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THE FUNCTION OF STOP-GAP AND PHASED REDEVELOPMENT OF THE BLOOD PRODUCTS LABORATORY

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SUMMARY

In response to increased demands for plasma fractions, notably factor VIII and albumin (PPF) a meeting was called at BPL in October 1977 to discuss future plans for developing the laboratory. A phased redevelopment of BPL was deemed feasible and became realistic at Elstree shortly after when the Lister Institute announced their intention to cease operations at Elstree in August 1978 and DHSS were able to negotiate for purchase of the site.

Phased redevelopment constitutes the following proposals:

1. A pilot production laboratory with associated research and development facilities. Capabilities include transitional development of new protein separation technology into pilot production scale operation - prepared fractions being suitable for clinical trial; to assess modifications to existing systems to improve yield etc; to manufacture small therapeutic batches e.g. rabies immunoglobulin.

2(a) New process areas for large fractions and the coagulation factor laboratory with self-contained support services, sterile filling area and packing, labelling and dispatch areas.

(b) New engineering maintainence and workshop areas; analytical quality control laboratory; records and data processing area; administrative area.

3. Redevelopment of existing BPL building after relocation of processes.

Production limits for the new laboratories are:

(a) 120M i.u.s factor VIII per annum.
(b) Albumin 650,000 containers per annum.

Required commissioning date 1984.

The interim period, pending transfer to new laboratories is designated Stop-Gap.

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Stop-Gap is a package which includes modest increases in production (outlined in Annex 2) with certain limited modifications to the existing buildings. Modifications are:

(1) Enlargement of the Coagulation laboratory process areas and an increase in plant capacity.

(2) Enlargement of the loading bay/reception/cold storage facilities; improvements in wash-up and assembly of equipment; upgrading of the terminal process area to assist throughput of final product.

The financial support for Stop-Gap is approved and planning is proceeding as fast as possible.

The reliability of Stop-Gap production has been assessed by an external systems-analysis team and is assured within the following conditions:

(a) That Stop-Gap is a finite period of not more than 4 years.
(b) That raw material supply is adequate.
(c) That staff recruitment is successful.

Within Stop-Gap, the following factors essential to efficient running of an enlarged laboratory must be provided for

(1) Selection of processes
(2) Implications of the Medicine's Act
(3) Future management and staff structure; terms and conditions
(4) Supply of raw materials
(5) Financial organization and administration
(6) Computerization and data processing

30/26

BLOOD PRODUCTS LABORATORY : STOP-GAP AND THE BASIS FOR PHASED REDEVELOPMENT

INTRODUCTION

This paper deals mainly with events at BPL dating from 1977 and with proposals for the future development plans. However, a new development should not be outlined without some consideration of the lessons and past experience gained from previous extensions to BPL, the last being planned in 1965 and completed in 1972. In his concluding report, the retiring Director, Sir William Maycock, commented that earlier extensions had been based on inadequate estimates of demand, had been severely constrained by the site and, inspite of these impediments, had had reductions on planned floor space imposed by the Department; summarizing, Sir William said "It takes at least 4 to 5 years to plan and build accommodation for a plasma fractionation or any other large laboratory. It is thus impossible for a fractionation laboratory to respond quickly to a new demand unless it has unused space at its command and unless it has been designed in a manner and uses techniques which allow flexibility in its accommodation and in the adjustment of production methods. I suggest two proposals concerning the BPL which will succeed "Stop-Gap" and provide accommodation that meets the requirements of Medicines Act, 1968:- firstly, the redeveloped BPL should have a capacity greater than that needed to provide for the latest estimates for plasma fractions available during the planning stage; secondly DHSS should take a long term view and consider a new BPL as a valuable investment which will save the Department much money".

Except that 4 to 5 years will now be an unacceptably long time to phase in new process laboratories at BPL, Sir William's conclusions are shared by the present Director.

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THE BACKGROUND TO STOP-GAP (1977-78)

During this period, the manufacture of blood products has remained essentially static, albumin production fluctuating about 130,000 containers and Factor VIII varying between 12.5 and 15m i.u. per annum. Other products have showed similar changes in rate of output.

This stasis has continued inspite of the regular and in some instances considerable increases in the NHS requirement for plasma protein fractions. The main deficiencies in BPL production are in the two main products, Factor VIII and albumin, although it must be stated that any major extra demand arising now for other products could not be met, e.g. extra normal human immunoglobulin, anti-HBs or anti-D immunoglobulin and dried plasma.

Causal factors for this static situation need to be defined.

(1) The present unacceptably high level of occupancy of production capacity stems from past failures in planning and financing of laboratory redevelopments. Constraints were imposed by the inadequate BPL leasehold on the Lister Institute site which contributed to the failure to re-define production requirements and coordinate these with forward planning of buildings. Financial requirements and the factor of reliability in the process tended to be overlooked. In short, past laboratory practice was more academic and less like production based on sound manufacturing practice.

(2) Deficiency in provision of raw material. BPL was developed for the primary purpose of utilising time-expired (i.e. waste) plasma from transfusion centres. The philosophy, established then, has continued in that RTCs tend to pass on to BPL (when it is convenient) the plasma for which there is no further regional use. Even with the advent of frozen fresh plasma (FFP) supply for BPL, the method of collection and distribution was co-opted, inappropriately, from existing practice and, as observed by the Working Party on Cryoprecipitate Production, 5-litre pooling of FFP for BPL has the lowest order of priority in the daily affairs of most regional centres.

Thus, in a manner totally contrary to good manufacturing practice, BPL still remains something of a dumping ground for various grades of plasma.

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(3) Lack of a contractual arrangement for plasma supply. The supply of raw material to BPL from RTCs has remained a matter of 'grace and favour' and has never established a regularized contractual supply. The reason for this past failure has stemmed from weak central policy for the transfusion service and anomalous financial arrangements.

Here, a fundamental defect in the NBTS system is apparent: collection and distribution of whole blood and red cells have remained within RTCs and their regional administrations, yet plasma collection, fractionation, distribution and financing have remained with BPL and the DHSS system of administrction and financing. This anomaly has been clearly recognised but remained uncorrected while the increasing growth in requirement for plasma products has accentuated the defect and forced the regional and central issues wider apart.

Within the regional transfusion centres, comparable with BPL, there exists an incapacity to raise plasma production. Inadequate forecasting, deficient forward planning and absence of a secure financial investment programme are the causes. Like BPL, regional centres have reached an unacceptably high level of occupancy of production capacity and cannot respond to new requirements without further money being spent.

The regional problem was defined in a DHSS report dealing with 'The Handling of the Trends Working Party Report' (26 April 1978) where it was noted that most RTCs were approaching maximum capacity with present resources. The additional point was made that BPL should be in control of its raw material supply. In this DHSS report, attention was also drawn to the salutory effect on FFP collection of £0.5m injected into NBTS as a result of direct Ministerial action in 1974 and earmarked for this purpose. This action, although it proved its point, should be criticised: it verified an already established need for FFP and Factor VIII concentrate for the home treatment of haemophiliacs and paved the way for full home prophylaxis of haemophilia with factor VIII concentrate to become a desirable practice in the U.K. as in other Western countries. However, there was no sequel to the first financial initiative and therefore no on-going DHSS provision for the inevitable increase in use of Factor VIII which ensued. Increasing purchase of expensive commercial Factor VIII has filled the gap.

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While it is tempting in this paper to concentrate solely on the development of BPL, experience show this to be unwise. Plasma collection and therefore the collateral development of regional transfusion services must be planned together and ways of correcting long standing anomalies quickly found.

DEVELOPMENT OF STOP-GAP

The Working Party on Trends in the Demand for Blood Products, formed early in 1977, made recommendations about future needs for blood products projected over the ensuing 5-10 year period. These recommendations, in line with the findings published in the Council of Europe Report "The Indications for the use of Albumin, Plasma Protein Solutions and Plasma Substitutes", were approved with minimal alteration by the Standing Medical Advisory Committee and in a later paper were recorded as 60 million i.u's Factor VIII and between 100-200g albumin per 1000 population per annum. Theoretical analyses were made showing the increase in whole blood collection which would be needed to provide the plasma to sustain this extra protein fractionation.

Already the 'Trends' Working Party figures are suspect in that current Factor VIII use approximates to the projected 5-10 year figure and there is no evidence that demand is levelling off. In addition, it will be debated later whether a reliance on whole blood donation for FFP supply is a rational approach to the problem.

The 'Trends' figures did accentuate the deficiency in BPL's output - increases in production of five times for both Factor VIII and albumin being needed to meet the required levels. Appreciative that such increases were impossible in the existing building, a meeting was called in October 1977 at Elstree when, in company with DHSS representatives from HS2A and finance branch, the immediate and long term future of BPL was discussed. In the minutes, it is recorded that three principal determinants influenced BPL's future:-

(1) The continuing pressure, both from the field and the Department, to produce more Factor VIII concentrate. BPL had almost reached the limit of its present production capacity, and, as a prerequisite, RTCs would have to increase the supply of plasma.

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(2) The implications of the recommendations of the 'Trends' working group, which pointed to a substantial expansion of the existing production of Factor VIII and albumin over 5 to 10 years.

(3) The application of the Medicines Act to the NBTS and the probability that a number of processing units in RTCs and in BPL would not meet the standards being demanded by the Medicines Inspectorate, particularly in relation to open systems for handling blood and plasma.

It was suggested that development at BPL should be closely integrated with those at RTCs: for example, BPL might consider looking to the geographically close Thames RTCs alone for plasma supplies, perhaps with plasma collection by plasmapheresis being funded centrally through BPL. BPL could limit the implications of the Medicines Act for the Regions by redeveloping production facilities at Elstree which would enable RTCs to send single packs of plasma there, obviating the need for sterile areas for plasma pooling at RTCs. At BPL, the redevelopment would take place in 3 phases:

IMMEDIATE: The pilot scheme for chromatographic separation, including associated R & D laboratories, storage and anlytical quality control.

PHASES I/II. Factor VIII. Increased production and support services, including the processing of the associated cryosupernatant. PPF/albumin production plus support services.

PHASE III. Reworking of existing BPL shell, including provision for quality control, bacteriology, pharmacology, physiology, administration and storage.
The plans would take account of the production requirements for all BPL products.

The Department thought that the phased redevelopment solution was worthy of further examination and proposed preparation of realistic development plans, based on agreed production targets.

In the interim, however, the Department wondered whether some immediate action should not be taken in view of the fact that phased redevelopment would take some years to complete.

30131

STOP-GAP was initiated and proposals from BPL were requested. In conjunction with BPL staff, a document was compiled and submitted to DHSS in December 1977 - a copy of these Stop-Gap proposals is appended as Annex 1.

Several aspects of development were seen to fall within Stop-Gap and were divided into two broad categories: (1) interim production levels as described in Annex 1; (2) a critical review of the laboratory as a basis for future improvements associated with Phased Development.

STOP-GAP

(1) Interim production (Annex 1)

The two stages of target production levels falling within the designated 4 year period differed significantly in that the first was feasible within the existing laboratory conditions given adequate staff recruitment at process-worker and technician levels. The second stage of production would be dependent on limited structural and plant alterations and additions in the Terminal Process Area, Loading Bay, Wash-up and Cold storage areas and in Coagulation Factor Laboratory.

Essential to the second stage was deemed an immediate survey of the building, plant, process, staffing and management systems by a professional managerial and systems-analysis consultant team. The objectives were

(i) an overall assessment of process capacity with recommendations on procedural matters and indications of reliability of the means to achieve target production levels.

(ii) examination of existing plant and machinery with a reliable assessment of capacity.

(iii) to work in conjunction with staff, architects and consultant engineers to advise on the most productive structural developments to the Terminal Process Areas and Loading Bay etc.

(iv) to assess lines of communication, feed-back in production systems and managerial practice.

Raw material supply was felt to be outside the remit of this study group due to the interaction with RTCs.

The survey is now complete with the exception of the final analysis of part (iv). The result is a reworked set of production targets deemed feasible within the second stage of Stop-Gap, but conditional upon the structural redevelopments listed above being completed according to plans and at the earlist opportunity.

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It should be noted that these are integrated targets which include all products made at BPL while incorporating the basic estimates for Factor VIII and albumin at 28m i.u. and 240,000 containers respectively per annum (see Annex 2). This level of albumin production approximates to 85g per 1000 population, i.e. it is still below the lower limit set by the 'Trends' Working Party.

(2) Structurual development within Stop-Gap

At the date of the October 1977 meeting, two developments were currently under discussion; first, an extension to the Loading Bay which had reached the stage of being offered out to tender and second, a Pilot Laboratory for Chromatographic research and development. The latter did not fit in at that time with the concept of Stop-Gap and will be discussed separately as an initial feature of the proposals for phased redevelopment of the laboratory. However, it is pertinent that both projects were severely constrained by the existing BPL leasehold on the Lister Institute site: structural/functional relationships in planning the loading bay extension were highly compromised by the need to contain the plans within BPL's boundaries and the pilot laboratory would have needed negotiation of a new leasehold area on the Institute site.

Coincident with submission of Stop-Gap proposals to DHSS and their receiving financial approval in June 1978, the Lister Institute announced its impending closure of operations at Elstree. The implications for BPL were many but most significantly, purchase of the site for DHSS would add a new dimension to future planning potential since a major redevelopment of BPL at Elstree had previously been excluded by the Lister Institute's own interests on the site. This period of change also coincided with the changeover of BPL Directors consequent upon Sir William Maycock's retirement in September 1978 and with the acceptance on an interim basis of a new legal employing authority for BPL staff, namely, N.W. Thames RHA.

With so much change and uncertainty, it was deemed prudent by the new director to jettison any past redevelopment plans compromised by the old conditions of BPL leasehold. In accordance with Stop-Gap planning, new project designs were initiated for the Loading Bay and Terminal Process areas which took full account of their functional content. These plans have reached the position of Capricode Stage 1 and 2 submissions and have been lodged with DHSS for approval. An early start on detailed drawings is awaited. Financial requirements for these developments within the 1979/80 budget have been approved.

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(3) Other aspects of Stop-Gap development

(i) Coagulation Factor Laboratory. Work is in progress on the provision of extra clean-working space to accommodate production of pure protein fractions, fibrinogen and albumin for delivery to The Radiochemical Centre, Amersham. This will in turn release space into the general process area of the Coagulation Factor Laboratory and provide extra facilities for development work on intake of FFP units in single transfer packs.

An extra Sharples continuous-flow centrifuge has been installed and commissioned providing the capacity to process 4 x 600 litre pools of FFP per week, i.e. the second stage Stop-Gap target.

N.B. It should be stressed that, under now outdated agreements, the work for The Radiochemical Centre, Amersham is carried on free of charge although the radio-labelled protein tracers are distributed by the Amersham laboratory on a worldwide profitable basis.

(ii) Freeze drying capacity will be increased by the addition of a small plant (EF6 Edwards High Vacuum) in the immediate future and delivery of a large plant (EF10) for installation in the autumn. Total installation will safeguard the second stage Stop-Gap production levels.

(iii) Development within Stop-Gap required by takeover of the Lister Institute site.

(a) Refurbishing the sewage plant - expert advise is being taken pending submission of a report.
(b) Alterations to the Virology Laboratory to accommodate the increased requirements for Hepatitis B screening and provision of the BPL radioimmune assay for HBsAg for the NBTS.
(c) Internal restructuring of Lister Institute Serum and Vaccines Laboratories to provide bulk storage capacity for bottles and containers at present stored on the loading bay.

(4) Operation of plant during Stop-Gap

(i) Addition to the York compressor system controlling the glycol-cooling plant.
(ii) Provision of a new borosilicate neutral-glass container with automated machinery for closures and seals: improvement of storage and distribution of PPF.

3934

Both matters are covered by reports placed on the agenda of the Scientific and Technical Committee's Meeting, June 7th. 1979.

THE LONGER-TERM ASSESSMENT OF LABORATORY NEEDS AND PRACTICE: A FUNCTION OF STOP-GAP.

Stop-Gap provides a modest interim improvement in production, pending realization of a Phased Redevelopment programme. However, it is essential during Stop-Gap to examine the future needs of a larger production unit with respect to:-

(i) The new fractionation process and its associated research and development.

(ii) The implications of Medicine's Act requirements.

(iii) Future management and staff structure and conditions.

(iv) Future supply of raw materials.

(v) Financial organization and administration (the inter-relationship of BPL within NBTS).

(vi) Computerization and data-processing.

(i) and (ii) The fractionation processes, research and development programme and the Medicine's Division requirements for safe processing will be dealt with in the section on Phased Redevelopment. It must be stressed, however, that, in the assessment of these vital areas of the laboratory's future programme, the early provision of a Pilot Production Laboratory was recognised to be of greatest importance. This matter is reviewed later.

(iii) Management and Staff structure at BPL reflects the piecemeal development of the laboratory over twenty-five years. The past lack of emphasis on the manufacturing process and attachment to academic bodies (MRC and Lister Institute) as legal employing authorities has done little to ensure that BPL staff receive the terms and conditions appropriate to their work, in that these should recognise production responsibility and enable rates of pay to be sufficiently attractive to gain employment at BPL in competition with local industry. Likewise, management is deficient in production/process skills and has failed to relate annual budgetary needs to production targets; there has been an absence of investment, a lack of accountability and worst of all, a

3013

failure to realise the equivalent commercial value of the BPL process.

Deficiencies in Management have arisen from not meeting needs in the areas of factory supervision, engineering maintainance, process/plant design, environmental control and analytical quality control. Ironically enough, it is improbable that management in several of these areas could be recruited within existing terms and conditions and the NHS parallels fail to provide grounds for optimism.

Attached to this paper, (Annex 3) is an example of the type of staff structure needed to run an enlarged BPL, infact, several positions could be gainfully employed within the existing laboratory.

A review of staffing is needed and attention is again drawn to a condition for success in Stop-Gap, namely, that staff positions at process and technical levels are fully recruited. Difficulty persists here threatening the entire operation and is entirely due to inability to offer a competitive wage within existing terms and conditions.

At a recent meeting with DHSS and RHA representatives to consider the future problems of staffing, job evaluation and appropriateness of NHS pay scales to the BPL staff, the following feelings were expressed:-

(a) that a job evaluation which principally sought a lateral transfer into NHS grades from existing Lister Institute grades assumed a status quo which was hardly the case while important decisions on the future of BPL were deemed imminent.

(b) that proposals in this paper for future systems of staffing necessary to run a redeveloped BPL as an efficient manufacturing organization should be considered along with other redevelopment plans by the Scientific and Technical and Joint Management Committees.

(c) that staffing evaluations should await a decision in principal on the future of BPL.

(d) that, following a decision to redevelop BPL, staff recruitment, according to an agreed system, should commence as early as possible within Stop-Gap i.e. during the planning and commissioning

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of new laboratories and plant, so that the new members would be fully involved from the outset.

Insofar that an enlarged BPL will always be compared with its industrial competitors on a wide range of matters from quality of product, product cost and safety of process, the means to attract a cohesive work force are required: competition with industry requires a start on equal terms.

(iv) Future supply of raw materials. Within Stop-Gap, the future raw material supply programme must be decided and the means whereby it can be financed. This matter is an essential and integral part of forward planning and needs to be resolved during the time a new fractionation laboratory is commissioned. It is a matter for a coordinated approach by DHSS, the regional transfusion centres and RHAs and the BPL.

Three main parameters can be defined:

(a) projected needs - quantity and quality

(b) methods of collection

(c) financing

(a) Projected needs

The 'Trends' Working Party fixed a level of 60m i.u. Factor VIII as concentrate in production and use by the mid-80s. However, annual returns from the Haemophilia Centres show first, that current Factor VIII use is in a period of rapid growth; second, that total use in 1977 was 48.5m i.u.; third, that the increase in use is wholly at the expense of Factor VIII concentrate. The true position of cryoprecipitate is hard to assess: data from the West Midland Haemophilia Association returns for 1976-77-78 show a decrease in cryoprecipitate use from 1.4m i.u. to 550,000 i.u. per annum during this period.*

* The decline in cryoprecipitate production at Birmingham RTC has been associated with a considerable rise in output of FFP to the extent that, if the region were to receive pro rata the Factor VIII concentrate attributable to their FFP supply, BPL would return 2.5m i.u's, a considerable proportion of the 3.1m i.u's total Factor VIII at present used in the West Midland Haemophilia region:- almost an example of self sufficiency.

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In practice it is likely that cryoprecipitate production will be maintained at falsely high levels by the occasional emergency fall-back on its use, i.e. after complicated surgery etc. when further continued use of commercial Factor VIII is proving to be prohibitively expensive.

In 1976, approximately £1.2m was spent on commercial Factor VIII purchase and this rose to nearly £1.8m in 1977. 1978 figures are not available yet but, with output of NHS concentrate static, the purchase price is likely to be considerable.

To assess future growth, the trends in haemophilia management must be considered. Gradually increasing numbers of haemophiliacs diagnosed and treated, expected increase in life span and associated increased incidence of concomitant illness and surgery, a move towards home therapy and prophylactic care all suggest a continued growth in Factor VIII use.

The latest complete treatment breakdown is for 1976 and the 1977 figures will be of interest since they will indicate the extent of growth in home treatment, in particular the home treatment of the severe haemophiliacs with less than 2% of procoagulant activity. These patients numbered 1,787 in 1976 and would be the group most naturally placed on full prophylaxis.

It must also be realised that, as with the regional transfusion services, haemophilia care varies between the supra-regions, financial policy obviously being an influence. Since prophylaxis is a desirable aim which is inhibited by commercial costs, a cheaper NHS equivalent is not only highly desirable but would inevitably stimulate increased use.

For a new fractionation laboratory at Elstree a production ceiling of 120m i.u. Factor VIII has been set with an intermediate target of 90m i.u. to be reached by the mid-80s. In consultation this is thought of as realistic; the plasma required would be 375,000L for 90m i.u. and 500,000L for 120m i.u. factor VIII per annum at current yield rates of 250 i.u. per kg. plasma.

The above estimates assume that the existing linear growth in annual rate of use of Factor VIII continues only for a further 2 to 3 years after which a plateau situation would develop.

Plasma needs for factor VIII provide sufficient raw material for fractionation of albumin in accordance with the 'Trends' Working Party estimates and based on current yield rates of albumin by Cohn fractionations. This situation would continue unless purification methods to retrieve factor VIII from FFP improved to the extent where yield was more than doubled i.e. source plasma input could be substantially reduced for this purpose. An equation of this kind is necessarily incomplete at present, since improvements in yield of albumin from plasma are currently under investigation. 30/3

(b) Methods of collection

In a paper to DHSS (9 August 1977) Sir William Maycock elaborated on the implications of the levels set by the 'Trends' Working Party for NBTS. The paper dealt with albumin and the assumptions were that plasma supply would depend on whole blood collection as carried on by RTCs except that a much higher proportion (80%) of blood going to hospitals would be as concentrated (plasma reduced) red cells. Even so, an increase in total donations from 1.9m to 3.03m would be required. Sir William observed that this latter figure was unremarkabe in that it corresponded to 61.7 donations per 1000 population in England and Wales, a donation rate only just comparable with existing donation rates in most other European countries.

DHSS expressed the view that the growth in regional blood donation rate would be constrainted by the fact that most centres appeared to be approaching maximum capacity with present resources. That this is so is evidenced by the static level of FFP supply to BPL during the past 24 months.

A new approach to plasma collection is needed at two levels : first, to satisfy the more modest needs of Stop-Gap i.e. an increase in FFP supply from 360,000 to 750,000 donations per annum; second, the long-term supply for an enlarged laboratory up to the levels of self sufficiency in blood products.

FFP for Stop-Gap. Proposals are based on the existing whole blood donation rate of 1.9m per annum. Of 1.9m donations, approximately 360,000 (19%) are used to prepare FFP i.e. plasma is removed and frozen within 24 hours of donation and supplied to BPL in 5-litre pools. This plasma is currently fractionated at 1200 litres per week to provide between 12.5 and 15m i.u. factor VIII per annum.

Of these 1.9m blood donations, approximately 1.0m (53%) are converted to source material for albumin fractionation (this includes the FFP above). Approximately 180,000 litres plasma yield 26g/litre albumin or 4680 kg equivalent to 95g/1000 population. At present only half this potential is utilized, Stop-Gap aims to make use of the total material.

It is argued that the present percentage of plasma which goes time-expired with red cells is unacceptably high and that during Stop-Gap a move should be made towards presenting plasma to BPL as FFP only thus phasing out time-expired plasma as much as possible.

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If completely successful, BPL could call on 1.0m → 1.2m donations of FFP from the existing whole blood donation of 1.9m, requiring that up to 60% of cells went to hospitals as concentrated red cells (a lower figure than the 80% referred to earlier).

Within this conversion to FFP, Stop-Gap requirements to produce 28m i.u. of factor VIII could be met, since approximately 730,000 donations of FFP would suffice to meet this target: additionally, the total input of plasma to BPL would not increase, this being of strategic importance until the proposed extra coldroom facilities are in operation.

To facilitate this approach by RTCs are needed money and a more streamlined approach to FFP collection. On the latter point, the agreed view among RTDs is that the 5-litre pooling system used to collect FFP should be phased out with the centres freezing single transfer packs of plasma obtained under sterile 'closed' conditions. To this end, the BPL Director formed a Working Party in September 1978 to design and negotiate provision of a new plasma transfer pack, functionally dedicated to provision of FFP in the most ideal condition. The prototype of this pack is now available for inspection by the Working Party and it is significant to note that the concept has received wide support from blood bank operators in the USA, Europe and Scandinavia. The Working Party should be able to report to transfusion centre directors by this autumn, following field trials.

Given a simpler procedure, there is little doubt that RTCs could rapidly increase the quantity and quality of FFP supply to BPL given sufficient incentive and financial support.

FFP for a redeveloped BPL. From existing blood donations, approximately 240,000 litres of FFP could be collected per annum. To achieve the two levels defined for an enlarged laboratory, i.e. 375,000 litres and 500,000 litres, an extra 135,000 and 260,000 litres of FFP respectively would be required per annum. Accepting that 60% of blood for hospitals is used as red cell concentrates, it is clear that the total plasma requirements could be met by an approximate doubling of the annual rate of whole blood donations.

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Before this approach is accepted, however, it will be essential to discuss general contraversial matters:

(1) Does the NHS require twice the existing amount of red blood cells and, if not, what are the ethical considerations concerning their wastage?

(2) Does the existing strategic approach to whole blood collection provide a sound basis for developing FFP collection at the quality and quantity required and at the most economical rate?

(3) New systems of plasma collection exist which are already widely used. Equally, procedures are being developed which enable all the plasma to be removed from a donation of red cells and provides for a replacement fluid which reconstitutes the cells at the desired haematocrit and in a protective environment.

Plasmapheresis either by conventional plasma bag systems, by newer developments along similar lines or by automated separation techniques requires urgent and serious appraisal by an expert group. It is important to reconcile new methods of plasma collection, decoupled from existing whole blood collection with the increased quantities of fresh plasma required. Equally important is the notion that fresh plasma collection logically should be associated with areas of high population density and short transit time between place of collection and site of processing and freezing. For this reason, it is likely that plasma collection is centred on large urban zones in Greater London, Bristol, Birmingham, Manchester, Sheffield, Newcastle etc. and not promoted in the regions with large rural donor catchment areas.

The initial developments for improving plasma collections for an enlarged BPL need to start now if there is to be a concomitant planning of redeveloped laboratories and improved raw material supplies. It is worth considering areas like S.E. Thames and Newcastle, where, either the transfusion service is not represented or is pending redevelopment, as suitable for pilot schemes in plasmapheresis.

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(c) Financing

The regional transfusion service will require extra money to finance plasma collection at two levels, within Stop-Gap and at the higher levels commensurate with self-sufficiency in Factor VIII. In the latter instance, a major reorganization of policy will be required; this is well realized, but it must be re-stressed that the time for reorganization needs to fall within Stop-Gap so that a basis is laid for a paid-up contractual supply of FFP to BPL before a new laboratory is ready to receive the increased supplies.

Within Stop-Gap, much can be done to improve arrangements between BPL and regions. For too long, certain regions have been penalized by inadequate return of finished product in relation to the considerable quantities of raw material sent to BPL: this is while other regions have sent little FFP but received equal quantities of factor VIII and albumin i.e. they have been in effect subsidized by more productive regions.

The inequality of this arrangement is now widely realized and does not stimulate good regions to do better. Regions that do not finance plasma at present, should pay for commercial plasma products until some more satisfactory long-term financial arrangements are worked out. Regions that do supply large amounts of FFP should receive pro rata the factor VIII and albumin attributable to their source material; in so doing, certain regions would have achieved already a considerable measure towards the goal of self-sufficiency. RTD's could justify their expenses by real savings to regional treasurers and maintain the regional initiative.

In recent meetings with DHSS Regional Principals, this view has been expressed and well received only after the internal requirements and organization of NBTS have been patiently explained. Before satisfactory financial arrangements can be made for the long-term, all parties involved will need to be fully informed.

(v) Financial organization and administration. Where this concerns the contractual arrangements for supplies of plasma from RTCs, this has been covered in (iv)(c) above. It should be added that any final arrangements will have to take into consideration the cost of production of various purified protein fractions.

During Stop-Gap the financial arrangements for operating BPL will need to be reviewed. It is realized at this point that decisions

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relating to future redevelopment of the laboratory and its future forms of legal employing authority and management will largely determine financial arrangements. However, it should be stressed that the existing system of budgeting and operation within strict cash limits do not conform with a production orientated unit where growth in output relates to increased revenue expenditure and long-term plans for capital redevelopment. A state of no-growth in the NHS may be a policy matter, but increasing use of blood products is a matter of fact. Unless the BPL can retain the operational flexibility to meet this extra use of factor VIII etc., the hospital service will continue to purchase increased amounts of commercial products.

(vi) Computerization and data-processing. Existing record systems have grown with BPL and are now limiting in their efficiency and with respect to coping with any further increases in output. Within Stop-Gap, the advantages of computerization in record keeping, stock inventory control, raw material handling and process control will need to be assessed.

Up to the present, no move into this field has been made at BPL because a group of RTDs has been installing into their centres, computors capable of handling the blood programme. Commonality in use has been actively defined at RTC level within NBTS and within the wider context of European and International blood control and documentation. Wide areas of agreement have been reached, so the fractionation laboratory can now fit into the regional programme without creating anomalies and with maximum benefit from regional experience.

30/43

PHASED REDEVELOPMENT OF BPL:

A phased redevelopment programme at Elstree became possible when a firm committment was reached by DHSS to purchase the Lister Institute site. At present, completion of purchase is awaited.

The advantages of developing BPL at Elstree have always centred round its position in relation to the Greater London area and its ease of communication by road and rail with most of the regional transfusion centres. Equally, in any redevelopment programme, it would be essential to involve existing staff in the planning of buildings, plant and process details, since they would eventually have to commission and run the new laboratories. Finally, new laboratory development would need to be concomitant with existing production and phased to cause minimal disturbance to building, staff or environment.

Although obtaining staff is at present difficult because Elstree is centred in an area of high employment, maintaining a new laboratory on the same site excludes any need for staff relocation and allows for easier recruitment during the Stop-Gap period.

Positioned at Elstree, BPL can retain its established links with the Haemophilia Centre in Oxford, the Regional Blood Transfusion Centre at Edgware and the Clinical Research Centre, Northwick Park.

Phased redevelopment of BPL was first discussed in October 1977 and has subsequently come to include the following components:

(1) The pilot production unit, known initially as the pilot chromatography laboratory.
(2) Redevelopment of the main process areas with their full support facilities.
(3) A re-work of the existing shell of BPL buildings or their demoli tion and reconstruction to meet current requirements.

(1) The Pilot Production Unit

This proposal was first moved four years ago. The aim was to provide research and development facilities to assist in new chromatographic methods of protein separation being tested up to pilot production level. The proposal was well received and authorization given to proceed with architects to a content/design study, drawing up of site plans and diagrammatic sketches of the proposed unit.

30144

Following the preliminary report, no permission to proceed was forthcoming and by November 1977 it was decided to stage an exhibition and demonstration of chromatographic procedures at BPL for the Subcommittee on Central Laboratories of the Central Committee of the NBTS. The committee was joined for the day by an outside expert adviser Dr. Peter Dunnill and the minutes of the meeting that followed (held on February 21st 1978) recommended to DHSS that there was an urgent need to provide a pilot chromatographic laboratory.

By July 1978, it was apparent that no money was to be readily forthcoming under normal budget heading and the matter lapsed until January 1979 when BPL received an urgent request to resurrect proposals as a submission for funding as a Special Medical Development. The new proposals, made on 24th January 1979 took into consideration the future purchase of the Institute site by DHSS; the documents are attached as Annex 4.

The new proposals were equally unsuccessful and in a letter 6th March 1979 the Department considered that application for support should be made to those responsible for the centrally financed Research and Development Programme. The matter rests there.

As an example of management procedure, the handling of this proposal cannot be seen as a satisfactory basis for future development of new laboratories at Elstree. Apart from the fact that there was no real sense of urgency outside BPL, there was a failure to realise that, in the same way that R and D merges into pilot scaled production and then into the full production process and involves many of the same staff throughout, the financial arrangements for such a unit need to relate to the main operating budgets of the laboratory, both revenue and capital, so that developments can be coordinated. Certain highly valuable blood products now made at the pilot chromatographic levels are sufficient to meet NHS requirements e.g. Factor IX and specific immunoglobulins.

The pilot production unit (as it is now termed) still forms an essential initial step in phased redevelopment and is being incorporated into the overall initial project plans so that it is properly related to existing facilities but also new process areas.

30/45

A final important point is that on the understanding that pilot facilities were provided, a senior biochemist, staff and equipment were taken on to develop chromatographic separations, in particular, affinity chromatography. The rapid success with albumin is well known to all who have visited Elstree. Progress is hampered by lack of space at a crucial time when American commercial operators are publishing the first major patent claims on this and related processes.

(2) Redevelopment of the main process areas with their full support facilities

The approach is twofold based on the functional content of a rebuilt laboratory capable of processing 120M in factor VIII per annum and the albumin and other products pro rata or according to need.

The first approach deals with the financial motivation for re-development and has been carried out in conjunction with Mr. Smart of the Scientific and Technical Committee. The report is independent of this paper.

The second approach is being taken into consideration by our initial project team of BPL staff with Architects and their consultant advisors. The preliminary report which has been prepared since the last meeting of the Scientific and Technical Committee is attached as Annex 5.

The initial project plan deals with the distribution of three main development areas, 5000 sq. metres allotted to coagulation factor production, 5000 sq. metres to Cohn fractionation of immunoglobulin and albumin and 5000 sq. metres to provide facilities for analytical quality control, maintenance and engineering, records and administration etc.

The main process areas are to be of flexible design so that constraints on the type of plant and process eventually selected would not be significant.

This approach to project planning has allowed basic estimates of capital costs to be made with approximate estimates for the increased revenue needs of the enlarged output (at current prices) and the extra requirement for staff. These details have been passed on to Mr. Smart.

3046

(3) Re-work of the existing shell of BPL

Little can be reported at this stage, a major determinant being whether the fabric would easily conform to new requirements bearing in mind that numerous alterations have already been made since the original construction. Redevelopment could be uneconomical depending on the functional content needed for the laboratory during the final stages of its enlargement.

(4) The fractionation processes, research and development programme and the Medicine's Division requirements.

At BPL, in keeping with most major plasma fractionation centres in Europe and USA, albumin and immunoglobulins are fractionated by a batch process utilizing a modification of Cohn's cold-ethanol process. For many years this process has shown itself to be highly dependable. Processing 3,500 litres plasma per week in 3 batches has resulted in sufficient output of immunoglobulin to meet needs and an albumin solution, termed Plasma Protein Fraction, consistently in excess of 95% purity. Complications in the basic process have been minimal and the yield of albumin approximately 70% - encouragingly high at the level of purity specified. Of almost equal importance, the batch process has shown itself to fit in well with the basic requirements for staffing, these being daytime working with some extensions to the normal day paid as overtime. The batch Cohn system has minimal dependence on a staff structure which is top-heavy in highly skilled technical and scientific persons and this requirement is reflected in the economic nature of the process.

A new laboratory with a capacity scaled up to five times the present level requires at the outset a process meeting of three essentials:-

(1) reliability
(2) specifications of Medicines Act
(3) compatible with the needs for Health and Safety at work.

(1) Reliability is best secured by experienced staff managing a process with which they are familiar and which has been shown to be consistently capable of providing output of sufficient

30/47

quality and with acceptable efficiency. It is argued that in a new scaled-up plant, there will be sufficient problems inherent in its size during the commissioning stage. Working knowledge of the process will be a major factor in obtaining a satisfactory product at the earliest opportunity. This approach does not exclude improvements in plant design and in support procedures of established value being incorporated into a new system. However, the basic remit for a new laboratory must be reliable production so that the earliest returns on the capital investment are shown.

(2) Process, plant and equipment will be significantly influenced by the new requirements for clean and/or sterile working. At present, these requirements are largely unknown, but require early detailed consideration. The Medicine's Inspectorate are mid-way through their inspection of BPL and a report will be forthcoming in the autumn. In the interim, the Director has placed an informal report before DHSS which is available to the Scientific and Technical Committee. It is clear that the existing laboratory has severe deficiencies, many being inherent in the building design and in a defective staff structure for a production unit. More important, the visit of the Inspectorate was viewed as an opportunity for them to become acquainted with the process so that they could advise better on future plant and process area design.

Apparent from the Inspectorate's visit was the pressing need for experimental design and this point was made forceably in connecting with early development of a pilot production laboratory at Elstree. A role of the pilot laboratory was the reconciliation of the implications of the Medicine's Act with the requirements of fractionation systems.

(3) The Health and Safety at Work Act now plays an important part in new laboratory design in that there is a requirement to disclose plans for inspection by relevant committees. This will inevitably influence building and plant design and is perhaps the best insurance that, once commissioned, the new plant is successfully managed and operated.

To augment the Cohn fractionation process in future the following processes are currently under development or await the extra space proposed in a pilot production unit.

(1) Conventional chromatography by ion exchange to be considered for specific immunoglobulin preparation with possible application in production of immunoglobulin suitable for intravenous use.

(2) Affinity Chromatography: Cibacron-blue-sepharose now functioning at pilot scale and capable of saving 95%+ of albumin wastage in Cohn fraction IV. Studies on potential toxicity are proceeding in conjunction with Medicine's Division. Serological uses for human albumin are established pending approval of the preparation for human use.

(3) Continuous electrophoresis: Seen mainly as a possible future system for factor VIII preparation, the project is currently aimed at producing a sample factor VIII concentrate for analysis within the next twelve months.

(4) Polyelectrolyte purification of factor VIII from cryoprecipitate.

Future research and development on the Cohn cold-ethanol process has been keenly advocated but awaits commissioning of a pilot production unit with appropriate R & D facilities.

30149

Annex 1

STOP-GAP REQUIREMENT FOR FACTOR VIII PRODUCTION 1978-1982

NBTS Central Laboratories
BPL: Blood Products Production Meeting, 25 October 1977.

Minutes p.2, para 6 (enclosure): The Department wondered whether some immediate action should not be taken in view of the fact that even the first phase of the rebuilding (BPL) would take some years to complete.

This immediate action has been termed "stop-gap" and is described as follows:

Stop-gap provision aims at:

(a) Maintaining present production rate
(b) Enabling stepwise increases in fractionation
(c) Preserving co-ordination between factor VIII and albumin production.

The aims for BPL during the next decade have been fixed at 1000 i.u. factor VIII concentrate and 200 g albumin as PPF per 1000 population. A phased redevelopment of BPL is envisaged to meet these targets but, during the interval before new production laboratories can be planned and built, production of factor VIII and PPF can both be increased using the continuously improving supply of frozen fresh plasma.

This paper deals with the immediate requirements for increasing factor VIII production. Albumin fractionation is considered separately. Planning on both subjects has been closely co-ordinated.

Factor VIII Concentrate

Production will be increased by a gradual rise in the processing of frozen fresh plasma (FFP) from 1200L/week to 2400L/week over a four year period. This is considered in three stages:

I 1200L → 1800L/week

II 1800L → 2400L/week

III Research and development.

The division is based upon the expected supply of FFP, stage I accommodating the bulk of FFP still in 5L pools but with a small proportion in single plastic bags; stage II is associated with a change from 5L pools to single donations.

Accordingly, requirements for stage I include:

(a) Space (re-allocation)
(b) Equipment
(c) Methods
(d) R & D for stage II (stage I R & D pilot plant)

Stage II requirements include:

(a) Equipment
(b) Methods

Stage III R & D for new coagulation laboratory methods.

30/51

STOP-GAP DEVELOPMENT FOR FACTOR VIII AND ALBUMIN

PRODUCTION 1978-1982

Contents:

Blood Products Laboratory,
Elstree,
Herts.

December 1977.

30152

STAGE I Space

Appendix 1, prepared from a document by Dr. Ellis, includes a proposal for re-allocation of space in the coagulation factor wing shown in fig. 1 of the Appendix. Main aspects are the inclusion of Room 12 in the main processing area with upgrading of Rooms 16, 16b, 16c for intermediate and final processing of factor VIII. Rooms 18 and 19 are then released for research and development, and assay and control. Fibrinogen for isotopic labelling for Amersham will be prepared in Room 12 and further facilities are available in Room 11 if required for coagulation research and development and for the pharmacological work at present carried out in Room 12.

Estimated cost

Appendix 2 shows the estimated cost of emptying and refurbishing Room 12 to provide a clean air-conditioned environment for flexible working: work surfaces will be mobile and localised working conditions provided to a high specification by laminar downflow systems. Process equipment costs are not included, but are discussed separately under the Stage I equipment heading in Appendix 1.

Rooms 16 and 16c in the main process area will be upgraded by incorporating a ceiling-vented clean air system providing temperature regulation and a positive pressure gradient where 16c > 16b > 16 > 13 and adjoining corridor. Room 16c is the final process area for factor VIII and the process will be further assisted by local laminar downflow of 0.02 µm filtered air. Room 16b will be used as a changing area for final process staff. Intermediate process work in Room 16 will be further safeguarded by local air filtration systems. Costs of air filtration for Rooms 16, 16b, 16c are shown in Appendix 2.

Equipment

Main items are shown on page 4 of Appendix 1, the limiting factor being availability of supply of a Sharples continuous-flow centrifuge (9 months). Supplies Division may be able to help by accelerating delivery.

Equipment for stage I R & D pilot plant work are also shown on page 4 of Appendix I and have been estimated to cost approximately £9,650 and were submitted in 1978-79 forecast estimates for coagulation factor R & D work.

Methods

This relates directly to the process but also includes certain suggested ways in which process-time and/or efficiency of yield could be improved. At present, process-time restricts production by limiting throughput to 3 x 400L pools/week. Without increasing working hours, this can be increased to 6 x 400L pools/week or 4 x 600L pools/week if the process is modified.

Several modifications are under consideration which could be adopted to give the desired work-flow. These modifications include:

(a) Initial process - Duplication of thawing vessels or increased pool size to 600L.
Increased centrifugation equipment.

(b) Intermediate process - Improved factor VIII recovery vessels with efficient heat exchange.
$Al(OH)_3$ separation by filtration.
Freezing of clarified stabilised factor VIII for batching into large pool final processing.

(c) Final process - Increased specific activity allowing freeze-drying and reconstitution in vials smaller than 65 ml as

2015?

R & D process methods in this area of production carry the highest priority.

Research and Development

This section in stage I is chiefly concerned with acceptance of FFP in single packs and incorporation into a quick-thaw process to obtain the expected improvements in yield.

Other research projects are concerned with improving the end-product in terms of volume, solubility and specific activity. Large parts of this work will be done in close collaboration with PF Lab Oxford.

STAGE II

To enable 2400L FFP/week to be fractionated in stage II, attention will also have to be given to changes in other parts of BPL.

(1) Maintaining the supply of FFP
(2) Integration with albumin production (Appendix 3i)
(3) Interactions with other departments in BPL.

Reference to items (2) and (3) in stage II at this point is not intended to imply any time scale for the overall operation. It does indicate, however, that as factor VIII and albumin production approach their stop-gap limits, the restraints imposed by other sections of BPL will become more and more apparent. These other sections include some needing specialised facilities, e.g. bacteriology, freeze-drying, and others less specialised, e.g. storage and inspection, labelling, packing and despatch.

Equipment

A firm statement of all the requirements for stage II equipment cannot be given now as shown and explained in the list in appendix 1, page 5. The need for additional freeze-drying plant in particular has to be considered in conjunction with terminal processing of other fractions.

Methods

This will be mainly concerned with accommodating an increasing proportion of FFP in single units and a reduction in 5L pools, this changeover being incorporated into a revised system for rapid thawing of plasma and improved yield of factor VIII.

Stage II in the development of stop-gap factor VIII production is likely to make a significant impact on facilities in other sections:

(1) The gradual acceptance of single donations of FFP by BPL will depend upon the response of the RTCs and the extent of their collaboration. Thus the change from 5L pools to single units cannot be entirely controlled by BPL.

(2) Single donor units will be RIA tested for hepatitis B (HBsAg) and will have been prepared by a closed process. This will remove part of the workload in bacteriological screening and will permit rapid use of FFP after its receipt at BPL.

(3) Acceptance of single units will enable a higher proportion of plasma obtained at RTCs to be available as FFP. The likely outcome is a shift from whole plasma to cryoprecipitate supernatant as a starting material for PPF production and a gradual overall increase in FFP supply due to a higher capture of plasma from whole blood donations.

30/54

(4) Increased pyrogen testing at intermediate and final process levels.

(5) Increased final RIA testing for HBsAg.

(6) Enlarged capacities for ancillary services - Method Study Survey.

The methods and developments in stage II will have important bearings on the plant and process incorporated into new laboratories and therefore merges with the proposed stage III which represents Research and Development associated with these processes.

Preserving co-ordination between factor VIII and albumin production

Requirements for raising PPF output are fully detailed elsewhere so that this section deals generally with the problems of integrating these two production activities.

The matter of immediate significance is that, while factor VIII production is a process with shortage of raw material in relation to fractionation potential and therefore of finished product, this is not so with PPF preparation where annual input of raw material at present exceeds production by approximately 5% and fractionation exceeds ability to complete terminal processing by a somewhat larger proportion.

A second point is that the expected increases in pool size in factor VIII production over the next two year period are relatively small when compared with the pool sizes and turnover of raw material for PPF.

As with factor VIII, considerable increases in PPF production can be phased in as described in Appendix 3ii. An analysis of the proposed phasing shows that stage I deals mainly with the problems in terminal processing, which relate to staffing and are being tackled within establishment.

Relief of this constraint on PPF production would enable an integrated work flow study involving the daily work schedules in albumin fractionation and factor VIII preparation at the proposed new levels, i.e. 195,000 litres of plasma for albumin and PPF and 130,000 litres of FFP for factor VIII per annum.

The daily work schedule should include, apart from the immediate process, details of all other laboratory services involved, materials used, quality control, bacteriological testing and pyrogen testing.

To analyse these schedules within the context of the existing laboratories it is proposed that an approach should be made as soon as possible to obtain the advice of external consultants (as originally carried out in 1965 for the BPL extension) in the first quarter of 1978.

The timing of this work study is important in that it could coincide with the agreement being reached in fact to allow planning of the Pilot Chromatography Laboratory and associated services to proceed. A Works Study on albumin and factor VIII might by that time have indicated the extent by which increased production would overflow existing space and facilities both quantitatively and qualitatively. Some accommodation for this overflow could then be included in the planning of the Pilot Laboratory. The stop-gap programme could then be secured.

Costs

Immediate costs for factor VIII are itemised in Appendices 1 and 2 and relate to refurbishing and purchase of new equipment. No immediate need is apparent at present for more staff above establishment to facilitate stop-gap increases in production. 30/5

Increased factor VIII production in relation to raw material supply

Increase in fractionation by 1200L/week represents an increase in single FFP donations of 6000/week, i.e. 312,000 per year. This number of donations equals the existing input of FFP to BPL and is equivalent to 17% of whole blood donations made in 1976 in England and Wales. Doubling this figure for FFP input increases the national commitment to red cell concentrates to 34% of all donations without other plasma requirements at RTCs being taken into consideration. When 5L pooling is discontinued, improvements in capture of FFP can be expected from blood component separation procedure at RTCs: from some centres increases in FFP are likely to be considerable, e.g. N.E. Thames have indicated an increase from 35,000 units to between 60-70,000 units annually as a result of abolishing 5L plasma pooling. Additionally, certain RTCs have yet to reach the targets set in 1975, e.g. Mersey 6,000 donations instead of 21,000 annually and North Western 9,000 donations instead of 25,000 annually. Doubling production of factor VIII will be achieved gradually due to constraints and costs in FFP separation.

Cost effectiveness of stop-gap production

The projected increase in PPF production over a four year period is of the order 60% over present fractionation limit i.e. from 140,000 bottles PPF to 230,000 bottles PPF p.a.

The increase of 90,000 bottles represents a commercial saving of approximately £1.8 million p.a. (PPF = £20 per bottle).

The annual increase in factor VIII will rise to 12.5 million i.u. at a mean current commercial rate of 13p per i.u. This represents £1.625 million p.a.

These increases will be largely achieved by internal reorganization of facilities and space, increase of more specialized equipment and modest increases in staff and materials. Certain services will need extra provision outside the present building. These are mainly for storage and terminal processing i.e. packing etc. and could be incorporated into the proposed Pilot Chromatography laboratory development. Extra facilities will be needed for increasing deep freeze storage capacity first for accommodating single unit FFP; second for storage of plasma for albumin fractionation. The latter requirement would be short term during the stop-gap period.

30/56

PROPOSAL FOR INCREASE OF FACTOR VIII CONCENTRATE PRODUCTION AT ELSTREE
(Precis of comments by Dr. Ellis)

Introduction

During the last 18 months the following developments have taken place:

(1) An additional fractionation step which gives a product with improved solubility so that 200 to 250 iu can be contained in a 65 ml vial and be reconstituted in 15 ml. By using a suitably designed container it is possible to freeze-dry this product in the existing drying plant.

(2) Production was increased in accordance with the planned expansion programme, the target set for mid-1977 being the fractionation of plasma from 343,100 donations (307,100 at Elstree; 36,000 at Oxford). The present facility has reached the limit of its capacity and to effect an increase it would be necessary to:

(a) provide additional areas in the coagulation laboratory and in storage and packaging
(b) instal a fourth fixed continuous-flow centrifuge
(c) instal additional freezing and freeze-drying plant: a small additional plant has been requested for 1978-79.

Expansion will be considered in three stages, as follows:

I. (a) 50% increase in production
(b) provision of pilot plant for the study and development of production and improved methods of fractionation.

II. 100% increase in production using the existing type of 5L bag for plasma and a proportion of plasma in single packs.

III. Changeover to single-donor plasma bag processing.

STAGE Ia 50% INCREASE IN PRODUCTION

Detailed Requirements for Expansion

Figure 1 shows a plan for the redistribution of work zones with the inclusion of additional area, namely room 12, and available laboratory facilities in room 11.

Alterations allow for the resiting of the segregated laboratory used at present for preparation of fibrinogen for isotopic labelling. With this arrangement, all routine process work would be within a single "clean" working area into which no external traffic need come - outlined in blue in figure 1 of the Appendix. The plan does not allow for plasma storage facilities which would become necessary when major fractionation of factor VIII took place from single donor packs. Cold storage is discussed later in this Appendix.

Alterations:

Refitting Room 12
Moving two sets of doors in W. corridor.
Air cooling and filtration Rooms 16, 16b, 16c.

Pilot plant work would be distributed between N-end of Room 13 and cold laboratory CR2 and R & D laboratory Room 18.

3957

Modification of Rooms 18 and 19 for use in assay and control and R & D.

Alteration costs are shown in Appendix 2.

Additional equipment:

Continuous-flow centrifuge (fixed installation	£5,500
Installation	500
Refrigerated laboratory centrifuge	4,500
Cartridge filter-holders (3)	1,500
Filling vessels	200 (estimated)
Controlled temperature process vessels	To be developed
	1,000 (estimated)
Filtration equipment ($Al(OH)_3$)	1,750
Second thawing vessel	1,500 (1st vessel £750 July 1975)
	16,450

Additional freezer in Drying Plant
(in addition to one in 1978-79 estimates)

Equipment for Room 18 can be met from provision of £500 small equipment costs forecast estimate 1977/78 R & D page 13(12).

STAGE Ib PILOT PLANT EQUIPMENT AND REFRIGERATION

(These have already been listed under "R.D. CONTINGENCY 1978-79")

Storage facility (-35°C) for single-donor bags *	£9,650 **
-80°C freezer	
Bag-stripping machine	
Plasma crusher	
Controlled temperature thawing vessel	

* Size to be decided (approx. 1000 cubic feet)
** BPL revised estimates 1977/78 p.4 and 17.

STAGE II 100% INCREASE IN PRODUCTION

Refrigerated laboratory centrifuge	£4,500
Second thawing vessel (Possibly of new design for "rapid-thaw")	1,500
Plasma softening rack (not required if the changeover to rapid-thaw procedure were made)	
Additional freezing and drying plant	To be estimated
Additional filtration equipment	1,100

30/58

STAGE III CHANGEOVER TO SINGLE BAGS

Bag-stripping equipment Plasma crusher Thawing vessel Other items	To be decided.

NOTE:

Single-donor packs are space consuming and a substantial input storage space at -35°C would be required in addition to existing deep-frozen storage space.

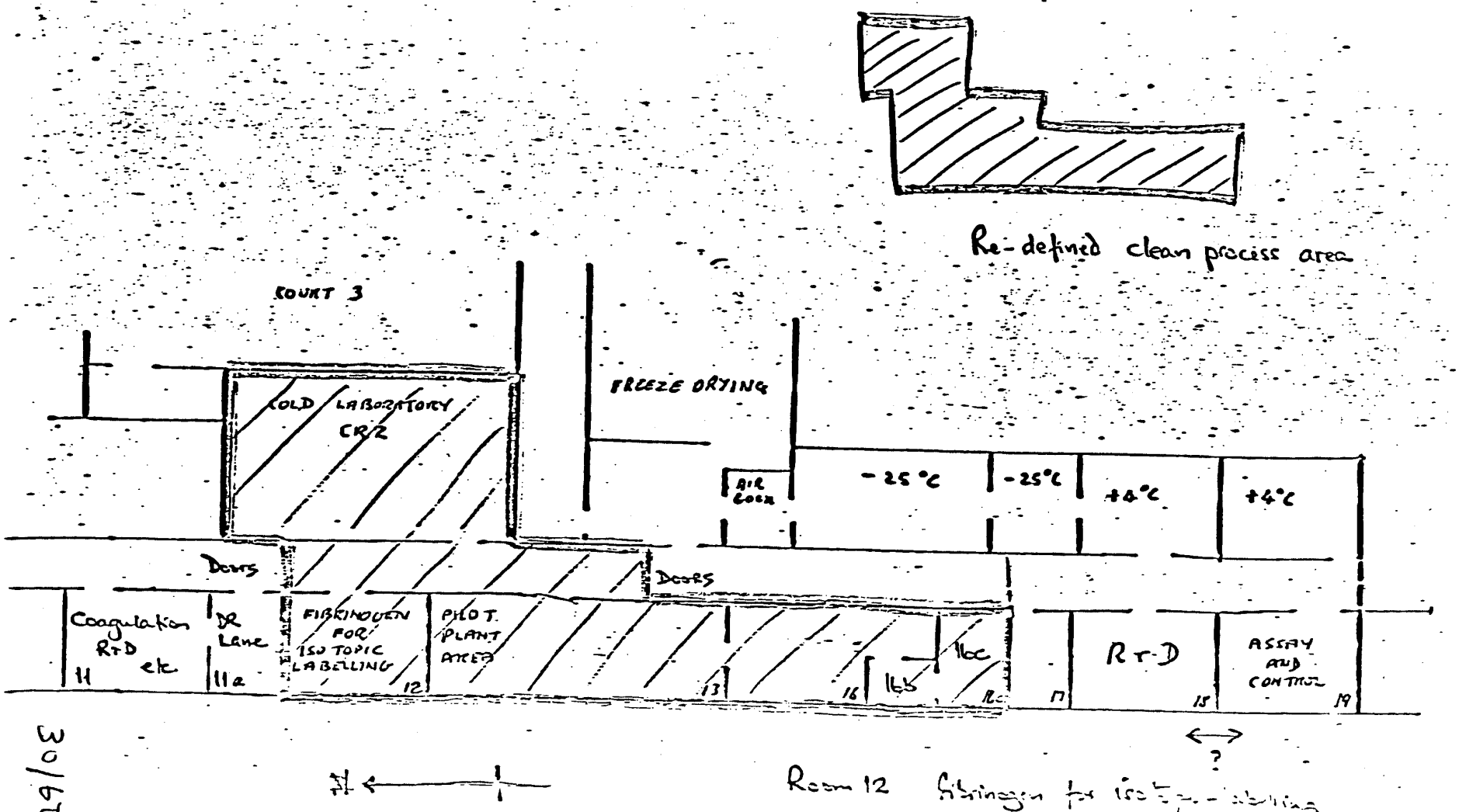
At the fractionation rate envisaged, i.e. approx. 2400 litres per week, the storage of, say, two weeks input of plasma would require a walk-in deep-freezer at -35°C large enough to store about 1000 cubic feet of plasma containers. (This would require an area about the size of an average room of 20' x 15', plus a site for compressors, e.g. Oxford walk-in freezer £7,500).

The siting of such a store will require further discussion, and no provision has been made for it either on the plans or as a cost item.

30/59

Appendix 1 Figure 1.

COAGULATION FACTOR LABORATORY : PROPOSED REVISED LAYOUT



30/6/83

1. Cost Estimate for Upgrading Room 12

Expenditure will be generated under the following heads:

(a) Installation of an air conditioning system
(b) Builders work for (a)
(c) Provision of localized air filtration equipment
(d) Builders work necessary to upgrade room surfaces.

Estimates:

(a)	Individual air conditioning system	2,100 *
(b)	Installation of (a)	500 *
(c)	Purchase of Microflow (or similar) Filters	
	2 x 4' x 2' overhead units	1,200
	1 x 1' x 1' portable unit	210
(d)	Upgrading room, clearing benches, covering ceiling, replacing windows, removing radiators, chasing in pipework, making good painting etc. Electrical work, removing plumbing.	2,000
		6,010

2. Moving doors in corridor to provide new process area 200

3. Cost of providing air filtration in Rooms 16, 16b, 16c

Ceiling vented positive pressure air filtration	2,400 **
Microflow Filters	1,200
Labour and installation	1,500 **
	5,100

4. Refurbishing of Room 18 accomplished by re-allocation of provision for Room 16c of £1,000 set aside in forecast estimates 1977/78 /page 19(14)/

5. Room 19 provision of £500 forecast estimates 1977/78 /page 19(13)/

Note: A quotation (copy attached) now received for items* in Room 12 and items** in Room 16:

Room 12	£2,594
Room 16	3,862

30/61

ENVIRONMENTAL CONTROL WESTERN LTD

83 NORTH STREET
BEDMINSTER
BRISTOL BS3 1ES

Telephone: Bristol (0272) 633321 & 633322

YOUR REF

OUR REF JB/77/518/LEH

8th December 1977

The Lister Institute,
Blood Product Laboratory,
Dagger Lane,
Elstree,
Herts.

For the attention of Mr. B. Montgomery - Maintenance Engineer

Dear Sirs,

Air Conditioning of Laboratories

Further to the visit by our Mr. R. Stanley to your premises regarding the above project, we have pleasure in reporting upon your requirements.

Requirement

Room 12

We are required to provide cooling to the area, limiting maximum summer temperatures to the range 68°F to 85°F, with air filtered down to 5 microns.

Room 16C

We are required to again provide cooling to the area, limiting maximum summer temperatures to the range 68°F to 85°F, with air filtered down to 2 microns. Air spillage to travel to rooms 16B and 16.

Recommendations

As a flat roof is available over both areas involved, we recommend the installation of roof top type packaged air conditioners, one to each area.

This type of air conditioner has a cooling only function and contains all necessary plant within one casing (i.e. compressor, condenser, evaporator plus both indoor and outdoor fans).

Contd./

Sheet metal ductwork will link the units to the room, via prepared openings in the roof structure and distribute the air into the areas concerned.

Room 12 will have a return air duct again rising through a prepared opening in the roof structure, back into the unit with a small fresh air supply duct connecting. The filter for this plant will be a bag type disposable filter giving an efficiency of 95% against 5 micron dust.

The plant serving Room 16C is working on full fresh air, distributing mainly to the 16C area but with a small bleed duct to 16B. Pressure relief flaps will allow 16C to be slightly pressurised, relieving to 16B and 16C.

If the plants are to be run continuously throughout the year, we would recommend the inclusion of heater coils within both systems. We believe low pressure hot water heating is available, and therefore we have priced for hot water coils and associated controls as an additional price.

The controls included within the cooling side are room thermostats plus a pressure switch across the filter to give an alarm signal when the filters require changing.

We trust the above and enclosed are to your requirements and look forward to your further instructions.

Yours faithfully,
for ENVIRONMENTAL CONTROL WESTERN LIMITED

GRO-C

J. Barnett
Manager

Enc.

30/63

ESTIMATE AND SPECIFICATION

AIR CONDITIONING UNIT - ROOM 12

To the supply of one 50MH048 roof-top packaged air conditioning unit with a nominal cooling capacity of 51400 b.t.u's per hour @ 90°F ambient.

Unit suitable for operation on 380/440 Volts 50 cycles three-phase electrical supply.

AIR CONDITIONING UNIT - ROOM 16C

To the supply of one 50DG006 roof-top packaged air conditioning unit with a nominal cooling capacity of 55000 b.t.u's per hour @ 90°F ambient.

Unit suitable for operation on 380/440 Volts 50 cycles three-phase electrical supply.

MAIN FILTERS

To the supply of one set of bag type and one set of Absolute type filter elements as manufactured by Auchard Developments. Each filter bank to include a visual manometer and a pressure switch to activate signal (by others).

FILTER AUXILIARY FAN

To the supply of one duct mounted axial flow fan to room 16C filters, to overcome resistance of Absolute filter elements.

Unit suitable for operation on three-phase 380/440 Volts 50 cycles electricity supply.

DUCTWORK

To the supply of three ranges of ductwork fabricated from galvanised mild steel sheet. Where supply air duct is exposed external surfaces will be insulated with glass-fibre mat and vapour sealed with metal foil finish.

Grilles generally to be of aluminium frame and components.

INSTALLATION

All of the above equipment will be installed in a first-class workmanlike manner. This will include all anti-vibration mountings and brackets, but does not allow for any builders work or electrical work.

The systems will be started, tested and left in working order.

30/64

ESTIMATE & SPECIFICATION (contd.)

DELIVERY

6-8 weeks from receipt of firm order.

PRICES

Room 12	-	Cooling only	- £2026.00	
Room 12	-	Addition for heating	- £ 568.00	2594
Room 16C	-	Cooling only	- £3141.00	
Room 16C	-	Addition for heating	- £ 721.00	3862

GUARANTEE

The above equipment is guaranteed for twelve months.

EXCLUSIONS

(i) Any builders work, such as preparing holes in building structure, and making good, etc.

(ii) Supply of switchgear, electrical wiring of units and controls.

(iii) Lifting equipment onto roof.

(iv) Supply of pipework, etc. to heater units.

(v) Working outside of normal hours.

TERMS OF PAYMENT

80% of the Contract Price is due upon delivery of materials to site before installation commences. 20% of the Contract Price is due upon completion.

CONDITIONS OF SALE

This quotation is subject to the Conditions of Sale as printed on the enclosed sheet.

3-/65

ENVIRONMENTAL CONTROL WESTERN LTD.

CONDITIONS OF TRADING

1. **GENERAL** – Our contract with you will be subject to the following conditions which will prevail should they conflict with any others, and which can only be varied or waived in writing by a Director of Environmental Control Western Ltd. ("the Company").

2. **PERIOD OF TENDER** – This tender is conditional upon the acceptance in writing within thirty days of the date hereof or such longer period as may be agreed in writing.

3. **CONTRACT VARIATIONS** –
(a) **Materials, Labour and Transport** – This tender is based on the prices of materials, labour and transport ruling at the date of tender, and we reserve the right to amend the tender prices to meet any variations in these prices due to Legislation, Government Orders, Regulations or Directions, changes in the National Agreements covering wages and conditions in the industry or any other cause beyond our control.
(b) **Additional Work or Variations** – Any additional works (not being the subject of separate tender) or dayworks will only be executed on the written authority of the purchaser and will be charged for at our standard daywork rates.
(c) **Additional charges** will be made if extra work is involved through your site or site access not being ready to receive our materials when delivery is made upon an agreed date.
(d) **Hours of Work** – This tender is based on wage rates for work done during recognised working hours specified in the current National Agreement of the industry. If overtime is worked at the request or with the approval of the Customer, his Architect or other Agent, the additional cost will be charged as an extra.
(e) **Discounts** – All prices are strictly nett and no discounts will be given.

4. **EXCLUSIONS – WORKS AND FEES NOT COVERED IN THE TENDER** – This tender covers the items of the Specification only and, unless otherwise expressly stated, does not include any of the following (for whatever purpose they may be required), viz: Builders', Joiners', Masons', Plumbers', Painters', Electricians', Stoking (except for testing the installation or parts thereof), or any other trades works: supply and erection of scaffolding, ladders or movable platforms, hoisting and/or lowering gear; fuel, water, gas or electric current; lighting fees of District Surveyors, Insurance Inspectors or any other Inspecting Authority.

5. **TERMS OF PAYMENT** – United Kingdom & Eire, 80% of the total contact value is due immediately on delivery of material to site and 20% on the completion of the installation. When the contract is for supply only, payment is due in full on delivery.

6. **MATERIALS** – The property in unfixed materials shall not pass until all materials shall have been paid for in full. All materials on the site fixed or unfixed are at the sole risk of the Customer and in the event of any of the same being damaged, destroyed, or stolen, we shall be entitled to full payment therefor and also for any work damaged, destroyed, or lost, and the cost of replacing any such material and of reinstating or restoring any such work shall be charged as an extra under clause 3(b) provided that the Customer shall not be responsible for any loss occasioned solely by the negligence of our employees.

7. **FIRE RISK EXEMPTION** – Notwithstanding anything contained in clause 6, hereof, the Customer shall be solely responsible for all loss or damage to the contract works arising from fire howsoever caused including unfixed materials on site for the purpose of carrying out the contract works and shall indemnify the Contractor against such loss or damage.

8. **GUARANTEE** – In place of any other conditions or warranties whether imposed by Statute or implied by Common Law, we undertake free of charge any materials or work found to be defective as follows: We will repair, or if necessary, replace if the defect is due to faulty manufacture or bad workmanship and is brought to our attention within six months of the completion of the work provided nevertheless that:–
   (a) We accept no responsibility for any drawing, design or specification not prepared by us, and submission of this tender does not constitute any warranty, guarantee, representation or opinion of the practicability of construction or of the efficancy, safety or otherwise of materials to be supplied or work to be executed by us in accordance therewith and the cost of any additional work caused by defect in any such drawings, designs, or specifications shall be chargeable as an extra under clause 3(b) hereof.
   (b) We shall not be liable for any consequential loss or damage caused directly or indirectly by any defect or otherwise howsoever.
   (c) We shall not be liable for any loss or damage direct or indirect nor for any extra work entailed due to the apparatus being put into operation by the Customer or by us at his request before it is handed over for beneficial use.

9. **COMPLETION AND DELIVERY** – We shall make every effort to complete the work by the time stated but we shall not be liable for delays due to strikes, lock-outs or other causes beyond our control.

10. **DRAWINGS** – Unless expressly stated drawings submitted with this tender shall not be binding as to detail.

11. **THIRD PARTY LIABILITY** – We shall not be liable for any claim whether brought against the Customer or against us either under any Statute or at Common Law by any person arising from any cause other than our negligence or that of our employees and the Customer shall indemnify us against any such claim and the costs of any legal proceedings.

12. **COMPLIANCE WITH LAW AND GOVERNMENT REGULATIONS** – Acceptance of this tender constitutes a warranty and representation by the Customer that he has complied with every applicable Statute, Order in Council, Regulation or Direction, Bye-Law or other lawful requirement or instruction, whether of the Government or of any local or other lawful authority and in particular that he has lawfully obtained every necessary licence, permit or authority that may be required in connection with the work.

13. **REVOCATION OF CONTRACT** – Should you:
   (a) fail to make payment of any amount when due, or
   (b) if a natural person, die or be certified mentally incapable, or
   (c) become insolvent, commit an Act of Bankruptcy, or have a receiving order in Bankruptcy made out against you, or
   (d) being a company, go into liquidation whether compulsory or voluntary, other than for the purpose of and followed by amalgamation or reconstruction, or have a Receiver of any part of your business or assets appointed,

   then we reserve the right:
   (i) to treat all sums due or to become due from you to us on any account whatsoever as immediately due and payable:
   (ii) to cancel any contract we have with you or to cancel or suspend delivery of goods and materials, execution of work, etc., and
   (iii) to enter on your sites and remove any of our property.

14. **LAW AND ARBITRATION** – These conditions and this contract shall be construed and governed in accordance with English law, and if any dispute or question between us cannot be settled by agreement it shall be referred for determination to a single referee pursuant to the provisions of the Arbitration Act 1950; should we not be able to agree upon the appointment of the referee he shall be appointed by the President of the Law Society of England.

15. Not withstanding any previous statement or condition unless expressly stated for a specific term not exceeding six months, all material and labour costs will be charged at the rate applying at the date of the supply of the equipment and installation.

30/66

BPL STOP-GAP PRODUCTION 1978-82

Meeting: Dr. Lane, Mr. Vallet. 8th November 1977.

Proposals for increasing PPF and factor VIII production made by Mr. Wesley and Dr. Ellis respectively were discussed to assess their feasibility during the stop-gap period.

Both proposals include a two-phase increase in final output as follows:

PPF and Albumin	140,682 →	155,000 →	195,000L plasma per annum
Factor VIII	62,500 →	93,600 →	124,800L FFP per annum

PPF and Albumin — Phase 1 is constrained by staff shortages in terminal processing (final solutions)

Phase 2 exceeds the ancillary services available

Factor VIII — Phase 1 requires internal reorganization of space and equipment within the coagulation factor laboratory

Phase 2 exceeds the ancillary services available.

On discussion, the priorities appear to be self-evident:

(1) The rapid relief of constraints on terminal processing of PPF by recruitment of staff from available establishment or by placing requests for further establishment.

(2) Incremental increases in plasma throughput for Factor VIII production are small in relation to plasma used for albumin production. Rate of increase in raw material for Factor VIII is likely to be gradual i.e. rising by 100 → 250L/week during the ensuing 24 - 36 months. The extra cryoprecipitate supernatant is unlikely to cause difficulties with albumin production if the terminal process has adequate capacity.

(3) Both proposed phase 2 operations require basic work study involving detailed work schedules. These would include requirements for all laboratory services, materials, quality control, bacteriological and pyrogen testing.

(4) Internal work study data should be made available for an external method study survey. Permission should be sought if necessary for such a survey to be made, hopefully in the first quarter of 1978. The approaching visit of Mr. Miller (ICI Method Study Group, 1965) is fortuitous in that advice may be sought.

(5) It would be advantageous for a Method Study Survey to coincide with the anticipated approval in fact that the Chromatographic Pilot Laboratory and associated services can be planned and built. Certain requirements for the stop-gap programme as indicated by method study could then be included in the Pilot Laboratory services.

Proposed objectives
(1) Staffing in final solutions
(2) Work schedules for PPF and Factor VIII
(3) Method Study Survey for Stop-gap programme.

30167.

Salt-Poor Albumin/Plasma Protein Fraction Production

E.D. Wesley

I. 1977

(a) estimated plasma intake to large fractionation laboratory (LFL)

= 148,625 L (total source material)

(b) estimated plasma fractionated

(based on Jan-Sept. figures) = 140,682 L (source material used)

i.e. excess of 5% in starting plasma.

(c) PPF production (estimated 4.11.77) = 130,000 x 400 ml bottles +

6250 x 25g albumin

equivalent to 113,500 L plasma as bottled end product.

(i) more plasma came into LFL in 1977 than was fractionated (a-b)

(ii) more plasma was fractionated than was processed to albumin and PPF (b-c)

(d) The increase in PPF production during 1977 was from the 1976 figure of 83,000 x 400 ml bottles to 130,000x400ml bottles. For a number of reasons, at the beginning of 1977 it was uncertain whether it would be possible to produce more than 130,000 bottles in a year:

(i) would sufficient plasma be available?

(ii) was the Final Solutions Section capable of producing more than 130,000 bottles PPF/year?

From 1977 experience, it is clear that the Final Solutions Section can produce more than 130,000 bottles/year. Sections II and III deal with how much more may be produced.

II. Theoretical upper limit of Albumin/PPF production in Large Fractionation Laboratory at 4.11.77.

Neglecting questions posed by (d) i and ii, it appears that the present limiting factor to albumin/PPF production is +30°C and +20°C incubation storage.

The upper limit is calculated as being approx. 190,000 containers per year, the calculation being based upon a maximum of 6 batches being stored for 2 weeks in the existing +30°C room. (6 x 1300 x 25 weeks)

1977 production experience suggests that this figure can be achieved only by further increase to the Final Solutions Section staff, to

1 Senior Chief Technician
1 Technician
4 J.L. technicians (1 extra to number @ 4.11.77)
2 Lab. Assistants
5 Filling room staff (2 extra to number @ 4.11.77)

30/68

(other than minor items) in production equipment would be necessary.

Therefore, assuming 190,000 containers to be feasible, then the following calculations may be made:

(a) 190,000 containers albumin/PPF = 180,000 x 400 ml PPF
& 10,000 x 25 g albumin.

180,000 bottles PPF @ 1.25 bottles/L. plasma = 144,000 litres
& 10,000 x 25 g albumin = 11,000 litres

155,000 litres plasma.

(b) annual plasma intake to LFL = 148,625 litres
(Jan-Sept. 1977 = 111,469 litres)

(c). Extrapolating increases in plasma supply by up to 1,000 L per week from additional factor VIII production, then a total of approximately 200,000 L plasma will be available for fractionation. This increase assumes that there is no associated decrease in intake of time expired plasma. Likewise the increase is optimistic when related to the projected stop-gap period of 4 years.

(c)-(a) = 45,000 litres plasma excess per year.

III. Theoretic upper limit for albumin/PPF production in LFL after modification to +30°C and +20°C storage

Of the 45,000 litres of excess plasma shown in (c)-(a) above, how much could be processed to PPF/albumin and/or freeze-dried factor VIII, assuming extra space +30°C and +20°C were made available?

Assuming extra space were available, the maximum production, based upon current experience is calculated at 240,000 container/year. This figure is based upon experience of 3 batches produced per week during part of 1977, suggesting that 4 batches per week could be produced for much of the year.

Such an increase would involve both an increase in the staff in the Final Solutions Section, and the purchase of more equipment (500 L sterile storage vessel, 40 x 40 cm Carlson Ford filter process). Autoclave, oven and heat-treatment capacity will be satisfactory, providing their reliability does not decrease.

Note See notes of meeting between Mr. Vallet and EDW concerning how +30°C incubation should be transferred to room 1.08 and +20°C storage transferred to room 1.13.

(a) 240,000 containers per year.

e.g. 230,000 x 400 ml PPF = 184,000 litres plasma (125 bottles/L)

10,000 x 25 g Albumin = 11,000 litres plasma

approx. 195,000 litres plasma

(b) II(c) above suggests that sufficient plasma will be available, although this will limit the amounts to be sent to PFC Liberton or freeze-dried as cryoprecipitate supernatant.

(c) The success of the fractionation programme started for a limited period (to test its feasibility) recently suggests that 195,000 litres of plasma can be fractionated within a year with the existing fractionation equipment providing sufficient staff were available to work the necessary overtime, and to maintain equipment.

30/69

7 November 1977.

SUMMARY OF ESTIMATED COSTS, STAGES I & II

A	Capital expenditure	£
	Room refurbishing factor VIII (Appendix 2)	11,310
	Stage I process equipment (approx) (Appendix 1 p.2)	16,450
	Stage I R & D Pilot Plant Forecast Estimates 1978/79	9,650
	Grant refrigerated water bath	1,500
	Stage II Process Estimate (Appendix 1 p.4)	7,100
	2 x 20' x 15' walk-in -40°C freezers	15,000
		61,010

Estimates for the following capital items have still to be obtained: controlled temperature vessels, additional freeze-drying plant.

B	Annual Revenue Expenditure Estimate	£
	Staff	20,000
	Supplies etc. as factor VIII production rises from ca 12 to ca 24M iu p.a. will increase to	47,000
	Associated overheads at maximum production	4,000
	Estimated total revenue expenditure:	71,000

30/70

Annex 2

(i) Summary of Integrated Recommendations

In this section are the recommendations by Systems-Analysis Consultants in conjunction with BPL staff.

(ii) Primary objectives

Production output of products listed below of

adequately high quality

with sufficient flexibility (including maintenance down-time)

to give adequate reliability

coupled with the development of a more effective management team (looking beyond 1982)

(iii) Aim to specific realistic levels of production for 1982, coupled with study to sustain/improve reliability of the system.

(iv) Specific production output objectives

PPF	230,000 x 18g bottles
'Salt-poor albumin'	12,000 x 20g bottles
Fraction II paste - for anti-D diluent and as n-immunoglobulin	80,000 x 250 mg
	60,000 x 750 mg
	2,000 x 15 mg (for use with measles vaccine)
Albumin 10% soln.	7,000 x 2.5 ml
	3,000 x 10 ml or 100 ml
Re-precipitated albumin (10% soln.)	500 x 10 ml
Factor VIII (Elstree alone) + Oxford	28.75m i.u. as 115,000 x 250 i.u.
Factor IX	7.5m i.u.
Fibrinogen for isotopic labelling	150 x 500 mgm
Fibrinogen	2,000 x 200 ml
	1,000 x 10 ml
Fibrin foam	1,000 x 4 x 4 cm
	300 x 2 x 2 cm

30/71

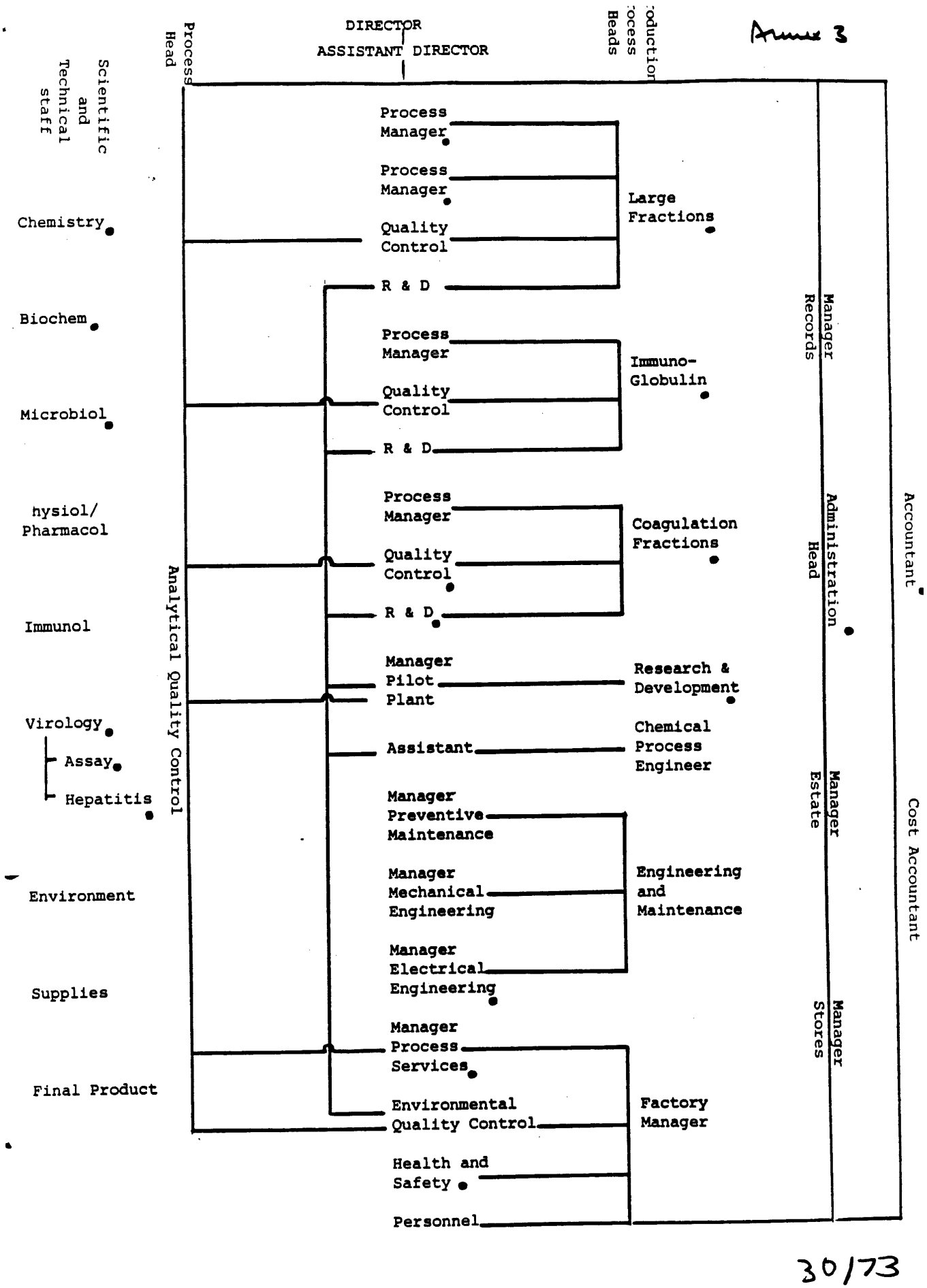
Thrombin	1,200 x 100 i.u.
	1,500 x 500 i.u.
	1,000 x 1000 i.u.
Anti-D equivalent to	72,000 x 100 ug
Anti-tetanus	30,000 x 250 i.u.
Other specific immunoglobulins	20,000 vials p.a. (to include up to 11,000 chickenpox)
Whole dried plasma	up to 15,000 (includes some flexibility)

An essential part of the package of recommendations are follow-up studies (a) to sustain/improve reliability, with special reference to both staffing and key items of equipment and (b) to develop adequately effective management, with special reference to an organisation structure appropriate to the current and future needs of BPL and integrated with effective production planning and control systems.

Further work is also recommended regarding quality assurance.

30/72

Annex 3



30/73

Annex 4

BPL Pilot Laboratory for Chromatographic and Fractionation Development
Submission for funding as a "Special Medical Development"

The enclosed documents outline the background to the development details and purpose of the pilot laboratory. Included is an estimate of cost attributable to

1) Building
2) Major plant and equipment
3) Annual forecast revenue cost for staff with main running costs based on November 1978 prices.

General Introduction

The pilot Laboratory was first envisaged over three years ago and, although supported in principle, it received no firm financial commitment during the ensuing two years. Permission was given for a feasibility study and this was carried out but in retrospect was hampered by the then existing constraints imposed by leasehold agreements with the Lister Institute.

To reactivate this matter, a special meeting was called at BPL in February 1978 at which a demonstration of the proposed scientific development was laid on for the Advisory Sub-Committee reinforced by experts. Details of this demonstration and of the minutes of the meeting of the Advisory Sub-Committee which followed are with the Department but it should be added that the pilot scheme was given the full support of the committee with the instructions that the matter should be taken up forthwith. Another year has passed by without further advance.

Significantly, during the past year, the Lister Institute has closed and the site is shortly to be acquired by the Crown, thereby releasing the constraints on the Pilot Laboratory programme.

In accordance with the new requirements, the Pilot Laboratory is presented in the new form (enclosed) with the best guesstimate of costs at current rates. The need for this laboratory is now critical and it is essential that this proposal does not represent another paper exercise resulting possibly in a further delay.

R. S. LANE
24 January 1979.

30/74

CHROMATOGRAPHIC PILOT LABORATORY

FORECAST ANNUAL REVENUE COSTS FOR
FIRST 3 YRS AT NOV. 1978 PRICES

1. PERSONNEL COSTS (excluding Dr. Havey and 1 technician)

4 Scientific Officers	£ 26,092	
2 Senior Technicians	12,410	
3 Technicians	14,658	
2 Lab. Assistants	6,497	
1 Fitter - Elect. or Mech.	4,156	
1 Secretarial Staff	3,348	
		67,171

2. BUILDING RUNNING COSTS

Rates	1,250	
Building Maintenance	500	
Plant Maintenance	1,000	
Heat and Light	5,000	
Cleaning	1,500	
Misc. Admin Support	1,000	
		10,250

3. SUPPLIES

a) Research based on 11 technicians and current consumption rates of £2,734 p.a.

11/2 x £2,734	say	15,000

b) Process

estimated		30,000
	Annual total	£122,421

30/75

24.1.79.

EQUIPMENT BUDGET

		£
1.	Conn Fractionation Suite	33,200
2.	Affinity Chromatography Unit	17,768
3.	Ion Exchange Chromatography Unit	52,272
4.	Additional Fractionation Suite	24,289
5.	Analytical Laboratory	17,471
6.	Water production and storage	23,000
7.	Freeze-drying	10,000
8.	Sterile filtration and bottling	10,500
9.	Autoclave	14,000
10.	Instrumentation	7,500
11.	Four clean laboratories @ 10,000	40,000
	TOTAL	£250,000

30/76

			Running total £
1.	Cohn Fractionation Suite		
	Sharples centrifuge (x 2)	£12,000	
	Fractionation vessels	10,000	
	Pumps	1,200	
	Centritherm (or equivalent process)	10,000	
	Sub-total	33,200	33,200
2.	Affinity Chromatography Unit		
	Column	1,000	
	Adsorbent	900	
	Pump (Sera)	500	
	Uvicord (Pharmacia)	1,710	
	Recorder	1,086	
	Pellicon Cassette System	2,700	
	SSP Pump (ND Handy)	772	
	Filter press (20 x 20)	1,500	
	Vessels	3,200	
	Automation	4,400	
	Sub-total	17,768	50,968
3.	Ion exchange chromatography		
	Pharmacia system	38,200	
	Filter press (20 x 20)	1,500	
	Sharples centrifuge	6,000	
	Stirrers (x 2)	100	
	Pellicon Cassette System	2,700	
	SSP Pump (ND Handy)	772	
	Vessels	3,000	
	Sub-total	52,272	103,240
4.	Additional Fractionation Suite		
	Flexible budget to accommodate		
	i) Continuous electrophoresis		
	ii) Batch ion exchange and gel filtration		
	Sub-total	24,289	127,529

30177

5.	Analytical Laboratory		
	Electrophoresis tanks, power pack etc.	200	
	Gelman Densitometer	4,000	
	Spectrophotometer	8,600	
	Columns and adsorbents	75	
	Fraction collector	1,150	
	Pump	380	
	U.V. detector (Pharmacia)	1,710	
	Recorder	1,086	
	Flame photometer	270	
	Sub-total	17,471	145,000
6.	Water production and storage		
	Still	15,000	
	Storage vessel	8,000	
	Sub-total	23,000	168,000
7.	Freeze-drying - Edwards EF 6	10,000	178,000
8.	Sterile filtration and bottling		
	20 x 20 Filter press (x 2)	4,000	
	Accessories (e.g. vessels)	2,000	
	Hot-air cupboard	2,500	
	Laminar flow air bench (x 2)	2,000	
	Sub-total	10,500	188,500
9.	Autoclave	14,000	202,500
10.	Instrumentation for process areas 1 - 3		
	Stirrers	200	
	Balances	3,600	
	pH meters (x 4)	2,000	
	Conductivity meters (x 2)	1,700	
	Sub-total	7,500	210,000

11. C. aboratories (4)

uire a flexible budget to accommodate new ideas

rial processes, e.g. PEG fractionation
heat processing
Sephacryl fractionation
Electrophoresis

Budget £10,000 for equipping each lab. 40,000

30/78

1. Cohn Fractionation

100L plasma pool

Assume 3.5g% HSA i.e. 3,500g HSA/100L

Assume 75% yield i.e. 2,625g HSA

Bottle as 20g% HSA i.e. 131 bottles

48 week year gives 6,288 bottles (27,946 bottles PPF)

£30/bottle yields £188,640

2. Ion exchange chromatography

150L plasma/week at 3.5g% HSA

Theoretical yield >90% i.e. 4,725g HSA

i.e. 236 bottles 20g% HSA per week

48 week year gives 11,328 bottles 20g% (50,346 bottles PPF)
£30/bottle yields £339,840

At 75% efficiency 9,440 bottles 20g% HSA

41,955 " PPF

Value £283,200

3. Affinity chromatography

340L Fraction IV/week (i.e. 68kg F.IV ppt)

Assume 1.5g% HSA i.e. 5,100g/340L

Theoretic yield >90% i.e. 4,590g HSA

i.e. 229 bottles 20g% HSA per week

48 week year gives 10,992 bottles 20g% HSA (48,853 bottles PPF)

£30/bottle yields £329,760

At 75% efficiency 9,160 bottles 20g% HSA

40,710 " PPF

Value £274,800

SUMMATION (1 - 3)

75% efficiency: 24,888 bottles 20g% HSA; 110,611 bottles PPF; value £746,640

Operational capacity: 28,608 bottles 20g% HSA; 127,145 bottles PPF; value £858,240.

30179

CHROMATOGRAPHY PILOT LABORATORY

BLOOD PRODUCTS LABORATORY, ELSTREE

REPORT No. 1 - ORDER OF COST

Contents :

Hutchison, Locke and Monk, -
Chartered Architects
19, The Green, Richmond, Surrey.
01-948 - 3136

in conjunction with
James Nisbet and Partners, -
Quantity Surveyors
Halco House,
28-30, Great Peter Street, S.W.1.
01-222-6271

DAH/AS/346.C.1.
2018D

1.00. Introduction

1.01 We have been asked to make a preliminary strategic assessment of location of accommodation to provide a Chromatography Pilot Laboratory related to the existing facilities of the Blood Products Laboratory, together with an order of cost estimate of the new facility related to a preliminary schedule of accommodation.

2.00 Background

2.01 Whilst an earlier study for the provision of some accommodation for Chromatography Research on a phased basis was carried out in October 1977, this was then limited by the restraints brought about by the control of the major area of land being within the Lister Institute; these limitations no longer exist, and so a wider range of solutions can be considered.

2.02 The attached drawing no. 346.D.1 shows the extent of existing Blood Products Laboratory buildings, and also shows the vicinity and plan areas of limited extensions to the two levels of the southern end of the Laboratory planned for commencement on site in 1979 to resolve the present congested situation in regard to delivery of materials and dispatch of products; this is known as the "Stop-Gap Project" in regard to Terminal Processing.

3.00 Site Analysis

3.01 The same drawing no. 346.D.1 also identifies these potential site areas - A,B, and C - for further growth of the existing Laboratory buildings, whilst acknowledging that the larger area to the south of the present road access does not offer the prospect of physical connection to the existing buildings, and in any event, if developed now, would prejudice development of a new laboratory facility if required in the long term.

3.02 In regard to the sites hatched and marked A,B and C on the attached drawing no. 346.D.1, and acknowledging discussion with representatives of the Blood Products Laboratory, we comment as follows:-

Site A - Due to its location in relation to the existing PPF laboratory and to the east of overall buildings this area is considered to be most suitable for medium term expansion of the PPF production area which is the major products of the complete Laboratory; ready physical connection is possible to existing PPF production facilities, and the facilities for improved dispatch of products offered by the current "Stop Gap" Project would be immediately available.

30181

Site B - This is adjacent to the research facilities which exists to the north of the present Laboratory, and as such, would seem to offer the maximum benefit for extension to provide new research facilities for Chromatography, with potential immediate physical connection, and without apparent limitation to further expansion if subsequently shown to be necessary.

Site C - This area offers scope for connection and contact to the existing Laboratory along its western frontage, and the land at present is only occupied by a small building providing canteen facilities; after consideration, it is thought that this land might best be reserved for medium expansion of Factor VIII, particularly if developed towards the southern end of the Laboratory where it could share the benefits of the roadway for transit of materials and end products.

3.03 Thus, from the above, it will be seen that Site B is the presently preferred area of the overall site for location of the Chromatography Pilot Laboratory.

00 Accommodation Requirements

4.01 We have been advised of an outline schedule of accommodation requirements as set down below:-

A - Therapeutic Pilot Process Area		sq. ft.
i)	Cohn Process Area - (same process as large fractionations in PPF Laboratory)	550
ii)	Affinity Chromatography area - (tall production columns)	750
iii)	Ion Exchange Chromatography area (no columns)	440
iv)	Additional Fractionation (uncommitted - parental use)	260
v)	Process Services - Freeze Drying, Vessel washing, Assembly, Sterilizers, Equipment Storage, Cold Room, -4°c to-30°c, Reagent Store	2000
vi)	Changing Area, Sterile Filling	900

30152

	sq. ft.
B - Clean Laboratory	
Storage) Reagents) Wash-up) Cold Room) Services)	800
C - Staff Provision	
Lecture facilities) Offices/Laboratories)	900
	6800
D - Undesignated space allowances - 6800 x 25%	1700
	8500
E - Circulation including plant space allocation - 8500 x 40%	3400
	11900 sq. ft.

5.00 Order of Cost

5.01 Related to the above accommodation requirements, Messrs. James Nisbet and Partners, Quantity Surveyors, have prepared an order of cost statement related to a notional understanding of technical and services requirements for the new Laboratory as follows:-

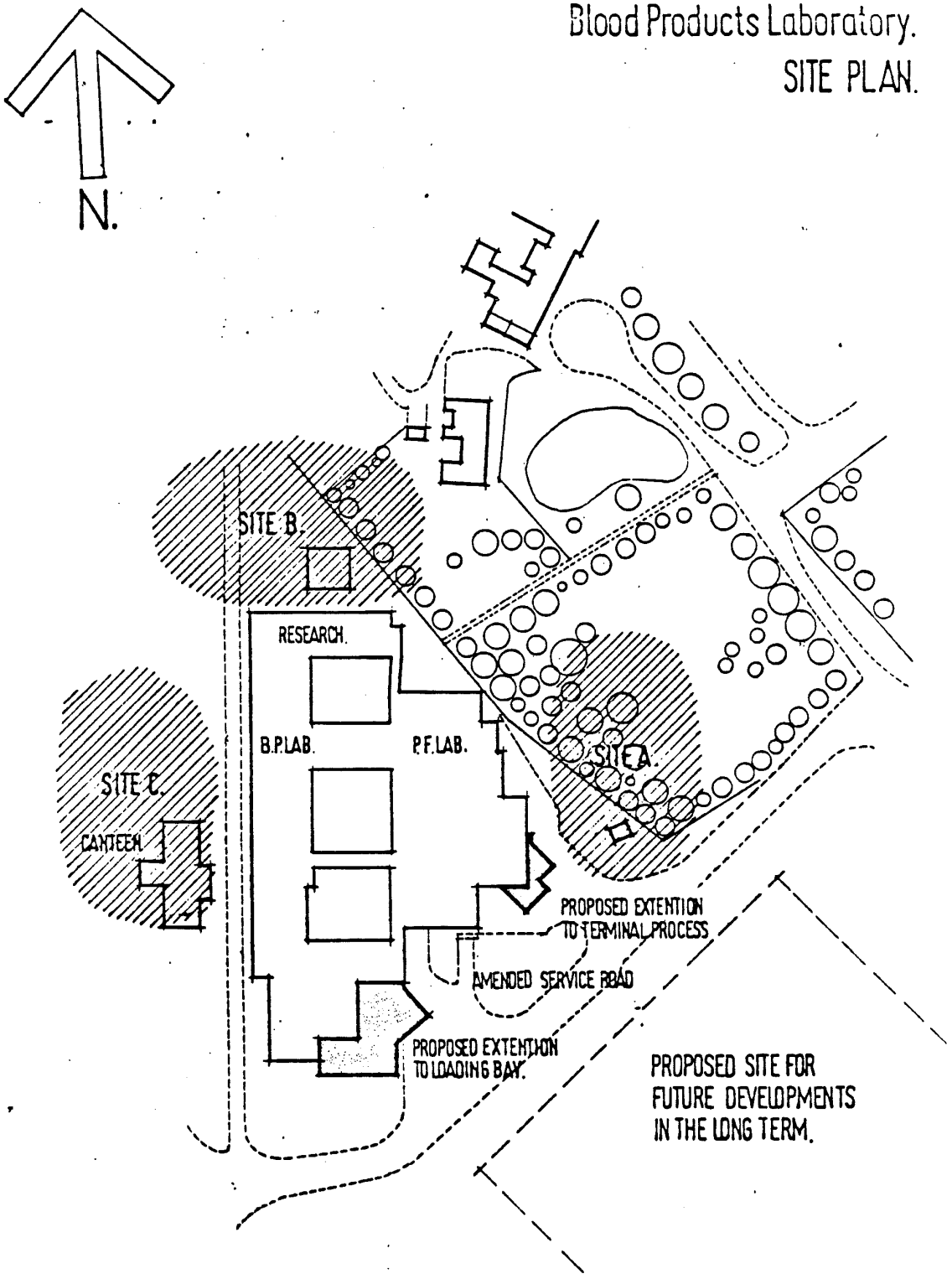
Total usable area as set down in schedule		8500 sq. ft.
Allowance for circulation, plant space - 40%		3400 sq. ft.
Total area		900 sq. ft.
	say	12000 sq. ft.
	=	1117 sq. metres
Assessed cost of £400 per sq. metre at January 1979 provides building cost of 1117 sq. m at £400	=	446,800
External works, say 10%		44,680
		£491,480
	say	£490,000

5.02 The above figures are exclusive of professional fees and expenses, equipment, furniture, and fittings, and are subject to variation in price after January 1979.

5.03 The above figures also acknowledge our understanding of the functional need for a two-storey building with relatively demanding technical requirements in regard to floor finishes, services related to sterile conditions, and knowledge that previous buildings have required piled foundations.

30183

Blood Products Laboratory.
SITE PLAN.



ALTERNATIVE DEVELOPMENT SITES.

SCALE 1:1250. 346. D. 1.

30/84

BPL PHASED REDEVELOPMENT

Outline Proposals

Factor VIII capacity 120 million (M) iu p.a.

Albumin pro rata based on source material from F.VIII process.

Production scheduled levels:

(i)	Factor VIII	90 M iu p.a.	1988
	Albumin	510,000 containers p.a.	
(ii)	Factor VIII	120 M iu p.a.	
	Albumin	675,000 containers p.a.	

Source Material frozen fresh plasma (FFP)

Production requirements:

Level i	1.9 M donations	≡	375,000 L
Level ii	2.5 M donations	≡	500,000 L

Process Area Expansion

Coagulation Laboratory	5,000 sq.metres
Cohn Fractionation Laboratory	5,000 sq.metres
Support Services Development	5,000 sq.metres

29/b

ESTIMATED REVENUE AT INCREASED OUTPUT LEVELS

General Rateable Services . . . . . (1)

Rates, electricity, fuel etc.
£115,000 / 5,000 sq.m. x 3 = £345,000
based on (projected) current laboratory costs.

Consumables . . . . . (2)

Increased levels assume 6 x current production.
Current expenditure £275,000 p.a. A factor is applied to expansion costs since it is believed that projections should be non-linear with respect to accrued costs due to increased process efficiency of large batches and process equipment.
∴ at 6 x current output

$$£275,000 \times 6 \times {}^{2}/_{3} = £1.1\ M$$

Increment due to expansion = £825,000.

Administration

Staff . . . . . (3)

Secretarial	4
Supply	5
Cleaners	6
Telephone	1
Building Maintenance	5
Engineers Maintenance	8
Estate Workers	2
Security personnel	4

Transport?

Total administrative staff costs based on numbers x standard British Industrial mean wage £4,683 p.a. = £163,905.

Coagulation Factors

Staff . . . . . (4)

Based on existing process with modification to provision of FFP in single packs instead of 5L pooled plasma units.

Present staff = 27 producing 15 M iu p.a.

Projected staff = 79 : increment = 52. Cost = £243,516 p.a.

29/7

Consumables: . . . . . (5)

equipment chemicals record keeping		£350,000
i.	Cartridge filters	54,000
ii.	Vials, seals, labels	150,000
iii.	Chemicals	20,000
iv.	Prefiltration equipment	15,000
v.	Tubing, bowl liners etc.	50,000
vi.	Quality control disposables	10,000
vii.	Data processing, records	50,000

Comment: Item (5) related to (2) represents superimposed costs. The breakdown in 5i → 5vi are accurate, based on projected methods and current prices. Compared with (2), the total in (5) is relatively large and probably results from assumed linear growth of costs in (5) as opposed to the non-linear growth of costs in (2).

The costs in (5) also include current production costs attributable to 15 M iu F.VIII p.a.

Cohn Fractionation

Staff: . . . . . (6)

Estimated levels are based on numbers of staff required for 1978 production levels and applying a 'scale-up' factor.

	Incremental increase	
Graduate staff	2	
Fractionation plant	27	
Final solutions	36	
Specific immunoglobulins	8	
Quality control	4	
R & D	4	
	81	Cost = £379,323 p.a.

Consumables: . . . . . (7)

Revenue assumed to fall within (2).

2918

Inspection, Packing and Despatch

Staff . . . . . (8)

Chief technician	1	
Data process	2	
Machine control	2	
Process staff	20	
General assistants	2	
Total	27	Cost £126,441

Washup and Autoclaves

Total	13	Cost £ 50,000

Comment: To accommodate the increased throughput in this section, a radically new approach will be needed including computerised recorder systems and automated machinery for labelling and packing etc. Staffing will therefore depend on the outcome of available equipment.

TOTALS . . . . . (9)

	Ref	£
Staff	3	163,905
	4	243,516
	6	379,323
	8	176,441
		963,185
General Services	1	345,000
		1,308,185
Consumables	2	825,000
		£2,133,185

CONCLUSION . . . . . (10)

Based on an initial view that total costs would be disposed as follows

Building	£10 M
Major plant etc.	£5 M
Small equipment + revenue	£5 M

24/9

the revenue costs leave £2.9 M for small equipment and furnishings.

DEPARTMENT OR SECTION
C.F. DEPARTMENT

24/10

Room	Item	Cost	1980/81 Budget Provision (similar)	Note No.	Note
23) 22) 21b) 21a)	General office furniture, most probably obtainable from store at second hand or redistribution from existing C.F. rooms.	500			
Assay Lab. (Vic Hallam)	Spectrophotometer Automatic pipettes	9900 200	8500 200	1.	1. See 'Quickspend' application.
19) (New tank) work))	Sink unit, PFW supply, pressure washing, shielded area etc.	(5000)		2.	2. Probably covered in 'Accommodation' aspects of reworking this room.
18 (Plasma intake)	Single-pack opener (Travenol) Waste washer Steel bins for plasma units) Trolleys to carry bin)	(see RSL) • 1000 • 3000	 1000 5000		
Modular Cold Store	Code bar checking 81/82. ? VDU & printer	5000 (see RSL)		3.	3. Probably a QC function rather than CF.
C.F. Corridor	2 Dycem tacky mats	• 800	400		
17/16 (New changing)	11 Lockers 2 Clean garmet cupboards	500 200			
16	2 LF cabinets on trolleys 1 LF unit, mobile 2 Process filter holders & parts Piped refrigerant (parts) Piped warn water (parts) 2 Sterile securing vessels 2 Jacketed vessels for controlled temp. pressures 2 Pressure vessels with innter liners 2 Lab. stools	2200 420 2000 200 150 1500 1500 5000 80	100 500 		

DEPARTMENT OR SECTION
C.F. DEPARTMENT

24/11

Room	Item	Cost	1980/81 (similar)	Note No.	Note
13	3 Steel trolleys	• 450	1000		
	1 LF cabinet	1200			
	2 S/S tanks	600			
	2 Lab. stools	80			
12	1 LF cabinet	1400	1000		
	2 Lab. stools	80			
	1 pH meter	600			
	Temp. measurement	300	300		
11a (existing 2nd office) for F.IX.	1 LF unit (suspender)	1400			
	2 stools	80			
	Pressure controllers	250			
11 (clean eg. store)	Racking	• 1000			
Cold Room 2	PFW vessel	(2000)	1500 + 1200		May not be required when Room 19 gets PFW point.
	Plasma washing	• 12000)	1400		
	Plasma thawing	• 5000)			
	Controlled temp. glycol 2 points	300)			
	Sharples cooling	1250			
Vial finishing suite	3 Vial driers	• 210000			
	1 Automatic dispenser/copper/sealer	• 25000			
	Racking, furniture, etc.	• 2000			
		264,990			
		39,150			
		304,140			

DEPARTMENT OR SECTION

LARGE FRACTIONATION LABORATORY

Room	Item	Cost	1980/1 Budget Provision (Y.
MARP 01 does not apply to this Section.			
STEP-OVER FACILITIES			
i) Upper Fractionation Laboratory	3 x full length lockers	£80	No
	Racking for boots, discarded, clothing etc.	£30	No
ii) Main L.F. area (ground floor), and offices to be established in corridor 2B			
a) Process area office 2.09	Desk	£80	No
	2 Chairs	£30	No
	2 x 15 drawer cabinets (Mathews MD15)	£88	No
	2 x Terifold Display & Inf. Wall Units	£35	No
b) New Fractionation Managers Office	(Desks, chairs, filing cabinets from previous office 209)		
	Visitors Chair	£15	No
	Stationery cupboard (Mathews)	£80	No
	Magnetic Board MW32	£28	No
	Notice Board AF32	£15	No
	Terifold Wall Unit (as above)	£18	No
	Clock	£11	No
c) New General Office	(Chairs, desk & notice board from present lobby clock)	£11	No
d) New Rest Room	Table, chairs, cupboard from present rest-room, with sink, work top etc. If not		
	1 new sink, work top, cupboard	£250	No
	Clock	£11	No
e) Corridor 2A, outside entrance to step-over & air-lock.	25 Full length lockers, with shelves	£650	No
	Wall cupboard for disposable clothing dispenser	£80	
	Clean clothing cupboard	£80	No
f) Room 3.05 (formerly rest room, to be converted to office)	Desk	£80	No
	Filing Cabinet	£100	No
	Chairs	£15	No
	Shelving	£50	No

29/12

DEPARTMENT OR SECTION

FINAL SOLUTIONS SECTION

Room	Item	Cost	1980/1 Budget Provision (Y.
MARP 01 (Stop-gap)			
2.19	Heat-treatment cabinet (Pickstone Eng. to quote)	£15,000 Estimated (8/79)	Yes
2.17	Stainless Steel Vessels (Sinclair Stainless to quote)	£7,000 Estimated (8/79)	Yes
2.24	Automatic filling, stoppering & clenching system for 400ml PPF bottles (Schubert & Co. to quote)	£40,000 Estimated (8/79)	Yes
2.17	100L stainless steel vessel	£1,000	No
2.17	Carlson Ford Filter	£2,000	Yes
	Pall Filter Housings x2	£1,500	Yes
STEP-OVER FACILITIES and IMPROVEMENTS to F.S. area			
a) 2.24, 2.22, 2.26	3 stainless steel benches to replace existing wooden benches	£1200	No
	Bottle skates	£600	No
b) Changing rooms upgrading	Wire cages for boot and clothing storage	£100	No
	Shelving for gloves and masks	£30	No
c) Step-over facilities and changing room - process area			
	10 full length lockers with shelves	£250	No
	Wall cupboard for disp. clothing dispenser	£80	No
	Clean clothing cupboard	£80	No
New Office tech. I/C FINAL SOLNS.			
	Desk	£80	No
	2 Chairs	£30	No
	Filing cabinet	£100	No
	Shelving	£50	No
		£ 70,937	

29/13