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BLOOD PRODUCTS LABORATORY

REPORT

April 1982 - April 1983
April 1983 - December 1983

R.S. LANE, Director.

16th January 1984.

INDEX

SUMMARY

This Report covers 21 months from April 1982 to December 1983 and its presentation to the Central Blood Laboratories Authority coincides with completion of the Authority's first year of management. The Report incorporates activities of the Blood Products Laboratory, Elstree (BPL) and Plasma Fractionation Laboratory, Oxford.

During this period, £2.5M has been spent on modernisation and extension of the existing buildings to allow increased output of factor VIII and albumin solutions to occur with safety while a new production building is completed. This project, called the Medicines Act Redevelopment Project (MARP) was finished by November 1982 and the post-MARP production targets met in 1983.

Annual factor VIII output has doubled to 30M iu and units of Plasma Protein Fraction and Albumin have increased from 130,000 to 220,000. The shelf value of this extra production is about £3.5M which has already greatly offset the capital expenditure involved.

To support the extra production, Regional Blood Transfusion Centres (RTCs) have doubled the input of fresh frozen plasma (FFP) taken from voluntarily donated whole blood: FFP intake is now 150,000 kg per annum.

Outputs of other main products have shown a tendency to increase as in past years, anti-D and tetanus immunoglobulin and factor IX being examples.

To cover these manufacturing activities, revenue expenditure was £3.439M in 1982/3 and is £2.79M after thefirst nine months of 1983/4: capital expenditure for the two periods was £.916M and £.1M respectively.

The development of a new production building commenced on site at Elstree in April 1983 and will cost in excess of £21M. Final estimates of costs and date of completion will not be ascertained until April 1984, but production is scheduled to commence during 1986. The project is proceeding on a 'design and construct' basis and will be finished to a specification compatible with high-grade pharmaceutical processing and Good Manufacturing Practice. Nominal capacity is 450,000 kg FFP throughput annually to provide 100M iu factor VIII and 200 kg albumin per one million population deemed necessary to give self-sufficiency to the NHS in these products.

Priorities in Research and Development have been directed towards improved product safety (inactivation or exclusion of hepatitis virus) and increased yield through more efficient processes. A full account is included in this Report.

Staff recruitment during 1982/3 and 1983/4 has increased numbers from 186 to 240. Appointments have been in all disciplines and grades. Important appointments of Mr. G.E. Mallory as Deputy Director, with responsibilities in Production Control and Administration, Dr. T.J. Sanpe as Head of Quality Control, and Mr. W.I.T. Ling as Head of Engineering, deserve mention.

Industrial Relations have shown a decline in accord during 1983, and this is due to the increasingly unsatisfactory conditions of work unsupported by an appropriate system of pay grades and conditions of

service compatible with manufacturing. The impending closure of PFL Oxford has heightened uncertainty at Oxford and Elstree in spite of reassurance. Considerable efforts will be needed in 1984 to avoid disruption of services.

The Report therefore covers a period of marked transition andgrowth in activities at all levels. Although targets have been met, there is still cause for dissatisfaction in areas of safety and quality assurance which reflect the strained resources and shortage of competent middle management.

Groundswell of discontent.

Recast functional + highlights

Low: problems of staff + management levels, due to

(1) Salary structure uncertainties.

no set of terms to advertise for recruitment

(2) Lack of key specialists - turned down 3 yrs ago

MANUFACTURING AND ADMINISTRATION

In 1982, impetus of manufacturing and laboratory development again increased although these efforts were not equally matched by corresponding output. Production problems resulting from MARP building works caused this discrepancy between June and November. From January 1983 onwards there began a marked rise in throughput as successful recommissioning showed its effect. Staff in all areas worked extremely hard throughout the year and are to be congratulated on their total effort.

The completed MARP project, apart from remedial works, provided an upgraded Coagulation Factors Production Suite, a new Loading Bay, increased heat treatment and incubation capacity for albumin, together with an Inspection and Packaging area with its own transit facility.

1982/3 product dispatches of factor VIII were +5% over 1981/2; 400 ml Plasma Protein Fraction (PPF) increased by an equal increment. Products released were valued at £9.708M of which £3.61M represented the notional value of source plasma. In the initial nine months of 1983/4, products released have been valued at £9.235M of which £3.07M represents the notional value of the source plasma. Production data are listed in the ensuing Tables.

Quality Control has undergone major rationalisation and expansion of services during the first year of appointment of the new Head of Department. The entire programme remains severely compromised, however, by the poor premises occupied. This critical matter is dealt with in the final commentary to this Report.

The engineering and maintenance services have been fully reviewed by the new Head Engineer. Recruitment has occurred into several engineering disciplines and the department has taken over all planning of small building works.

PRODUCTION SECTION REPORTS

COAGULATION FACTORS (Manager, Mr. P.J. Prince)

Factor VIII

1982/3: 116,890 kg fresh frozen plasma were processed, from which 102,694 vials of factor VIII were filled. Of this in-process number, 90,594 vials were released. During the year, 107 batches were started, but production in 30% was interrupted by freezing at an intermediate stage either due to MARP building works or because of staff shortages. Freezing of intermediates is associated with a 15% loss of yield and the step is only used where no other manufacturing alternatives are available.

Plasma supply remained in balance with an input of 131,000 kg. It is probable that input would have realised 150,000 kg FFP but for industrial action in the Health Services which affected some RTCs.

April - December 1983: 113,840 kg of FFP have been processed to obtain 96,703 vials of factor VIII. These vials have been released and stocks currently remain equivalent to supply for one week. This is inadequate.

Plasma supply is on schedule to reach 150,000 kg during the full year. Since manufacture from FFP cannot exceed 150,000 kg per annum, additional plasma will be stockpiled to assist commissioning of the new BPL production building. FFP stocks at 31st December 1983 were 29,952 kg.

Progress with the Single Plasma Pack

An automated pack opening machine has now been operating successfully at BPL for 18 months. During this period, the intake of FFP in single plasma packs has increased considerably. During the past 12 months more than 650,000 single plasma units have been received. All CF personnel (notably Mr. J. Williams) have contributed considerable efforts to establish the single plasma pack as the standard method for transport and storage of FFP.

LARGE FRACTIONATION (Manager, Mr. A.P. Butcher)

1982/3: A record level of production was achieved during this year: 170,681 kg plasma (or plasma equivalent) were fractionated, an increase of 27% over the previous year. The use of a new Westfalia BKA28 centrifuge (see below) was partly instrumental in achieving this record volume.

All plasma fractionated was converted to either fraction V or albumin concentrate. Conversion of fraction V to PPF was limited by building work in the Final Solutions Section; therefore fraction V accumulated throughout the year.

Fraction II production was geared to meet demand.

1983 April - December: 175,000 units of PPF and salt-poor albumin have been released during the nine month period which represents fractionation from approximately 140,000 kg of source plasma or an equivalent of 185,000 kg in the full year. This throughput is the maximum that current capacity can accommodate, thus Large Fractions now limits the volume of source material which can enter the Coagulation Fractions department to 150,000 kg annually.

Process Modification

(a) Westfalia BKA28 Centrifuges

During 1982 and 1983 an evaluation of two Westfalia centrifuges (one bought by BPL) was performed by Mr. M. Tucker and the Large Fractions staff. Approximately 100 runs were performed using plasma precipitates intended for use in final product. Separations of Kistler and Nitschmann A1, IV and V precipitates were studied for optimal suspension flow rates, bowl capacities, supernatant and precipitate characteristics, and the

results were compared with those of existing Sharples AS26 centrifuges.Experience has now shown that the Westfalia system is preferable and that benefits increase with scale of operations. The study was an essential precursor to decisions to place Westfalia BK45 centrifuges in the new BPL production building.

It should be noted that new equipment evaluation is carried out in routine production areas of necessity than out of choice, in the absence of a pilot development laboratory.

(b) Ultrafiltration Equipment

During 1983, investigations were made by Mr. M. Beeton with production-scale ultrafiltration systems used to remove water from factor IX supernatants prior to ethanol precipitation, and for the removal of water and ethanol from albumin/fraction V solutions. Amicon Hollow-Fibre Systems were evaluated and calculations indicate processing 3500L pools will be feasible. It is advantageous to remove bulk water prior to fractionation and ultrafiltration will be incorporated into the process used in the new BPL.

SPECIFIC FRACTIONATION

(i) Production

During the twenty-one months under review, sufficient quantities of specific immunoglobulin have been produced to meet most of the major needs of the NHS. (See Tables 2 and 5.) The major product was Anti-D(Rh) immunoglobulin, followed by tetanus immunoglobulin. An increased demand for varicella-zoster immunoglobulin was met by increased production. The demand for HBs immunoglobulin continues to rise and for some time has exceeded the amount that can be produced from the plasma received. Up to the summer of 1983, the demand was met by drawing on stocks of plasma and freeze-dried fraction II but these are now exhausted. The Regional Transfusion Centres were warned that unless a two to threefold increase in high-titre anti-HBs plasma supply to BPL was forthcoming, we would be no longer able to supply sufficient immunoglobulin to meet demand. We are now in a sitution of shortage of HBs immunoglobulin.

During 1983, the supply of HBs hyperimmune plasma has become further aggravated by uncertainty of donor selection. Antibody to hepatitis has become an associated marker of victims of AIDS (Acquired Immune Deficiency Syndrome) since most promiscuous homosexuals contract hepatitis.

From the Regulatory standpoint, plasma from homosexual donors may be used to prepare HBs immunoglobulin since fraction II products are believed not to transmit virus. This is not established for the putative virus of AIDS and therefore, at BPL, homosexual donor plasma will be used to prepare immunoglobulin when current work has established chemical modification methods with virucidal potential.

(ii) Human normal immunoglobulin for Intravenous Use (HNI iv)

Human normal immunoglobulin for intravenous use was produced in preparation for a clinical trial in an eighteen month programme of treatment of hypogammaglobulinaemic patients at the Clinical Research Centre, Northwick Park Hospital which began in April 1983. The product was an unmodified immunoglobulin preparation in which thelevels of immunoglobulin aggregates (as measured by gel permeation chromatography) and anti-complementary activity were very low. It was freeze-dried from a solution containing 10 g% added maltose. In addition to the full clinical trial, this product was used on a number of occasions on a named-patient basis in the treatment of hypogammaglobulinaemia, Felty's syndrome and idiopathic thrombocytopaenic purpura (ITP); the successful treatment of ITP in particular called for large infusions (0.4 g/kg/day for 5 days) and these were tolerated well by the recipients.

Issues were stopped and the product was recalled at the end of August following the report of short-incubation non-A non-B hepatitis in four patients in the Northwick Park trial.

An investigation of hepatitis associated with this preparation of intravenous immunoglobulin is being undertaken and a full report will follow its conclusion.

Initial observations confirm that the process used to prepare immunoglobulin for intramuscular use remains capable of preparing a safe product - assurance in this respect goes back thirty years. A minor process modification to circumvent early freeze-drying of fraction II paste, known to denature a proportion of immunoglobulin molecules, used for intravenous immunoglobulin is believed to have permitted virus transmission.

Audit of the process by Medicines Division Inspectors failed to reveal a failure in GMP as the cause for problems with intravenous immunoglobulin.

Work of high priority is now in hand to incorporate the process modification of incubation of immunoglobulin with a trace of protease at pH 4. This step, aimed at reducing immunoglobulin aggregation, coincidentally inactivates virus.

(iii) Further Developments: Cytomegalovirus (CMV) Immunoglobulin

During 1982/3, arrangements were made with four Regional Blood Transfusion Centres (Yorkshire, N.W. Thames, S.E./S.W. Thames and Oxford) to begin screening and selecting out blood donations with high-titre CMV antibodies. These donations are being sent to BPL where they are re-assayed for complement fixation titre (CFT). Any donation with an anti-CMV CFT of >1:64 is set aside for future fractionation. Plamsa supplies were sufficient to permit the first fractionation and production of CMV immunoglobulin in May 1983. The product and preparation method was planned to be the same as for intravenous immunoglobulin, the starting material being plasma containing high levels of antibodies to CMV. The initial proposal was to use this material in a controlled clinical trial of its value as a prophylactic agent in sero-negative bone marrow transplant recipients. This scheme has been deferred following the association of hepatitis with Human Normal Immunoglobulin for intravenous use. Because homosexual activities and AIDS are related and also carry

an association with high-titre antibody to cytomegalovirus, donor selection for this hyperimmune plasma becomes problematical. The same approach, now being adopted to handle plasma from donors with high-titre antibodies to hepatitis, will apply to cytomegalovirus antibody donors.

FINAL SOLUTIONS (Manager, Mr. B.T. Kennedy)

During the MARP project, the Final Solutions area was completely refurbished, resulting in a nine-week shut-down of operations in 1982. Difficulties with commissioning of autoclaves for preparation of essential sterile equipment further delayed the return to full production.

Supply of finished product at this time was maintained from stocks which were nearly exhausted by December 1982.

Following MARP alterations in January 1983, the supply of albumin and PPF has increased to levels beyond the targets set. New equipment in use since September 1983 has increased batch size by 50% and the increased throughput can be accommodated in enlarged facilities for pasteurisation and incubation. The increased throughput of this production area is reflected in the product data shown in Tables 5 and 7.

FREEZE DRYING (Manager, Mr. K. Kinnarney)

Installation of three new Lyomax freeze driers was completed in April 1982 but the new systems were not fully operational until mid-October. Since that time, the new freeze-drying suite has worked efficiently and provided a high level of security to the final freeze-drying step for coagulation factors.

Increased freeze-drying capacity has enabled factor VIII output to double and permitted development work on intravenous immunoglobulin preparations. The older EF10 freeze-driers now provide separate capacity for processing immunoglobulin intermediates.

TECHNICAL SERVICES (Manager, Mr. P.S. Leavens)

The MARP project closed Technical Services from June to September 1982 and considerable difficulties were experienced with commissioning of autoclaves and a new pyrogen-free water system (Finn Aqua). Sterile equipment and water services were not regularised until December 1982.

The entire area was reorganised and re-equipped to permit basic adherence to GMP procedures. Hygiene through the area now improves with unidirectional flow and entries for staff and equipment are separated. Staff are required to undergo a full change into uniform. Air handling has been improved and maintenance requirements have been separated from clean process areas.

Production levels and standards have increased to meet the requirements of current increased fractionation of plasma. The area remains compromised by the main structure of the old building and by its geographical separation from the two main process areas it serves.

Staff have been retrained and a move to uniform full-time working is being established. The change in work content has been followed by regrading but this has precipitated industrial relations difficulties in other groups of process staff. The dispute is unresolved and is currently being further assessed by external job evaluation of process grade workers.

TERMINAL PROCESS SECTION (Manager, Mr. D.T. Bennett)

This section was substantially upgraded by the MARP project during which time there was complete close-down of activities.

From January 1983, throughput of filled containers has increased 70% and the percentage of filled units rejected on inspection has shown significant reductions. The current position reflects the generally improved standards in preparation of containers and closures and in the environmental control of the Terminal Process Area.

Closure of albumin and PPF has remained a manual procedure following serious complications with the use of a new automated bottle closing and oversealing machine. Air filtration aimed at giving Class I conditions at the time of bottle closure has been unable to prevent repeated contamination of sterile broth runs and a serious design fault is evidenced by poor performance.

As in an earlier section, it should be noted that an attempt to commission new equipment in the Sterile Filling Area of Terminal Processing was totally unsatisfactory and contrary to GMP. However, in the absence of pilot development facilities, there is no alternative.

INSPECTION, PACKING AND DISPATCH (Manager Mr. G. Sharman)

During MARP, this area was rebuilt and extended to permit unidirectional flow of procedures and to create secure storage of products at defined stages of release procedure in line with GMP and Quality Control requirements.

Increased space has enabled a considerable increase in throughput of products without risk to product and batch definition. Secure and discrete label storage has enabled proper labelling procedures to be adopted.

A separate transit area for dispatch of products enables the maintenance of a clear zone between finished products and source plasma reception which was not possible prior to completion of the MARP project.

QUALITY CONTROL REVIEW

During the period in question, there have been changes in staff structure, procedures and staff responsibility and the concepts of good manufacturing and good laboratory practice in line with the Orange Guide have been progressed.

Analytical Laboratory

In addition to providing coagulation asay and anlytical chemistry support for BPL, for product development at PFL, and similar testing on PFL finished products, this section participated in a number of national and international collaborative studies, including:

April 1982	Calibration of Third British Concentrate Standards for Factor VIII.
May 1982	Ph.Eur. collaborative study on the NAPTT test.
June 1982	Stability study on Third International Standard for Factor VIII.
July 1982	Internal collaborative study comparing Factor IX concentrates (jointly organised by T. Snape and G. Mariani (Rome) on behalf of the International Committee on Thrombosis and Haemostasis).

A number of techniques, new to the Laboratory, were put into routine operation, including:

Sept. 1982	Immunoelectrophoretic assay for Factor XIIIa.
Feb. 1983	Immunoelectrophoretic assay for fibronectin.
March 1983	Spectrophotometric assay for glycine.

An assay for sorbitol is under development, and a calcium ion selective electrode is being evaluated for suitability in determination of the concentration of calcium ions in a coagulation reaction mixture.

Bacteriology Testing

The facilities in the Bacteriology Laboratory have been improved by the refurbishment of two rooms providing extra laboratory space (freeing the old Bacteriology Laboratory for use by the Environmental Control Group), and by the installation of a viewing window to the sterile room. Finished product sterility testing has been improved by the introduction of membrane filtration testing for albumin products. Extensions of the technique to other products are being investigated. In January 1983 a fundamental change was introduced in the technique for screening incoming plasma for microbial contamination: the test for sterility was replaced by a total viable count, allowing the degree of contamination to be determined. This change has dramatically reduced the number of plasma packs rejected (many packs previously rejected were only lightly

packs rejected (many packs previously rejected were only lightly contaminated) and has provided quantitative information on which basis individual RTCs can begin an improvement programme. Contaminant classification has been widened and a more rapid system of identification of contaminants introduced by February 1983. An otherwise good year was marred by a serious breach of GMP by a member of staff who was subsequently dismissed: the task of retesting many batches of product was well handled by remaining staff.

Animal Testing

The fabric of the animal house building continues to deteriorate and is a cause for serious concern. Notwithstanding, the section has increased the number of pyrogen and abnormal toxicity tests commensurate with increased output: e.g. the number of tests performed in the period January to March 1983 represented a 60% increase over the number of tests performed during the same period of the previous year. The unit continues to provide an anti-serum production service on demand, and also provides large volumes of rabbit serum to Brentwood RTC to provide complement for the HLA-testing programme. The section collaborated with the R & D section in the performance of a study on the metabolic decay of radio-labelled albumin in rabbits. An outbreak of pseudotuberculosis in the guinea pig colony in February 1983 caused disruption of the testing service. The infection was traced to a delivery of animals from one supplier (no longer used) and has been eliminated.

Hepatitis Testing

This section continues to produce the BPL HBsAg RIA kit for sale in the UK, as well as providing an HBsAg testing service to BPL and BGRL.

Growth in use of the BPL RIA test has steadily progressed: fifteen Regional Blood Transfusion Centres in England and Wales now use the test, as does the RTC in Belfast and several Centres in Scotland. PHLS Laboratories at Bristol, Cardiff, Leeds and Leicester receive supplies and latest recipients are the Army Blood Supply Depot, Aldershot, and Edinburgh University Medical School.

Production figures in the attached Tables show the income from this test which is likely to exceed £600,000 in 1983/4.

Progress in developing contractual collaboration with the Wellcome Foundation to merge production and development interests have remained unacceptably slow, but it is hoped that a commencement may be made in the financial year 1984/5.

A total of 27,459 tests for HBsAg were performed on plasma pools, in-process and finished product of BPL and BGRL. Seven positives were detected, including four positive plasma pools (but none in BPL products). The positives in plasma pools prompted an investigation into the security of RIA testing at the RTCs involved. This has been combined with a planned programme of visits to RTCs by the Head of Section and the HQC. Only four centres have been visited to date. It is recognised that, with the shift from 5L packs to single plasma packs, increased emphasis on QA at the Transfusion Centres is required, since screening of individual donations at BPL is unnecessary in a well-ordered system.

Anticipated Developments

It is proposed to continue the restructuring of the QC organisation. The Factory Control Unit will be formalised with the appointment of a Factory Control Manager, responsible for Process and Product Quality Control Documentation, Regulatory Affairs and GMP training. The Control Laboratory will be divided into two, more manageable units, each with a unit head. The posts of Factory Control Manager and Microbiological Analytical Services Manager are unlikely to be filled until 1985/6 and initial attempts at recruitment have not been successful.

The functions of the Oxford Control Section will be incorporated into the section 'Coagulation/Biochemistry'. Although in practice the Oxford Control section will still provide a service for product development at PFL, it will no longer perform finished product testing, and will be managed by the head of the Coagulation/Biochemistry Section, who will divide his time equally between BPL and PFL.

PFL REVIEW

April 1982 - December 1983

The function of PFL has been changed to meet the transitional needs of BPL which take into consideration the experience of PFL in process and product development and in coagulation assay design and control.

During the MARP project at BPL, PFL took a major role in maintaining factor VIII production and persisted with process developments and minor products where possible. In 1983, Dr. J.K. Smith transferred from production responsibilities at BPL and became Chief Project Scientist in R & D with principal activities at PFL.

PFL production now handles such volumes of plasma required to provide sufficient starting material for process evaluation and product development. Approximately 300 kg per week of fresh plasma enters fractination: from this plasma, factor VIII and IX is routinely prepared and, on alternate weeks, factor VII anti-thrombin III and factor XIII.

The bulk of plasma deliveries to PFL are special, coming from selected donors or from new automated systems for plasmapheresis. Product which incorporates novel characteristics is specially labelled and distributed to specified physicians for fully documented use.

A full report of the development work at PFL is included in the R&D section of this Report.

To match the production at PFL, the unit is fully maintained and air-conditioning has been upgraded, new equipment provided and the production area refurbished. In relation to the available facilities at BPL, PFL remains invaluable as the only area where pilot-process development in coagulation factors can take place. Although closure is programmed during 1986, there can be no firm date until the entire functional potential of PFL can be transferred to Elstree.

It is likely that expertise at PFL will be called on to assist with training of staff and commissioning duties in relation to the new BPL productin unit and, for this purpose, resources at PFL will have to receive careful planning, attention and financing until effective closure dates are defined.

ENGINEERING REVIEW

Mr. W.I.T. Ling was appointed Chief Engineer on 2nd January 1983. His appointment has strengthened our Engineering Services and permitted important reorganisation and recruitment of additional staff.

The several maintenance workshops are now better integrated on a temporary basis in building number 11, pending authorisation of a proper facility since MARP reorganisation of production eliminated the previous engineering maintenance facility. The maintenance section remains one of several weak areas and over the next two years will need to be considerably strengthened to provide full services to the new factory and other departments on site.

The Chief Engineer has taken control of all minor capital developments on site which are not part of the main rebuilding programme. This has removed an inappropriate burden from general administration where these responsibilities had previously been held.

With the Head of Production, the Engineer has had a full commitment to the front-end design of the new BPL. That the appointment coincided with this stage of redevelopment is of critical importance in that build-up of engineering commissioning services will underwrite any success in early operations in the new BPL. Because engineering and maintenance at BPL have been weak throughout, the Chief Engineer's task is probably greater than that in other departments.

Full support of engineering resources is needed and will include proposals in 1984 for new extensions to the engineering workshops.

ADMINISTRATION

Administration functions changed in December 1982 when BPL moved from the employing authority of North West Thames RHA to that of the Central Blood Laboratories Authority. Following this move, administration which includes accounts has served a dual purpose to provide services to the Authority in appropriate areas and to the Director BPL for all administrative and financial matters relating to the management of BPL and PFL. Within this organisation, it has been possible to define lines of responsibility without creating excessive duplication of administrative effort.

Since April 1982, salary and ledger payments have been committed to computer data process and data retrieval. Staff were trained externally for this purpose and the system now operates successfully.

Stock manipulation and laboratory inventory continue to be troublesome due to incorrect programming of software for computerised

control. The problems continue to receive attention.

Increased mechanised automation will become the main challenge for administrative managers, in particular the requirements associated with the new BPL. Full advantage of computerised data handling must be taken to prevent a parallel proliferation of administrative staffing with growth in production.

INDUSTRIAL RELATIONS REVIEW

Two levels of consultation have been regularly maintained at Joint Consultative and Local Consultative levels and the process of discussuion and communication has been generally satisfactory.

In 1982/3, staff were careful to preserve the BPL interests when faced with the repercussions of industrial action in the NHS. No work time was lost, so keeping intact the excellent record of this organisation.

In the past year, frustration has continued to increase because no decision has been reached about the long-term conditions of employment for staff. The matter has been under discussion for three years, although several fully supported proposals have been issued from BPL.

Since completion of the MARP project, working conditions have changed quantitatively and qualitatively for staff and the trend is towards the standards needed to operate the new BPL successfully in 1986. These staff changes have generated grievances, based on comparability, which cannot receive a long-term solution until approved pay structure and terms and conditions are available which are appropriate to the manufacturing status of this organisation.

It is significant that local staff, management and Authority officers are in general agrement on the form of pay structure and pay-related terms and conditions needed for effective employment at BPL.

NEW BUILDING PROJECT

Following the Feasibility Study in Autumn 1981 and further additional front-end design during the latter half of 1982, a contract was signed by CBLA and Matthew Hall Norcain Engineering in 1983 to commence work on building a new production facility for BPL.

Work commenced with site clearance and grading in April 1983. The project is controlled for CBLA by a Project Control Committee headed by Mr. W. Jackson with Mr. W.P.N. Armour and Mr. S. Hibbert for the Authority, the Director BPL land Mr. G.E. Mallory as supporting members.

The progress report will be provided by the CBLA Project Manager, but some pertinent comments are appropriate in the Director's Report.

The input from BPL staff at technical, process and scientific levels during front-end design has been considerable, as expected, but a greater reliance than anticipated in areas of engineering design and specification has been placed on BPL staff following project discussions with Matthew Hall consultants. The effect has been to reduce internal management resources for existing BPL manufacturing to a bare minimum for a period of nine months following completion of MARP. In this compromised situation, effective inputs to current BPL production and to Matthew Hall have been at risk. It is felt that Matthew Hall have been inflexible in their approach to the client, which has exacerbated problems.

Within BPL it is evident that serious deficiencies exist at middle management and some senior management levels; thus it is anticipatedthat developing a full commissioning team for the new production unit, while maintaining full, secure manufacture in the old BPL, will impose great difficulties.

Resources planning and allocation for bringing the new BPL on-stream will commence in 1984 and should have reached definitive levels by the time of the next Annual Report.

MEDICINES INSPECTORATE

In the period Mr. J. Ayling, our Inspector, was promoted and a new Inspector, Mr. D. Haythornthwaite, took his place. The Inspectorate in general remained dissatisfied with the GMP status of BPL. These dissatisfactions concern the following:

1) The buildings: the MARP upgrading of the buildings was insufficient to give improvement in all areas. In fact, proper organisation of the building, upgrading of the Large Fractions area, a new reception and changing area and QC laboratory were not attempted due to cutback in available funds.

2) The QC buildings remain sub-standard despite the changes mentioned in the Report on that section.

3) Storage conditions for process and packaging materials, raw materials and final product are either not to GMP standards, or are too distant (third party based) for satisfactory supervision and control, with available manpower.

4) Documentation: continued dissatisfaction was expressed on this front although staff are moving as quickly as possible to remedy this situation. Progress would be more adequate if it were possible to strengthen our staff structure to permit more consistent work in this area. Inability to progress more quickly is a source of strong local dissatisfaction. However, significant improvements have been made as indicated in the Quality Control Section above, and further improvements are programmed.

The elements all appear in a Report of the Inspector's informal visit to BPL during the Summer 1983. A response to this Report is made available to CBLA under separate cover.

MANUFACTURING RECORDS 1982/3

Tables 1 - 4

Table 1 shows the amount of plasma feedstocks processed during the year with 1981/2 values in parantheses.

Table 2 shows the amount of products issued for clinical use in 1982/3 with previous year figures in parentheses.

N.B. Output figures are not related to quantities of plasma processed due to existence of intermediates in stock and to the length of the production process.

In spite of MARP building delays in 1982/3, modest increases in main product despatches were achieved.

Table 3 shows the products in stock at the end of the fiscal year. Most stocks were low, although some recovery had been achieved with PPF during the last quarter.

Table 4 shows the feedstock position at March 1983.

Interruptions to production during the year resulted in an excess of FFP input over processing. While it was intended to absorb this stock during the following year, it has proved difficult since input of FFP in 1983/4 has approached the current working capacity of BPL at a level of 150,000 kg.

The FFP stock represents 2.5 months supply and does contribute significantly to security in the process by allowing a proper quarantine period for late notification of hepatitis contracted by donors at about the time of blood donation. The Quality Control Department is pressing for this FFP stock to be preserved.

Time expired plasma stocks accumulate slowly. This trend is maintained to permit an adequate feedstock input into the new BPL production building to support commissioning.

TABLE 1

PRODUCTION 1982/83

Plasma Processed

Fresh Frozen Plasma (BPL)	116,890 kg			
Fresh Frozen Plasma (PFL)	14,209 kg			
FFP Total		131,099 kg	(116,228)	
Time Expired Plasma	53,791 kg			
Total Plasma Processed				184,890 kg (138,230)

PRODUCTS PASSED TO FREE STOCK	DOSE SIZE		UNITS
Plasma Protein Fraction (PPF)	100 ml		3,611
Plasma Protein Fraction (PPF)	400 ml		135,305
Salt-poor Albumin 20g%	100 ml		8,380
Albumin 10g%	2.5 ml		9,440
Normal Immunoglobulin	250 mg		99,440
	750 mg		21,510
(for use with measles vaccines)	15 mg		1,690
Normal Immunoglobulin for Intravenous use	1 mg		190
	5 mg		184
Specific Immunoglobulins			
Anti-D	250 iu		34,400
	500 iu		69,235
	2000 iu		960
Anti-HBsAg	500 mg		1,150
Anti-tetanus	250 iu		33,080
Anti-varicella-zoster	250 mg		5,000
	50 mg		440
Factor VIII (BPL)	250 iu		80,002
Factor VIII (PFL)	250 iu		8,405
		Total	88,407
Factor IX	600 iu		18,420
Fibrinogen (as reprocessed batches)	2 g		37
Accredited donor fibrinogen	180 mg		133

TABLE 2

PRODUCTS DISPATCHED FOR CLINICAL USE 1982/83

PRODUCT	DOSE	UNITS	(1981/82)
Plasma Protein Fraction (PPF)	100 ml	2,449	(2665)
Plasma Protein Fraction (PPF)	400 ml	159,987	(152793)
Salt-poor Albumin 20g%	100 ml	6,701	(6028)
Albumin 10g%	2.5 ml	5,046	(9000)
	100 ml	100	(284)
Reprecipitated Albumin	10 ml	130	
Normal Immunoglobulin	250 mg	97,600	(97595)
	750 mg	37,320	(50515)
(for use with measles)	15 mg	3,949	(1225)
Normal Immunoglobulin for Intravenous use	465 mg	229	
	600 mg	200	
	1 g	190	
	5 g	151	
Specific Immunoglobulins			
Anti-D	250 iu	36,021	(42795)
	500 iu	79,671	(68220)
	2500 iu	510	(1010)
Anti Tetanus	250 iu	33,318	(23020)
Anti-HBsAg	100 mg	4,720	(4220)
	500 mg	3,942	(5520)
Anti-varicella-zoster	50 iu	220	(470)
	250 iu	3,400	(5710)
Anti-mumps	250 mg	770	
Anti-rabies	500 iu	700	(3560)
Factor VIII	250 iu	90,594	(86101)
Factor IX	250 iu	19,324	(19835)
Thrombin	500 iu	627	(367)
	1000 iu	27	
Fibrinogen	2 g	52	
Accredited fibrinogen for Isotopic labelling	180 mg	95	

TABLE 3

PRODUCTS IN STOCK - MARCH 1983

		Units
Factor VIII	250 iu	1,756
Factor IX	600 mg	300
Fibrinogen	200 ml	7
Thrombin	500 iu	359
	1000 iu	3
Plasma Protein Fraction	100 ml	1,939
	400 ml	27,053
Salt-poor human albumin 20%	100 ml	2,544
Human albumin in saline 10%	2.5 ml	10,604
10%	100 ml	64
Reprecipitated human albumin	10 ml	160
Normal Immunoglobulin (im)	250 mg	11,350
	750 mg	9,850
Normal Immunoglobulin (iv)	1 g	26
	5 g	33
Anti-D Immunoglobulin	250 iu	13,371
	500 iu	17,909
	2,500 iu	790
Anti-rabies	500 iu	1,925
Anti-varicella/zoster	50 mg	290
	250 mg	2,510
Anti-HBs	500 mg	39
Anti-tetanus	250 iu	12,204

TABLE 4

PLASMA STOCKS - MARCH 1983

		kg
Time Expired Plasma	Beginning of month	133,570
	Into process	4,530
	Rejected	325
	Received	7,220
	End of month stock	135,570
Fresh Frozen Plasma	Beginning of month	33,733
	Into process	12,897
	Rejected	NIL
	Received	11,848
	End of month stock	32,684
Special Plasma	Beginning of month	627,1
	Into process	493,1
	Rejected	NIL
	Received	535,8
	End of month stock	669,6
Total receipts in month		19,603.8
Total into process in month		17,920.1
Total plasma stock end of month		168,923.6

MANUFACTURING RECORDS APRIL - DECEMBER 1983

Tables 5 - 7

Table 5 shows the amount of products issued for clinical use in the first nine months of 1983/4 fiscal year.

During this uninterrupted period of production following the MARP project, there are major increases in outputs of certain main product lines in keeping with targets set for the Laboratory.

Table 6 shows the feedstock position at December 31st 1983. During the time period, FFP has been fractionated at a rate slightly above input but the 1982/3 trend has been maintained.

Table 7 shows the post-MARP targets referred to above and sets down the state of current performance.

The data are satisfactory indicating a balance between plasma input and processing at the rate required. Factor VIII and PPF outputs have passed targets.

TABLE 5

PRODUCTS DISPATCHED FOR CLINICAL USE APRIL - DECEMBER 1983

PRODUCT	DOSE	
Plasma Protein Fraction (PPF)	100 ml	5,100
Plasma Protein Fraction (PPF)	400 ml	176,952
Salt-poor Albumin 20g%	100 ml	8,590
Albumin 10g%	2.5 ml	4,806
	100 ml	103
Reprecipitated Albumin	10 ml	165
Normal Immunoglobulin	250 mg	70,200
	750 mg	28,325
(for use with measles)	15 mg	2,192
Normal Immunoglobulin for Intravenous use	465 mg	0
	600 mg	0
	1 g	474
	5 g	505
Specific Immunoglobulins		
Anti-D	250 iu	32,510
	500 iu	69,890
	2500 iu	402
Anti Tetanus	250 iu	30,318
Anti-HBsAg	100 mg	0
	500 mg	1,584
Anti-varicella-zoster	50 iu	390
	250 iu	3,362
Anti-mumps	250 mg	0
Anti-rabies	500 iu	300
Factor VIII	250 iu	108,308
Factor IX	250 iu	16,842
Thrombin	500 iu	317
	1000 iu	0
Fibrinogen	2 g	7
Accredited fibrinogen for Isotopic labelling	180 mg	50

TABLE 6

PLASMA STOCKS - DECEMBER 1983

		kg
Time Expired Plasma	Beginning of month	159,140
	Into process	0
	Rejected	0
	Received	3,865
	End of month stock	163,005
Fresh Frozen Plasma	Beginning of month	28,227
	Into process	10,882
	Rejected	48
	Received	12,655
	End of month stock	29,952
Special Plasma	Beginning of month	942
	Into process	436
	Rejected	0
	Received	380
	End of month stock	886
Total receipts in month		16,900
Total into process in month		11,318
Total plasma stock end of month		193,843

TABLE 7

MANUFACTURING TARGETS 1983/4

	Annual	Per Month	Third Quarter
FFP receipts	150,000 kg	121,500 kg	112,500 kg
Factor VIII	30×10^6 iu	2.5×10^6 iu	22.5×10^6 iu
Albumin/PPF 400 ml	170,000 units	14,166 units	127,494 units

PERFORMANCE

	November	December	Third Quarter
FFP received	12,655 kg	12,121 kg	110,169 kg
FFP processed	10,882 kg	13,277 kg	113,620 kg
Factor VIII (245 iu)	2.25×10^6 iu	3.8×10^6 iu	23.83×10^6 iu
FFP (400 ml)	15,160 units	18,210 units	164,262 units

FINANCIAL STATEMENTS 1982/3

Tables 8 - 10

Table 8 shows the notional and actual income of BPL during the year and values processed plasma on-cost at market rates. Products are priced at a very competitive rate, i.e. about 30% below mean commercial rates across the whole product range. Therefore, no products are priced above existing market prices for that product, while some products are considerably reduced in price on their market counterpart. The pricing strategy reflects the fact that only some listed products have commercial competion in the U.K.

Normal value of the released products for 1982/3 was £9.7M with stocks rated at £1.9M.

Plasma on-cost was valued at £3.6M and BPL revenue and capital expenditure for the year can be seen in Tables 9 and 10.

Sales of BPL RIA tests for hepatitis B markers made £.494M.

Tables 9 and 10 show the revenue and capital outturns for 1982/3. Expenditure was retained with cash limits.

Revenue expenditure for BPL and PFL was £3.07M.

Capital expenditure of £.898M on completion of the MARP project raised the final cost of this refurbishment to approximately £2.5M against an original cash limit of £1.3M.

TABLE 8

PRODUCTS ISSUED AND IN-STOCK:

NOTIONAL AND ACTUAL INCOME - MARCH 1983:

APRIL - MARCH 1982/83

PRODUCTS ISSUED	MARCH 1983 £K	APRIL-MARCH 1982/83
PPF/Albumin	305	3,736
Factor VIII	192	1,534
Factor IX	145	1,155
Normal Ig (im)	42	522
Normal Ig (iv)	5	24
Specific Ig (Anti-D)	139	1,629
Other Products	119	1,108
	947	9,708
INCOME FROM SALES		
BPL RIA test for HBsAg	52	494
Supplies to Amersham International		33
Royalties	-	-
PRODUCTS IN STOCK (March 31st)		1,895
PLASMA VOLUME PROCESSED		
FFP (Recovered plasma human)	117	2,925
TEP	47.2	684
Shelf price of plasma fractionated:		3,609

TABLE 9

BPL/PFL REVENUE OUTTURN 1982/83

Expenditure:-	BPL £	PFL £	TOTAL £
Staff Costs (salaries and employees N.I. and Sup'n contributions)	1,325,958	186,387	1,512,445
Non Staff Costs, Staff expenses (Incl. Transport, Canteen, Travelling and Subsistence etc.)	77,655	3,355	81,010
General supplies	733,574	65,183	798,757
Overheads (Rates, Oil, Electricity, Machinery M'tance Cleaning)	510,521	33,788	544,309
Admin RHA. Rent OAHA etc etc	10,500	3,000	13,500
Equipment Purchases	293,031	46,557	339,588
Building & Estate M'tance	77,136	7,555	84,691
V.A.T.	189,064	18,817	207,881
	3,217,439	364,742	3,582,181
Cash limit (revised)	3,092,000	347,000	3,439,000
Receipts			
Rents	16,963	-	16,963
Grants & Services	41,598	-	41,598
Sundries	9	44	976
RIA Tests	404,690	-	404,690
Sales of Products	51,337	-	51,337
	515,520	44	515,564
Net Revenue Outturn	2,701,919	364,698	3,066,617

BPL CAPITAL EXPENDITURE OUTTURN 1982/83

B.P.L.	Contract £	Equipment £	Sundries £	Fees £	Total £
Large Fractions MARP 01	466,195	69,471	3,565	43,894	583,125
C.F. Lab. Reconstr.	26,625	99,550	3,791	25,441	155,407
C.F. Lab Re-Roofing	4,993	-	-	-	4,993
C.F. Lab Modular Cold Store	-	-	-	2,125	2,125
Pyrogen Free Water	13,134	6,396	205	5,168	24,903
New Hepatitis Lab	2,085	-	-	333	2,418
Glycol Cooling	1,392	-	-	3,211	4,603
Virology Centrifuge	-	71	-	495	566
Cottages Upgrading	1,563	-	-	-	1,563
Fulton Boiler Replacement	-	-	881	2,068	2,949
Computer Installation	-	274	5,492	-	5,766
Technical Services Equipment	-	12,012	-	-	12,012
Vaccine Lymph Bldg	46,800	-	-	-	46,800
Freeze Dryers & W'shop Improv.	-	-	-	328	328
	562,787	187,774	13,934	83,063	847,558
V.A.T.					36,720
					884,278
N.W.T. R.W.O. Fees					14,530
				TOTAL	898,808
				Cash Limit	941,000

New Laboratory Project Preliminary Expenses	253,080	
V.A.T.	22,735	275,815
Cash Limit		320,000

P.F.L. CAPITAL EXPENDITURE OUTTURN

Equipment	-	4,280	-	-	4,280
Air Conditioning Prep. Area	4,659	6,268	869	-	11,796
	4,659	10,548	869	-	16,076
V.A.T.					947
				TOTAL	17,023
				Cash Limit	34,000

Financial Statements April - December 1983

Tables 11 - 14

Table 11 shows the notional and actual income of BPL during the nine months period. The basis for presentation is the same as that used for data shown in Table 8; thus the two Tables are comparable.

Notional value of the released products is £9.2M which is 25% greater than in the equivalent period of the previous year. Stock values have risen to £3.05M.

Plamsa on-cost is valued at £3.07M and BPL revenue and capital expenditure is shown in Table 12.

Sales of BPL RIA tests has reached £.45M and other product sales are £.1M. The composition of these other product sales is shown in Table 14.

Table 12 shows revenue and capital outturn for the first three quarters of 1983/4 fiscal year. Revenue expenditure has reached £2.79M with minor capital expenditure at £.1M. Cash limits are raised as indicated following meetings between CBLA, DHSS and Ministers in November 1983.

Table 13 shows budget expenditure presented in the more useful format of fixed and variable costs of manufacturing at BPL.

Variable costs of manufacturing are 74.5% of budget.

The fixed on-costs of Research and Development represent 3.5% of the budgetted expenditure. This level is considered to be undesirably low if a secure technology-based manufacturing process is to be guaranteed.

Table 14 shows an anlysis of product sales in the nine month time period.

Sales to the MoD will need to be renegotiated in 1984/5 since the Army Blood Supply Depot is now making a significant contribution of FFP into production.

PRODUCTS ISSUED AND IN-STOCK

NOTIONAL AND ACTUAL INCOME - APRIL-DECEMBER 1983

PRODUCTS ISSUED	OCTOBER £K	NOVEMBER £K	DECEMBER £K	APRIL/DECEMBER £K
PPF/Albumin	471	371	449	3 870
Factor VIII	278	166	281	1 789
Factor IX	105	124	205	1 011
Normal Ig (im)	43	37	48	385
Normal Ig (iv)	0	0	0	66
Specific Ig (Anti-D)	149	150	162	1 336
Other Products	85	98	68	778
	1 131	946	1 213	9 235

INCOME FROM SALES				
BPL RIA Test	49	52	49	451
Amersham International	3	3	3	33
Others	0	0	0	65
Royalties	0	0	0	0

PRODUCTS IN STOCK	2 871		3 049 (Dec. 31st)	

PLASMA PROCESSED (COST £K)				
FFP	285	332	272	2 846
TEP	41	13	0	227
				3 073

BPL/PFL EXPENDITURE & INCOME FOR 9 MONTHS APRIL-DECEMBER 1983 COMPARED WITH BUDGET PROVISIONS

		BPL	PFL	TOTAL
		£	£	£
Revenue				
Salaries etc.		1 194 039	170 581	1 364 620
Staff Expenses		104 625	1 788	106 413
Lab Supplies		654 518	59 857	714 375
Overheads		263 524	8 774	272 298
Equipment		95 173	14 924	110 097
Buildings & Estate		47 795	2 453	50 248
VAT		98 860	12 287	111 147
		2 458 534	270 664	2 729 198
Creditors				
Rates (proportion)		52 875	-	52 875
Rent (proportion)		-	10 575	10 575
Revenue Exp 9 mths		2 511 409	281 239	2 792 648
Cash Limit and retained income for 9 months	old =	2 529 000	299 250	2 828 250
	new =	2 805 000	330 000	3 135 000
Capital				
New Lab Project		2 359 402	-	2 359 402
Cash Limit 9 mths	old =	4 457 925	-	4 457 925
	new =	3 750 000		3 750 000
Other Capital Expenditure		85 451	15 180	100 631
Cash Limit 9 mths	old =	256 500	31 500	288 000
	new =	259 500	42 750	302 250
Receipts				
Rents		8 006	-	8 006
Sales of Products		98 367	-	98 367
Sales of RIA Tests		419 520	-	419 520
Sundries		2 188	-	2 188
WHO Grant		-	-	-
Sale of Services		-	-	-
Grants R & D		2 532	-	2 532
Receipts 9 months		530 613	-	530 613

STATEMENT OF SPENDING AGAINST BUDGET
PERIOD APRIL - DECEMBER 1983 - 9 MONTHS

Revenue

82/3 £	BPL & PFL	83/4 £	£	%
	1. Variable Costs			
822 967	Salaries and Employers NI & Supn	998 110		
677 813	Supplies	795 628		
170 956	Overheads	187 739		
28 686	Staff Expenses (proportion)	53 206		
100 869	VAT	92 034		
			2 126 717	74.5
	2. Fixed Costs			
235 179	Salaries and Employers NI & Supn	285 229		
9 959	Supplies	11 690		
134 777	Overheads	148 009		
18 128	VAT	16 540		
20 759	Building & Estate - M'tnce & Improv	50 248		
28 686	Staff Expenses (proportion)	53 206		
			564 922	19.8
101 664	3. Research & Development		101 009	3.5
6 470	4. CBLA HQ		61 570	2.2
2 356 913			2 854 218	100.0
2 609 000	Budget Provision (Cash Limit)	old =	2 895 250	
		new =	3 214 000	
	Receipts			
321 690	RIA Test Kits	419 520		
-	Sale of Products	98 367		
30 670	Other Income	12 726		
352 360		530 613		

ANALYSIS OF PRODUCT SALES APRIL - NOVEMBER, 1983

Product Analysis	£
PPF 400 ml & 100 ml	14 742
Salt poor albumin	7 940
10 G% albumin sol. 100 ml	1 075
Normal Immunoglobulin	28 322
S.F. products	4 290
Factor IX	10 102
Fibrinogen for Isotope Labelling	27 984
Reprecipitated albumin	4 007
Whole plasma	84
	98 546
Less credit for 82/3 overcharge to MOD	7 080
	91 466

Customer Analysis	
MOD	47 366
Amersham International	33 150
British Airways	4 400
Belfast R. Vict. Hospital	12 092
Other	1 538
	98 546

RESEARCH AND DEVELOPMENT

Contents

Mechanical thawing of FFP for cryoprecipitate

An electrically heated vessel, equipped with a powerful motor driving a helical mixing blade, has been constructed by Technical Services Group and was commissioned early in 1983. It has been successful almost immediately in achieving factor VIII yields at least as good as those obtained by manual thawing, in reducing unpleasant and potentially hazardous manual stirring, and in liberating about 10 man days per week for more illuminating work. Its use has now become routine. Work on design and construction of crushing equipment has been deferred since it may be unnecessary for this mode of thawing.

Special Plasmas

Haemonetics plasma in PVC packs is received from Leeds and the Bradford model plasmapheresis centre, and 150-300 kg pools fractionated every few weeks. Variations have included FFP recovered from Haemonetics platelet concentrate, and the use of a new polyolefin pack which can be opened without liquid nitrogen. All of these innovations are, or promise to be, very successful. A small amount of Haemonetics plasma and conventional plasmapheresis plasma from Oxford RTC has also been fractionated. Mersey and South Thames RTCs are starting Haemonetics programmes and the first plasma has been received for small-pool fractionation. Plasma continuously pheresed by filtration rather than centrifugation will shortly be collected in other RTCs for fractionation.

Heparin plasma

Parallel collections of blood from the same donor into citrate and heparin anticoagulants have continued with the assistance of Oxford and Yorkshire RTCs, and the separated plasma subjected to cryoprecipitation at PFL. Results so far suggest that, under any blood collection system feasible in most English RTCs, the substitution of heparin for citrate anticoagulant will not provide significantly increased recovery of factor VIII in cryoprecipitate, and that there are serious obstacles to the use of heparin as a primary anticoagulant in the RTCs.

Factor VII

Production has been scaled up to 300 kg plasma equivalent in one run each fortnight. Fraction I-C is now removed routinely before recovery of factor IX and factor VII, in order to minimise contamination of factor VII with fibrinogen. Progress has been made in controlling contamination of factor VII with the coloured protein caeruloplasmin, by a programme of variations in the content and volume of wash buffer.

The increased emphasis on factor VII production reflects a wish to build up stocks for direct clinical use and prepare for attempts to make a factor VIIa concentrate for patients with inhibitors of factor VIII.

Factors II IX and X

The routine use of Haemonetics plasma and the introduction of new column-monitoring equipment prompted a re-examination of the resolution of factor IX from undesired activated factors. This has resulted in valuable insights into the existing chromatographic separation and very substantial improvements in the process which may, moreover, be generally applicable to other concentrates prepared in a similar way.

Fraction I/Factor XIII/Fibrinogen

Fraction I-C is now recovered in alternate weeks from 300 kg cryosupernatant, primarily as a source of factor XIII but also to assess more closely its value as a source of fibrinogen.

The problems encountered last year in pasteurising factor XIII concentrate have been overcome by using new heat-protective agents and recovery of the pasteurised protein has been improved by establishing our first use of ultra-filtration. The variable appearance of PKA activity during processing has been controlled by a novel adsorption process which may have wider application to other products. The method has now passed into routine production, giving a yield of approximately 100 (plasma) units of factor XIII per kg plasma from an essentially 'waste' fraction. Agreement has been reached on clinical trials to start early in 1984.

Further sets of reference materials, this time including concentrates, have been prepared at PFL and circulated at the request of the Factor XIII sub-committee of ISTH.

Fibronectin

Work has continued on recovery of Fibronectin from 'waste' cold precipitate from the factor VIII process. A stable, freeze-dried concentrate, soluble at 10 mg/ml has been developed and appears to be safe for human infusion, but there is no consensus that in vitro assays of biological activity will predict a valuable function in replacement therapy, e.g. in burns, trauma or septicaemia. Perfection of a clinical concentrate and the addition of pasteurisation stage have therefore been deferred but the production of a 'technical' grade of fibronectin for laboratory and industrial use has been pursued.

Two grades of fibronectin have been developed as laboratory reagents. The first is prepared by a precipitation method at >90% purity. The second is purified by affinity chromatography to electrophoretic homogeneity. Both reagents have been used successfully as cell-attachment and cell-migration factors in the growth of mammalian cells in serum-free medium.

In conjunction with the process development, a range of tests has been set up to assess the quality of the fibronectin, including polyacrylamide gel electrophoresis, immunoelectrophoresis and agarose gel electrophoresis. Quantitation is by rocket immunoelectrophoresis; the effect of plasmin, trypsin and heparin addition to fibronectin samples has been studied using this assay. A solid phase, enzyme-linked gelatin binding assay is being adopted and characterised in pursuit of a routine BPL assay for fibronectin.

HPLC is being used to identify degradation products in complex mixtures of proteins. Direct applications of fibronectin fragments, in diagnostics and in therapeutics, are being investigated. This involves the development of assays for binding activity and the isolation of fibronectin fragments.

Fibrinogen

The selective recovery of fibronectin from cold precipitate leads readily to a fraction depleted of fibronectin and rich in fibrinogen. This fraction has been refined as a source of fibrinogen for clinical use, since it appears to be soluble at higher concentrations and may be less denatured than some alternative preparations from Cohn Fraction I. The yield is approximately 200 mg fibrinogen per kg plasma, from a 'waste' fraction, and it is expected to be adequate to meet the reduced but persistent clinical demand for fibrinogen concentrates. Several batches of the new product, in vials containing approximately 500mg fibrinogen, have been released for clinical use. Six

batches have now been used in six patients with excellent tolerance, the expected range of recoveries and half-lives, and no sign of transmitting hepatitis.

The use of HPLC for FPA assay and two dimensional electrophoresis, with and without immunological detection methods, for fibrinogen chain and degradation product anaylsis has been explored, but has yet to be used on a routine basis. The development of analytical crosslinking tests to examine the quality of fibrinogen continues and has been applied to preparations from BPL and PFL. There were no apparent differences in crosslinking, however, quantitative differences in the levels of plasminogen, fibronectin and fibrinopeptide A have been observed for the different preparations.

Antithrombin III/Factor XI

A potent, pasteurised concentrate of AT III is now in routine production, from approximately 400 kg Factor IX supernatant in alternate weeks, and yielding approximately 300 (plasma) units per kg plasma. There is considerable interest in clinical trial for congenital deficiency and various acquired deficiencies of this protein.

In support of larger scale production, optimal conditions for synthesis of the heparin-Sepharose affinity reagent have been extended to at least two litre batches with new equipment.

Before pasteurisation, Antithrombin III concentrate fortuitously contains Factor XI activity. Some batches retaining this activity have been prepared to treat congenital deficiency of Factor XI, for which alternative concentrates are no longer easily available.

Factor VIII

A pilot study has been started, aimed at combining Alhydrogel adsorption and cold precipitation in the Factor VIII process, currently involving two long sedimentations in expensive and inappropriate centrifuges, and substituting a single in-line filtration. Results are promising and the effects of this possible variation on the recovery of fibronectin and fibrinogen will continue to be assessed.

Work has continued on the project concerning fibrinogen in Factor VIII concentrates especially with regard to evidence of destructive enzymic activity. 2D-immunoelectrophoresis has been used to analyse concentrates and their intermediates for fibrinogen degradation products. Results suggest that some proteolysis does occur, probably before or during the initial cryoprecipitation steps. The effect of fibrinopeptide A (FPA) and fibronectin in factor VIII concentrate on end product solubility and pyrogencity has also been investigated. High FPA levels are found in pyrogenic samples; but there is no one point in the production process that causes a significant increase in FPA levels. Cross reactivity with the FPA antibody led to the investigation of HPLC as an assay method, currently insufficient sensitivity prevents its adoption in routine screening tests. Initial results suggested that poor solubility may be related to high fibronectin levels when expressed as a percentage of the total protein content. Analysis of a wider sample volume suggests that this may only be one of several contributing factors. The fibronectin contamination of intermediate purity factor VIII can be removed using gelatin-Sepharose, but at the expense of diluting the factor VIII.

Inactivation of Hepatitis viruses in Coagulation Factor Concentrates

Reference has already been made to the pasteurisation of Antithrombin III and Factor XIII concentrates.

NHS concentrates of Factor VIII and Factor IX continue to transmit Non A, Non B hepatitis to susceptible patients (usually those receiving large-pool concentrates for the first time) and there is considerable interest in the possible transmission of Acquired Immune Deficiency Syndrome through intravenous concentrates. Ways of reducing the transmission of viral diseases have been extensively reviewed and programmes started with the aim of reducing or removing infectivity by heating under the protection of amino-acids and sugars.

So far, it seems likely that Factor IX, II and X can be pasteurised with less than 50% reduction in overall yield, but these observations have to be confirmed on a larger scale before clinical trials of reduced infectivity. Factor VIII and fibrinogen present more problems but progress has been encouraging. The protective agents have been suggested by Protein Fractionation Centre in Edinburgh, and close liaison is maintained with their independent efforts.

Meanwhile, conditions have been established for heating concentrates in the dry state and trial of these products is expected to precede that of concentrates heated in solution.

Thrombin

A new preparation of more highly purified thrombin has been made by venom inactivation of factor II, IX, X concentrates rejected from clinical use. The new concentrate promises to be extremely potent and stable. It can be made from a pasteurised source for clinical applications but the major use is expected to be as a laboratory or research reagent. Alternative activation systems are being investigated to achieve an even greater degree of homogeneity.

Albumin

Studies on the interaction of Albumin with Cibacron blue-Sepharose have shown that the adsorbent capacity is dependent on the interelationship of pH, ionic strength and immobilised ligand concentration. Cibacron blue has been purified by organic solvent extraction, contaminating dyes could not be immobilised to agarose with the established coupling regime.

Four Cibacron blue samples have been tested for mutagenic potential by Dr.J.M.Parry, University College Swansea. The negative results obtained in this study have encouraged the continued use of this adsorbent. To proceed to animal toxicity studies the capacity and binding strength of Cibacron blue-Sepharose for 17 animal albumins has been compared to the human albumin values; results suggest the use of the following test animals; rat, rabbit and marmoset. Human and rabbit albumins prepared by affinity chromatography were isotopically labelled and injected into rabbits as part of the study on clearance rates. No toxic effects were found and clearance from the rabbits was normal when compared with monomeric albumin prepared from PPF samples supplied by BPL, PFC and Travenol. The study also demonstrated that high M.W. contaminants of PPF, probably albumin aggregates, were cleared more rapidly than monomeric albumin.

Work has continued on the development of Cibacron-affinity purified albumin as a serological reagent. The pilot-scale production of albumin has been streamlined using a new column and microcomputer based process control. All batches from the pilot-scale system tested at Brentwood RTC have good red cell agglutination enhancement properties. Washings from out-dated red cells, supplied by Brentwood RTC, have been investigated as an alternative source of albumin. Despite early problems with the purity of the albumin prepared from this source, results are encouraging and serological performance is excellent.

Detailed investigation of the factors influencing the performance of albumin as an agglutination enhancement reagent have continued. BPL human albumin has been compared with conventional BSA in manual serology at Brentwood RTC and in the autoanalysers at Manchester RTC and BGRL. Parameters studied include fatty acid content concentration, ionic strength, polymer content and batch variation. Polymer content of the current reagent is low and a second reagent is now being developed with enhanced polymer content. Three aggregating techniques are currently being reviewed, chemical cross-linking, heat-treatment and alkali treatment. All three are characterised by the production of over-reactive albumin species. The final albumin reagent will contain minimal amounts of this species. The significance of albumin bound fatty acids in serology is being investigated using conventional defatting techniques and a new chromatographic process.

The international working party on albumin reagents reported in June 1982. Although the BPL affinity purified albumin preparations were satisfactory, the results were, in many respects, equivocal and implied that human albumin (BPL) behaved in a different way to bovine albumin (commercial). Further samples have been supplied for the 1983 trial.

Development has continued on the multi-element column (MEC) of Cibacron blue-Sepharose for the recovery of albumin from pathological plasma. A full scale prototype, capable of recovering albumin from a typical programme of therapeutic plasmapheresis, has been designed and is under construction. Samples of pathological plasma have been tested for suitability on Cibacron blue-Sepharose.

α -1-Antitrypsin

Alternative source materials for α_1-AT have been investigated; no significant difference was found between Kistler and Nitschmann fraction IV paste and Cohn fractions IV-1 and IV-4 with respect to the α_1-AT content. The removal of large plasma proteins, especially lipoproteins, from Cohn Fraction IV has been investigated. α_1-AT recovery from ultrafiltration experiments was poor, however, current studies on the use of Aerosil are promising. The weak interaction of α_1-AT with Cibacron blue-Sepharose has been investigated at different ligand substitutions with a variety of matrices. Both parameters having an apparent effect on protein recovery, as does the ionic strength of the application buffer. Zinc-chelate chromatography of α_1-AT was investigated without success, however, the presence of zinc increased the affinity of α_1-AT for Cibacron blue-Sepharose, but with poor recoveries. If α_1-AT recovery could be improved this would provide a useful tool in the purification regime.

LAL endotoxin assay

The LAL clot assay for the detection of endotoxins has been investigated as an alternative to the rabbit pyrogen quality control test. The tube and microgelation methods validate for water and albumin products, but not for coagulation factors. Test failures observed with the more economic microgelation method have been investigated and reasons established.

An alternative microtitre plate assay using a chromogenic peptide substrate has been developed. Parameters for a statistically valid assay have been established for albumin (PPF). Anomalous results, on comparison with the clot method and the sensitivity threshold for the rabbit, are being investigated.

Additional Projects

(a) Investigations have begun on the potential of the affinity adsorbent albumin-Procion blue-Sepharose. We have found that pyrogenic endotoxins can be selectively removed from intermediate purity factor VIII on this

adsorbent. In addition hepatitis B surface antigen, in factor VIII concentrate, can be selectively adsorbed by Procion blue-Sepharose or by albumin-Procion blue-Sepharose.

(b) The programme on protein distribution during plasma fractionation has been completed. Some 40 samples, products and waste fractions, have been assayed for 25 plasma proteins. The results of this study have been compiled for distribution and assessment with the production units. The programme on the utilisation of waste fractions in the development of a substitute for animal sera in cell culture has been shelved due to lack of resources.

(c) The preparation of magnetic microspheres for use in the batch production of albumin from fraction IV is being investigated, in an attempt to eliminate the problems associated with the filtration of this source material. Small batches of magnetic affinity gels have been prepared; albumin binding capacity is equivalent to non-magnetic counterparts.

(d) The interaction of plasma proteins with Cibacron blue-Sepharose has been investigated using albumin-depleted source material. Using a competetive albumin gradient the proteins were eluted as follows; orosomucoid, prealbumin, α-1-antitrypsin, haptoglobulin, α_2HS glycoprotein, Gc globulin, caeruloplasmin, IgA, transferrin, ATIII, IgG and haemopexin.

(e) The purification of Factor VIII by ion-exchange chromatography has been investigated. Model studies, using Cytodex microcarriers, indicate that the substitution level of the ion-exchange matrix has considerable bearing on the recovery of factor VIII. Problems with in-process clotting have been overcome, current work is aimed at preventing non-specific protein adsorption.

(f) In collaboration with Dr.M.Preece, Institute of Child Health, we are investigating the fractionation of somatomedin C from Cohn Fraction IV, during the purification of albumin on Cibacron blue-Sepharose. The bound state of somatomedin C is being investigated by gel filtration chromatography and ultrafiltration technology.

(g) Transferrin, for Edgware RTC, has been prepared from albumin-depleted Cohn Fraction IV by ion exchange chromatography. The preparation appeared pure by HPLC, although immunoelectrophoresis indicated contamination with γ-globulin.

Personnel and Department

In the past year the structure and composition of the R & D department has changed to meet the terms of reference established for the department by the CBLA. The Oxford laboratory (PFL) has been organised as a pilot production laboratory contributing conventional clinical products and intermediate fractions to BPL stocks, and using the same source plasma for the evaluation of new process technology or the development of new products for clinical trial. Dr.J.K.Smith has been appointed to the position of Chief Project Scientist (R & D), being responsible for all routine and development production at PFL. This move has been accompanied by the transfer of Mrs.L.Winkelman (PFL) and Miss.R.Baker (BPL) to the R & D staff. Dr.P.Feldman joined the staff at PFL to work on vitamin K-dependent proteins, including the prothrombin complex of coagulation factors. Dr.L.Singleton has recently been appointed to the position of Senior Scientist (BPL) in charge of the Toxicology Unit; to include a collaborative study with Quality Control department on the use of the Limulus assay for the detection of pyrogens. Mr.S.Price has joined the technical staff, being responsible to Dr.R.A.Brown for the development of a large-scale system for the chromatographic separation of albumin. There have been no other staff changes in the year.

Conversion of the R & D wing has been completed to give three new laboratories, a central instrument room, a radioisotope laboratory, and a modernised cold room.

Collaboration in progress with outside laboratories

Scientist	Institute	Interest and aims
Drs. Schor	Christie Hospital, Manchester	Fibronectin in cell culture
Dr. Webster	CRC, Northwick Park	Fibronectin : opsonic function and mycoplasma
Dr. Lever	" " "	Fibronectin and Haemophilus
Dr. Heath	Dept. Zoology, Oxford University	Fibronectin in cell culture
" "	" "	Somatomedin-like growth factors (common interest only)
Dr.F.Barrelle	Dunn School of Pathol. Oxford University	genetic engineering of fibronectin ("consultative")
Drs. Melamed & Hughes-Jones	ARC, Cambridge	Transferrin for cell culture
Dr. Gordon	Dunn School of Pathol.	Fibronectin for cell culture
Dr.J.Hall	Chester Beatty, Sutton	Fibronectin as an opsonic agent with monocytes
R.Kirkham	Brentwood RTC	Serological albumin from red cell washings
K.Macdonald	" "	Serological albumin-testing
Drs. Gunson & P.Howell	Manchester RTC	Serological albumin as an auto analysis reagent
Dr. Fogg	Sheffield RTC	Serological albumin, substitute for BSA
Dr.M.J.King	BGRL	Development of serological albumin-polymer content
Dr.V.Anyoku	St. Mary's Hospital Paddington	Use of human albumin in RIA
Dr. Preece	Institute of Child Health	Somatomedins and fraction IV
Dr. Lockwood	Hammersmith Hospital	Recovery of albumin from pathological plasma
Dr. Kumar	Christie Hospital, Manchester	Fibronectin in leukaemia

Representation at International Meetings

Dr.J.K.Smith, 24th April 1982, Speywood Symposium on Factor VIII, Uberlingen. (JKS invited discussant).

Dr.J.K.Smith, L.Winkelman, 16-17th July 1982, First International Conference on Factor XIII and Fibronectin, Marburg. (JKS & LW Speakers).

Dr.J.K.Smith, Dr.T.J.Snape, 27-30th July 1982, International Committee on Thrombosis and Haemostasis, Bergamo.

Dr.R.S.Lane, Dr.M.J.Harvey, 1-7th August 1982, International Congress ISH-ISBT, Budapest.

Dr.J.K.Smith, 7-9th October 1982, Symposium on Factor VIII/vWF, San Diego.

Mr.G.E.Mallory, Mr.K.Kinnarney, Mr.L.Vallet, 12-14th October 1982, Edwards 5th International Freeze Drying Symposium, Chesham, Bucks.

Dr.R.S.Lane, 6-11th November 1982, Annual Meeting of American Association of Blood Banks, California.

Mr.L.Vallet, 15-18th November 1982, WHO/IABS Symposium on Hepatitis, Athens.

Dr.M.L.Kavanagh, Mr.L.Vallet, 4-5th April 1983, Center for Blood Research: "Immunoglobulins - Genes, Receptors, Therapy". Boston, Mass.

Dr.J.K.Smith, 6-9th June 1983, American Blood Resources Association meeting, Arlington, USA.

Dr.T.J.Snape, Dr.J.K.Smith, Dr.R.Brown, 1-9th July 1983, International Congress on Thrombosis and Haemostasis, Stockholm.

Mrs.D.K.Harvey, 8-11th July 1983, International Congress on Thrombosis and Haemostasis, Stockholm.

Dr.R.S.Lane, 24th October - 4th November 1983, Annual Meeting of American Association of Blood Banks, New York.

Mr.L.Vallet, 27th November - 4th December 1983, WHO Int. Soc. Biol. Standardisation, Geneva.

Mr.G.Sims, 5-8th December 1983, Netherlands Red Cross: Workshop on detection of vasoactive side effects of plasma components, Amsterdam.

Representation at National Meetings

Dr.M.L.Kavanagh, Dr.R.S.Lane, Mr.L.Vallet, 6th May 1982, PHLS Technical Discussion Session "Update on Immunisation", Colindale. (L.Vallet Speaker).

Dr.R.S.Lane, Dr.J.K.Smith, 11th May 1982, Fourth annual Fenwal Symposium: "Trends in Transfusion", Cambridge.

Mr.L.Vallet, 23rd June 1982, Institute of Physics: "Aspects of Freeze Drying", Imperial College, London.

Dr.M.L.Kavanagh, Mr.L.Vallet, 22-23rd July 1982, British Society for Immunology. Summer Meeting, Nottingham University.

Mrs.J.Rott, Mr.C.McFarland, Mrs.D.Harvey, July 1983, Anachem course on protein HPLC.

Dr.R.A.Brown, 10th September 1983, Immunotechnology and Industry, Birmingham University.
Mr.L.Vallet, 5-6th October 1982, Institute of Chemical Engineers: "Bio-processing in the Eighties", Southampton.

Dr.R.A.Brown, 16th November 1982, LKB Seminar on "HPLC of Proteins", London.

Dr.R.A.Brown, 24th January 1983, Royal College of Pathologists seminar: "Vinyl Chloride and Liver Disease".

Dr.J.K.Smith, 11th February 1983, SNBTS Meeting on Procurement of FFP, Edinburgh.

Dr.R.S.Lane, 6th April 1983, British Burn Association Symposium, Newcastle.

Dr.R.S.Lane, 17-18th May 1983, Fifth annual Fenwal Symposium, Cambridge. (Dr.R.S.Lane Speaker).

Dr.R.S.Lane, 6th October 1983, Burns Symposium, Royal Society of Medicine, London.

Dr.J.K.Smith, 25th October 1983, Millipore/Waters Symposium on Separation Technologies for Biotechnology, London.

Dr.M.L.Kavanagh, Dr.T.J.Snape, Mr.L.Vallet, Mr.E.D.Wesley, Mr.N.Pettet, 28th October 1983, Pharmaceutical Society of GB: "Natural blood products and synthetic substitutes". Paper "Production of different blood products" given by N.Pettet, London.

Mrs.G.Cotton, Miss.R.Baker, 30th November 1983, Waters course on protein HPLC, Harrow.

Mr.S.Price, December 1983, Biochem. Soc. Meeting on Preparative Scale Chromatography and Electrophoresis.

Dr.M.J.Harvey, Dr.R.Brown, December 1983, British Blood Transfusion Society, Cambridge.

COMMITTEES

Dr.R.S.Lane served on the Biologicals Sub-Committee of the Committee on Safety of Medicines.

Dr.R.S.Lane, Dr.T.J.Snape and Mr.L.Vallet served on Committee K (Blood Products) of the British Pharmacopoeia Commission.

Mr.L.Vallet attended meetings of Group 6B (Blood and Blood Products) of the European Pharmacopoeia Commission (Strasbourg) as a consultant.

Dr.J.K.Smith was a member of Dr.H.H.Gunson's Working Party on Self-Sufficiency in Plasma Supply.

Publications

Robinson A.E., Penny A.F., Smith J., D.L. Tovey. Pilot study for large-scale plasma procurement using automated plasmpheresis. Vox Sanguinis 44; 143-150 (1983).

Austen D.E.G. and Smith J.K., Factor VIII Fractionation on Aminohexyl Sepharose with possible reduction in Hepatitis B antigen. Thrombosis and Haemostasis, 44; 46-48, (1982).

Winkleman L. Antithrombin III-binding capacity of Heparin-Sepharose as a function of activation temperature and duration. Thrombosis Research 29; 383-386 (1983).

Smith J.K. and Winkleman L. "A concentrate of factor XIII from Human Plasma", in "Factor XIII and Fibronectin - new clinical and biological approaches". Editors Egbring R and Klingemann, H.G., Die Medizinische Verlaggesellschaft, Marburg, 1983.

Winkelman, L., Smith J.K., Norman E. "Fibronectin as a by-product of large-scale factor VIII production", in "Factor XIII and Fibronectin - new clinical and biological approaches". Editors Egbring R. and Klingemann, H.G., Die Medizinische Verlaggesellschaft, Marburg, 1983.

Atkinson, A., Hammond, P.M., Hartwell, R.D., Hughes, P., Scawen, M.D., Sherwood, R.F., Small, D.A.P., Bruton, C.J., Harvey. M.J., and Lowe, C.R., Triazine-dye affinity chromatography, Biochem. Soc. Trans. 9, 290-293, 1981.

Scawen, M.D., Derbyshire, J., Harvey, M.J., and Atkinson, A. The rapid purification of 3-hydroxybutyrate dehydrogenase and malate dehydrogenase on triazine dye affinity matrices. Biochem. J. 203, 699-705, 1982.

Atkinson, A. and Harvey, M.J. Protein-binding affinity chromatography media U.K. Patent GB 2015552B, 1982

Atkinson, A. and Harvey, M.J. Purification of albumin by affinity chromatography on an immobilised triazine dye. U.K. Patent GB 2053926B, 1983

Harvey, M.J., Brown, R.A., Rott, J., Lloyd, D. and Lane, R.S. The purification of albumin by affinity chromatography. In "Separation of plasma proteins" Editor J.M. Curling, 80-88, 1983

Brown, R.A., Placental collagens. In "Collagen in Health and Disease". Editors J.B. Weiss and M.I.V. Jayson. Churchill Livingstone, 1982

J.B. Weiss, C.R. Hill, R.J. Davis, B. McLaughlin, K.A. Sedowofia and R.A. Brown. Activation of a procollagenase by low molecular weight angiogensis factor. Bioscience Reports 3, 171-177, 1983

R.Brown, G.Cotton, C.McFarland, L.Winkelman, M.J.Harvey, R.S.Lane. Suitability of a waste fraction from the preparation of factor VIII as a source of fibronectin. Thrombosis Haemostasis 50 ,433. (1983).

R.A.Brown. Failure of fibronectin as an opsonin in the host defence system : a case of competitive self-inhibition? Lancet (ii),.1058-60, November 5th 1983.

R.A.Brown, L.W.Tomlinson, C.R.Hill, J.B.Weiss, P.Phillips, S.Kumar. Relationship of angiogenesis factor in synovial fluid to various joint diseases. Annals of Rheumatic Diseases 42, 310-7. (1983).

J.B.Weiss, C.R.Hill, R.J.Davies, B.McLaughlin, K.A.Sedowotia, R.A.Brown. Activation of a Procollagenase by low-molecular weight angiogenesis factor. Bioscience Reports 3 ,171-7. (1983).

R.Brown. Fibronectin : Current models and trends. Transfusion Microbiology Newsletter, November 1983.

R.A. Brown, K. Mcdonald, C. McFarland, S. Price, J. Rott, M.J. Harvey. Albumin as a serological reagent: production by large scale affinity chromatography. B.B.T.S. meeting, Cambridge, 1983.

R.A. Brown, L. Winkelman, G. Cotton, J.K. Smith, M.J. Harvey. Fibronectin: recovery of a useful tissue culture reagent from waste plasma protein. B.B.T.S. meeting, Cambridge, 1983.

L.Vallet. The Preparation of Protein Fractions for Clinical Use from Human Blood Plasma. In "Bioprocessing in the Eighties", Institute of Chemical Engineers, 1982.

R.S.Lane, M.L.Kavanagh, L.Vallet. Human Immunoglobulin for Clinical Use. Lancet, 12th February, 1983, p.357-358, (letter).

R.S.Lane. Non-A non-B hepatitis from Intravenous Immunoglobulin. Lancet, 22nd October 1983, p.974-975 (letter).

Patents and Crown Records

Patent Filed : January 1983 "Affinity Chromatography Adsorbents Containing Collagen and Gelatin

Crown Records

1. "Enhancement of the Polymer Content of Human Albumin for use as a Serological reagent".
2. "Electrophoretic Assessment of the Gelatin Binding Activity of Fibronectin".
3. Process for removal and purification of hepatitis B particles from protein solutions.
4. Removal of pyrogens from plasma proteins using modified triazine dye affinity chromatography.
5. Use of Isolated Fibronectin Domains.

Management and Planning

This Report includes the first full year of management by the Central Blood Laboratories Authority: it covers a time of rapid transition and growth during which management co-ordination remained extended. Progress has been made in three of the four basic requirements for a new plasma fractionation unit, namely a new factory, a new employing authority and wider terms of reference for manufacturing and services. A new system of terms and conditions for employment has not been achieved and remains problematical.

Refurbishment of the existing production areas was completed with difficulty during 1982 and all new areas and equipment were commissioned by November. Interruptions to production varied between a few weeks up to five months. The standard of performance of new equipment was only moderate, notably with freeze driers, autoclaves and air filtration systems; the reasons were numerous, but the implications for commissioning the new BPL are obvious. Weak BPL engineering support during the MARP project was a major cause of the difficulties experienced.

Manufacturing in the refurbished BPL was uninterrupted during 1983. MARP 01 production targets were reached: considering only factor VIII and albumin, mean monthly output before MARP 01 was £.342M and increased during 1982/3 to £.476M, finally rising to £.629M in 1983/4. The approximate annual increase in shelf value of these two products is £3.44M which has already greatly offset the capital expenditure of £2.5M on the MARP 01 project. BPL, in its refurbished state, will need to manufacture at current rates until mid-1986, during which time, value of released products will have exceeded £40M.

Managing production in the old BPL and planning for commissioning the new BPL are two activities which will run side-by-side for a 36 months period. Planned growth of resources to commission and secure production in the new factory in 1986 is of paramount importance and includes:

Recruitment and training of staff
Additional buildings
Expansion of Quality Control Services
Implementation of GMP
Increased revenue and capital financial support
Expanded product and process development and research
Plasma supply.

The task is considerable in that the same staff have to fulfil responsibilities in both roles and management input may be overextended.

The CBLA's attention should be drawn to the present position as it relates to future growth in resources. During the past four years the MARP project and major redevelopment of BPL have required considerable energy and initiatives at local and external levels. Both projects received substantial political attention and reflected Treasury's policy relating to Central Government spending. In both instances, the capital programmes developed independently of equivalent revenue expenditure planning.

A serious deficiency has developed in that certain essential capital projects squeezed out of MARP proposals by financial cuts, have not been progressed in parallel with proposals to rebuild the main BPL production facility. The reasons for this lack of progression are in part logistical, but there was no wish to promote two capital programmes which might confuse or act prejudicially to the main endeavour of rebuilding BPL.

The capital projects in question are:

New QC and animal house and engineering facilities
Additional warehousing and cold storage
Enlarged restaurant and staff facilities
Extension of R & D laboratories.

Full proposals are near completion, but there is no allocated capital for implementation. In discussions with DHSS, there is now recognition that these projects are needed to support the functions of BPL prior to commissioning the new production unit: it is also recognised that commissioning the new plant will be at risk without full services from QC, environmental control and engineering services.

Following MARP, increases in production have taken BPL warehousing requirements beyond capacity with the result that hire of external contract warehousing is forming a significant additional item of expenditure.

For logistical, Regulatory and GMP reasons, extra warehousing is needed on this site.

It is intended that warehousing should incorporate -40 C storage to accommodate the buffer stock of FFP required from RTCs prior to January 1986. It would be a serious matter if BPL limited growth in plasma procurement due to lack of cold storage capacity.

Extension to R & D laboratories was strongly supported by management in 1977 when proposals were made for a pilot process and product development laboratory. Without PFL, development work would now be at a standstill; postponing decisions in 1977 has created a critical situation ahead of the new BPL development.

During 1984 and 1985 sufficient staff must be recruited and trained to run the new production unit in 1986. Approximately 100 extra employees will not be easy to attract, particularly for key positions. Any disincentives to recruitment must be removed. Thus it is essential that proper pay grades with agreed terms and conditions are obtained for BPL as soon as possible.

Negotiations with DHSS and Whitley Council representatives have continued for three years without resolution recognising that BPL has manufacturing requirements of staff which do not have equivalence within the NHS. To this end and to facilitate proper management of Industrial Relations difficulties experienced at BPL, DHSS must be pressed for an early decision favouring our interests.