DRAFT

COMMON SERVICES AGENCY

SCOTTISH HEALTH SERVICE

MEDICINES INSPECTORATE - PROTEIN FRACTIONATION CENTRE - REPORT OF AD HOC PROJECT STEERING GROUP

TRINITY PARK HOUSE
SOUTH TRINITY ROAD
EDINBURGH
EH5 3SE

OCTOBER 1982

CONTENTS

1. INTRODUCTION

During the period December 1979 to January 1980 two senior Medicines Inspectors made formal visits to the Protein Fractionation Centre at Liberton. The purpose of these visits was to ensure acceptable standards of Good Manufacturing Practice from which would emerge a Manufacturing Licence and, as a consequence, specific product licences. The Inspectors' definitive report was received in July 1980 and a formal written response was submitted in April 1981. In the meantime the Director and his staff, in consultation with a new team of Inspectors and as necessary with the Building Division, had taken action to remedy those deficiencies which could be dealt with within the existing resources of the Centre and had reached agreement on the action requiring to be taken in respect of more than 95% of the items outstanding. In November 1981, therefore, the Medicines Inspectorate, following further visits to the Centre to progress matters, issued a further report which inter alia drew attention to the deficiencies which remained outstanding. This final report is reproduced at Appendix (I).

Against this background, at its meeting on 24 February 1983, the Sub-Committee agreed that an ad hoc Project Steering Group be established to advise the Sub-Committee on the detailed brief for the proposed works at the Protein Fractionation Centre and to identify the notional capital and revenue implications of the programme. Subsequently, in a letter dated 30 April 1982, the Scottish Home and Health Department indicated inter alia that the Medicines Inspectorate would like to see:

(i) an itemised list of the improvements and alterations proposed for the upgrading of the existing production facilities with, if possible, some tentative costings to give an indication of the scale of the exercise;

(ii) a timetable indicating the items to be tackled before the proposed shutdown/...

shutdown, those to be carried out during the shutdown and any which it was proposed to undertake after operations had restarted;

(iii) the identification, as appropriate, within the list and timetable referred to at (i) and (ii) above, of proposals for the extension of the production facilities.

Further, at its meeting on 26 May 1982, the Sub-Committee extended the remit of the Group to include examination of the associated staffing proposals.

The proposals which are described in the report, therefore, have been developed in consultation with appropriate officers of the Building Division and, informally with the Medicines Inspectorate, to meet the criticisms of the Protein Fractionation Centre by the Medicines Inspectorate as identified in Appendix (I) but have been framed in such a way as to meet the terms of reference given to the Project Steering Group by the Sub-Committee and provide the information requested by the Scottish Home and Health Department. The proposals also assume that a production capacity of 80 tonnes of plasma per annum is required ie. the estimated requirement for Scotland and Northern Ireland by 1986. It should be noted, however, that with appropriate adjustments to the staffing arrangements and the provision of additional equipment a production capacity of up to 200 tonnes per annum could be achieved. Furthermore, an alternativ staffing structure and further expansion of the extension programme would realise the demonstrated fractionation capacity of the process plant of up to 450 tonnes per annum. For the information of the Sub-Committee the resource implications of meeting the latter requirement are summarised in Appendix (II). The proposals further assume that any necessary additional land will be made available by the Lothian Health Board.

2. PROPOSALS/...

2. PROPOSALS

(a) Building and Engineering

Phase 1

The construction of a Microbiology Laboratory is nearing completion and it is anticipated that the building will be handed over in February/March 1983. The necessary additional equipment is being ordered at the present time and the formal commissioning of the laboratory will commence as soon as the overall staffing arrangements for the Protein Fractionation Centre have been agreed.

Phase 2

This phase is designed to meet the most important immediate requirements identified by the Medicines Inspectorate to improve the staff control and environmental conditions in the finishing areas.

A new automated tunnel washer/steriliser/filling machine is to be located within the present sterile equipment store. Supervision of the filling procedure will be achieved by an observation panel in the south wall of the room. Material will be piped from the existing re-solution area to the new filling room and the product will be passed through the existing pass-through hatches to pasteurisation and to freeze drying as appropriate.

The crystalloid manufacture will be carried out in the present filling clean room and the plasma crushing area will be upgraded.

Phase 2(a)

The/...

Phase 2(a)

The upgrading of the existing environmental conditions in the preparation, production and quantity control department.

Drawing no 2 illustrates the work to be carried out in Phases 2 and 2(a).

Phase 3

The construction of further storage, filling, labelling, packaging, office and staff facilities and, in a separate building situated to the east of the new extension, a reagent manufacturing facility for the provision of quality control material and an engineering workshop for the use of the maintenance staff of the Centre. In addition the provision of a new sub-station to complete the energy needs and a further emergency generator.

It is considered essential that the unloading and loading of materials and product should take place undercover and one delivering point has been specifically attributed to the delivering of plasma. This gives direct access to the new - 40°C cold rooms to be located on the east side of the present production building. In this way the plasma will arrive by way of a new ante-room to the reception area of the production department.

All the remaining materials entering the building would be by way of the general goods reception o; and sorted and passed either to the General Store and Bottle Store or the Packaging Materials Stor.. Contiguous with general store is the Equipment Preparation/...

Preparation Area for the washing, assembly and sterilising of equipment for the clean aseptic finishing of albumin solution.

The clean area in the proposed extension will handle the finishing of large volume parenterol products. These products will then proceed to pasteurisation, inspection, bond storage and through packaging and labelling to dispatch.

Drawings no 5 and 6 illustrate the proposals.

Phase 4

In this final phase the new extension will be commissioned and the present building will be shut down to allow further alterations to be carried out on the present finishing area. The completed department illustrated on Drawing no 6 shows a tunnel washer/steriliser/filling machine for the finishing of small volume products only (Immunoglobulins and Factor VIII and Factor X). This is a rededication of the tunnel washer/steriliser/ filling unit installed during Phase II.

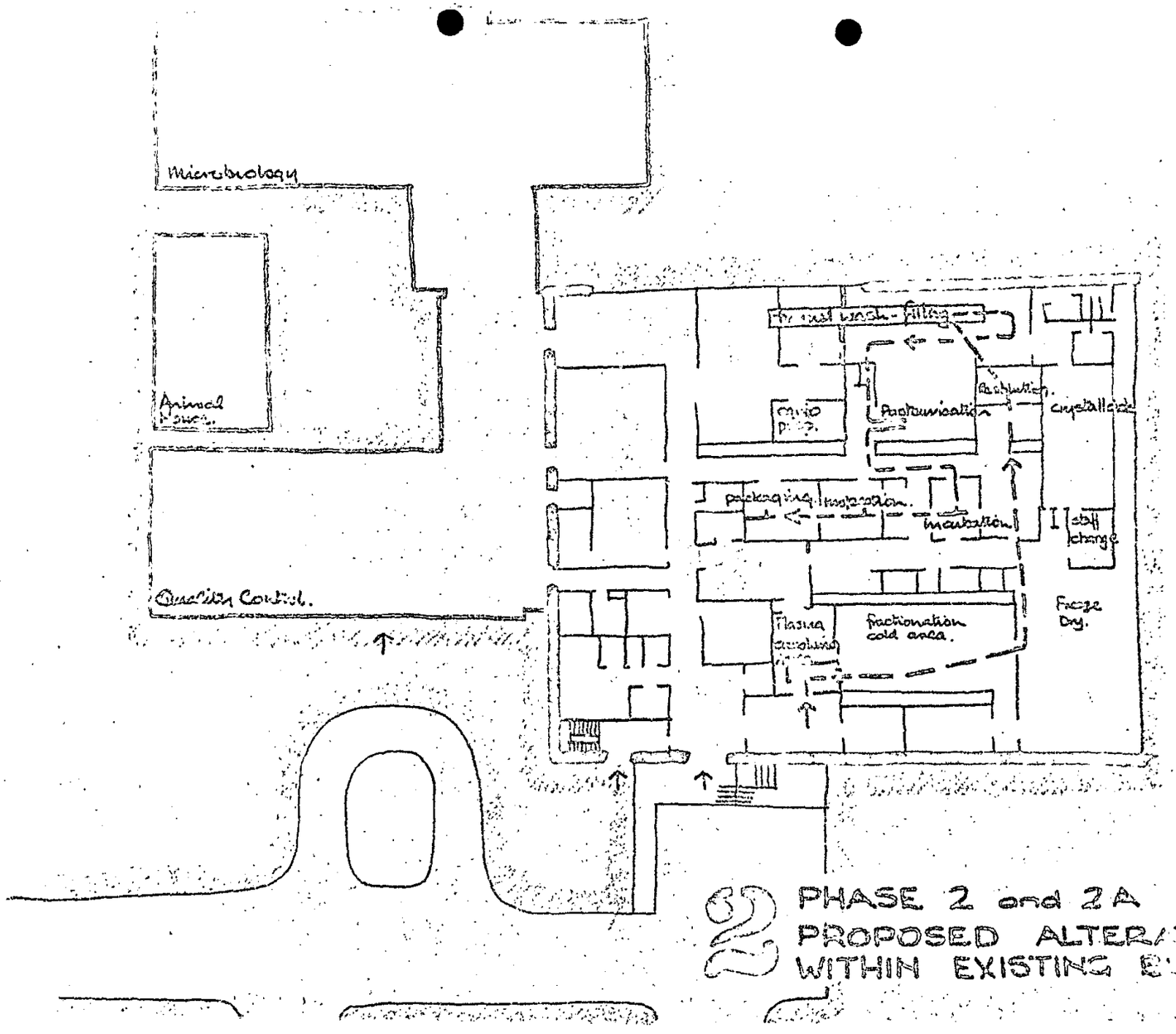
The changing area has been relocated and freeze drying machines will be placed to give access from within the new clean area. In the area of the old changing rooms a drying area will be added for the clarification of plastic packs containing crystalloid solution. In this way both the Proteinacious products and the Crystalloids arrive at a new delivery point, through /...

through pass-through hatches, to a corridor giving direct access to Inspection and the Product Bond Stores. Also during this period of closedown the present -40°C Cold Room Process Store will be renewed unless further deterioration requires more urgent action.

(b) Staffing

A new staff structure was already under development at the time of the initial visit by the Inspectorate. This has been extended and researched in consultation with the present Inspector in the light of his criticisms of the range and quality of staffing at the Centre. The structure has been constructed to take account of maximum utilisation of production capacity on the basis of a 120 hour working week and the employment of individuals of the calibre usually associated with pharmaceutical manufactures.

EXISTING BUILDINGS
Quadrangle Control.



2 PHASE 2 and 2A
PROPOSED ALTERATIONS
WITHIN EXISTING BUILDING

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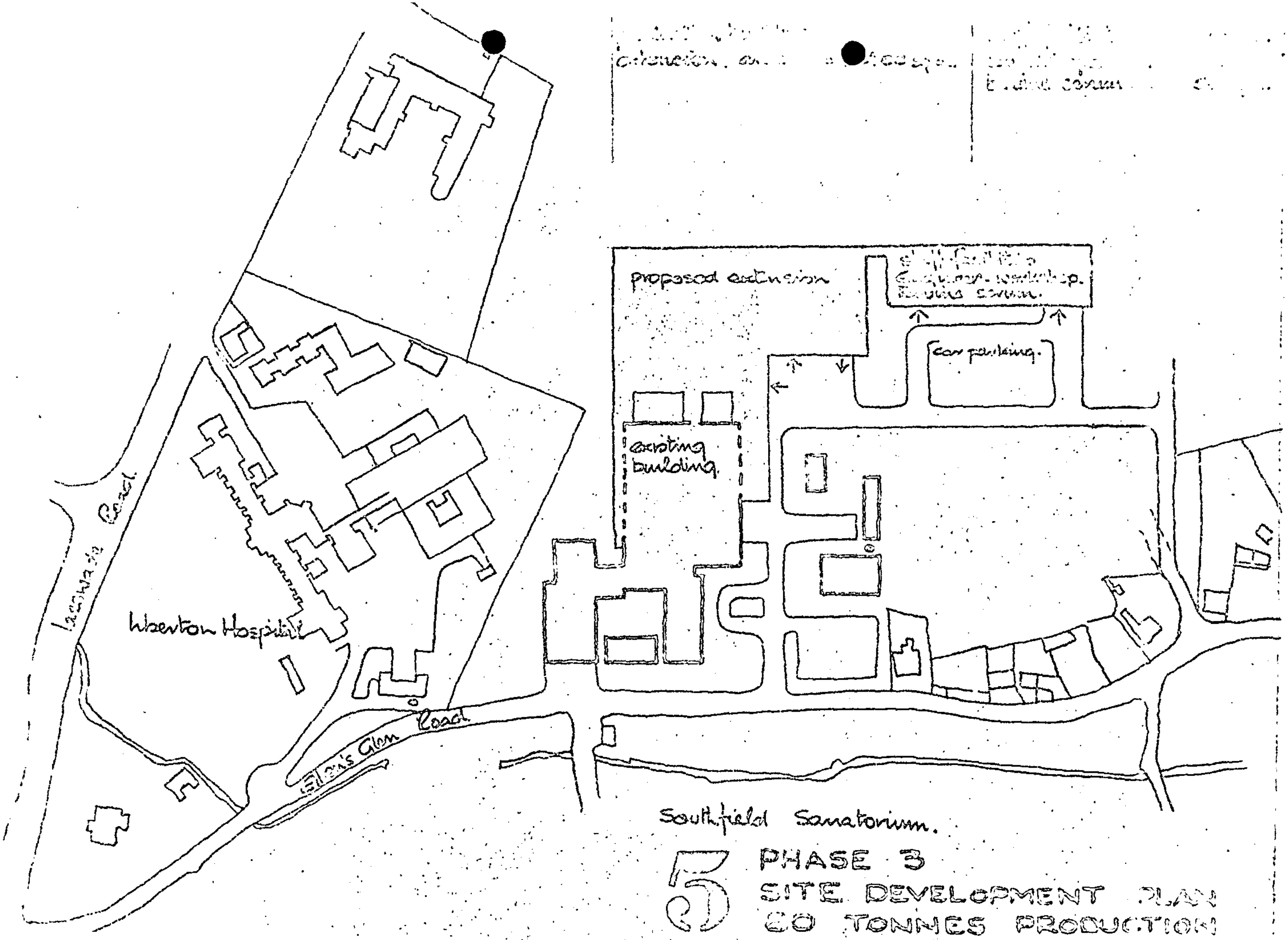
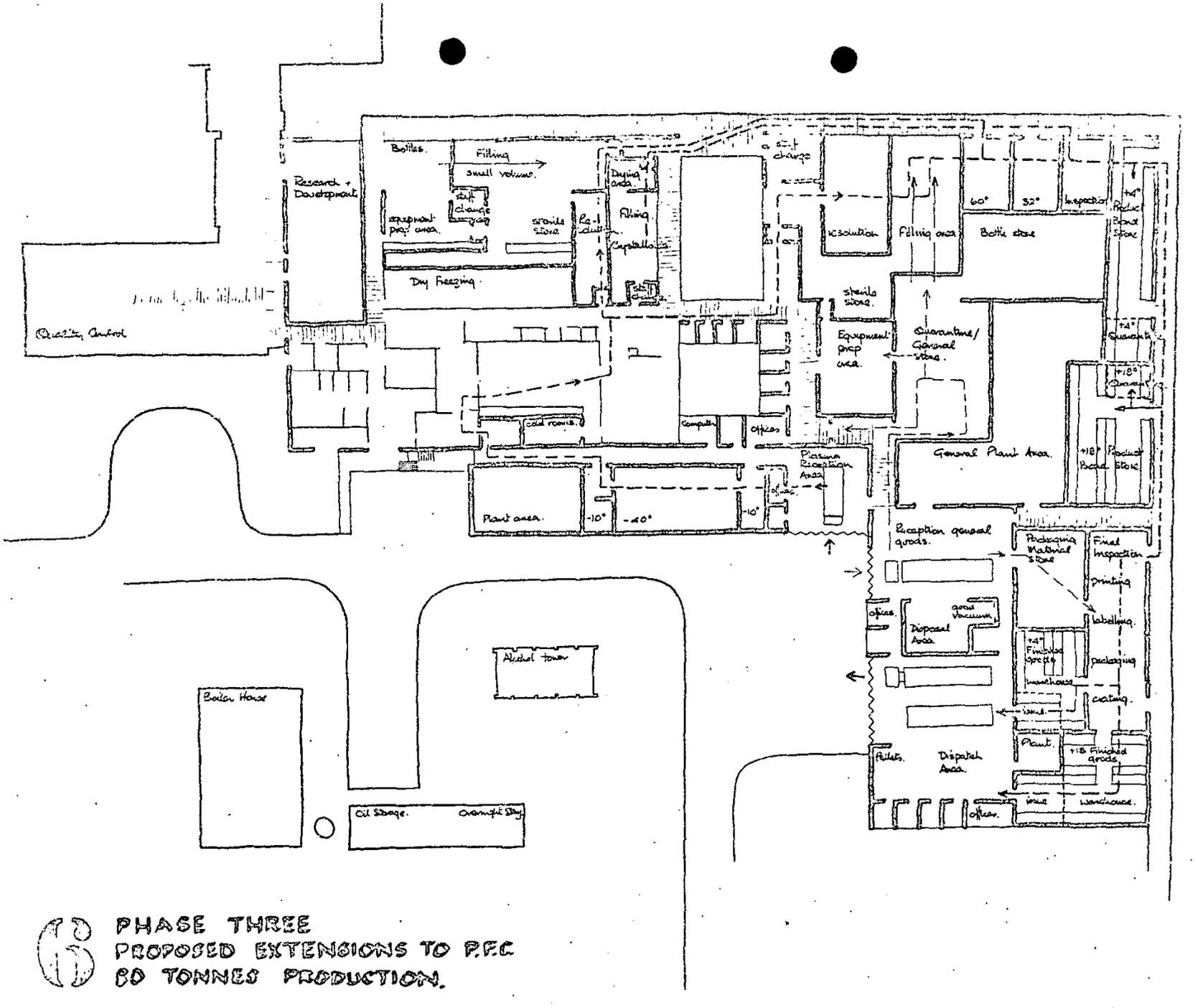

proposed extension
car parking.
existing building
Liberton Hospital
Lasswade Road
Ellen's Glen Road
Southfield Sanatorium.
5
PHASE 3
SITE DEVELOPMENT PLAN
60 TONNES PRODUCTION

SNB.008.7288



PHASE THREE
PROPOSED EXTENSIONS TO P.F.C
80 TONNES PRODUCTION.

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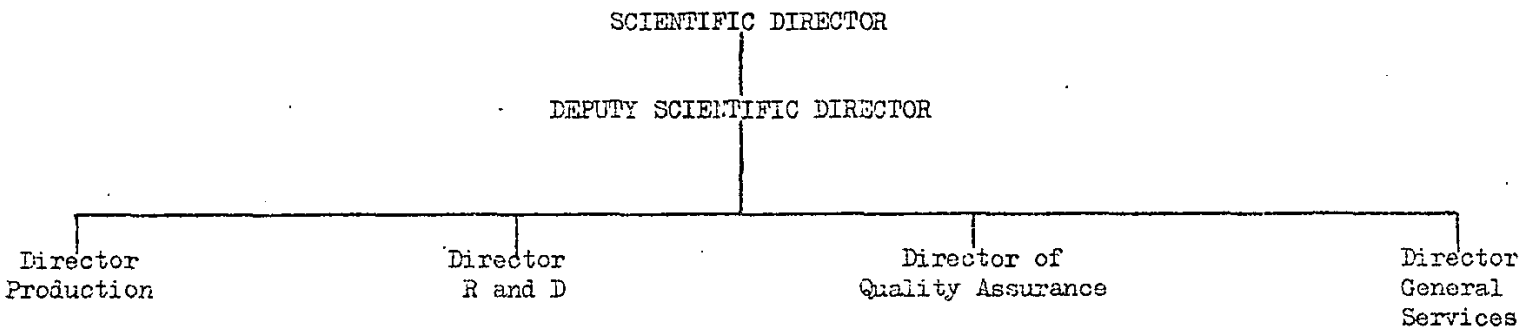
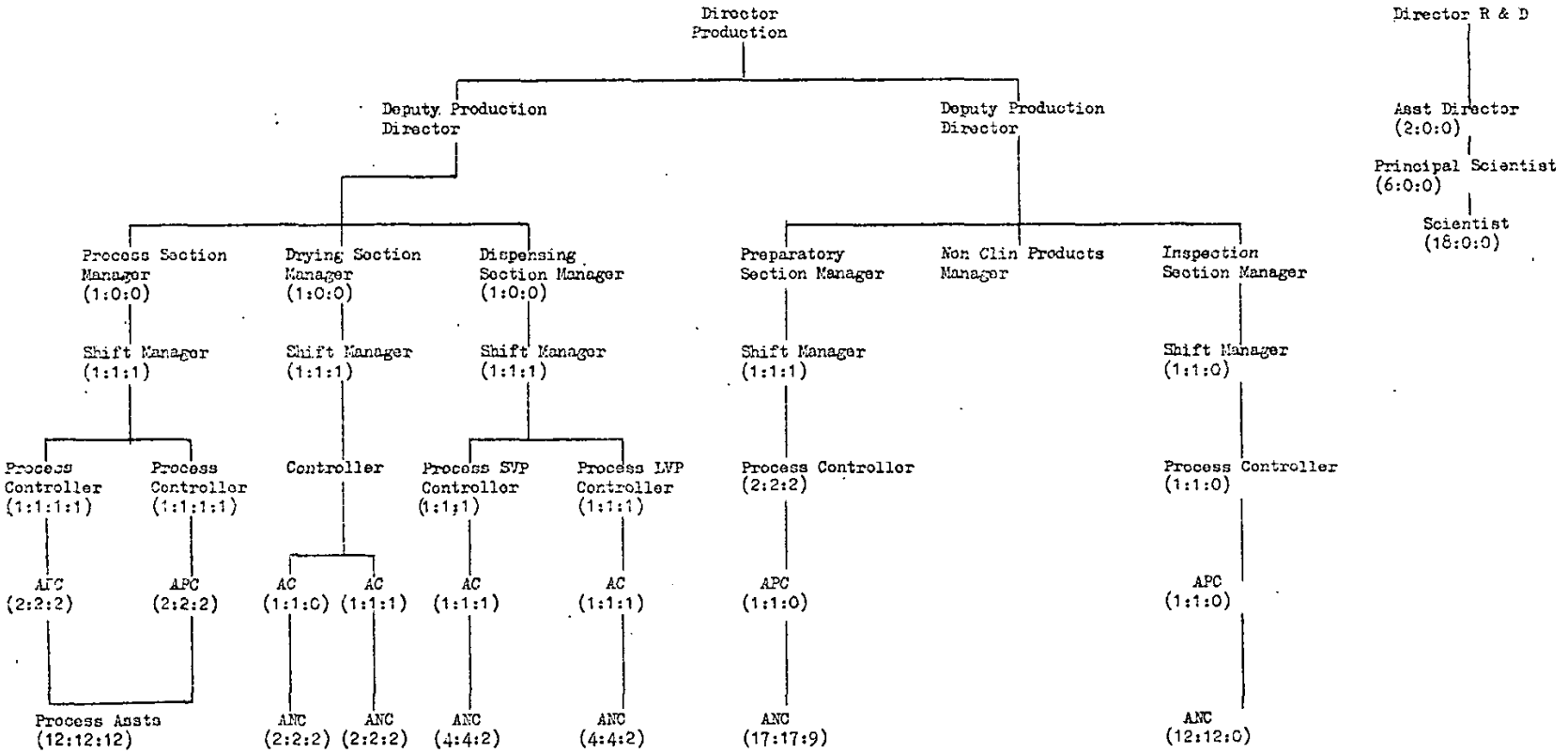
PROPOSED NEW STAFFING STRUCTURE - PROTEIN FRACTIONATION CENTRE




Director
Production
Deputy Production
Director
Deputy Production
Director
Process Section
Manager
(1:0:0)
Drying Section
Manager
(1:0:0)
Dispensing
Section Manager
(1:0:0)
Preparatory
Section Manager
Non Clin Products
Manager
Inspection
Section Manager
Shift Manager
(1:1:1)
Shift Manager
(1:1:1)
Shift Manager
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Shift Manager
(1:1:1)
Shift Manager
(1:1:0)
Process
Controller
(1:1:1:1)
Process
Controller
(1:1:1:1)
Controller
Process SVP
Controller
(1:1:1)
Process LVP
Controller
(1:1:1)
Process Controller
(2:2:2)
Process Controller
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AC
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APC
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Process Assts
(12:12:12)
ANC
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ANC
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ANC
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ANC
(17:17:9)
ANC
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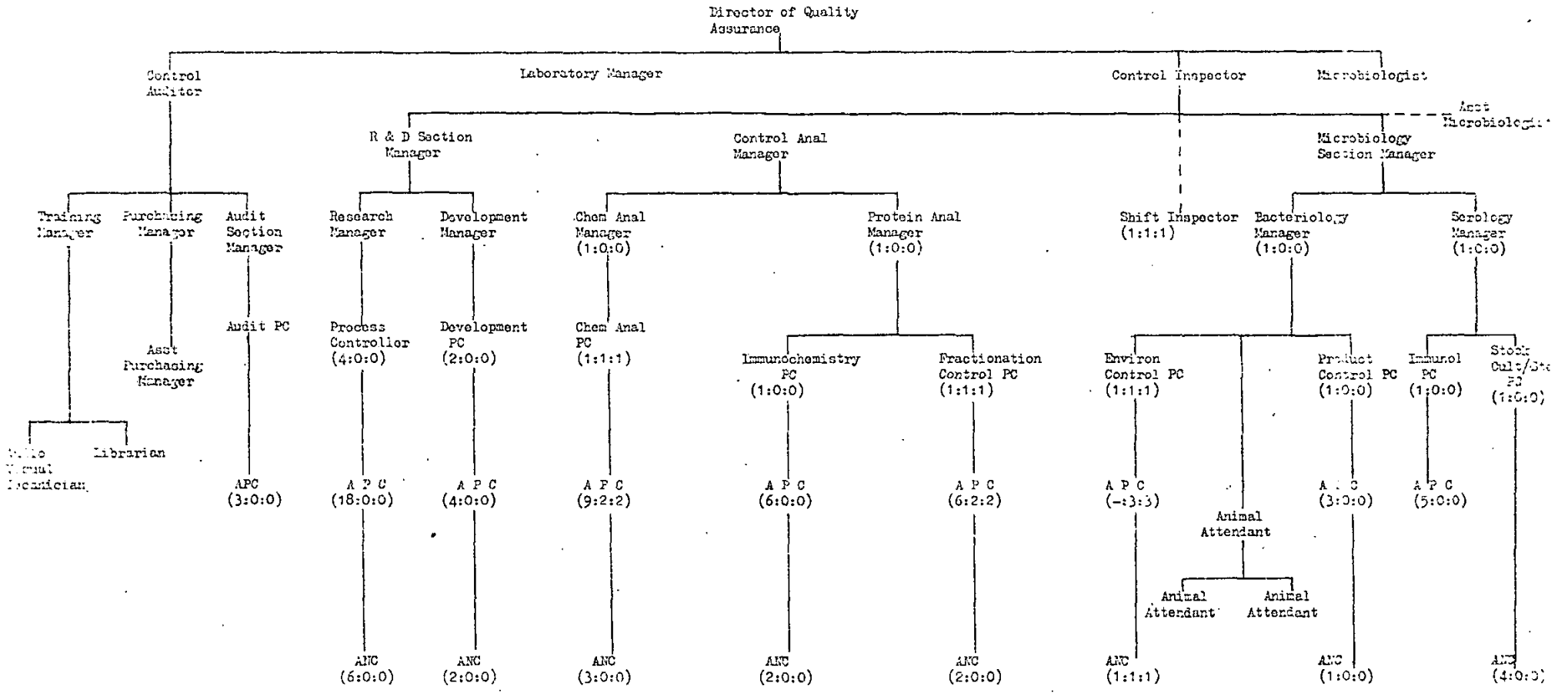
Director R & D
Asst Director
(2:0:0)
Principal Scientist
(6:0:0)
Scientist
(18:0:0)


Director of Quality Assurance
Control Auditor
Laboratory Manager
Control Inspector
Microbiologist
Asst Microbiologist
R & D Section Manager
Control Anal Manager
Microbiology Section Manager
Training Manager
Purchasing Manager
Audit Section Manager
Research Manager
Development Manager
Chem Anal Manager (1:0:0)
Protein Anal Manager (1:0:0)
Shift Inspector (1:1:1)
Bacteriology Manager (1:0:0)
Serology Manager (1:0:0)
Asst Purchasing Manager
Audit PC
Process Controller (4:0:0)
Development PC (2:0:0)
Chem Anal PC (1:1:1)
Immunochemistry PC (1:0:0)
Fractionation Control PC (1:1:1)
Environ Control PC (1:1:1)
Product Control PC (1:0:0)
Immunol PC (1:0:0)
Librarian
APC (3:0:0)
A P C (18:0:0)
A P C (4:0:0)
A P C (9:2:2)
A P C (6:0:0)
A P C (6:2:2)
A P C (-:3:3)
Animal Attendant
A P C (3:0:0)
A P C (5:0:0)
ANC (6:0:0)
ANC (2:0:0)
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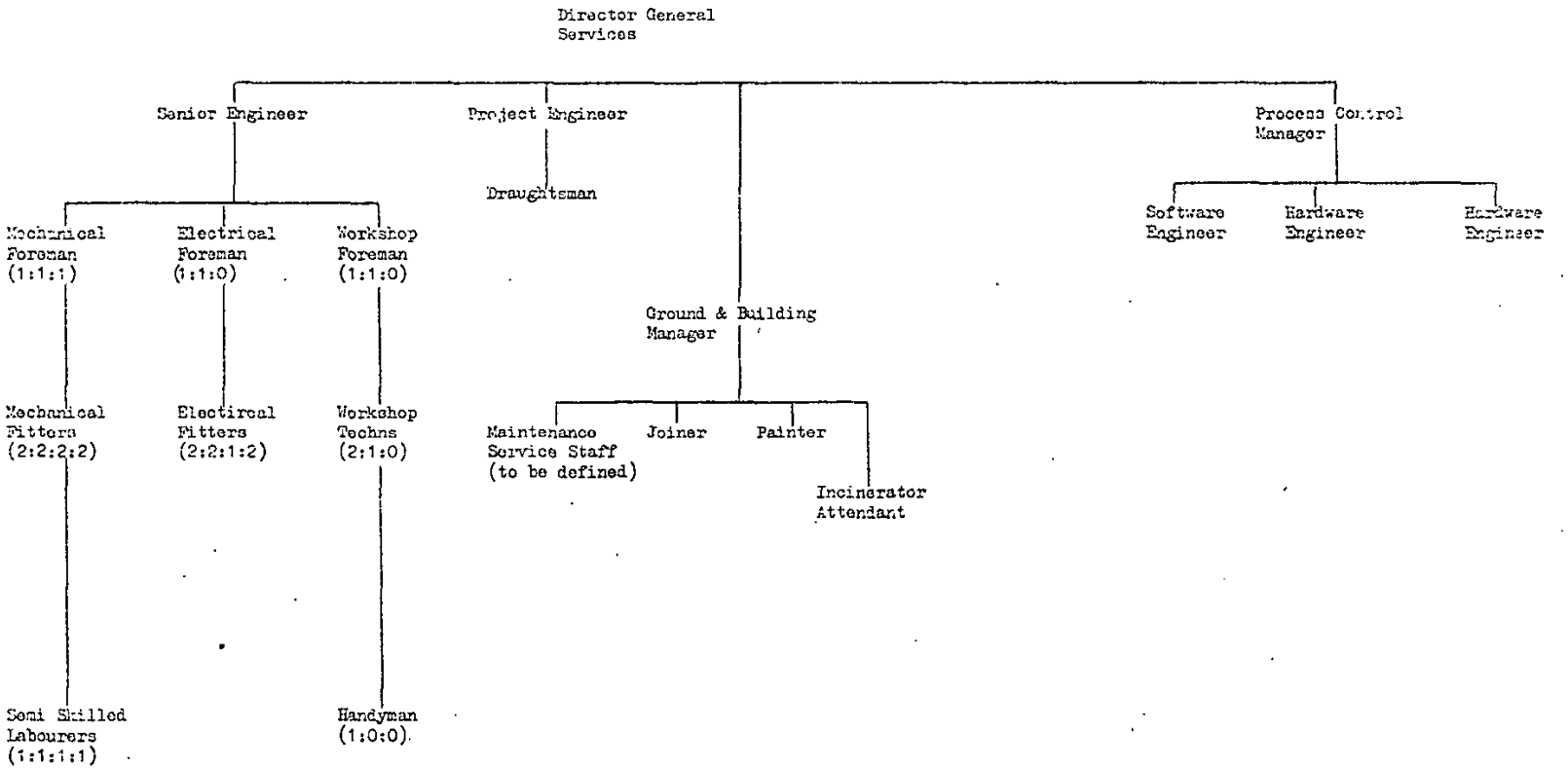

Director General
Services
Senior Engineer
Project Engineer
Process Control
Manager
Draughtsman
Software
Engineer
Hardware
Engineer
Hardware
Engineer
Mechanical
Foreman
(1:1:1)
Electrical
Foreman
(1:1:0)
Workshop
Foreman
(1:1:0)
Ground & Building
Manager
Mechanical
Fitters
(2:2:2:2)
Electrical
Fitters
(2:2:1:2)
Workshop
Techns
(2:1:0)
Maintenance
Service Staff
(to be defined)
Joiner
Painter
Incinerator
Attendant
Semi Skilled
Labourers
(1:1:1:1)
Handyman
(1:0:0)

3. COST INFORMATION

(a) Capital

(i) Building and Engineering

	£000s	
Phase 1	-	
Phase 2	60	
Phase 2(a)	340	
Phase 3	6,300	
Phase 4	520	
		7,220

(ii) Equipment

Process	152	
Preparation	990	
Filling	566	
Laboratory	125	
Process Control	100	
Engineering	308	
Administration	280	2,521
TOTAL		9,741

(b) Revenue

	£000s
Operational Costs	1,400 to 2,100
Salaries and Wages	2,950
TOTAL	4,350 to 5,050

APPENDIX (I)

MEDICINES INSPECTORATE REPORT ON THE CURRENT STATUS AT THE PROTEIN FRACTIONATION CENTRE, EDINBURGH AS OF OCTOBER 1 1981

D HAYTHORNTHWAITE
K J AYLING

1. Introduction and Background

Following the response of The Protein Fractionation Centre (PFC) to the inspection of Messrs Flint and Purves a series of visits for discussions at PFC has taken place to progress matters. These were held on the following dates:-

11th and 15 June 1981 - D Haythornthwaite
30th September-1st October - K J Ayling and D Haythornthwaite

The discussions were principally with

Mr J Watt - Scientific Director
Dr R Perry - Quality Controller

During the visit of 11th June the DRG Flexpack process was examined, since a product licence for this has been issued recently. A separate draft report on this was issued to SHHD.

Detailed comments have been received upon the draft, and the Medicines Inspectorate response to this is therefore included in this report.

2. General Comments

With the appointment of Dr Perry as Quality Controller, progress towards a fully integrated Quality Assurance system as would be expected of an equivalent industrial company has been progressed rapidly bearing in mind the resources available.

Detailed comments are therefore not offered at this stage regarding Quality Control, general documentation, and standard operating procedures, with the exception of sections 3.7 and 3.8 of this report.

Routine visits in the future will review progress of these aspects and an in-depth inspection in approximately three months will be scheduled to cover these aspects and offer any necessary advise and recommendations as is normal M.I practice.

Areas where progress towards acceptable levels of GMP are still not adequate are as follows.

1. Inadequate space in some production and storage areas

2. Unsatisfactory processing conditions

3. Poor surface finishes

4. Unsatisfactory work flow patterns, which could lead to product mix-up

5. Unacceptable staff movements through production areas, which could lead to contamination of components and product

It is stressed that the comments in this report are made regarding the present level of output, and the present facilities.

Where alterations of the facilities have been positively scheduled then account of these is taken.

For ease of reference the section numbers used in the PFC "Response To Medicines Inspectors' Report 1980" are used where necessary. The specific references are found in book I, pages 19-69.

3. Specific Comments on Premises and Facilities

3.1. Storage Areas (ref 3.16.4; 3.29.9 of PFC Response). There is insufficient cold storage on site and plasma is stored in contract cold storage facilities. It is understood that locked tamper proof cages are being purchased to store plasma.

Such contract facilities are difficult to control and should not be longterm.

On site stores are generally unacceptably overcrowded and congested.

The cold rooms suffer badly from a surfeit of "snow" produced by the refrigeration system which covers shelves and products. This problem is worst in cold stores G87 and G86.

3.2 Processing Areas

Processing areas should in general conform to the WHO Guidelines (1978) or where appropriate to the Guide to Good Pharmaceutical Manufacturing Practice (1978).

Air filters should normally be terminal, ie immediately prior to the air entry to the room. Where design restrictions make this impractical then the filters should be as near to the room inlet as possible.

3.2.1 Plasma Processing Areas (G89/G92) (ref 3.1 of PFC response)

A great deal of traffic proceeds through these areas, but with present work patterns this is inevitable. Plans to alleviate this were discussed. Some rebuilding is necessary

Greater assurance would be obtained by converting the plasma pooling process into a more closed system (plans to provide a cleaner method of stripping of plastic, pooling and crushing of plasma have been discussed).

3.3 Preparatory Area (G66/G68) (ref 3.20 of PFC response)

Critical handling points should meet BS 5295 class 2 conditions. A general air supply of HEPA (0.5 micron) filtered air is recommended, and provision of air locks and changing facilities.

Staff are not wearing hats necessary in order to avoid the shedding of particles onto components and equipment.

The area is used as a general throughfare by staff not working in this area. A satisfactory area cannot be maintained under these conditions.

3.4 Solution Preparation and Filling Area (G67)

The proposed equipment layout (drawing 169) as detailed in the PFC Responce to the Draft Report of 11 and 16 June is acceptable.

The surface finishes of the walls and the crevice between wall and ceilings is still not acceptable.

3.5 Clean Room G104 (Preparation for Aseptic Area G77) (ref 3.8 of PFC response)

Critical handling points is this area should meet BS 5295 Class 2. The installation of HEPA filters (0.5 micron) is recommended for this area.

Air locks and changing facilities should be provided.

3.6 Freeze Drying Areas (G83/G94) (ref 3.10 of PFC response)

Installation of a LAF module over the entrance to the freeze dryers is scheduled for early completion. This is considered to be an interim solution and will be reviewed once it has been installed.

3.7 Inspection and Labelling Area (G98/G96) (ref 3.17 of PFC response)

The labelling area (G98) and the corridor outside is chronically overcrowded, and product flow is not easily controlled.

As a matter of urgency, the use of roll fed labels should be instituted to immediately alleviate the risk of mix up of labels and/or product.

.8 Label Stores and Bag Printing (G63)

The storage area required for "cut" labels in this small room means that the space available for printing of PVC bags for large volume parenteral (LVP) solutions is very restricted.

Old printed PVC bags were on a shelf near to the printing equipment. This is a serious breach of GMP and a check list for change over of products and batches should be instituted immediately.

With the very cramped conditions provided, the implementation of upgrading of room G67 to accommodate bag printing must be a priority (see 3.4).

3.9 Autoclaves

These have now been brought up to a better standard by PFC but replacements should be planned for the early 1980's to ensure greater reliability and safety.

4 Conclusions

4.1 Progress towards implementing necessary standards of GMP in general Quality Assurance matters including provision of standard process documents and standard operation procedures is generally acceptable.

A major effort regarding these aspects is now coming to fruition

Two major exceptions to this were noted.

(i) 3.7 of this report. Labelling room G96.
(ii) 3.8 " " Old PVC bags left in Bag printing/store room G63. Lack of SOP to cover this aspect

4.2 Firm proposals to remedy those deficiencies regarding buildings and facilities as reported in the first inspection are still awaited, with dates of implementation.

These deficiencies are as defined in section 3 of the report.

4.3 The present buildings and facilities continue to fail to reach minimum standards of GMP, and a licence would not be recommended for an industrial equivalent unless agreed upgradings were instituted as a matter of urgency

Possible satisfactory alterations to the buildings and facilities have been discussed, on site, but provision of detailed plans by you is still awaited.

4.4 The use of a closed system for plasma stripping, pooling and crushing would substantially upgrade this part of the operation and lead to clearer starting material for extraction of coagulation factors and fractionation products.

4.5 Staff responsibility regarding autoclave validation and control is unusual in that the Section Manager is very actively involved. The total assurance given by his involvement with the Engineering Department does however provide a high general overall standard in this field, and is therefore quite acceptable.

Recommendations

The report should be forwarded to the appropriate Authority for remedial action as a matter of urgency.

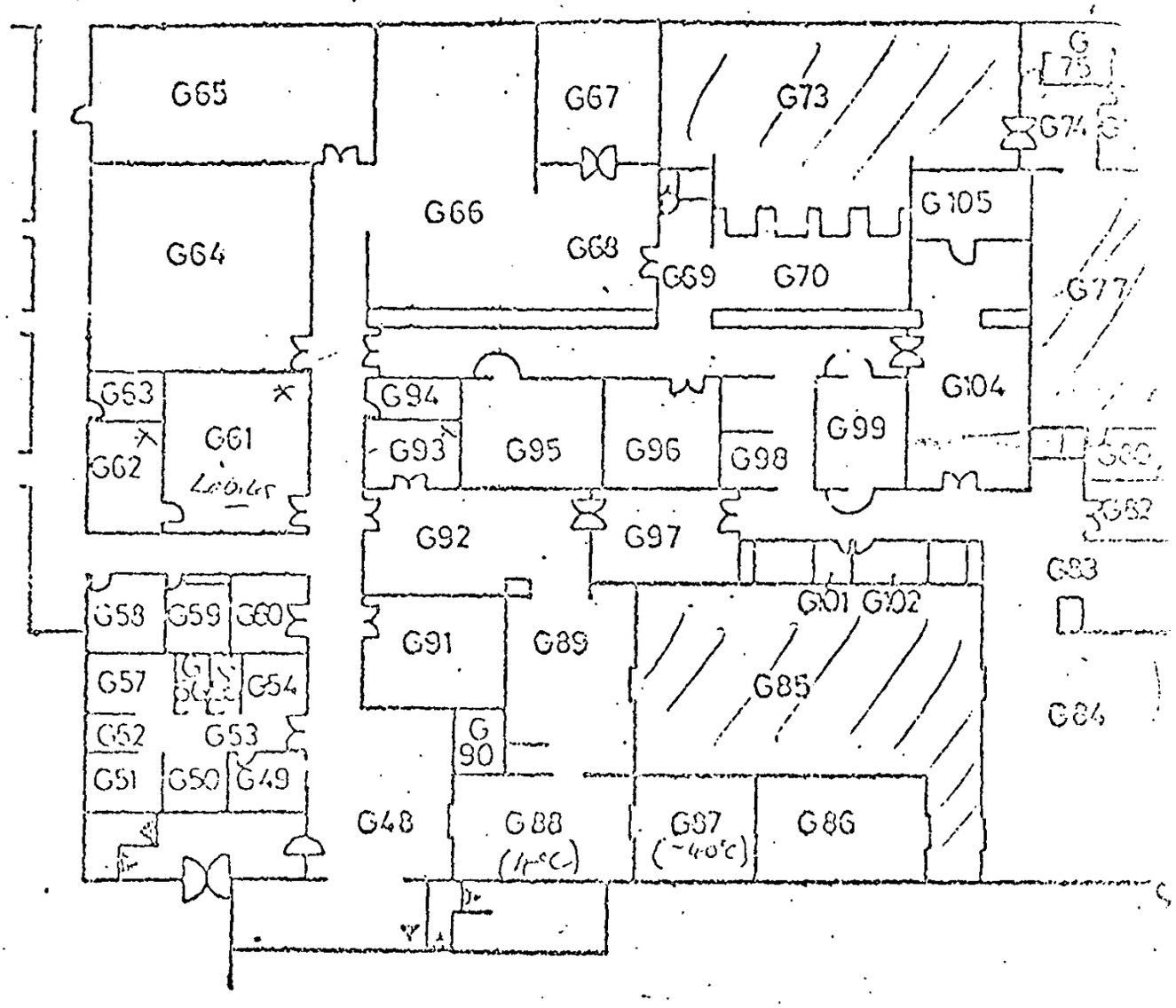
Where complete solutions to the deficiencies are not immediately available, then the interim proposals should be specified, and a timetable provided for implementation.

The Medicines Inspectorate is prepared to discuss on site or at SHHD any draft proposals so that unnecessary delays are avoided.

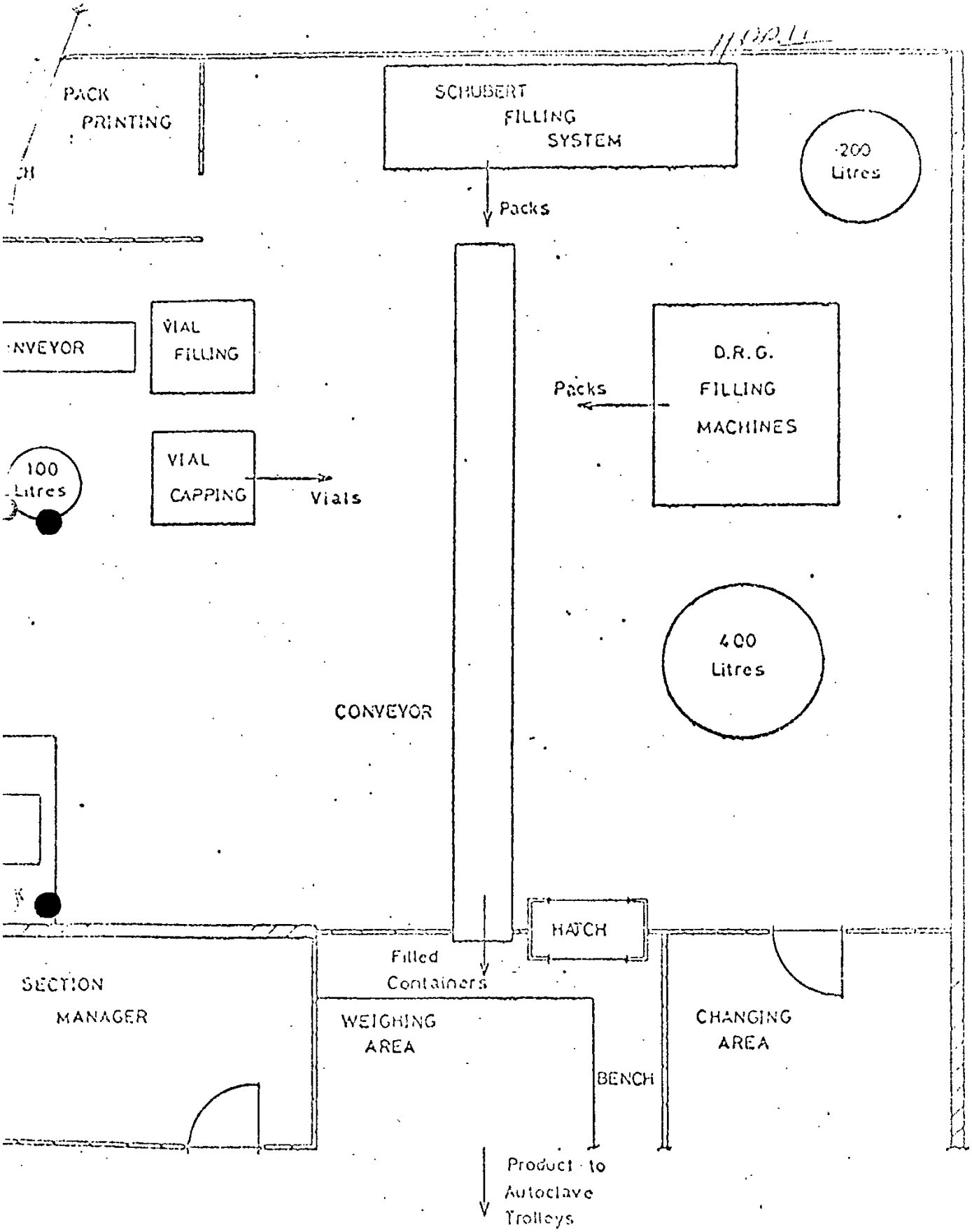
K J Ayling 26 Oct 1981

D HAYTHORNTHWAITE
K J AYLING

refs K J A - 121081 (D1)
- 201081 (D2)
- 261081 (DF)



PRODUCTION BUILDING – GROUND FLOOR PLAN



12-9-81 SK	REVISIONS	Date	Name	Protein Fractionation Centre EDINBURGH
	Title PREP FILLING AREA (S.67)			Drg. No 169

APPENDIX (II)

The 450 tonnes option - resource implications

To realise the demonstrated fractionation capacity of the process plant of up to 450 tonnes it would be necessary to:-

(i) Expand the Phase 3 main extension of the production building from 6,400 sq metres to 8,300 sq metres.

(ii) Extend the existing boiler house to enlarge the capacity by a further boiler. This would require major alterations to, or the rebuilding of, the BTS Headquarters building.

Drawings No 3 and 4 illustrate the proposals.

Resource implications

(a) Capital

(i) Building and Engineering

	£000s
Phase 3 - additional cost	1,900

(ii) Equipment

Process - additional cost	673
Preparation "	662.5
Filling "	200
Laboratory "	36
Engineering	50
Administration	200
TOTAL ADDITIONAL COST	3,721.5

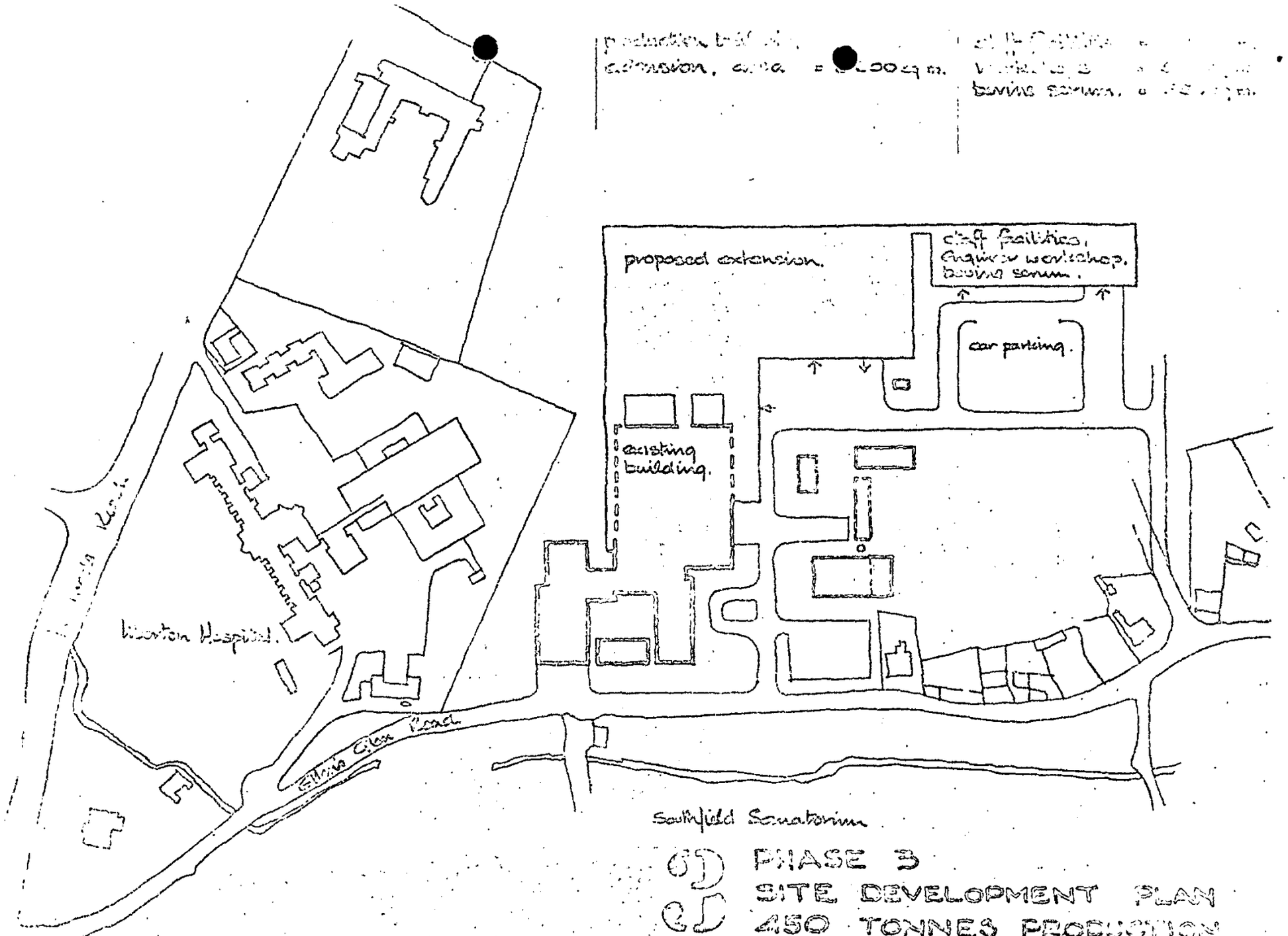
(b) Revenue

Operational Costs	4,000 to 5,600
Salaries and Wages	1,258
TOTAL ADDITIONAL COST	5,258

NB/...

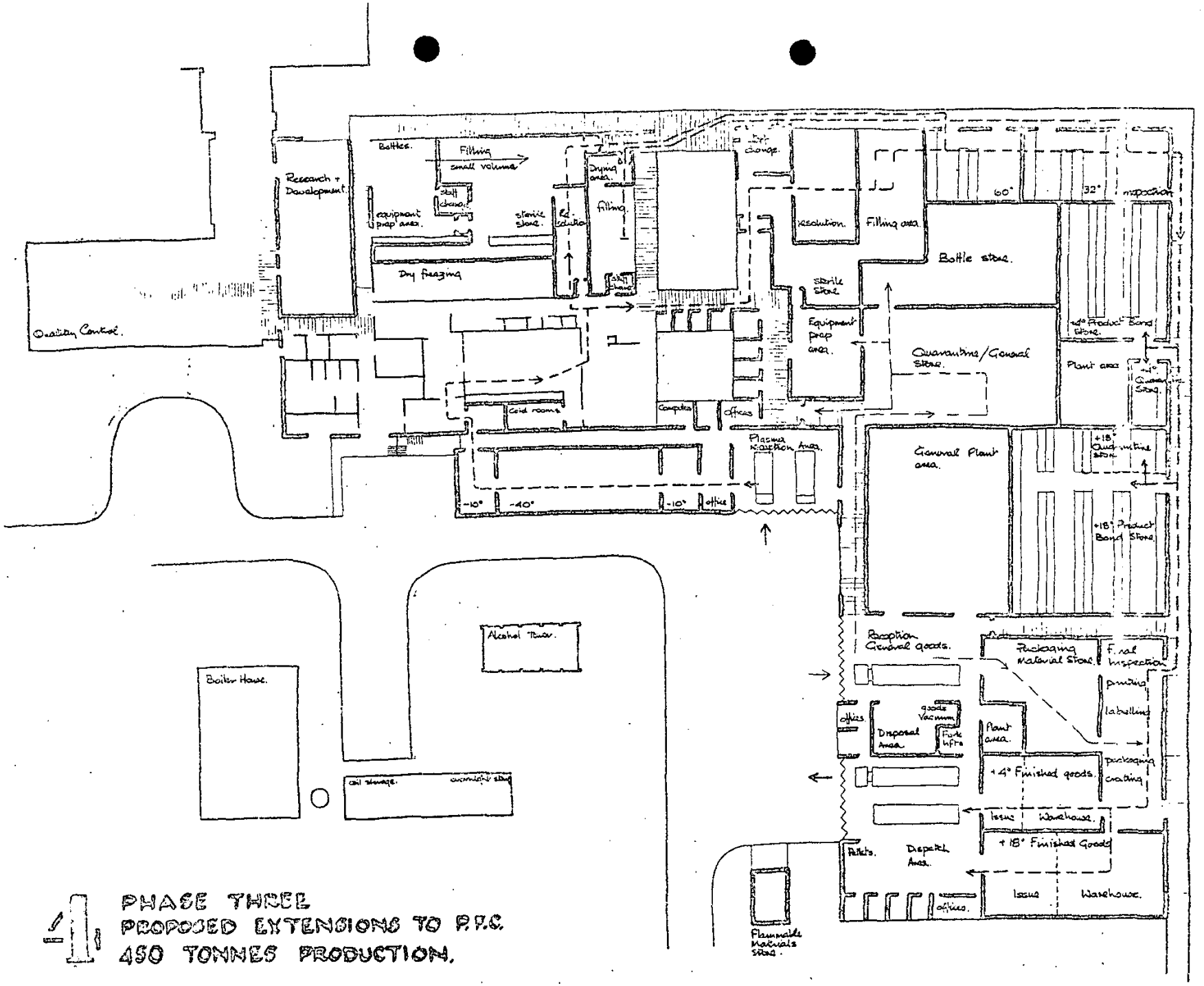
NB (i) The building and engineering cost information is based upon estimated sizes for each department and represent costs for comparative purposes;

(ii) all costs are exclusive of fees.



PHASE 3
SITE DEVELOPMENT PLAN
450 TONNES PRODUCTION

SNB.008.7307



PHASE THREE
PROPOSED EXTENSIONS TO P.F.C.
450 TONNES PRODUCTION.

SNB.008.7308