrypsin: chromatographic fractionation
* PMG/01 Lys-plasminogen preparation and production
* PMG/02 Plasminogen: preparation of a reagent-grade product
SMC/01 Somatomedin C, purification and assay
TCS/01 Development of tissue culture supplements
Tf/01 Transferrin: distribution and fractionation
Clq/01 Isolation of complement component: Clq

Topic : Analytical Developments

Project Code — Estimated Budget : £32,850

HEP/02 Antibody to hepatitis B surface antigen
LAL/01 Validation of LAL assay for albumin and other blood products
LAL/02 Chromogenic substrate test: validation for selected blood products
LAL/03 Coagulation factors: LAL tests and anomalous rabbit pyrogen tests
IGG/05 ELISA for determination of antiviral IgG
IgG/06 Antiviral/antitoxin antibody assay development
* IgG/07 Bacterial lipopolysaccharide: antibody screening
* BM/01 Screening test for β2-microglobulin
HPLC/1 High pressure liquid chromatography: protein analysis
HPLC/2 High pressure liquid chromatography: analysis of low molecular weight compounds

Topic : Process Development

Project Code — Estimated Budget : £84,300

3GA/02 Cibacron blue-Sepharose: ligand leakage
3GA/03 Cibacron blue-Sepharose: toxicity studies
MM/01 Production of a magnetic matrix for chromatography
* ADC/01 Ampholyte displacement chromatography and chromatofocussing: plasma protein fractionation
* CHR/01 Chromatography adsorbents: comparative studies
* MAB/01 Monoclonal antibody/cell culture facility
* COM/01 Computer Applications

Topic : Concluded Projects

Project Code

8/08 Factor VIII: Chromatography in relation to ligand substitution
8/09 Factor VIII: Immunoadsorbent chromatography
FG/03 Fibrinogen: qualitative analysis
FN/03 Fibronectin: as a non-immune opsonin
FN/05 Fibronectin: assay kit development
ALB/03 Albumin: development and characterisation of serological reagent
ALB/04 Albumin: polymer enhanced serological reagent
3GA/01 Cibacron blue-Sepharose: affinity of hepatitis B particle and pyrogens
HEP/01 BPL-radioimmunoassay for hepatitis B surface antigen
HEP/03 Screening tests for markers of hepatitis infectivity
AT/02 α_1-Antitrypsin: conventional chromatographic fractionation
AT/03 α_1-Antitrypsin: affinity chromatography adsorbents
IgG/04 Immunoglobulin: evaluation of Westfalia BKA6 centrifuge
EF/01 Ethanol fractionation: concentration of factor IX supernatant by ultra-filtration
EF/03 Ethanol fractionation: filtration of albumin solutions using non-asbestos filter media
EF/04 Application of Westfalia bowl centrifuges in cold ethanol fractionation
PP/01 Distribution of plasma proteins in BPL products and waste fractions

SCIENTIFIC PUBLICATIONS, PRESENTATIONS, ABSTRACTS AND LETTERS

Heat treated NHS factor VIII concentrate in the UK - a preliminary study

Colvin, B.T., Machin, S.J., Mackie, I., Ainsworth, M. and Smith, J.K.
British Society for Haemostasis and Thrombosis, March 1985.

Microcomputer control of liquid chromatography

McFarland, C.D., Price, S., Brown, R.A. and Harvey, M.J.
Biochem. Soc. Trans. 12 (1984) 1098

Factor VIII concentrate as a source of fibronectin for replacement therapy

Smith, J.K., Brown, R.A., Harvey, D.K. and Harvey, M.J.
J. Clin. Pathol. 37 (1984) 1196

'Plasma Proteins of the Future'

Smith, J.K.
Sixth Annual Fenwal Symposium, Cambridge, 1984.

'Plasma quality - the effect of some blood processing choices on coagulation factor concentrates'

Smith, J.K., Evans, D.R. and Prince, P.J.
18th ISBT Congress, Munich, 1984.

'Plasma Products for the Future'

Smith, J.K.
Second Annual BBTS meeting, Manchester, 1984.

'Processing Criteria for Recovery of FFP for Fractionation'

Smith, J.K.
Ninth Annual Symposium on blood transfusion, Groningen, Netherlands, 1984.

Microcomputer controlled, automatic production of human albumin by affinity chromatography

McFarland, C.D., Price, S., Brown, R.A. and Harvey, M.J.
Second Annual BBTS meeting, Manchester, 1984.

Analysis of human plasma fibronectin by size exclusion high performance liquid chromatography

Cotton, G., Brown, R.A. and Harvey, M.J.
Second Annual BBTS meeting, Manchester, 1984.

A pasteurised antithrombin III concentrate for clinical use

Smith, J.K., Winkelman, L., Evans, D.R., Haddon, M.E. and Sims, G.E.C.
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CROWN RECORDS AND PATENTS

Plasma protein fractionation for clinical use: separation of factor VIII from fibrinogen and fibronectin by precipitation with heparin.
L. Winkelman, May 1984, Crown Record.
Separate patent application currently being submitted.

CONFERENCES AND VISITS

Dr. R.S. Lane	
January 10-12	Visit to HemaScience Laboratories, Santa Ana, California.
March 8-10	1984 International Symposium on Viral Hepatitis, San Francisco.
July 22-27	International Society of Blood Transfusion 18th Congress, Munich.
August 6-7	Visit to Immuno Limited, Vienna.
October 15-27	ISBT Working Party on Automation and Data Processing, Toronto; American Association of Blood Banks meeting in San Antonio; Visit to Travenol Laboratories in Chicago.
Mr. L. Vallet	
February 20-23	Group 6B (Blood Products) meeting, European Pharmacopoeia, Strasbourg.
July 22-27	International Society of Blood Transfusion 18th Congress, Munich.
September 26-29	2nd Annual BBTS meeting, Manchester.
October 30-31	Group 6B (Blood Products) meeting, European Pharmacopoeia, Strasbourg.
Dr. M.J. Harvey	
May 15-17	Biotech '84, Wembley.
September 26-29	2nd Annual BBTS meeting, Manchester.
Dr. J.K. Smith	
March 8-9	Haemonetics Symposium, New York.
April 2-13	Invited visitor to Commonwealth Serum Laboratories, Melbourne, to present and discuss BPL/PFL experience on plasma procurement, development of factor VIII, IX, VII, XIII, AT3, fibrinogen and fibronectin concentrates, and to exchange views on hepatitis-safer concentrates.
May 14-15	Invited speaker at Sixth Annual Fenwal Symposium, Cambridge. 'Plasma proteins of the future'.
July 23-25	Invited speaker, 18th ISBT Congress, Munich. 'Plasma quality - the effect of some blood processing choices on coagulation factor concentrates', J.K. Smith, D.R. Evans, P.J. Prince. Co-authors.
September 26-29	Invited speaker, 2nd Annual BBTS meeting 'Plasma products for the future'.
November 1-2	Invited speaker and session co-chairman, 9th Annual Symposium on blood transfusion, Groningen, Netherlands. 'Processing criteria for recovery of FFP for fractionation'.

May 7 and November 22	Visits to Protein Fractionation Centre, Edinburgh, to discuss hepatitis-safer factor VIII and IX concentrates.
Dr. P. Feldman	
November 15-17	ICTH Plenary sessions and sub-committee meetings, Miami, Florida.
Mrs. L. Winkelman	
April 13	British Society on Haemostasis and Thrombosis Meeting, Sheffield.
October 3	Haemostasis Club meeting, Oxford, on Fibrinolysis.
Mrs. J. Keen	
October 3	Haemostasis Club meeting, Oxford, on Fibrinolysis.
Dr. L. Singleton	
July 3-5	Pathological Society meeting, Leeds. Bacterial Endotoxin.
April 17	Robens Institute of Toxicology open meeting, Surrey University.
Dr. R.A. Brown	
June 26-29	3rd International Symposium on 'The Biology of the Vascular Endothelial Cell', Boston, U.S.A.
Dr. G.G. Neal	
July 19	Transmissible Diseases in Blood Transfusion, Edgware.
September 21	British Society for Haemostasis and Thrombosis AGM, Middlesex Hospital.
October 3	Haemostasis Club meeting, Oxford, on Fibrinolysis.
Miss A-M. Brady	
October 3	Haemostasis Club meeting, Oxford, on Fibrinolysis.
Mrs. J. Rott	
October 24	Course on FPLC (Pharmacia).
Dr. J.E. More	
June 26	Interphex '84, Brighton.
August 10	Somatomedin Club meeting, Oxford.
Mr. C.D. McFarland	
April 11-12	Biochemical Society meeting - Microcomputers in Biochemistry, Keele University.
September 26-28	2nd Annual BBTS meeting, Manchester.