LP1

Department of Health and Social Security
Medicines Division Finsbury Square House
33-37a Finsbury Square London EC2A 1PP
Telex 883669
Telephone 01-638 6020 ext

V J Harley Esq
Department of Health and Social Security
Room 1209
Hannibal House
Elephant and Castle
LONDON
SE1 6TE

Your reference

Our reference

Date
10 September 1979

Dear Sir

MEDICINES ACT 1968

1. An inspection of the pharmaceutical manufacturing facilities of the Blood Products Laboratory, Elstree was carried out on 23 - 27 April and 16 - 19 July 1979. Shortcomings observed during the course of the inspection are summarised at various points in the enclosed copy of the inspection report.

2. The report was considered by the Inspection Action Group of the Division in accordance with the procedure described in my minute of 20 July to you. The conclusions and recommendations of the Group are set out in the appendix to this letter.

3. I should be grateful if you would submit the report, conclusions and recommendations to the Joint Management Committee for the laboratory and let me have as soon as possible proposals for remedial measures, setting out where appropriate a time-table for their implementation and completion.

Yours faithfully

GRO-C

G E J FIRSTBROOK

ENC

918.

19/201

BLOOD PRODUCTS LABORATORY - ELSTREE

CONCLUSIONS AND RECOMMENDATIONS OF MEDICINES DIVISION

CONCLUSION

1. The Blood Products Laboratory was developed in stages over a number of years as new products were introduced and new buildings were erected to facilitate their manufacture.

2. With the exception of the Large Fractionation Laboratory, the buildings were designed as laboratories for small scale manufacture and as production increased could not readily be adapted to large scale manufacture.

3. The three main manufacturing departments have operated as separate units; each developing in its own way, and this has resulted in the lack of an integrated manufacturing operation.

4. The key personnel are scientists with research and development experience but have not had the opportunity to gain experience of modern large-scale sterile production requirements in the pharmaceutical industry. This was no doubt the correct policy in a development situation when production was small and research and development was an important feature of the laboratory.

5. Production is now on a scale which must be regarded as a large scale factory-type operation and has out-grown the premises in which it is undertaken.

6. The Laboratory is so short of space for cold storage; quarantine of raw materials, in-process materials and finished products; receipt and despatch; packaging; and warehousing generally, that it is not practical or safe to increase throughput even if the necessary production facilities were available. For these reasons it is not practicable to consider a double-shift system of working if it were possible to employ the appropriate additional staff.

7. If this were a commercial operation we would have no hesitation in recommending that manufacture should cease until the facility was upgraded to a minimum acceptable level.

M/203

8. However, as blood products are essential to the health and well-being of the nation and as alternative sources of supply are severely restricted, production at Elstree may continue provided certain aspects of the standards of production and control are improved immediately and that the planning of certain other essential improvements in these standards commences immediately with a view to very early implementation.

RECOMMENDATIONS

9. Our recommendations are therefore as follows:-

a) Under no circumstances should production of any product be increased under the existing manufacturing conditions.

b) There is special need for the manufacture of Freeze-Dried Plasma to be upgraded immediately by locating it elsewhere on the premises as the present facility is totally unacceptable. The alternative is to cease manufacture of this product as the operation as currently undertaken is microbiologically hazardous.

10. Immediate upgrading of product procedures and control must include:-

a) An improvement in hygiene cleaning procedures to be established, written down, evaluated and regularly monitored.

b) Manuals of manufacturing and testing procedures to be drawn up.

c) Specifications for raw materials, eg time-expired plasma, fresh-frozen plasma, plasma specifications to include microbial limits.

d) Packaging components to be clearly defined.

e) Environmental monitoring to be introduced and action taken when the results are outside acceptable (specified) levels.

f) Documentation to be revised and standardised throughout the Laboratory.

g) Standardised procedures to be introduced for scrutinising production and test records, with a nominated person responsible for this task and for the release of products.

h) Job descriptions and responsibilities to be clearly defined.

j) Training procedures to be introduced.

19/203

k) Steps to be taken to establish the following key posts and appoint appropriate staff as:

Factory Manager; with industrial experience of the manufacture of sterile pharmaceutical products and preferably blood products or biologicals processing.

Quality Controller; as defined in the Guide to Good Pharmaceutical Manufacturing Practice.

Microbiologist; to provide a fully integrated microbiological service.

Engineer; to provide an engineering service and planned preventive maintenance throughout (should have experience of clean rooms, clean air systems, sterilization, filtration etc).

11. Planning of essential improvements must commence forthwith and, take into consideration the following:-

a) The present facility is totally unsuitable for manufacture of sterile products and incapable of being upgraded to the required standards.

b) The existing buildings would be suitable as, or could be adapted for use as:
in-process and control laboratories, research and development laboratories, office accommodation, warehousing, receipt and despatch, packaging.

c) A new factory-type manufacturing facility is required.

ADDITIONAL COMMENT

12. The arrangements originally intended for increased production (known as "Stop Gap Proposals") should be proceeded with as quickly as possible to provide additional cold storage space, warehousing, goods receipt and despatch, container washing and preparation, but only if such a development can be incorporated into a new manufacturing facility. However, in proceeding with 'STOP GAP' there should be no intention of increasing production in the

19/204

present facility as it is already overloaded and seriously deficient in standards. We do not see the need to develop a green-field site for the new manufacturing facility. Instead we would advise that the existing buildings to the north of the Blood Products Laboratory should be demolished and this area utilised. Production could be continued at existing levels in the upgraded existing Laboratory during building of the new production facility. Adequate precautions would need to be taken during such a period to prevent contaminnation of products from the environment. When the new production areas are in operation the existing buildings could be adapted for the ancillary operations. Consideration should be given to amalgamating production from the Plasma Fractionation Laboratory at Oxford, but in the meantime that Laboratory too should be inspected.

19/205

retyped from doc dated from HL (see attached)

APPENDIX 2

MEDICINES DIVISION RECOMMENDATIONS FOR ACTION TO BE TAKEN AT THE BPL ELSTREE	DETAILS OF ACTION TAKEN IN RESPONSE TO THE RECOMMENDATIONS	MEDICINES DIVISION'S COMMENTS ON ACTION TAKEN AND ESSENTIAL SHORT-TERM REQUIREMENTS
1. Under no circumstances should production of any product be increased under the existing manufacturing conditions.	1. Freeze-dried plasma The production of freeze-dried plasma is to cease forthwith.	1. Production of freeze-dried plasma should have ceased already.*
2. There is special need for the manufacture of Freeze-Dried Plasma to be upgraded immediately by locating it elsewhere on the premises as the present faility is totally unacceptable. The alternative is to cease manufacure of their product as the operation as currently undertaken is micro-chemically hazarous.		2. As production has ceased upgrading does not apply.
3. Immediate upgrading of product procedures and control must include:-		
a. An improvement in hygiene cleaning procedures to be established, written down, evaluated and regularly monitored.	a. Cleaning Arrangements for the provision of adequate cleaning facilities are being undertaken with the advice of Domestic Services Branch of the Department.	a. Details are required of the measures taken before comment can be made.
b. Manuals of manufacturing and testing procedures to be drawn up.		b. Details required.
c. Specifications for raw materials, eg time-expired plasma, fresh-frozen plasma, plasma specifications to include microbial limits.		c. " "
d. Packaging components to be clearly defined.		d. " "

* Confirmed that production has ceased.

MEDICINES DIVISION RECOMMENDATIONS FOR ACTION TO BE TAKEN AT THE BPL ELSTREE	DETAILS OF ACTION TAKEN IN RESPONSE TO THE RECOMMENDATIONS	MEDICINES DIVISION'S COMMENTS ON ACTION TAKEN AND ESSENTIAL SHORT-TERM REQUIREMENTS
e. Environmental monitoring to be introduced and action taken when the results are outside acceptable (specified) levels.		e. Details required.
f. Documentation to be revised and standardised throughout the laboratory.	f. Documentation Heads of departments of the Blood Products Laboratory, in conjunction the Director and with Dr Smith of the Plasma Fractionation Laboratory, Oxford, are currently drawing up standardised documentation appropriate for use in the up-graded facility. The Medicines Inspectorate has offered every assistance in compiling and reviewing such documentation.	f. It is essential that standardised documentation be prepared for operations in the existing facility. Revised documentation will be required for the fully upgraded facilities.
g. Standardised procedures to be introduced for scrutinising production and test records, with a nominated person responsible for this task and for the release of products.		g. He should like to have details of procedures and to know who will be responsible.
h. Job descriptions and responsibilities to be clearly defined.	h. Job description Job descriptions for each staff post are being drawn up and these will clearly define individual responsibilities.	h. Noted and welcomed.

MEDICINES DIVISION RECOMMENDATIONS FOR ACTION TO BE TAKEN AT THE BPL ELSTREE	DETAILS OF ACTION TAKEN IN RESPONSE TO THE RECOMMENDATIONS	MEDICINES DIVISION'S COMMENTS ON ACTION TAKEN AND ESSENTIAL SHORT-TERM REQUIREMENTS
j. Training procedures to be introduced.	j. Staff training Staff training in good pharmaceutical manufacturing practice has already commenced. Staff will also have the opportunity of observing these standards in opcration within the pharmaceutical industry.	j. Details of the programme of staff training and by whom it would be carried out are required. It is hoped that staff would be seconded to industry to gain experience in good pharmaceutical manufacturing practice.
k. Steps to be taken to establish the following key posts and appoint appropriate staff as: Factory Manager; with industrial experience of the manufacture of sterile pharmaceutical products and preferably blood products or biological processing. Quality Controller; as defined in the Guide to Good Pharmaceutical Manufacturing Practice. Microbiologist; to provide a fully integrated microbiological service. Engineer; to provide an engineering service and planned preventive maintenance throughout (should have experience of clean rooms, clean air systems, sterilization, filtration etc).	k. Head of the Coagulation Dept. The present head of the Coagulation Department is to retire shortly. His duties will be taken over by Dr J K Smith of the Plasma Fractionation Laboratory who is already spending a substantial proportion of his time at the Blood Products Laboratory revising documentation and manufacturing procedures. Quality controller. The phasing-in of the amalgamation between the Plasma Fractionation Laboratory and the Blood Products Laboratory has the added advantage that Dr Ethel Bidwell will shortly be able to provide a full analytical quality control service and appropriate staff training in quality control for the two laboratories.	k. The appointment of Dr Smith seems entirely appropriate. However, he is unlikely to have the expertise in pharmaceutical manufacture expected of a Director of production. This can be corrected by the appointment of a production manager with biopharmaceutical experience with a firm such as Evans, Wellcome or Pfizer and with a commensurate salary. While we do not question Dr Bidwell's expertise in the analytical control aspect of quality assurance it is very doubtful whether she has the experience of a person responsible for quality assurance in the large scale manufacture of sterile products. We are not in a position to comment objectively on the value of this proposal, therefore. We are looking for the appointment of an expert in the field of quality assurance.

MEDICINES DIVISION RECOMMENDATIONS FOR ACTION TO BE TAKEN AT THE BPL ELSTREE	DETAILS OF ACTION TAKEN IN RESPONSE TO THE RECOMMENDATIONS	MEDICINES DIVISION'S COMMENTS ON ACTION TAKEN AND ESSENTIAL SHORT-TERM REQUIREMENTS
		Microbiologist: This post should be filled. Engineer: This post should be filled.
4. Planning of essential improvements must commence forthwith and, take into consideration the following:- a. The present facility is totally unsuitable for manufacture of sterile products and incapable of being to the required standards, b. The existing buildings would be suitable as, or could be adapted for use as: in-process and control laboratories, research and development laboratories, office accommodation, warehousing, receipt and despatch, packaging. c. A new factory-type manufacturing facility is required.		4(a)-(c) We would like to know what is planned and of progress made.
	5. The improvements documented above will, it is hoped, go a considerable way towards improving the good manufacturing practiceat the Blood Products Laboratory, although it must be emphasised that no serious hazard	5.I It is not accepted that the suggested improvements go a considerable way towards improving g.m: p at the laboratory. It is essential that further measures be taken in the short-term to

MEDICINES DIVISION RECOMMENDATIONS FOR ACTION TO BE TAKEN AT THE BPL ELSTREE	DETAILS OF ACTION TAKEN IN RESPONSE TO THE RECOMMENDATIONS	MEDICINES DIVISION'S COMMENTS ON ACTION TAKEN AND ESSENTIAL SHORT-TERM REQUIREMENTS
	to patients has ever been identified as arising from the administration of these products. Further short-term improvements are being considered for implementation as soon as money can be made available.	provide minimum safeguard in the production of the preparations. It is understood that the "stop-gap" proposals have been dropped. We understand alternatives have been considered and would like to have details.
	6. Up-grading of freeze-drying area A new EF 10/10 freeze-drier is currently being installed together with a new workshop and office in the freeze-drying area. Plans are being drawn up for the provision of a changing room for staff entering the freeze-drying area.	6. These proposals refer to the area for production of Factor VIII and immunologicals. The purchase the freeze-drier had originally been arranged to provide stand-by facilities. The changing room for personnel is an improvement as it will separate people and product. It does not improve the air quality. The resiting of the workshop may provide extra space in the packing area. The possibility of installing a larger fun to increase the number of air changes should however be explored. The quality of air supply does not meet the standards for a permanent installation.

as received from MD !

APPENDIX 2.

MEDICINES DIVISION RECOMMENDATIONS FOR ACTION TO BE TAKEN AT THE B P L ELSTREE	DETAILS OF ACTION TAKEN IN RESPONSE TO THE RECOMMENDATIONS	MEDICINES DIVISION'S COMMENTS ON ACTION TAKEN AND ESSENTIAL SHORT-TERM REQUIREMENTS
1. Under no circumstances should production of any product be increased under the existing manufacturing conditions.	1. Freeze-dried plasma The production of freeze-dried plasma is to cease forthwith.	1. Production of freeze-dried plasma should have ceased already. *
2. There is special need for the manufacture of Freeze-Dried Plasma to be upgraded immediately by locating it elsewhere on the premises as the present facility is totally unacceptable. The alternative is to cease manufacture of the product as the operation as currently undertaken is micro-biologically hazardous.		2. As production has ceased, upgrading does not now apply.
3. Immediate upgrading of product procedures and control must include:-		
a. An improvement in hygiene cleaning procedures to be established, written down, evaluated and regularly monitored.	a. Cleaning Arrangements for the provision of adequate cleaning facilities are being undertaken with the advice of Domestic Services Branch of the Department.	a. Details are required of the measures taken before comment can be made.
b. Manuals (annual) of manufacturing and testing procedures to be drawn up.		b. Details required.
c. Specifications for raw materials, eg time-expired plasma, fresh-frozen plasma, plasma specifications to include microbial limits.		c. " "
d. Packaging components to be clearly defined.		d. " "
e. Environmental monitoring to be introduced and action taken when the results are outside acceptable (specified) levels.		e. " "
f. Documentation to be revised and standardised throughout the laboratory.	f. Documentation Heads of departments of the Blood Products Laboratory, in conjunction the Director and with Dr Smith of of the Plasma Fractionation Laboratory, Oxford, are currently drawing up standardised documentation appropriate for use in the up-graded facility. The Medicines Inspectorate has offered every assistance in compiling and reviewing such documentation.	f. It is essential that standardised documentation be prepared for operations in the existing facility. Revised documentation will be required for the fully upgraded facilities.
g. Standardised procedures to be introduced for scrutinising production and test records, with a nominated person responsible for this task and for the release of products.		g. We should like to have details of procedures and to know who will be responsible.
h. Job descriptions and responsibilities to be clearly defined.	h. Job description Job descriptions for each staff post are being drawn up and these will clearly define individual responsibilities.	h. Noted and welcomed.
j. Training procedures to be introduced.	j. Staff training Staff training in good pharmaceutical manufacturing practice has already commenced. Staff will also have the opportunity of observing these standards in operation within the pharmaceutical industry.	j. Details of the programme of staff training and by whom it would be carried out are required. It is hoped that staff would be seconded to industry to gain experience in good pharmaceutical manufacturing practice.
k. Steps to be taken to establish the following key posts and appoint appropriate staff as:		
Factory Manager; with industrial experience of the manufacture of sterile pharmaceutical products and preferably blood products or biologicals processing.	Head of the Coagulation Department The present head of the Coagulation Department is to retire shortly. His duties will be taken over by Dr J K Smith of the Plasma Fractionation Laboratory who is already spending a substantial proportion of his time at the Blood Products Laboratory revising documentation and manufacturing procedures.	The appointment of Dr Smith seems entirely appropriate. However, he is unlikely to have the expertise in pharmaceutical manufacture expected of a Director of production. This can be corrected by the appointment of a production manager with biopharmaceutical experience with a firm such as Evans, Wellcome or Pfizer and with a commensurate salary.
Quality Controller; as defined in the Guide to Good Pharmaceutical Manufacturing Practice.	Quality controller The phasing-in of the amalgamation between the Plasma Fractionation Laboratory and the Blood Products Laboratory has the added advantage that Dr Ethel Bidwell will shortly be able to provide a full analytical quality control service and appropriate staff training in quality control for the two laboratories.	
Microbiologist; to provide a fully integrated microbiological service.		
Engineer; to provide an engineering service and planned preventive maintenance throughout (should have experience of clean rooms, clean air systems, sterilisation, filtration etc).		

* Confirmed that production has now ceased

paragraph 3 ..

MEDICINES DIVISION RECOMMENDATIONS FOR ACTION TO BE TAKEN AT THE B P L ELSTREE	DETAILS OF ACTION TAKEN IN RESPONSE TO THE RECOMMENDATIONS	MEDICINES DIVISION'S COMMENTS ON ACTION TAKEN AND ESSENTIAL SHORT-TERM REQUIREMENTS
Planning of essential improvements must commence forthwith and, take into consideration the following:- a. The present facility is totally unsuitable for manufacture of sterile products and incapable of being upgraded to the required standards. b. The existing buildings would be suitable as, or could be adapted for use as: in-process and control laboratories, research and development laboratories, office accommodation, warehousing, receipt and despatch, packaging. c. A new factory-type manufacturing facility is required.	5. The improvements documented above will, it is hoped, go a considerable way towards improving the good manufacturing practice at the Blood Products Laboratory, although it must be emphasised that no serious hazard to patients has ever been identified as arising from the administration of these products. Further short-term improvements are being considered for implementation as soon as money can be made available. 6. Up-grading of freeze-drying area A new EP 10/10 freeze-drier is currently being installed together with a new workshop and office in the freeze-drying area. Plans are being drawn up for the provision of a changing room for staff entering the freeze-drying area.	While we do not question Dr Fidwell's expertise in the analytical control aspect of quality assurance it is very doubtful whether she has the experience of a person responsible for quality assurance in the large scale manufacture of sterile products. We are not in a position to comment objectively on the value of this proposal, therefore. We are looking for the appointment of an expert in the field of quality assurance. Microbiologist: This post should be filled. Engineer: This post should be filled. 4(a)-(c) We would like to know what is planned and of progress made. 5. It is not accepted that the suggested improvements go a considerable way towards improving G.M.P. at the laboratory. It is essential that further measures be taken in the short term to provide minimum safeguard in the production of the preparations. It is understood that the "stop-gap" proposals have been dropped. We understand alternatives have been considered and would like to have details. 6. These proposals refer to the area for production of Factor VIII and immunologicals. The purchase of the freeze-drier had originally been arranged to provide standby facilities. The changing room for personnel is an improvement as it will separate people and product. It does not improve the air quality. The refitting of the workshop may provide extra space in the packing area. The possibility of installing a larger fan to increase the number of air changes should however be explored. The quality of air supply does not meet the standards for a permanent installation.

MEDICINES DIVISION RECOMMENDATIONS FOR ACTION TO BE TAKEN AT THE BPL ELSTREE	DETAILS OF ACTION TAKEN IN RESPONSE TO THE RECOMMENDATIONS	MEDICINES DIVISION'S COMMENTS ON ACTION TAKEN AND ESSENTIAL SHORT-TERM REQUIREMENTS
1. Under no circumstances should production of any product be increased under the existing manufacturing conditions.	1. Freeze-dried plasma The production of freeze-dried plasma is to cease forthwith.	1. Production of freeze-dried plasma should have ceased already.*
2. There is special need for the manufacture of Freeze-Dried Plasma to be upgraded immediately by locating it elsewhere on the premises as the present faility is totally unacceptable. The alternative is to cease manufacure of their product as the operation as currently undertaken is micro-chemically hazarous.		2. As production has ceased upgrading does not apply.
3. Immediate upgrading of product procedures and control must include:-		
a. An improvement in hygiene cleaning procedures to be established, written down, evaluated and regularly monitored.	a. Cleaning Arrangements for the provision of adequate cleaning facilities are being undertaken with the advice of Domestic Services Branch of the Department.	a. Details are required of the measures taken before comment can be made.
b. Manuals of manufacturing and testing procedures to be drawn up.		b. Details required.
c. Specifications for raw materials, eg time-expired plasma, fresh-frozen plasma, plasma specifications to include microbial limits.		c. " "
d. Packaging components to be clearly defined.		d. " "

* Confirmed that production has now ceased.

MEDICINES DIVISION RECOMMENDATIONS FOR ACTION TO BE TAKEN AT THE BPL ELSTREE	DETAILS OF ACTION TAKEN IN RESPONSE TO THE RECOMMENDATIONS	MEDICINES DIVISION'S COMMENTS ON ACTION TAKEN AND ESSENTIAL SHORT-TERM REQUIREMENTS
e. Environmental monitoring to be introduced and action taken when the results are outside acceptable (specified) levels.		e. Details required.
f. Documentation to be revised and standardised throughout the laboratory.	f. Documentation Heads of departments of the Blood Products Laboratory, in conjunction the Director and with Dr Smith of the Plasma Fractionation Laboratory, Oxford, are currently drawing up standardised documentation appropriate for use in the up-graded facility. The Medicines Inspectorate has offered every assistance in compiling and reviewing such documentation.	f. It is essential that standardised documentation be prepared for operations in the existing facility. Revised documentation will be required for the fully upgraded facilities.
g. Standardised procedures to be introduced for scrutinising production and test records, with a nominated person responsible for this task and for the release of products.		g. He should like to have details of procedures and to know who will be responsible.
h. Job descriptions and responsibilities to be clearly defined.	h. Job description Job descriptions for each staff post are being drawn up and these will clearly define individual responsibilities.	h. Noted and welcomed.

MEDICINES DIVISION RECOMMENDATIONS FOR ACTION TO BE TAKEN AT THE BPL ELSTREE	DETAILS OF ACTION TAKEN IN RESPONSE TO THE RECOMMENDATIONS	MEDICINES DIVISION'S COMMENTS ON ACTION TAKEN AND ESSENTIAL SHORT-TERM REQUIREMENTS
j. Training procedures to be introduced.	j. Staff training Staff training in good pharmaceutical manufacturing practice has already commenced. Staff will also have the opportunity of observing these standards in opcration within the pharmaceutical industry.	j. Details of the programme of staff training and by whom it would be carried out are required. It is hoped that staff would be seconded to industry to gain experience in good pharmaceutical manufacturing practice.
k. Steps to be taken to establish the following key posts and appoint appropriate staff as: Factory Manager; with industrial experience of the manufacture of sterile pharmaceutical products and preferably blood products or biological processing. Quality Controller; as defined in the Guide to Good Pharmaceutical Manufacturing Practice. Microbiologist; to provide a fully integrated microbiological service. Engineer; to provide an engineering service and planned preventive maintenance throughout (should have experience of clean rooms, clean air systems, sterilization, filtration etc).	k. Head of the Coagulation Dept. The present head of the Coagulation Department is to retire shortly. His duties will be taken over by Dr J K Smith of the Plasma Fractionation Laboratory who is already spending a substantial proportion of his time at the Blood Products Laboratory revising documentation and manufacturing procedures. Quality controller. The phasing-in of the amalgamation between the Plasma Fractionation Laboratory and the Blood Products Laboratory has the added advantage that Dr Ethel Bidwell will shortly be able to provide a full analytical quality control service and appropriate staff training in quality control for the two laboratories.	k. The appointment of Dr Smith seems entirely appropriate. However, he is unlikely to have the expertise in pharmaceutical manufacture expected of a Director of production. This can be corrected by the appointment of a production manager with biopharmaceutical experience with a firm such as Evans, Wellcome or Pfizer and with a commensurate salary. While we do not question Dr Bidwell's expertise in the analytical control aspect of quality assurance it is very doubtful whether she has the experience of a person responsible for quality assurance in the large scale manufacture of sterile products. We are not in a position to comment objectively on the value of this proposal, therefore. We are looking for the appointment of an expert in the field of quality assurance.

MEDICINES DIVISION RECOMMENDATIONS FOR ACTION TO BE TAKEN AT THE BPL ELSTREE	DETAILS OF ACTION TAKEN IN RESPONSE TO THE RECOMMENDATIONS	MEDICINES DIVISION'S COMMENTS ON ACTION TAKEN AND ESSENTIAL SHORT-TERM REQUIREMENTS
		Microbiologist: This post should be filled. Engineer: This post should be filled.
4. Planning of essential improvements must commence forthwith and, take into consideration the following:- a. The present facility is totally unsuitable for manufacture of sterile products and incapable of being to the required standards, b. The existing buildings would be suitable as, or could be adapted for use as: in-process and control laboratories, research and development laboratories, office accommodation, warehousing, receipt and despatch, packaging. c. A new factory-type manufacturing facility is required.		4(a)-(c) We would like to know what is planned and of progress made.
	5. The improvements documented above will, it is hoped, go a considerable way towards improving the good manufacturing practiceat the Blood Products Laboratory, although it must be emphasised that no serious hazard	5.I It is not accepted that the suggested improvements go a considerable way towards improving g.m: p at the laboratory. It is essential that further measures be taken in the short-term to

MEDICINES DIVISION RECOMMENDATIONS FOR ACTION TO BE TAKEN AT THE BPL ELSTREE	DETAILS OF ACTION TAKEN IN RESPONSE TO THE RECOMMENDATIONS	MEDICINES DIVISION'S COMMENTS ON ACTION TAKEN AND ESSENTIAL SHORT-TERM REQUIREMENTS
	to patients has ever been identified as arising from the administration of these products. Further short-term improvements are being considered for implementation as soon as money can be made available.	provide minimum safeguard in the production of the preparations. It is understood that the "stop-gap" proposals have been dropped. We understand alternatives have been considered and would like to have details.
	6. Up-grading of freeze-drying area A new EF 10/10 freeze-drier is currently being installed together with a new workshop and office in the freeze-drying area. Plans are being drawn up for the provision of a changing room for staff entering the freeze-drying area.	6. These proposals refer to the area for production of Factor VIII and immunologicals. The purchase the freeze-drier had originally been arranged to provide stand-by facilities. The changing room for personnel is an improvement as it will separate people and product. It does not improve the air quality. The resiting of the workshop may provide extra space in the packing area. The possibility of installing a larger fan to increase the number of air changes should however be explored. The quality of air supply does not meet the standards for a permanent installation.

Report of Inspection of	:	The Blood Products Laboratory Elstree Hertfordshire
Dates of Inspection	:	23 to 27 April 1979 and 16 to 19 July 1979
Objective	:	To assess the manufacturing operation from a pharmaceutical viewpoint.
Senior Personnel met	:	Dr Lane, Director Mr Vallet, Deputy Director Mr Wesley, Head of Large Fractionation Laboratory Dr Ellis, Head of Clotting Factors Laboratory Dr Singleton, Microbiologist and Head of Freeze-dried Plasma Laboratory Mr Montgomery, Engineer Mr Sharman, Packaging Mr Pettet, Chief Technician C F Laboratory Mr Williams, Senior Technician C F Laboratory Mr Greulich, Quality Control Chemist
DHSS representatives	:	Dr Holgate (part time) Mr Flint Dr Purves

19/18

INDEX

3.4 Freeze Drying Department

INTERIM SUMMARY 5

3.5 Washing and Sterilization of Equipment etc

INTERIM SUMMARY 6

3.6 Engineering aspects of plant and equipment

INTERIM SUMMARIES 7 and 8

4. SUMMARY SESSION OF THE VISIT OF 23 - 27 APRIL

5. PASTEURISATION OF P.P.F ; INSPECTION AND PACKAGING - MR SHARMAN

5.1 Pasteurisation of P.P.F.

5.2 P.P.F. Incubation

5.3 Inspection and Packaging

5.4 Transit Cartons Store

5.5 Final Products Ambient Store

5.6 Quarantine Stores

5.7 Small Orders Despatch Section

5.8 Complaints

INTERIM SUMMARY 9

6. ANALYTICAL LABORATORIES

INTERIM SUMMARY 10

7. DOCUMENTATION AND FINAL PRODUCT RELEASE

7.1 Plasma Protein Fraction Documentation

19/20

7.2 Freeze - Dried Factor VIII Documentation

7.3 Freeze - Dried Small Pool Plasma Documentation

INTERIM SUMMARY 11

8. CONCLUSIONS AND RECOMMENDATIONS

Part 2 - BIOLOGICAL QUALITY CONTROL FACILITIES

Appendix 1 Large Fractionation Production Methods

Appendix 2 (a - c) Plans of Production Areas

Appendix 3 Clotting Factors Production Methods

Appendix 4 Large Scale Production of Human Plasma Fractions (Publication)

Appendix 5 Product List

PART 1 - GENERAL REPORT

1. INTRODUCTION

Dr Lane, Director of the Blood Products Laboratory (BPL) took over the responsibility of running the Laboratory only about 6 months ago on the retirement of Sir William Maycock.

Brief discussions of a general and introductory nature were held prior to starting the inspection for the benefit of Dr Purves, who had not visited the site before. It was intimated that production throughput in the unit has far exceeded the original design capacity. In an attempt to rectify some of the immediately apparent deficiencies a 'stop gap' project has been initiated to partly improve the buildings and alleviate difficulties concerning storage. Some of these measures are intended to be temporary, but others, such as cold stores, are being planned for long term use. In general, the impression gained from Dr Lane was that he fully appreciates his major problems lie in staffing, limitations imposed by premises and having to run the laboratory as a factory.

1.1 Inspection Format

Messrs Flint and Purves have inspected and reported on this site as they would have done were it a pharmaceutical operation.

2. STORES AND RECEIPT OF CHEMICAL RAW MATERIALS, COMPONENTS ETC

*The storage area allocated for the receipt of general goods and chemical raw materials is severely congested to the extent that areas, although designated for quarantined and passed goods are not used as such. Congestion is such that it precludes good storage and proper stock rotation of components such as vials, bungs etc. On the whole the area is dry and weatherproof, although some leaks were evident through part of the roof behind the loading bay.

Analytical control over chemical raw materials, instituted only in 1978, has been organised by Mr Greulich, who is in charge of the analytical department. Each container is identified and one from each manufacturer's batch is fully *assayed according to laid down specifications. These specifications appear to be those of the EP or BP but as yet have not been written in a formal manner.

Components such as bottles, vials, bungs etc are, as yet, not routinely tested: there are no formal specifications. Some vials stored behind the loading bay were left open to atmosphere.

A limited amount of in-process testing is done using mainly electrophoresis and ethanol determinations.

A series of standard analytical methods have been prepared for the analysis of raw materials, in process samples and finished products.

Because of the inordinate time taken to inspect the production of this operation, it was not possible to have a comprehensive look at the analytical laboratories during the first week of the visit. A report on this will be prepared after a follow-up inspection planned for the week beginning Monday 16 July 1979.

3. PRODUCTION PREMISES, EQUIPMENT AND PROCEDURES

3.1 Mr Wesley's Department : Large Fractionation and Final Solutions

Mr Wesley, who is in charge of the Large Fractionation Laboratory (LFL), joined the BPL 16 years ago direct from Nottingham University, where he obtained a B Pharm degree. He is responsible for large scale protein fractionation and the production of immunoglobulins. His deputy oversaw the latter production, but has left for a post in industry: he has not yet been replaced.

Staff presently working to Mr Wesley include a Mr Butcher who has worked in the laboratory for 25 years and was in charge of ether fractionation when it was in operation: Mr Butcher is the chief technician. Three technicians (with various O and A levels, doing day release) and laboratory assistants, employed for manual work report to Mr Butcher. There is no formalised training for technicians or laboratory assistants other than that given by exposure to work in hand.

3.1.1 Products made

The major products made in this laboratory include:

3.1.1.1 Plasma Protein Fraction, PPF

3.1.1.2 Salt Poor Albumin 10g% and 20g%, and

3.1.1.3 Normal and specific Immunoglobulins

A summary of the production of these can be seen at page 3 of Appendix 1, using the standard cold ethanol fractionation method of Kistler and Nitschman (Vox Sang 7, 414-424, 1962). Starting materials used in this production include:

3.1.1.4 Time expired plasma: this comes from Regional Transfusion Centres (RTCs) in 5L plastic packs.

3.1.1.5 Cryoprecipitate supernatant: this also comes from RTCs. Materials 4 (3.1.1.4) and 5 (3.1.1.5) normally amount to about 1,200 litres per week which contributes about 50% of the plasma requirement.

3.1.1.6 Cryoprecipitate supernatant: a second source of this material is from Dr Ellis' laboratory [Clotting Factors Laboratory] and consists of plasma from which factor VIII has been removed. This is supplied to the LFL in bulk, in stainless steel fractionation vessels, 1000 litres per week. It is not routinely tested for Hb_s Ag or micro-organism count: it can have high microbial counts as some examinations have show.

3.1.1.7 Factor VIII/IX supernatant: a supply of this 120 litres/ week is obtained from Oxford Plasma Fractionation Laboratory in stainless steel churns.

3.1.1.8 Fraction 1 supernatant: this is plasma from which fibrinogen has been removed.

3.1.1.9 Precipitate A supernatant: this is plasma which has had antibodies removed (Specific 1gg) and contains albumin only.

3.1.1.10 Freeze dried, time expired plasma from Dr Singleton's laboratory.

3.1.1.11 Plasma from Belfast in 3L packs.

The composition of the starting plasma pools therefore varies according to source, the proportion of frozen time expired plasma and liquid plasma used. This, it was said, did not affect the quality of the end product even though Belfast plasma has been known to have organism counts up to 3 million per ml, other plasmas have also been found to have counts in the region of 500 per ml.

All plasma received from the RTCs is tested for Hb_s Ag by a radio immunoassay (RIA). If there is insufficient material in the testing pouch then this test is done in preference to a microbial count. Plasma, the microbial quality of which is unknown, can be used in production runs. Some RIA testing is done at Region and reported to the BPL. (i.e. North London and Brentwood).

Initially the turnover of time expired plasma was about 10 weeks but now the unit is being supplied with more plasma than can be handled by the existing staff on a single shift basis and turnover, it is estimated, is greater than one year.

Liquid plasma is normally used within 3 days but it could stand longer, perhaps over weekends, if this is to be so then alcohol (96% ethanol and 2% methanol) is added to a final concentration of 19%. The justification of different storage temperatures for liquid plasmas, that is $+2^{\circ}C$, $-3^{\circ}C$ and $-5^{\circ}C$ is due to the alcohol content (see page 4, Appendix 1).

As fraction II, used for immunoglobulin production, is produced at a frequency of 1 batch in 10 of large scale fractionation, fraction II starting material is selected with care to get the 'best'. Any potential fraction II material about which there is the slightest query is not used. 'Tropical pool' plasma, i.e plasma from coloured donors, is not used.

Every 5L pack of time expired plasma is an individual batch: it is made up to 28 donations, details of which are kept by RTCs but not passed on to the BPL.

3.1.2 Production Process

5L packs of time expired frozen plasma on receipt at the BPL is transferred within a short time period (30 mins) to $-25^{\circ}C$ stores on the upper floor of the large fractionation laboratory. Material is kept

on numbered pallets and details of batches on a pallet location are recorded. Pallet contents are not secure in that individual packs could be transferred from one pallet to another. This is not of any great consequence as batches are requisitioned the day before use and checked against the batch numbers on the outsides of cardboard cartons and, also on the pack inside. The 'production' batch record is ticked against each pack number and packs are transferred to a second pallet. On the day of use the packs are checked again and the ticks ringed. At the first checking stage material that has been defined as unacceptable is removed from the pallet, but not from the store. Acceptable material should always be kept secure i.e. on a caged pallet, segregated from rejected material.

Pooled material collated for processing consists of liquid plasma, which is always used first, and time expired frozen plasma to make up the volume for a given production run. Separation of the required portions is then by cold ethanol fractionation at various pH values and centrifugation.

3.1.3 Premises, Equipment and Procedures

Operations involved in large scale fractionation are split between two floors. The initial steps are carried out on the upper floor fractionation room (see Appendix 2c). All of the remaining steps are undertaken in a ground floor area shown at Appendix 2b.

5L packs of plasma in cardboard outers are transferred on wooden pallets into the upper fractionation room. Cardboard and wooden pallets should not be taken into this area: the latter should be easily cleanable and be of plastic or metal construction.

This production area houses the tops of four stainless steel processing vessels the bodies of which protude into the ground floor processing room in which centrifugation is done.

The room finish is of gloss painted plaster ceiling, three walls of a similar finish, one of welded vinyl and the floor is covered again with welded vinyl. The area is air-conditioned but the quality of air supplied was not known by Mr Wesley. Air enters at near ceiling level and is directed to the floor by fixed hoods and exhausts at a high level on the opposite wall. There is no changing room for staff entering the

area or air lock for the entry of goods and equipment. There is much exposed wood, cork, high level dust traps (pipework) and condensation on pipes.

There are no written cleaning schedules for the room or equipment. Production staff clean equipment but the room is cleaned by general staff: the frequency of this is floors weekly and walls and ceilings at indeterminate times. No procedure exists for the preparation of disinfectant used in this area: it is made up with tap water. There appears to be no standardisation of procedures. Funnels and troughs for use on thawing shelves - piped glycol solutions are used to facilitate heat exchange - for the collection of plasma are autoclaved in a ground floor area and brought to this processing room unwrapped, 24 hours before use. The autoclaving procedure is apparently used principally to eliminate hepatitis virus. Hypochlorite solution, made up by rule-of-thumb, is used to disinfect the thawing shelves; it is not made up in a pre-sterilized container. Cleaning cloths remain wet and could promote the spread of bacteria. Tap water supplied to this area is softened and of unknown microbial count.

Bags of frozen plasma are allowed to thaw on the stainless steel shelves. Plasma discharges into stainless steel chutes which lead to stainless steel funnels which feed into a holding vessel. All vessels are washed out but not to a written procedure: no record is kept that they have been washed. Apparently they are washed out with mains water from a hose-pipe which is hung on the wall in a coil fashion. They are left wet, then rinsed out with 75 litres of heated (80°C) distilled water: this wash water is checked for microbial count.

Some mould was growing in the vicinity of the sink.

A drain in this area is treated with lysol which had been made up some time ago: the drain is never cleaned. The sink drain is not disinfected.

Rubber tubing used as overflow tubes for the large reaction vessels are neither cleaned, changed nor examined microbiologically.

There are many possible sources of microbial contamination in this area that could enter the reaction vessels at the loading stage. No

19/27

baseline level has been established for the environment, tap water, cleaning solutions etc: the area should be monitored to establish this data.

Engineering support for maintenance of the fabric of the premises is inadequate e.g. defective plaster.

Short term improvements to this area should involve improving procedures, maintenance to premises, and cleaning in accordance with clean room technology. Longer term improvements would necessitate upgrading the environment to Class 2, with the incorporation of an air-lock and a personnel changing room.

The ground floor processing area is split into three main zones, cooled to varying degrees. A $+2^{\circ}C$ zone is used as a general preparation area e.g asbestos filters, storage and processing area (decanting of reconstituted fraction II solution into shallow stainless steel trays from winchester bottles, prior to freezing). The $-5^{\circ}C$ room houses the bases of the large fractionation vessels and the manifold fe ed,assembly of Sharples continuous centrifuges. The $-10^{\circ}C$ room houses the fractionation of immunoglobulins.

The criticisms already made to the initial processing area are also applicable to this which has additional deficiencies. Throughout this area which has no personnel changing room, the suspended ceiling is of long narrow perforated metal sections, which slot together in a tongue and groove manner. Wall surfaces are of a formica type finish with wooden 'protection' bars. The floor is of quarry type tiles with grouting between. In the $+2^{\circ}C$ room the ceiling sections were found to be poorly fitting and dirty: on closer examination this dirt was found to be confluent growth of mould, in all appearances showing growth from the hyphael to the sporing stage of its cycle.

This situation in a room where nutritive products are being processed in an open manner is totally unacceptable. Water for use in production was being cooled in an open top stainless steel vessel adjacent to such an area.

Air supplied to these rooms is virtually totally recirculated with a small percentage make up, the quality of which, i.e filtered or not,

was not known.

The temperature of the area is not conducive to good work over an extended period of time.

The area is particularly difficult to clean effectively. Cardboard is also brought into this area.

The transfer of centrifuge precipitate from the Sharples units to non-sterilized polythene bags is done in the open atmosphere of the -5°C room. Precipitate is stored in a cupboard in this room until it is required for solutioning, in lidded stainless steel tanks, which is done in the +2°C room. The resulting albumin solution is then passed through a series of coarse asbestos filters and a final of 0.22 micron filter.

Resulting filtrate is then further processed. If it is fraction V, which will eventually end up as Plasma Protein Fraction or Salt-Poor Albumin, it is subjected to thin layer vacuum distillation to remove process alcohol and concentrate the protein to the required level. Resulting solutions are then packed into 5L plastic packs which are frozen in one of two Grant freezers, in an adjacent room, before being stored at -25°C. If it is fraction II it will be transferred to shallow trays, as described above, for subsequent freezing and drying in the Edwards' freeze driers. Primary drying takes 1.5 days and the secondary drying (P_2O_5) is done overnight. Dried material on open trays is then tipped into ordinary polythene bags (not pre-sterilized). Bags of powder are then placed in lidded polythene buckets and stored at -25°C in a refrigerated room next to the PPF solutioning room.

The former operation is done in a Centritherm Unit which is housed in what appears to be a standard laboratory with a general air supply, not HEPA filtered. The Centritherm evaporator is virtually a closed piece of apparatus which is disinfected, using hot water, before use: the system would be much improved if its component parts were sterilized and the whole operation was carried out in a controlled area. There is no changing room or procedure for entering the laboratory: the ceiling is constructed of perforated tiles, the walls are of painted plaster and the floor of vinyl finish. Laboratory furniture is of wood (some unsealed) and cardboard cartons into which filled bags are put are taken into the area. The door to the area from a common corridor is not always closed during processing and staff do not wear gloves during processing.

While operators don special clothing in the plasma pooling area on the first floor - trouser suits, wellingtons and masks - to protect the operator from splashes of plasma, no clothing in addition to a standard laboratory coat is worn in this area.

There is no general changing procedure for staff entering the BPL so that they can exchange their outdoor clothes for factory clothes. The operator in the Centritherm room was wearing outside 'running shoes' and a process tube was hanging on the floor near these: this points to another potential source of microbial contamination in addition to that contributed by the general environment of the factory.

Some in-process control work is carried out on the Fraction V paste after centrifugation. The paste is made up into solution in sub-batches (one sub-batch per day). Solutions are filtered. Before evaporation the turbidity is examined (purely visually), electrophoretic tests are done and samples taken for microbial examination. Counts are determined and can lie between 100 and 500 organisms/ml: contaminants are not classified. /Poor material is used in production by being mixed with good material to "dilute the bug count out": this type of philosophy is totally unacceptable./

Small scale fractionation of specific immunoglobulins such as anti-bee venom is done in a $-10^{\circ}C$ room which is part of the suite housing the $-5^{\circ}C$ and $+2^{\circ}C$ processing rooms already mentioned: it is equally poor in the fabric of finish and standard of operation carried out therein. However, the environment and procedures used to pool the plasma are more inferior than those cited for large scale fractionation. Plasma is pooled in a general laboratory Appendix 2(b), with perforated ceiling tiles, wooden furniture and rough wooden crates (used for the carriage of bottled chemicals), fibreboard containers of chemicals etc: it is supplied with air the quality of which is probably extremely poor as manifest by black streaks of dirt surrounding the in-put grill. Again, there is no changing room or procedure for entry to this area. 5L bags of selected plasma are thawed out in a sink of hot water drawn from the general factory system.

INTERIM SUMMARY 1

In summary, the general standard of the Fractionation Laboratory operation is extremely poor. Processing involves open procedures at the

beginning and throughout the fractionation operation. Alcoholic fractionation is effected at various pH levels and with appropriate centrifugation plasma fractions are obtained as pastes in the Sharples centrifuges. These pastes are taken up into solution (using cooled distilled water previously stored at 80°C) and filtered (coarse asbestos plus a final 0.22 micron filter). Filtrate is then subjected to thin layer vacuum distillation or frozen. Much of the handling of this intermediate product is done in an open manner in the +2°C room which was found to be heavily contaminated with moulds. Plasma fractions are then held frozen or dried, awaiting further processing.

The attitude taken that, as the starting material is contaminated, it is pointless carrying out the rest of the processing under clean conditions is unacceptable, even if the end product has never been shown to elicit pyrogenic reactions. A change in attitude is required to collect the raw material under conditions as hygienic as possible pool it at RTCs under clean room conditions, commensurate with the nature of the operation, to ensure that the microbial load is minimal. All material used in production should be of known microbial load and plasma should be processed in such a way that its microbial load is not contributed to due to inferior premises, procedures and techniques. To achieve this it is imperative that the operation is upgraded,

SHORT TERM: improve handling within the present premises

LONG TERM: upgrade the premises to CLASS 1 or CLASS 2, commensurate with the nature of the operations to be done.

i. Staff training should be implemented/improved.

ii. Documentation should be improved ie. procedures.

iii. Equipment/premises should be improved.

iv. Environmental monitoring should be implemented to at least establish present particulate and microbial loads.

v. Cold storage should be increased to facilitate better segregation and stock rotation.

vi. Staff should wear processing clothing in critical production areas.

vii. Additional key staff is required as present staff are taking the responsibility for too wide a range and extent or production activities and therefore cannot spend the necessary time for supervising immediate production staff who are left too much to use their own initiative (see point i).

Final Solution Preparation

Preparation of the final solutions utilizes frozen Fraction V concentrate - for PPF - frozen albumin concentrate - for salt poor albumin - and freeze dried Fraction II for normal immunoglobulins etc. This activity involves opening bags of frozen material, swabbed with 96% alcohol, in the final solutioning room (see Appendix 2(b)) under vertical LAF and placing in a stainless steel vessel with half of the lid removed. The frozen concentrate is allowed to melt and is taken up into an isotonic solution in the adjacent +2°C room. Water used at this stage has been collected and cooled in another +2°C room, already mentioned which was heavily contaminated with moulds.

Staff working in this area wear ordinary laboratory coats, head covers and sterilized gloves.

The premises are poor. There is no staff changing room. The ceiling and walls have an imperfect painted plaster finish: the floor is of welded vinyl. Wooden furniture and desks are used throughout: they are not easily cleanable: there is a notice board on the wall and the area is used as an office as well as a production area. Air is supplied to the room through high-level wall grills around which is cracked plaster and black streaks, again indicating the poor quality of the air supplied. The vertical laminar flow bench is hung on overhead rails to permit its use over a considerable length of bench. Debris could fall from these rails, and, it is doubtful that this type of distant LAF source would protect the product. There is a great liklihood that it would promote contamination due to turbulence and the proximity of 'shedding' operatives. A fibreboard container of sodium chloride was found in the area: this salt is used to render bulk solution of product isotonic. The fabric of finish of the associated +2°C room is similar to those previously described in the large fractionation suite.

During the preparation of these solutions samples are taken, using 'sterile' beakers, for protein determinations. This is done using a refractometer. The use of the word 'sterile' for a beaker which has only been washed shows a lax use of the word, indicating a lack of understanding of the true meaning of sterility. This situation occurring so near to the final sterilization by filtration does pose several questions regarding staff training, appreciation of the nature of the work in hand, supervision etc.

Solutions are then filtered through a Carlson Ford asbestos depth filter unit (previously 'sterilized') into a pre-sterilized stainless steel vessel (121°C/1 hr). Because of the tubing (non-sterile) used post filter this stage of the operation is considered non-sterile. The solution is then filtered through a complicated network of tubes to a PALL filter (0.22 micron), before passing through the wall, in a pre-sterilized piece of tubing, to the 'sterile' filling suite. Procedures used in this area - manipulation of sterilized tubing from a dirty to a clean area - do not lead to good aseptic techniques.

Samples of solutions are taken before and after the penultimate filtration stage for microbial evaluation.

Smaller quantities of Gamma immunoglobulin solutions are pre-sterilized by filtration* into pre-sterilized hermetically sealed cans with filter air bleeds in the solution preparation area and these are taken into the sterile suite for filling, being transferred in the air lock from one wheel base to another which is kept in the clean room.
NOTE: The PALL filter and vessel are sterilized together.

A plan of the 'sterile' filling suite can be seen at Appendix 2(b). This area is cleaned thoroughly once per month. There is no daily or weekly cleaning procedure and this would explain the build up of dust on exhaust grills.

Product and equipment enter the area via an air lock: personnel enter via one of two designated changing rooms. Briefly the changing procedure is as follows: male operatives take off outdoor shoes only (ladies do not), overshoes are put on, hands are washed, head cover

*Under LAF in final solutioning room

(which is too small) is donned, then the mask (hands are not washed again), the operative puts on the one piece trouser suit closing it at ankles (outside overshoes) wrists and neck: sterilized gloves are put on, hair is tucked into hood with gloved hands. The dressed worker then washes the gloved hands with an alcoholic solution on entering the suite.

At the time of inspection the air extract unit in the ceiling, on the dirty side of the male changing room was open with no barrier between it and the outside atmosphere. Cracks were noted in the wall plaster and floor to wall coving was loose. There is an insufficient number of differential pressure manometers to permit the recording of pressures in the various rooms and show a gradation of flow of air from the more to the less critical areas.

Female staff wore the clean room clothing in an inappropriate manner, The hair was not totally covered, make-up was worn, earrings were worn, sleeves of suits were not tucked into gloves: this latter point would probably result in a pumping effect of debris from the sleeve into the critical filling zone.

The vertical LAF is suspended on overhead rails and is directed onto a solid bench which will result in a considerable amount of turbulence around the filling head. It is considered that horizontal LAF would be more appropriate for the type of filling head currently being used.

An alcoholic disinfectant for hand rinsing is not readily available for any operative that may inadvertently touch the face.

There is no LAF facility in the Factor VIII filling room.

Operatives complained that no training had been given for this type of operation but they did realise that specialist information should be sought.

The overwrapping of clothing to be sterilized and taken into this area has not been standardised. Each operative prepares his/her own clothing.

Bottles of diluted and concentrated Chloros in the suite were closed with CORKS.

INTERIM SUMMARY 2

In summary, the premises, operations and procedures carried out in the final solution preparation room are inadequate for the types of product being manufactured. There are indications that staff training should be implemented so that some of the potential trouble spots may be identified, and dealt with.

The 'sterile' filling suite should conform and be used as a CLASS 1 area for the aseptic operations being carried out. While the fabric of the premises in general is good, deficiencies have been noted: these should be rectified immediately. One of the major deficiencies exists in the way personnel dress and work in the area: this is highly significant when one notes that the greatest potential source of contamination is the operative. The choice of a vertical LAF has been questioned.

3.2 Dr Ellis' Department : Clotting Factors Laboratory.

Dr Ellis is in overall charge of the Clotting Factor Laboratory. Reporting to him is Mr Petett BSc, the chief technician, who acts as his assistant and deputy: he has worked at BPL for 6 years. A senior technician, a Mr Williams in post for 10 years, is in charge of the day-to-day operations in the Laboratory. Beneath these key people there are technicians, some qualified, others not, and, laboratory assistants.

3.2.1 Products made.

The major products made in this laboratory include: . .

3.2.1.1. Antihaemophilic Factor (AHF), 50-60,000 units/year.

3.2.1.2 Fibrinogen for intravenous use, 100 bottles/week.

3.2.1.3 Fibrinogen for isotope labelling. Highly selected starting material is used to prevent the passing on of hepatitis virus.

3.2.1.4 Fibrin foam (this is freeze dried fibrin which is put into a jar and baked in an oven) 1,000 pieces/year.

19/35

3.2.1.5 Preparation of an intermediate product, Factor IX, which is sent, refrigerated, to the Oxford BTC 2 x 200L batches/week, and,

3.2.1.6 Thrombin, 1,000 vials per year.

3.2.2. Production Process.

The above range of products are all made in a single suite of laboratories, a plan of which is shown at APPENDIX 2(b).

To illustrate the general types of procedures used the manufacture of AHF only will be considered.

Details of the procedures used in this area are given in a Master Method document which should be referred to, see APPENDIX 3.

3.2.3 Premises, Equipment and Procedures.

This production operation suffers criticisms similar to those already cited for the large scale fractionation unit.

Access of personnel, "tub-trucks" and equipment, from elsewhere in the Laboratory complex to this processing and adjacent areas is too lax.

There are no areas which act as equipment air-locks or changing rooms for personnel to don suitable clothing. There is no standardisation of attire for operatives entering processing room CR2, (i.e no SOP), although in mitigation process workers in close proximity to the process are better covered than others doing less critical operations. This attire consists of coveralls, boots, head cover, mask and gloves and can be used for more than one day. It is stored in metal lockers in the central corridor of the suite between sessions of use. Clothing would be changed at least once per week: it is laundered by a commercial laundry. Hats, masks and gloves are changed daily and boots are washed in Hycolin, infrequently.

Premises used for the primary preparation of AHF are poor. There is a metal plate ceiling in which there are trap doors; walls are of painted plaster, with cracks and the floor is of quarry tiles. There are numerous service pipes to various pieces of equipment which render the room not easily cleanable.

Air supplied to this room is not filtered it is merely conditioned and recirculated through wooden ducts. There is no forced ventilation of the corridor: any ventilation is merely by air loss from adjacent rooms.

It is in this room that frozen plasma is thawed for the initial stage of Factor VIII production. Melted raw material is then centrifuged (continuous Sharples units) to separate the cryoprecipitate which contains the required fraction. All of the processes undertaken may be described as open.

The aqueous heat exchanger used at 28°C, to aid plasma thawing has been known to leak: this could contaminate the product if it was not adequately maintained and tested.

There are no Standard Operating Procedures (SOPs) for the cleaning and disinfection of the environment or equipment. Disinfection of the cleaned environment is achieved by wiping down surfaces with 1% Hycolin, made up qs, using clean sterilized lint. Floors are cleaned once per week and walls infrequently. Vessels and certain pieces of equipment are steamed out after use (105°C), cleaned with Haemosol solution, then with pyrogen free water and finally with 70% ethanol. They are rewashed immediately before use with sterilized pyrogen free water.

On the completion of each piece of work, floors are mopped with Hycolin.

Laboratories 13 and 16 house further processing steps in Factor VIII production namely centrifugation of precipitate and resuspension of precipitate, and final sterilization by filtration, respectively (see APPENDIX 3 for more detail). The fabric of finish of ceilings and walls is of matt painted plaster, the surface of which is cracked at several locations. The floor is of welded vinyl and the furniture of wood. Laboratory 16 has an inner room in which the terminal aseptic

19/37

filtration of Factor VIII is done. Access to the latter which has a poor fabric of finish, is gained via a small changing room which is merely an ante-room without the facilities required to permit one to don sterilized clothing in the manner required for an aseptic operation. Work is done under the protection of a LAF bench, which, from appearances, is ill-maintained. In this room the overall pressure relative to ambient is 0.6" water gauge. Neither the room nor the associated equipment looked clean. Clothing used in this area is the same as that used in the processing area but is sterilized and changed on a daily basis.

Windows in laboratories 13 and 16 can be opened and heating of the areas is achieved by enclosed radiators, with top grills, adjacent to the windows.

Factor VIII production is monitored microbiologically. The environment is monitored on a daily basis. There are no seasonal fluctuations in results. Counts of 10 organisms per plate (half an hour exposure) are not uncommon. Samples of solutions are taken immediately prior to sterilization by filtration. This type of control is incomplete in that the quality of aluminium hydroxide gel used in production is not determined.

Filling of Factor VIII into the final vials is always done on the same day that the bulk solution is sterilized by filtration. Consideration should be given to carrying out this filtration stage in the "aseptic filling suite", where the filling operation is done (middle room).

Filled vials with loose fitting bungs are taken in aluminium trays with loose fitting lids from the filling room through the Laboratory to the Freeze Drying Department. Lockable caged trolleys should be used for the product security of unlabelled vials, which are in process: this is not done presently. A reconciliation of vials and bulk product etc. is done after filling but before labelling.

Fibrinogen for isotopic labelling is made on a small scale in laboratory 19. This is a standard laboratory with no filtered air supply, associated changing room etc. therefore the premises are not acceptable for the type of operations undertaken: it is of a similar finish to laboratories 13 and 16. Filling of the product into vials is done in the aseptic filling suite.

Documentation presently available covers Manufacturing Records, Apparatus Lists, AHF Filling Record, Residues and Rejects Disposal Record, Pyrogen Free Solutions and "Ambient Air Sterility", the title of the last document poorly describes collected settle plate data!

Staff training is merely by exposure to current manufacturing situations.

Dr Ellis recognises that the unit is suffering from chronic staff shortages and extremely poor facilities.

This situation has worsened over recent years owing to increased production and the constraints placed upon the operation by the premises, both in design and lack of appropriate facilities. He would like to totally separate the production of prothrombin and factor VIII, but again this cannot be done owing to the lack of space.

INTERIM SUMMARY 3

In summary, the premises, facilities and operations carried out in this area are inadequate for the aseptic preparation of any product. Immediate action should be taken to initiate steps to rectify these deficiencies. These should be short term to update and create new documentation, procedures etc to cover all procedures used in and associated with production. Steps (longer term) should also concurrently be taken to rectify the deficiencies in the premises. These it is considered could only be achieved by the erection of a purpose built factory complex, since the limitation of the present laboratory complex are blatantly apparent, both to the inspectors and scientists on site alike.

3.3. Dr Singleton's Department : Filling of Plasma for Freeze Drying

Dr Singleton is in charge of the microbiological testing laboratory and the manufacture of one product namely freeze dried plasma.

3.3.1 Production Process in brief.

2L pools of plasma, (10 donor pools), in glass Winchester bottles

19/39

are supplied by two Regional Transfusion Centres. The outsides of the Winchesters are washed prior to storage at 4°C. These pools may be stored for up to 4 months before use. All containers have samples removed on which RI assays and sterility tests are executed. About 30 of these are used for each filling session. Aliquots are "aseptically" filled into British Standard Transfusion bottles which are then closed with perforated plastic plugs and dust covers. The contents of these bottles are then spun and frozen to form a shell to aid the subsequent freeze drying operation, which is carried out in the freeze drying department. Following this bottles are labelled, inspected etc: these aspects will be examined at the follow up inspection which will take place during the week beginning 16 July 1979.

3.3.2 Premises, Procedures and Equipment.

Plasma for production runs is stored in the +4°C cold room in Dr Singleton's department. "Aseptic" filling is done in the innermost of twin rooms (see APPENDIX 2(b)). The door between these rooms is suspended and sliding in nature. The premises are of painted plaster walls and ceilings with old wooden laboratory type benching on which cardboard boxes were lying. The floor was of stone, terrazzo type finish. Air drawn from the corridor, where filthy aluminium crates were being stored, is filtered and supplied at high level at one end of the room and extracted at low level at the other end where a horizontal LAF bench is sited (see 3.5 for quality of air filters).

The floor is cleaned weekly with a machine used elsewhere in the BPL: there is no SOP for the cleaning/disinfection of these rooms.

Operatives clothing is re-sterilized without first being cleaned. Persons undertaking aseptic filling enter via the adjacent room, as does equipment, product etc, and don wellingtons, masks, headcovers and surgeon's type gowns. The sleeves of these gowns are not elasticated and gloves are not worn. Wooden trolleys used elsewhere are wheeled into this area.

Filling of plasma is not done under LAF protection but directly beneath the air-input which supplies air of doubtful quality. The LAF is used during the sterility testing of in-process and finished products.

Production and testing activities such as these should not be carried out in the same laboratory.

Materials supplied for each run consist of tested plasma in 2 litre Winchesters (30), sterilized filling heads, one for each Winchester - these are sterilized in bulk in one pack - sterilized freeze-drying caps and sterilized transfusion bottles capped with cotton wool/Gauze plugs, with paper dust covers. All of these enter the filling room through the ante-room area which is used as a storage/changing area where gowns are donned over outside clothing e.g. woollen jumpers etc. The filling operation is carried out around a bunsen burner, using "no touch" technique: it is not done under the protection of the LAF.

INTERIM SUMMARY 4

For a filling operation such as this, true aseptic facilities and procedures, with currently accepted techniques, are required, but are not being used. This is due to severe deficiencies in the premises, general facilities and procedures being used. Prompt action should be taken to initiate the steps required to rectify the failings and introduce quality assurance into the process.

3.4 Freeze Drying Department.

At the time of this inspection Mr Kinnarney was in charge of the unit in the absence of his immediate boss who was on sick leave.

Products supplied to this department for further processing, that is freeze drying, are as follows :

3.4.1 Fraction II and Specific Fraction II material from Mr Wesley's unit.

3.4.2 Factor VIII, Fibrinogen and Thrombin from Dr Ellis' unit, and,

3.4.3 Plasma from Dr Singleton's unit.

Items for freeze drying are held in cold storage awaiting the

19/41

availability of the appropriate freeze drying units.

A plan of the department can be seen at APPENDIX 2(b). Vertical freeze drying units, used for albumin and large bottles of fibrinogen and plasma, are housed in the main laboratory; the horizontal Edwards units (X2) are in an adjacent, recently upgraded area, which is supplied with air filtered down to 5 microns. This air is lost via the air-lock. The air lock and another adjacent room have also been upgraded to provide smooth, impervious, easily cleanable surfaces. The latter is to be used to house a small portable freeze dryer not yet on site; in the future fraction II will be dried there, while the former is used for equipment/product and personnel entrance; it is also used to store clothing for use in the area. Clothing used consists of a suitable hood, one piece suit, overshoes, mask and disposable gloves; it is donned in this area, but there are no handwashing facilities. Product taken in through this personnel changing area is poorly protected against potential contamination since vials are not sealed and they are held in trays which have only loose fitting lids.

Cleaning and sterilization procedures undertaken in this area are carried out but the details are not recorded. The Edwards units are sterilized by ethylene oxide using water and ethylene oxide (12% in halocarbon) at ambient temperature; the efficacy of this as a sterilization procedure has not been adequately validated, nor does there seem to be any logic in the choice in frequency of sterilizing the chamber.

Within the main freeze-drying laboratory, a small room designated as the Needling Room, has been built. This is where bottle caps used in freeze-drying are exchanged aseptically for sterilized caps with inserted needles and plugged with cotton wool, to permit nitrogen charging of the head space. On completion of the charging process, done in the vertical freeze-drying units, bottles are returned to the Needling Room where the needles are removed.

Air is supplied to this room from the freeze-drier room via 5 micron filters, only around the time that the room is to be in use. The use of vertical LAF units in this situation so far away from the aseptic manipulation is questionable as there is a high probability of turbulence occurring at bench level and consequent contamination from operatives. Clothing used in this area is donned in the freeze-drying room.

INTERIM SUMMARY 5

The premises used for loading vials into freeze-driers are not totally satisfactory for aseptic procedures e.g. entry of product and personnel. Adequate validation studies have not been undertaken to verify the adequacy and required frequency of the sterilization procedure currently used on freeze-drying chambers.

Premises, facilities and procedures used for the Needling Operation are totally unsatisfactory.

3.5 Washing and Sterilization of Equipment.

When Mr Smith left the BPL, no person was made responsible for the washing-up and sterilization of equipment, Mr Sharman, Mr Smith's deputy, is temporarily in charge.

Bottles, vials and bungs are washed in rooms 229 and 228, the latter of which adjoins the "sterile filling suite".

Vials are washed and dried in an ACIC machine to a programmed cycle after which they are packed under LAF into trays in which they are sterilized in one of the two hot air sterilizing ovens. These ovens have forced air circulation and at the end of the sterilization cycle cooling air is drawn in through HEPA (0.2 mincron) filter banks. They have been tested to ensure that sterilization temperatures are achieved uniformly throughout the load. Sterilizer charts form part of the production records.

Bungs are washed in a Schuco machine and then transferred into stainless steel baskets in which they are dried in the ACIC machine. Subsequently, they are put into nylon bags - with cotton bungs at their closures - and sterilized by steam. The sterilization procedure has <u>not</u> been validated.

Bottles are transferred in crates from the ante room to 229 to room 228 where they are washed in a Miller-Hydro machine. The washing cycle is as follows, boiling water, hot soda solution, two hot rinses and one cold - all mains - and a final rinse of distilled water. All bottles, vials and bungs have this final distilled water rinse.

19/43

Other components and items of equipment used in production are washed by hand in a general wash-up area, tubing is done in a second ACIC machine. The walls and ceiling of this area are of painted plaster and the floor is of quarry tiles. Ventilation of the area is natural, through open windows.

Assembly and wrapping of items for sterilzation is done in an adjoining room, the fabric finish of which is poor.

Three Manlove autoclaves are used for sterilization procedures, two are of the downward displacement type and one of the high vacuum type. Commissioning of these was done in 1973 and periodically they are challenged with spore strips. Sterilization cycles are normally 20lb./sq" (126°C) for 30 minutes or 60 minutes for the former units, and 134°C for 3 minutes for the latter. The downward displacement units have the facility to pull vacuums at the beginning and end of cycles and these cycles are used to sterilize nylon wrapped items. It has not been shown that items so wrapped have had adequate steam penetration to achieve sterilization.

Sterilized equipment found in a "clean" store designated for this purpose was found to be inadequately wrapped, that is not double wrapped.

INTERIM SUMMARY 6

The fabric of the premises which house the bottle/vial washing operation are reasonably good, with a filtered air supply and LAF cabinet, but the layout could be improved.

The processing and assembly of rubber bungs and cap bodies could be changed to minimise handling.

Hot air sterilizing ovens should have data books in which use and maintenance information can be recorded. One temperature chart should be used per cycle. The Gallenkamp hot air sterilizing oven has no record of commissioning. Suits used during aseptic filling operations are wrapped in this area, but, they are not washed prior to sterilization.

The premises of the general wash-up area are acceptable but those for the wrapping of equipment should be improved. The sterilization efficacy of items

19/44

which are wrapped in nylon should be validated. The double wrapping technique for sterilized components and equipment should be adopted.

3.6 Engineering aspects of plant and equipment.

Mr Montgomery, the chief engineer, has working for him one assistant engineer (previously a fitter), 1.5 electricians and one process fitter. He stated that his present staff allocation is totally inadequate.

The general air filtration system in the factory utilizes Microflow GA filters (95% efficient at 5 microns). Brief details of the systems used in different areas follows:

3.6.1 Fractionation Laboratory and Associated Areas.

The upper large scale fractionation room, centritherm room and adjacent areas are supplied with terminally filtered air (95% efficient at 5 microns). However, the ground floor part of the fractionation suite does not have a filtered air supply. Its air is in a total recirculation system without make-up. This situation was difficult to appreciate since some air is lost through extract grills which are fitted with filter material. When the unit is formalized once per year, or, periodically (unspecified) the 5μ filtered air is supplied to the unit to flush out traces of formalin. When this has been completed the inlet is blanked off and the system returned to total recirculation.

3.6.2 Room 207: Wash up area for large pieces of equipment.

This area has a separate heated and filtered air supply (total loss) with pre-filters and terminal GA filters.

3.6.3 Room 230: Initial wash up area and assembly zone for the wrapping of items to be autoclaved.

This area is supplied with air that has been pre-filtered only.

3.6.4 Rooms 228/229: Bottle and vial washing area.

This system supplies air that is pre-filtered at the plant room and is passed through terminal GA filters into the area.

3.6.5 Clean side of Double-Ended Autoclaves.

Air filtration here is through both pre-filters and terminal GAs and is a total loss system.

3.6.6 Final Solution Preparation Room.

Air supplied to this room is both pre-filtered and passed through GA filters.

3.6.7 The Sterile Filling Suite.

The system used in this area was designed by Mr J Furman. Air supplied to the suite is passed through pre-filters, GA filters and finally terminal GAA filters (99.997% efficient at 0.5 microns). Air is ducted back to the plant room via GAA filters placed at extract grills. Blanking off plates used on vents to atmosphere post formalisation of the room are not always adequately sealed.

No tests have been done to validate the effectiveness of the seal between terminal filters and trunking using dioctylphthalate, as evidenced by black streaks at the perimeter of filter housings. No other tests e.g. anemometer or microbiological have been done. Some smoke tests have been performed to determine air flow patterns.

3.6.8 Dr Singleton's Filling Room.

Air supplied to this room is drawn from the general microbiology corridor where filthy aluminium crates were being stored: it is passed through GA filters in the terminal position. The air flow rate from these is < 25 cu/ft/min. There is no air supply to the air lock other than that lost naturally from the filling room.

3.6.9 Dr Ellis' Laboratories.

Room CR2 has only partial air filtration which is afforded by the scavenging effect of a Microflow unit (GA) left running in the room. Air within the room is recirculated and conditioned: it is drawn up from the side of the room where the Sharples centrifuges stand and is cooled by passing over cold glycol coils, in wooden ducting, in the

19/46

ceiling void and passed back in at the other end of the room. The ducting has never been cleaned out.

The aseptic filling room in laboratory 16 has air supplied through a GA filter: the source of this may be corridor or roof air: apparently little is known of this system.

Laboratory 19 where albumin for the Radiochemical Centre is prepared has no filtered air supply; air is only conditioned.

3.6.10 Edwards Area Air Supply.

This is a separate system used purely to supply this area. Again the air is pre-filtered before passing through GA filters in the duct about 10' removed from the inlets to the room. Feed air is drawn from the corridor adjacent to the changing room.

3.6.11 Needling Room.

The quality of air filtered into this room was not known but was considered to be probably no better than 5 micron: feed air is drawn from the main freeze drying room.

Smoke tests are not routinely carried out to determine the general air flow within rooms: the only exception is the sterile filling suite where these tests were carried out at commissioning of the unit. Settle plates are used to determine microbial levels but a standard procedure applicable throughout BPL did not appear to be applied.

Control and maintenance of LAF work stations is exceptionally weak: that done will not give any assurance that the units are working as designed. Work stations are not on contract maintenance. Particle counts within the units are not determined. Air-flow rate determinations are undertaken, but readings are not taken at discrete points on the filter face, and, no action points have been defined. Mr Montgomery was not sure which class of filters were used in some of the older Microflow units (LAFs) but considered they could have an average porosity of 5μ.

19/47

The control exercised over air supply plants, filters etc and LAF units, and, the maintenance of these is totally inadequate for the types of operations carried out at BPL.

The responsibility for autoclave control and maintenance appears to have fallen between two stools. Control tests are not done by the engineers, they are organised by Mr Sharman. Methods used include the Bowie Dick Test, Brown's tubes and spore strips. Validation studies of the effectiveness of these units as sterilizers is ill-defined. Maintenance is breakdown in nature. Although a Planned Preventive Maintenance scheme is being prepared, Mr Montgomery does not have the staff to institute it, therefore maintenance of autoclaves is inadequate.

Hot air sterilizing ovens are multipoint thermo-couple tested by Mr Sharman's staff.

There are no routine inspections of equipment by autoclave and hot air oven manufacturers.

Similarly, control and maintenance over the freeze driers is the responsibility of staff in that department, and <u>not</u> that of the engineers. Mr Montgomery presumed that this was breakdown in nature.

Mistral centrifuges in Dr Ellis' department are in a maintenance contract.

Responsibility for ensuring the satisfactory operation of the Sharples Centrifuges was only recently taken over by Mr Montgomery, after Mr Smith left.

Maintenance and the control of equipment is inadequate and ill-defined. This is a severe deficiency.

1948

4. SUMMARY SESSION OF THE VISIT OF 23 - 27 APRIL

A summary session was held at which Dr Lane was the sole representative of the BPL. It was intimated to him that the inspection was carried out along the same lines as those used in pharmaceutical industry. Production only had been examined during this 5 day period of inspection and that a follow-up inspection would be required to cover documentation and laboratories.

Our disagreement with the attitude taken, in certain parts of the laboratory, that as the starting material is contaminated there is little point in the rest of the processing being done under clean conditions, was given. The type of sterile products made on this site should be produced to proven and accepted Good Manufacturing Practices.

In general our findings were that the operations carried out on this site were unsatisfactory from the following points of view:

4.1 Premises.

4.2 Procedures - lack of standardisation and those available incompletely cover operations.

4.3 Equipment and Plant - inadequate control and maintenance.

4.4 Lack of adequate documentation to control the production operation as per the Guide to Good Manufacturing Practice.

4.5 Inadequate Environmental Control - both particulate and microbial.

4.6 Staff Training - none at present.

Examples of these were given to Dr Lane to justify the statements: details of these may be found in the body of this report.

5. PASTEURISATION OF PPF; INSPECTION AND PACKAGING - MR. SHARMAN

Part of Mr. Sharman's duties include pasteurisation of Plasma Protein Fraction (PPF) and the packaging and despatch of this and all other products manufactured in the Blood Products Laboratory.

5.1 Pasteurisation of PPF

Plasma Protein Fraction is pasteurised by heating for a minimum period of 10 hours at a temperature of $60^{\circ} \pm 0.5^{\circ}C$ in order to inactivate hepatitis virus. The process is carried out in two large, floor mounted, hot air ovens in room 220 which is adjacent to the sterile filling room. The ovens are equipped with circulating fans and were manufactured specially by Westwood Major Ltd.

One batch of PPF occupies both ovens as sub-batches A and B.

There are three compartments in the body of the ovens, each of which takes two stacks of filled bottles in metal crates. Hot air from the fan compartment circulates via the airduct in the base of the oven and is forced upwards by baffles into the bottle compartments.

Temperatures are monitored by six probes and recorded on Cambridge temperature chart recorders. The probes are situated:-

in a bottle in the lower airduct
in the free air space in the lower airduct
left, front, top of the load
left rear top of the load
right front top of the load
right rear top of the load

The ovens were said to be commissioned in 1974 by Mr. Vallet and Mr. Montgomery and that temperatures at all points were within $\pm 0.5^{\circ}C$. They have not been re-commissioned since then but the probes are checked every month against a National Physical Laboratory (NPL) certified thermometer in a thermostatically controlled water bath.

19/50

Maximum reading thermometers are also placed in the front, top, left and right positions during each production load and the temperatures are noted on the Cambridge charts.

The door seal gaskets were in an extremely poor condition and the inspectors were worried that cold air could be sucked in and lower the oven temperature. This was said not to occur as the temperature throughout was maintained at $\pm$ 0.5°C. Inspectors were also worried that the temperature might be affected by a reduction in air velocity through failure of the fan but if this did happen then the heating up period would be unduly long and would be seen by Mr. Sharman when checking the records.

The ovens were not maintained on a planned preventive basis but the Cambridge recorders were serviced every two months by the supplier. Consideration should be given to servicing the ovens on a regular basis and at least twice yearly. More documented control is also needed over this critical stage of manufacture where hepatitis virus is inactivated.

5.2 PPF Incubation

After pasteurisation the bottles are transferred to the Incubation Room (1.07) and stored at a temperature of 32° $\pm$ 2°C for from 10 to 14 days. This room is heated by two fan heaters, placed high up on opposite walls, and circulation of the air is assisted by an auxiliary fan on the floor. The fan heaters are controlled by thermostats and the room temperature sensed from a point near the door and recorded on a chart.

From the positioning of the fan heaters there is a good possibility of localised overheating on some stacks of bottles and airflow patterns could fluctuate according to the number and positioning of the stacks and positioning of the floor fan.

As the room is completely full with one week's production additional space is required

19/51

After the requisite storage period at 32°C the bottles. which have been inverted during this period, are inspected for leakage and bacterial growth, and acceptable bottles are then transferred next door for a further three weeks storage at ambient temperature.

Each bottle is labelled with a batch number and whether pasteurised in the A or B oven.

As with the 32°C quarantine store extra space is likewise needed in the ambient store.

From the ambient store the P.P.F is removed to room 1.11 for inspection and packaging.

5.3 Inspection and Packaging

Inspection and packaging of all products is carried out in room 1.11. This is a T-shaped room with laboratory benches along the walls in the leg of the T, a bench along the end wall of one arm to serve as a despatch area, and in the opposite arm two labelling machines and a cartonning machine.

The room is well lighted with natural and artificial light but is an open-plan area which is not segregated or partitioned in any way for the various packaging operations.

Only one product at a time was said to be dealt with in the room, but two products were on the benches at the time of our visit although this was probably due to Mr Sharman being called away to assist us in the inspection. In any case it is standard procedure to inspect and package part of a batch of P.P.F in the morning, switch to a different product in the afternoon, and then subsequently to continue with the batch of P.P.F! This was said to reduce fatigue and improve inspection efficiency. Staff employed on inspection are not given eye sight tests including those for colour blindness.

P.P.F is inspected under polarised light (ALLAN viewers) for fibres, and for precipitation and other particles by swirling the bottles, shining a

light upwards through the base and viewing against a black background. Defects are classified and recorded but the operators do not have check lists of defects for specific products to which they can refer.

P.P.F is labelled on an EEC Autolabeller which is continuously set up for this product with the labels in position. The rationale for this was that no other product would be labelled on the machine. Inspectors pointed out, however, the problem of labels not being controlled in a secure manner and the possibility of bottles being coded with labels from previous batch runs.

The second labelling machine was a 'WHITEHALL MACHINERY LABELLER' which was also set up but for labelling anti-D Gammaglobulin. A fault had developed and the firm's engineer had been called for to examine it, but the labels had been left on the machine. This indicates a lack of discipline and inadequate control of the labelling operation.

The Vial cartonner was a BOSCH, HOFLIGER and KARG machine.

Inspection and labelling of P.P.F constitutes the major workload but the area was not laid out to facilitate a continuous flow of work or to prevent a crossover of product at the various stages. Other smaller product batches were inspected and labelled on the static benches.

The packaging operation for P.P.F was inspected as being representative of the handling of products generally. Although there was a packaging record it was insufficiently detailed and omitted some important aspects of the packaging operation, e.g line clearance checks prior to starting the operation.

Dried Human Plasma was being labelled during the afternoon of our visit and the labels were being batch coded in manuscript from a production record sheet. There were no written procedures for the operation and although there was said to be a system of cross checking it was not apparent to us and checks were not recorded.

Opening from the packaging room were ancillary rooms for the storage of transit cartons, storage of labels and printed packaging materials, finished goods and despatch.

19/53

5.4 Transit Cartons Store (room 1.13) and Labels Store

This room is used for storing and making up cardboard transit cartons, but, due to severe shortage of space in the packaging area generally, was also used for storage of packed stock, inspected stocks and non-inspected material. In fact it appeared to be a general storeroom. Drains run through the room at ceiling level and up to two months ago had been troublesome due to leaking but have now been repaired.

One corner of the room is caged off to provide a secure, locked area for printed labels printed cartons and leaflets. There were no written specifications for any of these materials and the only quality control checks were those carried out infrequently by Mr Sharman.

5.5 Final Products Ambient Store (Room 1.12)

This room has a floor area of approximately 144 sq feet and is totally inadequate for the purpose as only remnants of packed stocks are generally held here for supplying small orders on demand. P.P.F and Freeze Dried Plasma are stored in the D.H.S.S Store at Bristol and the packed product is despatched from Elstree weekly. Packaged stocks, prior to despatch to Bristol, are stored mainly in the corridors for lack of other storage space.

South East London and Wessex Regional Transfusion Centres take 200 and 100 bottles respectively of P.P.F per month made up from all batches produced in that period and these are used routinely on patients to test for any adverse reactions. These consignments are made up prior to despatch of the remainder to Bristol and are held in the Final Products Store.

Although it is an 'approved products' store it also contained :

Fibrinogen labelled as "not checked"
Fibrinogen labelled as "checked and sorted" and hence visually inspected only.
Time - expired albumin
Time - expired serum
Time - expired P.P.F.

19/54

Appropriate storage, other than in an approved products store, is needed for such materials.

5.6 Quarantine Stores (Rooms 1.09 and 1.10)

These two rooms, immediately outside the entrance to the packaging room, are in fact one room which has been divided almost to ceiling height by a wire grid. The rooms are maintained at +4°C and the temperature recorded on a CAMBRIDGE chart recorder which is checked daily and the chart changed weekly.

Normal and convalescent gamma globulins are quarantined in wooden trays with metal lids secured by crimped metal tags. Each tray is tag labelled with the contents and batch number and whether inspected or not. Inspected material is sealed again in the same way as non-inspected material until it is labelled. After labelling, the product is packed in fibreboard transit cartons and banded with plastic strapping.

Room 1.09 is the quarantine store and room 1.10 the released materials store, but material is only released against specific batch numbers so it is not possible to issue non-released material.

Rejected material was found in the quarantine store, and should either be returned direct to the production departments or held in a secure box labelled "REJECTED" until the entire consignment has been inspected.

As with other rooms there is a serious shortage of storage space.

5.7 Small Orders Despatch Section

Small orders are made up for despatch on a bench at one end of the packaging room (1.11).

There is a record book for each product which shows quantities produced and issued on specific dates, with a batch reconciliation carried out when batches are expended. The only exception to this was for Fibrin which is stored in a refrigerator in room 1.13 and which is not reconciled on a batch basis.

19/55

5.8. Complaints

Mr Sharman said that complaints were never received but if there were any that required recall then this could be undertaken immediately as the destinations of all batches were recorded. It was later suggested to us that complaints would be dealt with by Dr Lane but we did not have a chance to question him on this.

INTERIM SUMMARY 9

A better documented control is required over the pasteurisation process which is a critical stage of manufacture in which hepatitis virus is inactivated. Planned preventive maintenance of the operation is also required instead of breakdown maintenance.

It was very apparent that quarantine storage and despatch areas were far too small for the volume of production and this resulted in some other areas being used for purposes for which they were not intended and for corridors to be used for storage.

The temperature distribution in quarantine areas was suspect due to the positioning of fan heaters, variable stacking within the rooms and variations in the airflow patterns.

Printed packaging materials i.e labels, cartons and leaflets were not defined in written specifications and were not quarantined on receipt or adequately quality controlled.

Packaging operations were not defined by written procedures, were not organised in such a way as to prevent cross flow of products and various key procedures in the operations were not recorded.

Labels were left on machines in a non-secure manner.

All packaged stocks were not held in a quarantine store until the documents and records were checked and the products released by an appropriate person delegated for the task.

19/56

6. ANALYTICAL LABORATORIES

The analytical laboratories are in charge of Mr Greulich who in turn reports to Mr Vallet.

Staffing of the laboratories is as follows:

6.1 Quality Control Chemist:
Mr Greulich,B.Sc (Chemistry), M.Sc (Analytical Chemistry)

He has been with the Blood Products Laboratory for about ten years, having started as a junior technician.

6.2. Deputy Quality Control Chemist.
Mr R Brunsden, H.N.C (Chemistry), L.R.I.C (Analytical Chemistry)

Has been with the Laboratory since January 1979 and was previously at Bedford College, University of London.

6.3 Mr N Croad, H.N.C. (applied biology)

Responsible for elemental analysis of intermediate and finished products

6.4 Mr D Morris, Medical Laboratory Technician.

Seconded from production on a temporary basis to assist Mr Brunsden on gel filtration assays, electrophoresis, nephelometry, ethanol determinations and testing of raw materials.

There is a complement for a junior technician but there has been no success in filling the post.

Laboratory staff are responsible for taking their own samples of in-coming raw materials which are quarantined in the stores and notification of their receipt is by telephone. Analytical staff do not receive copies of purchase orders or delivery notes so do not know what consignments to expect.

19/57

The laboratory staff apply the quarantine labels to the containers.

Samples are taken into washed 50 ml. plastics universal containers for solids and glass screw-capped production bottles for liquids.

The sampling equipment is kept in the laboratory.

All containers are sampled and the contents identified and a full analysis done on a blended sample of up to five containers.

Consignments are sampled in the stores, which are overcrowded; methanol is sampled in the inflammables store and ethanol from tanker deliveries is sampled by the worker who supervises the delivery.

There are only about 18 chemical raw materials and these are purchased from approved suppliers on the basis of satisfactory performance over the years. The main suppliers are British Drug Houses and Hopkin Williams.

All chemicals have recently been given an expiry date of one or two years before re-testing. Most chemicals have written specifications prepared by Mr Greulich, but they were not dated or signed as being approved. All these specifications are to be re-written as time permits and they will then be dated and include analytical procedures.

Packaging components i.e. bottles, vials, closures, labels, cartons etc. are purchased either from D.H.S.S or from industry but in either case there are no specifications. no sampling and no testing.

Mr Greulich has recently started to date stamp outer containers of packaging components for stock rotation purposes. Printed cartons are given a life of one year 400 ml P.P.F bottles three years and 540 ml plasma bottles five years. There is no scientific basis for the periods chosen which corresponded only with the stock holdings at that time. In any case, bottles received from D.H.S.S. could already have been in store for an indeterminate period of time.

19/58

Analytical work is shared between two sections responsible for physical and biochemical testing respectively. Each laboratory maintains a register for booking in samples and progressing the tests. The test results are checked in one laboratory by Mr Brunsden or Mr Greulich and in the other by Mr Croad and then transcribed on to analytical data sheets. The sheets are checked and signed by Mr Greulich, who also comments on the results, approved and initialled by Mr Vallet and then submitted to the production departments.

Mr Greulich has no involvement in microbiology and the production departments collate all their own test results.

Analytical calculations are worked out on pieces of paper which are subsequently destroyed when the results are transcribed into record books for each test procedure. We suggested the use of personal laboratory note books and for all calculations to be seen and checked by Mr Greulich at regular intervals and the books signed and dated by him.

On checking through the raw materials specifications we discovered that those for aluminium hydroxide, water, ethanol and methanol have still to be written up.

Analytical results were invariably recorded by means of ticks as an indication of compliance whereas it would be more meaningful to record actual results. An analytical result for TRIS was reported as >99.8% against a required standard of 99.8% ; this again was unsatisfactory and the actual result should have been recorded.

The analytical suite comprises four separate laboratories in rooms 6, 6A, 5 and 1B.

Room 6 is the general laboratory which is used also for gel filtration determinations using three U.V Absorptiometers and associated columns manufactured by L.K.B.

Standard solutions were said to be made up freshly as required except those in regular use which would be used up within one week of preparation. Some solutions which should have been discarded had been retained and were undated. It was agreed that such solutions would either be dated with a shelf life or discarded after use.

19/59

Standard solutions made up from commercial concentrates are checked approximately every three weeks against other standard solutions for correctness of factorisation.

Room 6A - Instrumental Laboratory.

The instruments included the following:
Zone Electrophoresis by SHANDON
PYE UNICAM SP 1800 U.V. SPECTROPHOTOMETER
Water Bath.
AMINCO NEPHELOMETER
HILGER and WATTS U.V. Spectrophotometer for protein determinations.
RELEAS-O-MATIC Single Pan Balance.
Refrigerator.
METTLER Top Pan Balance.
GELMAN Electrophoresis Scanner for Slider.
JOYCE LOBEL Electrophoresis Scanner for Slider.
Moving boundary electrophoresis apparatus.

All equipment is serviced on twice yearly contracts with the manufacturers. Details are retained by the administrator Mr Bailey.

Volumetric glassware is washed in the laboratory, dried in a drying cabinet and stored in a cupboard.

Room 5 - Biochemistry Laboratory.

Equipment included:
KJELTEC System 1003 Distilling Unit.
TECHNICON, Heating Block, 40 unit.
BAIRD Atomic Absorption Spectrophotometer, A 3600.
pH Meter.
EIL 705 S pH Meter.

Room 1b

Contained:
PERKIN ELMER F17 Gas Chromatograph.
M.S.E Superspeed 75 Centrifuge
M.S.E Highspeed 18 Centrifuge
Melting Point Apparatus.

19/10

INTERIM SUMMARY 10

Not all chemical raw materials were defined in written specifications and some were insufficiently detailed.

There were no specifications for packaging components and the laboratory staff were not involved in quality controlling such materials.

Analytical calculations should be made in personal laboratory work books and not on pieces of paper which are destroyed. Work books should be checked regularly and signed by Mr Greulich.

It was apparent that the laboratory was inadequately staffed to undertake all the necessary analytical work, staff were transient and there was much dissatisfaction due to a lack of definition from top mangement of their job responsibilities.

The laboratories provide a service on demand from production departments but are insufficiently involved in the initiation of a comprehensive quality assurance system.

Some improvement in the recording of test results, e.g by giving the actual results, and improvement in the format of test reports, e.g by noting acceptable tolerance limits on reports is needed.

19/61

7. DOCUMENTATION AND FINAL PRODUCT RELEASE

Analytical and production records were examined for the three main production departments, i.e. Large Fractionation and Final Solutions Laboratories, Coagulation Factors Laboratory and Freeze-Dried Plasma Laboratory. The heads of these departments are Mr. Wesley, Dr. Ellis and Dr. Singleton respectively. As Dr. Ellis and his chief technician were attending a symposium we discussed the documents with Mr. Williams the senior technician.

To evaluate the systems in the three departments we examined the records of one batch each of Plasma Protein Fraction, Freeze-dried Antihaemaphilic Fraction (Factor VIII) and Freeze-dried Small (10 donor) Pool Plasma.

7.1 Plasma Protein Fraction Documentation - Mr. Wesley

As there is no single plasma pool throughout the operation we had to check the fractionation records of all those plasma pools taken to produce a specific batch of PPF (Fraction V).

The following points were noted and discussed:-

7.1.1 Quantities were in litres and although this was obvious to the staff the denomination was not shown on the production record.

7.1.2 Details crossed out and amended were not signed by the operators or any reason given for the amendments.

7.1.3 Plasma volumes in the production vessels are measured by hydrostatic pressure but this was not obvious from the records.

7.1.4 The 5-litre packs of frozen time-expired plasma are tested at the Regional Transfusion Centres and supplied as hepatitis negative. Except for supplies from North London (Edgware) and Brentwood Regional Transfusion Centres all other material is re-tested for Australian antigen at the Blood Products Laboratory by Mr. Combridge.

19/62

7.1.5 Packs reported as hepatitis negative by the Regional Centres could be found subsequently to be hepatitis positive.

7.1.6 In some cases a sample sachet is not supplied with the bulk material or else the sample is not available for Mr. Combridge to carry out an Australian antigen test. In such a case the plasma is used as part of the plasma pool on the argument that the PPF solution is pasteurised to inactivate any hepatitis virus that might be present.

7.1.7 Sterility testing of time-expired plasma, when first introduced, was not to protect the patient but to provide an indication of the quality of material supplied from the Transfusion Centres. The policy was to test 1 in 10 packs only.

Now all plasma is tested for the presence of micro-organisms except where there is insufficient sample in the sachet or the sachet is missing.

/5-litre packs of fresh frozen plasma for factor VIII are not tested for the presence of micro-organisms./

7.1.8 The production records showed that about 3 out of 40 packs were infected and not used, 16 out of 40 batches had no samples for testing and hence could have been infected but were used in the pool.

7.1.9 It is not possible to achieve proper stock rotation of the frozen plasma because the -25°C cold rooms are severely congested and it is thus impossible to use the oldest plasma first. Some plasma is also stored in commercial cold stores under contract and there is no indication of when it will be returned for processing.

There is no upper limit for the storage of this plasma and we were told that it has been successfully fractionated up to five years old.

19/63

7.1.10 Part of the plasma pool is made up of factor VIII supernatant from Dr. Ellis's laboratory and from the Fractionation Laboratory at Oxford.

7.1.11 Mr. Wesley takes a sample of plasma from the bulk pool for a microbiological count but the result is known only in retrospect after the pool has been fractionated.

Although the material initially brought from Oxford was highly contaminated its quality is now much improved.

7.1.12 The 5-litre packs of plasma used in the Coagulation Factors pools are often not tested for micro-organisms as Dr. Singleton cannot cope with the work load. However, all this material is tested for Australian antigen either by Mr. Combridge or the North London and Brentwood Regional Transfusion Centres.

7.1.13 In-process testing comprises:-

7.1.13.1 Pool from 5-litre packs of time-expired plasma is sampled for microbial counts.

7.1.13.2 Pool of supernatant plasma from Dr. Ellis is sampled for microbial counts.

7.1.13.3 The combined plasma pool is sampled for microbial counts but the organisms are not typed.

7.1.13.4 The combined plasma pool is sampled and tested for Australian antigen.

7.1.13.5 Retention samples of the plasma pool are taken and kept at $-35^{\circ}C$.

7.1.14 Results of calculations are recorded on the production sheets but not the actual calculations. These should be shown together with an indication that they have been checked and by whom.

19/64

7.1.15 Alcohol used in production is not tested for micro-organisms and neither are any of the reagents.

7.1.16 There is no routine maintenance of production equipment such as stirrers and centritherms.

7.1.17 From the analytical records it was difficult to decide whether Mr. Vallet or Mr. Greulich was in charge of the analytical laboratory as some test certificates were signed by one and some by the other. Staff were also uncertain of this point and had some difficulty in knowing with whom to deal.

7.1.18 Tolerance limits for e.g. pH ranges are not stated.

7.1.19 Solutions for concentration in the Centritherm could have microbial counts of 50 per ml prior to concentration and the same count after concentration. This appeared to be somewhat odd as higher counts would be expected on the concentrate.

7.1.20 Diluted solutions for bottling can also have microbial counts of 50 per ml and more. There is no upper acceptable limit and levels as high as 10^4 per ml are known; even at this level the final product was said not to be pyrogenic.

7.1.21 Batch numbers of the reagents used in production were not recorded on the batch production records.

7.1.22 Material rejected for particulate contamination was re-claimed by including in subsequent plasma pools.

7.1.23 Sterilised equipment used in the production process e.g. tubing, filters, vessels, caps etc is autoclaved as mixed loads which may be used in different production batches. It is therefore not possible to provide a temperature recorder chart with each production record and so pieces of sterilisation tape from the sterilised packs were attached to the records. As this is not necessarily indicative of a satisfactory sterilisation cycle either

19/55

photocopies of the charts should be attached or a statement included on the production record that the chart has been examined by a nominated person and is satisfactory.

7.1.24 Where repeat testing is carried out the reason for so doing should be stated on the records.

Before a batch of P.P.F is released, Mr Wesley collates the various production and test records and prepares a summary of the important parameters which he signs and submits to Dr Lane for his approval and signature of release. This is a good system.

The production documentation for P.P.F Solution was comprehensive and could with some relatively easy modifications be regarded as satisfactory. Shortcomings were the lack of adequate packaging information as mentioned previously under that section and inadequate environmental monitoring.

The preparation of a batch summary sheet is to be commended and likewise the fact that Dr Lane acts as quality controller in releasing the product.

We did not have time to examine other products for which Mr Wesley is responsible but we trust that the documentation for P.P.F is typical of his entire range.

7.2 Freeze-Dried Antihaemaphilic Fraction (Factor VIII) - Mr Williams.

The starting material is fresh frozen plasma supplied in 5-litre plastic packs.

When a delivery arrives at the Blood Products Laboratory the stores staff notify production by telephone and within half an hour the consignment is stored in the -25°C cold room.

Consignments are checked against the delivery sheets for damaged packs and correct labelling of packs and outer protective cartons. However, when damage occurs, the damaged packs are not always segregated from good stock.

19.66

There is no uniformity in the supply of sample sachets as some Regional Transfusion Centres leave them attached to the main packs, others separate them from the packs but supply them in the cartons with the packs, others pack the sachets all together in a separate container. Some Transfusion Centres have a higher damage rate of sample sachets than others and this often accounts for insufficient samples for testing. Standardisation of the method of supplying sample sachets should be considered.

The packs and sample sachets are labelled with specific batch numbers which are also imprinted into the plastics material. These details are transcribed from the consignment sheet into receipt books for each Regional Transfusion Centre. The reason for individual books was said to be to enable material from individual Regional Transfusion Centres to be processed separately, but this could also be achieved by recording the details on production record sheets.

Mr Combridge notifies the results of hepatitis testing by means of a hand written list and occasionally reports the absence of samples for testing. As batches are checked before sending to the hepatitis testing laboratory it is odd that some samples are missing. Mr Williams explained this by saying that he could not rely on his staff to do the job properly. The samples are occasionally found subsequently, but if not then a core sample is taken from the main pack. This is done in the open laboratory using a separate sterile sampling tool for each pack; there is a possibility though of contaminating the pack.

Material from Regional Transfusion Centres North London and Brentwood is hepatitis tested at these Centres and not re-tested at Elstree. All other fresh frozen plasma for Factor VIII is tested at Elstree by Mr Combridge who uses a modified method of the ABBOTT radio-immunoassay test.

No microbial counts are made on the samples except those from Regional Transfusion Centres Cardiff and Cambridge. The aim originally was to test material from all Centres but Dr Singleton could not cope with the work-load under nine weeks and storage of 5-litre packs then became a problem. As the Cardiff and Cambridge plasma was contaminated with large numbers of G negative organisms it was decided to keep a check on material from these two Centres. The quality is now said to have improved.

13/67

The manufacturing record sheets need to be revised as follows:

7.2.1 To provide space for recording the checking of batches on selection in the cold room and again when used in production.

7.2.2 The manufacturing record could with advantage be standardised with that for Large Fractionation material.

7.2.3 The pH of the cryo-supernatant is currently recorded in a laboratory notebook whereas this and other manufacturing parameters should be recorded on the manufacturing record.

7.2.4 Sterilising filters are not pressure tested as there is no convenient pressure lines, although this matter is being considered.

7.2.5 All sterilised equipment used in processing must be proved as such by a copy of the temperature chart record or by a statement in the production record that the process was checked and correct.

7.2.6 Positive action is not taken on settle plate results which indicate high numbers of micro-organisms.

7.2.7 When an analytical result is out of specification it is repeated once only even if the two results are widely different, e.g solution times of AHF were 36 minutes and 12.5 minutes. Duplicate results should not be relied on but done in triplicate.

7.2.8 The manufacturing record has been condensed into too small a space; procedures should be more specific e.g equipment such as stirrers should be clearly defined and quantities which are estimated should be clearly recorded as such.

7.2.9 There should be space on the record to show that it has been checked, and by whom, as the record goes from Mr Williams via Mr Pettet to Dr Ellis and is not signed by any of them until the batch us released by Dr Ellis.

7.2.10 Mr Pettet checks the test results and transcribes them into a book in order to compare trends but there should also be a summary sheet showing results against specification limits. There would be merit in having a standardised procedure on the format developed by Mr Wesley for P.P.F.

17/68

7.2.11 Responsibility for final release of products from the Clotting Factors Laboratory should also be standardised in line with Large Fractionation material.

7.3 Freeze-Dried Small Pool Plasma - Dr Singleton.

Documentation for this product was again different from that in the other two manufacturing departments. Being one of the oldest established products the documentation has developed in an ad-hoc fashion over the years and no thought appears to have been given to changing the system. In fact there was resistance to change from some of the staff.

Processing and testing details are recorded mainly in a series of production books but also on official record sheets and odd pieces of paper.

Much important information vital to an aseptic manufacturing procedure e.g. the cleaning of processing areas, environmental monitoring, medical checks on staff (known carriers have been used in production), records of sterilisation of equipment, was absent or the data not even collected.

After the freeze drying stage the bottles are released to Mr Sharman for packaging and Dr Singleton does not see the packaging record and has no say in the operation. Dr Singleton said there was no signed release of the product or scrutiny of the entire documentation but that batches "just left the building".

INTERIM SUMMARY 11

Documentation and records in use in the three major manufacturing areas were all different in format and comprehensiveness; and if any thought had been given to standardisation it was not apparent.

The records in the Large Fractionation Laboratory are the best and with minor modifications would result in an acceptable system whereas the records for Freeze Dried Plasma are totally inadequate.

14/5?

The the three manufacturing departments appear to operate as entirely separate units with little interchange between them and no overall management at top level.

There is no standardised system for the appraisal of manufacturing and testing records or for the final release of products; Dr Lane releases products from the Large Fractionation Laboratory and Dr Ellis from the Clotting Factors Laboratory, but the release of Freeze Dried Plasma is a grey area in which no one person has overall responsibility for release.

PART 2

Report of Inspection of:	Biological Quality Control facilities at the Blood Products Laboratory, Elstree, Herts.
Date of Inspection:	July 18th 1979.
Objective:	To determine the extent and nature of the activities within the biological control facility and to comment thereupon.
Senior personnel met:	Dr. L. Singleton Mr. Combridge Mr. Wilkinson
D.H.S.S. Inspectors:	Mr. J. Flint Dr. J. Purves Dr. J. A. Holgate

1. Areas of work

Dr. Singleton described his duties as including:

(1) the production of freeze-dried plasma and its quality control

(2) supplying a service for other departments who send him samples for various biological tests. These include

(a) the "sterility" testing of all incoming plasma except fresh frozen material

(b) in-process and final product sterility testing

(c) pyrogen testing of various end products and intermediates for B.P.L. and Oxford

(d) toxicity testing in mice and guinea-pigs

(e) the reading of sterility tests supplied from Oxford

(f) development activity

(g) an interest in certain processes

(h) some testing of the environment.

2. Staff

Dr. L. Singleton	- head of department
Mr. N. Wilkinson B.Sc.	- deputy (direct from University)
Mr. Wild	- development function. H.N.C. microbiology

19/7

2 technicians (female) carrying the bulk of the work load
2 junior laboratory technicians
2 process workers
1 general worker - washing up; cap making
2 animal attendants - one of which is an Associate of the Society of Animal Technicians
1 student

In addition Mr. Combridge is outstationed in a temporary building together with one technician entirely responsible for hepatitis testing. Mr. Combridge reports directly to Dr. Lane and is not part of Dr. Singleton's staff.

Dr. Singleton reported on the great difficulties experienced in recruiting and retaining staff at any level quoting that in one period of 100 days on only 3 was there a full complement. In 4 years there had been 3 different graduates in the deputy post. The animal technicians, the 2 female senior technicians and Mr. Combridge appeared to be the only experienced and reasonably permanent staff in the establishment.

Because of shortages medically unsuitable staff has been used on occasions.

3. Premises

The premises consist of

(a) A group of rooms at the end of a corridor in the main block consisting of Dr. Singleton's office; a laboratory for development work used by Dr. Singleton, Mr. Wilkinson and Mr. Wild; a ladies toilet; a first-aid room; the "sterile" suite in which "sterility" testing is carried out as well as plasma transfers (this is described in the main body of the report); a main bacteriology laboratory; a cold store for plasma; the plasma arrival and bottle washing room.

(b) An "outstation" temporary building near the main entrance containing an office and a small but very adequately equipped laboratory where Mr. Combridge and a technician carry out all the tests for hepatitis antigen.

(c) Two animal houses in the original Lister complex well removed from the main building. One is entirely self contained and consists of the main animal room housing the rabbit colony, a pyrogen testing area and an office containing the temperature recording equipment, record books etc. The other is a single room in which mice and guinea-pigs are housed and the toxicity tests are performed. Between the two separate areas is a large wash up room and cage store with a separate small food store.

19/72

There is no longer, since the loss of the Lister laboratories, a media kitchen - all media being bought in from Difco.

4. Details of testing

4.1 Sterility testing

All incoming plasma except for that fresh frozen is examined for micro-biological contamination if there is, in the case of the pooled plasma, a sample available of sufficient volume in the sample sachet. This is often not the case - some centres providing only about half the requisite samples to accompany the 5 litre pools while others lack only about 10%. The sample is tested on agar and in Brewers medium. If growth occurs the fact is reported as "less than 10" or as a series of plus signs. Any growth found is filmed and sub-cultured and identified eventually into a general group - corynebacterium, micrococcus, bacillus etc. Material having a contamination greater than 10/ml is indicated as not for use but there is no system to ensure that it is not used. Furthermore, material not tested as a result of 'no sample' or 'insufficient sample' is also used. The plant has never operated on a 'clean' plasma basis - the bacteriology would seem to serve only as a matter of side interest.

In-process samples are tested on request - the material (pre-filtration, post-filtration, pre-heating, bulk pre-filling) and final product being taken from batches to no particular design and not under the control of Dr. Singleton. From Oxford only final product sample tests are received.

No other starting materials are tested since in the case of many of them a filtration technique would be necessary and the facilities are not available to cope with this.

The testing of both incoming plasma (frequently contaminated) and of final product (expected sterile) is carried out in the sterile suite also used for plasma transfer. The only difference is that the former is done on the open bench while the latter is done under a horizontal laminar flow hood switched on some 10 minutes before testing starts. The transfer is done using plastic disposable syringes taken from cardboard boxes placed in the area. Technicians change in the outer room into sterilised (but not washed) front fastening gowns, rubber boots (washed in antiseptic solution to no particular formula once per week), paper caps (inadequate) and rubber gloves (washed in soap and water or 100% alcohol). There seem to be no written instructions and no training of technicians except on the job.

1973

The surface of the sample sachet is wiped with a cotton wool swab soaked in 100% alcohol - one swab being used for more than one sachet. The sample in addition to being placed in agar and Brewers medium is also in part put into a plastic Universal bottle for retention and a further part into a small tube for testing for Australia antigen. Freeze-dried materials are made up using internally prepared diluent.

The methods given in the European Pharmacopoeia are said to be employed but at present the incubation period is only 7 days, any repeat test is of the original number of samples and no positive growth control is carried out though Dr. Singleton is thinking of starting to do this. Sampling of final product is also said to be in accordance with Ph. Eur. but it was not possible to check this since Dr. Singleton did not know what proportion he receives.

Investigatory work, incubation of samples (in 3 incubators - one at 37°C, two at 30-32°C), record keeping, reading of results etc. all takes place in the laboratory opposite the 'sterile' suite. The equipment seemed adequate for the very elementary tasks being performed but it seemed strange not to see any membrane filtration apparatus.

4.2 Pyrogen testing

Every batch of every product except freeze-dried plasma is tested on rabbits for freedom from pyrogens. Since the products are immunogenic these tests involve fresh rabbits on every occasion - a total of some 1600 per year obtained from a number of dealers who have proved fairly reliable. Each rabbit remains on the premises on average 7-10 days and is merely subjected to a saline test before being used. The animal house, test facility and office are excellently kept - the only criticism being that the temperature of the rooms is not measured and recorded. However, since they are adjacent and on the same aspect of the purpose built premise the temperature of the two rooms is probably within the requisite range. The records kept were satisfactory and showed very few total failures although some were recalled - a leaking cooling coil accounting for one (the coils are not pressure tested) and entry of water from the warming baths the cause of another failure.

Dried plasma has not been tested since the batches are felt to be too small to sacrifice one unit for test. However, Dr. Singleton did accept the suggestion of random testing of such batches in order to examine the general state.

The Limulus test is being examined in parallel with the rabbit test - e.g. in testing of Factor VIII (where most problems arise) - if the final

19/74

product has had to have a repeat test then the limulus test will be carried out in parallel. It is hoped this might eventually be used as an in-process control.

Unfortunately no "trend" records are kept. Dr. Singleton reported this had been examined and not found useful as failures, when they occurred, were sudden plant failures and not gradual events.

The equipment is checked by the manufacturer once every 6 months but no laboratory checks are performed between these times.

Animal cages are cleaned twice a week and autoclaved at intervals, an autoclave being sited in the cage washing room. The general conditions of the animals and premises were excellent.

4.3 Toxicity testing

We were told that every batch of final product is submitted to a test for freedom from abnormal toxicity by the injection of the appropriate amount quoted in official texts into mice and guinea-pigs followed by observation for 7 days.

The conditions under which the animals are kept and the tests are performed are, as stated elsewhere, excellent and the technician in charge seemed capable of performing his duties efficiently.

4.4 Testing for presence or absence of hepatitis B surface antigen

Samples of all incoming plasma except from two regional centres - North London and Brentwood (where tests are performed and accepted by B.P.L.) are tested for HB_sAg. Except for fresh frozen plasma where Mr. Combridge samples for himself samples and lists are provided by Dr. Singleton's staff on intake of plasma. Results are supplied by Mr. Combridge to the production units involved with a copy to Dr. Singleton. Any positive results are notified to the centre supplying the plasma and such plasma is not passed into production but where plasma sample is absent or inadequate the plasma may still be used, though a core sample will be requested first.

Mr. Combridge and his technician employ a radio-immuno assay technique shown to be more sensitive (detecting down to 0.1 to 0.25 ng) than the commercially available kit. This they are about to make available to others within the service, the work having been done in conjunction with North London and the Middlesex Hospital. A very elegant microtitre technique is used utilising small plastic cups slotted into a preformed plastic tray. Although there are chances of transcribing errors any positive can be double-checked by using the retention sample. Doubtful results are also double-checked

using longer incubation periods and anything still in doubt is sent to Dr. Dane for further study.

Discussion relating to the use of untested plasma revealed that it was thought it was only used in a production involving heat treatment - but this seemed somewhat uncertain. However, study of the records did tend to indicate the order of risk of anything untoward arising as being low.

In-process samples are also tested but this did not seem to be on a very systematic basis.

4.5 Other biological testing and control

4.5.1 Environment

Dr. Singleton indicated that although settle plates have been in use in various production areas for a number of years only recently has Mr. Wild started to make any special study of an environment - starting with that of the sterile filling suite and using a slit sampler. No definitive results or action seems to have been taken on this work and, following examination of the records of settle plate counts no action would appear to be taken in that area either. Very high counts are recorded from time to time in sensitive areas - e.g. under the filling hood and in one of the smaller rooms in the sterile suite, and regular high counts are found in the changing rooms. One could not help be surprised at the little use which appeared to be made of a very considerable body of information.

4.5.2 Autoclaves

About once a month some study is made on autoclave loads using spore strips - but placed only in the free spaces and not incorporated within the wrapped articles. Further spore strips are placed in the coolest parts of the autoclave. It was not clear to whom the results were reported and what action (if any were necessary) was taken.

4.5.3 Ovens

Dr. Singleton expressed having some interest in thermometry tests carried out on the electric dry heat ovens and showed some understanding of the faults in design of those actually in use.

4.5.4 Freeze-driers

Again spore strips have been used to check on the efficacy of the ethylene oxide sterilisation of the Edwards freeze-driers. The problem of possible delayed germination of the spores was discussed.

19/7t

4.5.5 Other

Dr. Singleton admitted he had not been involved in any study of the bacteriology of cartons or clothing, nor in any planned maintenance programme concerning air filters or separation columns. He was also concerned regarding his lack of involvement in labelling matters.

5. Records

Detailed records extending back a number of years are kept in foolscap sized hard backed ledgers in the bacteriological laboratory. Each is clearly marked on the spine as to its purpose provided the system is fully understood.

5.1 Plasma

Here the ledgers are marked with the names of the various Regional Transfusion Centres from which the plasma comes. The details recorded differ slightly in the case of the Winchester bottles of time expired plasma used by Dr. Singleton for the preparation of freeze-dried plasma where the records can be considered part of the production documentation falling to his charge and will be described elsewhere in this total report, and those concerning the five litre pooled packs of plasma from other centres.

With regard to the sample sachets from these pool packs each has a number and a code letter to indicate source. They are entered by number into the appropriate book and this also indicates if there is either "no sample" or "insufficient sample". From these records Dr. Singleton has prepared tables showing the frequency (in percentage terms) of these events against the various centres. From the book the "first list" is prepared on pieces of paper and this list is transmitted to the areas where initial tests are performed (bacteriology, hepatitis testing) so that checks can be made against the actual sample labels and results can be reported. Any positive bacteriological finding is entered in the ledger in pencil and, if identification occurs into the broad groupings this is later entered in red ink. After the results are obtained from Mr. Combridge the whole information is entered into sheets for transmission to the production area.

Areas with a bad record with regard to leaking of sample sachets have been contacted but although in some cases this has resulted in considerable improvement, in others high (50-60%) rates of inadequacy of sample continue.

5.2 "Fraction" book

In this are recorded the results of tests performed on in-process samples sent by the production departments. In each case a report is returned

9/77

to the department of origin signed by Dr. Singleton. If he is away the report awaits his return for signature but the individual concerned in the production department is always free to consult the laboratory ledger. The same procedure applies to final product bacteriological tests.

5.3 Settle plate records

These have been discussed above.

5.4 Tests on water

Samples are taken each week from the "pyrogen-free" water outlet. These almost invariably show contamination - according to Dr. Singleton from the rubber pipe attached to the outlet.

5.5 Others

Other ledgers contain results of tests on the autoclaves and on the sterilisation of the freeze-driers.

6. Summary of comments and recommendations

6.1 "Sterility" testing

6.1.1 Sterility test proper

In-process and final product samples should be taken on a formal basis, should have proper recording and documentation, should be tested in accordance with official requirements by trained staff working in appropriate premises to the highest standards and thereby should fulfil their proper role as an essential element of product quality assurance.

6.1.2 Plasma testing

It should be decided at the highest levels exactly what the practise should be regarding use of contaminated plasma - whether by bacteria, moulds, mycoplasma or certain viruses. Acceptance levels should be set and testing designed to select intake material appropriately. Information obtained should be fully used by 'feed-back' to determine cause and cure. This testing (except in the case of hepatitis antigen) should be entirely separate from 6.1.1 and both should be totally divorced from any production process in physical terms.

6.2 Animal tests

Apart from some minor requirements relating to the premises used for testing for freedom from pyrogens there is nothing to criticise in this connection. However, the area should receive close attention from the point of view of yielding more interesting work and playing a more practical role in product assurance than simply routinely testing each and every batch. These remarks will apply more when total production is fully controlled.

6.3 Quality assurance

Any biological facility involved in pharmaceutical production and especially in cases where the products cannot be terminally sterilised has a major part to play in quality assurance. The head of any such facility must be totally involved in all decisions concerning the premises, plant, personnel and product and a fully equipped laboratory staffed by well trained persons should be fully occupied in monitoring every aspect of work. This would include testing of all incoming raw material, intermediates and final product, checking sterilisation techniques and equipment, checking air filters and the environment, watching personnel for carrier states or temporary increases in bacterial flora, examining any special clothing worn etc. The inspectors felt very strongly that few or none of these aspects at present apply to the Blood Products Laboratory.

GRO-C

J. A. HOLGATE

23 July 1979.

Copies to: Mr. Flint
Dr. Purves

19/74

INDEX

19/81

3.4 Freeze Drying Department

INTERIM SUMMARY 5

3.5 Washing and Sterilization of Equipment etc

INTERIM SUMMARY 6

3.6 Engineering aspects of plant and equipment

INTERIM SUMMARIES 7 and 8

4. SUMMARY SESSION OF THE VISIT OF 23 - 27 APRIL

5. PASTEURISATION OF P.P.F ; INSPECTION AND PACKAGING - MR SHARMAN

5.1 Pasteurisation of P.P.F.

5.2 P.P.F. Incubation

5.3 Inspection and Packaging

5.4 Transit Cartons Store

5.5 Final Products Ambient Store

5.6 Quarantine Stores

5.7 Small Orders Despatch Section

5.8 Complaints

INTERIM SUMMARY 9

6. ANALYTICAL LABORATORIES

INTERIM SUMMARY 10

7. DOCUMENTATION AND FINAL PRODUCT RELEASE

7.1 Plasma Protein Fraction Documentation

19/82

7.2 Freeze - Dried Factor VIII Documentation

7.3 Freeze - Dried Small Pool Plasma Documentation

INTERIM SUMMARY 11

8. CONCLUSIONS AND RECOMMENDATIONS

Part 2 - BIOLOGICAL QUALITY CONTROL FACILITIES

Appendix 1 Large Fractionation Production Methods

Appendix 2 (a - c) Plans of Production Areas

Appendix 3 Clotting Factors Production Methods

Appendix 4 Large Scale Production of Human Plasma Fractions (Publication)

Appendix 5 Product List

19/83

PART 1 - GENERAL REPORT

1. INTRODUCTION

Dr Lane, Director of the Blood Products Laboratory (BPL) took over the responsibility of running the Laboratory only about 6 months ago on the retirement of Sir William Maycock.

Brief discussions of a general and introductory nature were held prior to starting the inspection for the benefit of Dr Purves, who had not visited the site before. It was intimated that production throughput in the unit has far exceeded the original design capacity. In an attempt to rectify some of the immediately apparent deficiencies a 'stop gap' project has been initiated to partly improve the buildings and alleviate difficulties concerning storage. Some of these measures are intended to be temporary, but others, such as cold stores, are being planned for long term use. In general, the impression gained from Dr Lane was that he fully appreciates his major problems lie in staffing, limitations imposed by premises and having to run the laboratory as a factory.

1.1 Inspection Format

Messrs Flint and Purves have inspected and reported on this site as they would have done were it a pharmaceutical operation.

2. STORES AND RECEIPT OF CHEMICAL RAW MATERIALS, COMPONENTS ETC

*The storage area allocated for the receipt of general goods and chemical raw materials is severely congested to the extent that areas, although designated for quarantined and passed goods are not used as such. Congestion is such that it precludes good storage and proper stock rotation of components such as vials, bungs etc. On the whole the area is dry and weatherproof, although some leaks were evident through part of the roof behind the loading bay.

Analytical control over chemical raw materials, instituted only in 1978, has been organised by Mr Greulich, who is in charge of the analytical department. Each container is identified and one from each manufacturer's batch is fully *assayed according to laid down specifications. These specifications appear to be those of the EP or BP but as yet have not been written in a formal manner.

19/84

The composition of the starting plasma pools therefore varies according to source, the proportion of frozen time expired plasma and liquid plasma used. This, it was said, did not affect the quality of the end product even though Belfast plasma has been known to have organism counts up to 3 million per ml, other plasmas have also been found to have counts in the region of 500 per ml.

All plasma received from the RTCs is tested for Hb_s Ag by a radio immunoassay (RIA). If there is insufficient material in the testing pouch then this test is done in preference to a microbial count. Plasma, the microbial quality of which is unknown, can be used in production runs. Some RIA testing is done at Region and reported to the BPL. (i.e. North London and Brentwood).

Initially the turnover of time expired plasma was about 10 weeks but now the unit is being supplied with more plasma than can be handled by the existing staff on a single shift basis and turnover, it is estimated, is greater than one year.

Liquid plasma is normally used within 3 days but it could stand longer, perhaps over weekends, if this is to be so then alcohol (96% ethanol and 2% methanol) is added to a final concentration of 19%. The justification of different storage temperatures for liquid plasmas, that is +2°C, - 3°C and -5°C is due to the alcohol content (see page 4, Appendix 1).

As fraction II, used for immunoglobulin production, is produced at a frequency of 1 batch in 10 of large scale fractionation, fraction II starting material is selected with care to get the 'best'. Any potential fraction II material about which there is the slightest query is not used. 'Tropical pool' plasma, i.e plasma from coloured donors, is not used.

Every 5L pack of time expired plasma is an individual batch: it is made up to 28 donations, details of which are kept by RTCs but not passed on to the BPL.

3.1.2 Production Process

5L packs of time expired frozen plasma on receipt at the BPL is transferred within a short time period (30 mins) to -25°C stores on the upper floor of the large fractionation laboratory. Material is kept

Components such as bottles, vials, bungs etc are, as yet, not routinely tested: there are no formal specifications. Some vials stored behind the loading bay were left open to atmosphere.

A limited amount of in-process testing is done using mainly electrophoresis and ethanol determinations.

A series of standard analytical methods have been prepared for the analysis of raw materials, in process samples and finished products.

Because of the inordinate time taken to inspect the production of this operation, it was not possible to have a comprehensive look at the analytical laboratories during the first week of the visit. A report on this will be prepared after a follow-up inspection planned for the week beginning Monday 16 July 1979.

3. PRODUCTION PREMISES, EQUIPMENT AND PROCEDURES

3.1 Mr Wesley's Department : Large Fractionation and Final Solution

Mr Wesley, who is in charge of the Large Fractionation Laboratory (LFL), joined the BPL 16 years ago direct from Nottingham University, where he obtained a B Pharm degree. He is responsible for large scale protein fractionation and the production of immunoglobulins. His deputy oversaw the latter production, but has left for a post in industry: he has not yet been replaced.

Staff presently working to Mr Wesley include a Mr Butcher who has worked in the laboratory for 25 years and was in charge of ether fractionation when it was in operation: Mr Butcher is the chief technician. Three technicians (with various O and A levels, doing day release) and laboratory assistants, employed for manual work report to Mr Butcher. There is no formalised training for technicians or laboratory assistants other than that given by exposure to work in hand.

3.1.1 Products made

The major products made in this laboratory include:

10/96

3.1.1.1 Plasma Protein Fraction, PPF.

3.1.1.2 Salt Poor Albumin 10g% and 20g%, and

3.1.1.3 Normal and specific Immunoglobulins

A summary of the production of these can be seen at page 3 of Appendix 1, using the standard cold ethanol fractionation method of Kistler and Nitschman (Vox Sang 7,414-424, 1962). Starting materials used in this production include:

3.1.1.4 Time expired plasma: this comes from Regional Transfusion Centres (RTCs) in 5L plastic packs.

3.1.1.5 Cryoprecipitate supernatant: this also comes from RTCs. Materials 4 (3.1.1.4) and 5 (3.1.1.5) normally amount to about 1,200 litres per week which contributes about 50% of the plasma requirement.

3.1.1.6 Cryoprecipitate supernatant: a second source of this material is from Dr Ellis' laboratory [Clotting Factors Laboratory] and consists of plasma from which factor VIII has been removed. This is supplied to the LFL in bulk, in stainless steel fractionation vessels, 1000 litres per week. It is not routinely tested for Hb_s Ag or micro-organism count: it can have high microbial counts as some examinations have show.

3.1.1.7 Factor VIII/IX supernatant: a supply of this 120 litres/week is obtained from Oxford Plasma Fractionation Laboratory in stainless steel churns.

3.1.1.8 Fraction 1 supernatant: this is plasma from which fibrinogen has been removed.

3.1.1.9 Precipitate A supernatant: this is plasma which has had antibodies removed (Specific Igg) and contains albumin only.

3.1.1.10 Freeze dried, time expired plasma from Dr Singleton's laboratory.

3.1.1.11 Plasma from Belfast in 3L packs.

19/87

on numbered pallets and details of batches on a pallet location are recorded. Pallet contents are not secure in that individual packs could be transferred from one pallet to another. This is not of any great consequence as batches are requisitioned the day before use and checked against the batch numbers on the outsides of cardboard cartons and, also on the pack inside. The 'production' batch record is ticked against each pack number and packs are transferred to a second pallet. On the day of use the packs are checked again and the ticks ringed. At the first checking stage material that has been defined as unacceptable is removed from the pallet, but not from the store. Acceptable material should always be kept secure i.e. on a caged pallet, segregated from rejected material.

Pooled material collated for processing consists of liquid plasma, which is always used first, and time expired frozen plasma to make up the volume for a given production run. Separation of the required portions is then by cold ethanol fractionation at various pH values and centrifugation.

3.1.3 Premises, Equipment and Procedures

Operations involved in large scale fractionation are split between two floors. The initial steps are carried out on the upper floor fractionation room (see Appendix 2c). All of the remaining steps are undertaken in a ground floor area shown at Appendix 2b.

5L packs of plasma in cardboard outers are transferred on wooden pallets into the upper fractionation room. Cardboard and wooden pallets should not be taken into this area: the latter should be easily cleanable and be of plastic or metal construction.

This production area houses the tops of four stainless steel processing vessels the bodies of which protude into the ground floor processing room in which centrifugation is done.

The room finish is of gloss painted plaster ceiling, three walls of a similar finish, one of welded vinyl and the floor is covered again with welded vinyl. The area is air-conditioned but the quality of air supplied was not known by Mr Wesley. Air enters at near ceiling level and is directed to the floor by fixed hoods and exhausts at a high level on the opposite wall. There is no changing room for staff entering the

area or air lock for the entry of goods and equipment. There is much exposed wood, cork, high level dust traps (pipework) and condensation on pipes.

There are no written cleaning schedules for the room or equipment. Production staff clean equipment but the room is cleaned by general staff: the frequency of this is floors weekly and walls and ceilings at indeterminate times. No procedure exists for the preparation of disinfectant used in this area: it is made up with tap water. There appears to be no standardisation of procedures. Funnels and troughs for use on thawing shelves - piped glycol solutions are used to facilitate heat exchange - for the collection of plasma are autoclaved in a ground floor area and brought to this processing room unwrapped, 24 hours before use. The autoclaving procedure is apparently used principally to eliminate hepatitis virus. Hypochlorite solution, made up by rule-of-thumb, is used to disinfect the thawing shelves; it is not made up in a pre-sterilized container. Cleaning cloths remain wet and could promote the spread of bacteria. Tap water supplied to this area is softened and of unknown microbial count.

Sterilization
bacteriology
water
softeners.

Bags of frozen plasma are allowed to thaw on the stainless steel shelves. Plasma discharges into stainless steel chutes which lead to stainless steel funnels which feed into a holding vessel. All vessels are washed out but not to a written procedure: no record is kept that they have been washed. Apparently they are washed out with mains water from a hose-pipe which is hung on the wall in a coil fashion. They are left wet, then rinsed out with 75 litres of heated (80°C) distilled water: this wash water is checked for microbial count.

contaminated

↑ 35-40°

Some mould was growing in the vicinity of the sink.

A drain in this area is treated with lysol which had been made up some time ago: the drain is never cleaned. The sink drain is not disinfected.

Rubber tubing used as overflow tubes for the large reaction vessels are neither cleaned, changed nor examined microbiologically.

There are many possible sources of microbial contamination in this area that could enter the reaction vessels at the loading stage. No

19/8?

baseline level has been established for the environment, tap water, cleaning solutions etc: the area should be monitored to establish this data.

Engineering support for maintenance of the fabric of the premises is inadequate e.g. defective plaster.

Short term improvements to this area should involve improving procedures, maintenance to premises, and cleaning in accordance with clean room technology. Longer term improvements would necessitate upgrading the environment to Class 2, with the incorporation of an air-lock and a personnel changing room.

The ground floor processing area is split into three main zones, cooled to varying degrees. A +2°C zone is used as a general preparation area e.g asbestos filters, storage and processing area (decanting of reconstituted fraction II solution into shallow stainless steel trays from winchester bottles, prior to freezing). The -5°C room houses the bases of the large fractionation vessels and the manifold feed assembly of Sharples continuous centrifuges. The -10°C room houses the fractionation of immunoglobulins.

The criticisms already made to the initial processing area are also applicable to this which has additional deficiencies. Throughout this area which has no personnel changing room, the suspended ceiling is of long narrow perforated metal sections, which slot together in a tongue and groove manner. Wall surfaces are of a formica type finish with wooden 'protection' bars. The floor is of quarry type tiles with grouting between. In the +2°C room the ceiling sections were found to be poorly fitting and dirty: on closer examination this dirt was found to be confluent growth of mould, in all appearances showing growth from the hyphael to the sporing stage of its cycle.

This situation in a room where nutritive products are being processed in an open manner is totally unacceptable. Water for use in production was being cooled in an open top stainless steel vessel adjacent to such an area.

Air supplied to these rooms is virtually totally recirculated with a small percentage make up, the quality of which, i.e filtered or not,

19/9D

was not known.

The temperature of the area is not conducive to good work over an extended period of time.

The area is particularly difficult to clean effectively. Cardboard is also brought into this area.

The transfer of centrifuge precipitate from the Sharples units to non-sterilized polythene bags is done in the open atmosphere of the -5°C room. Precipitate is stored in a cupboard in this room until it is required for solutioning, in lidded stainless steel tanks, which is done in the +2°C room. The resulting albumin solution is then passed through a series of coarse asbestos filters and a final of 0.22 micron filter.

Resulting filtrate is then further processed. If it is fraction V, which will eventually end up as Plasma Protein Fraction or Salt-Poor Albumin, it is subjected to thin layer vacuum distillation to remove process alcohol and concentrate the protein to the required level. Resulting solutions are then packed into 5L plastic packs which are frozen in one of two Grant freezers, in an adjacent room, before being stored at -25°C. If it is fraction II it will be transferred to shallow trays, as described above, for subsequent freezing and drying in the Edwards' freeze driers. Primary drying takes 1.5 days and the secondary drying (P_2O_5) is done overnight. Dried material on open trays is then tipped into ordinary polythene bags (not pre-sterilized). Bags of powder are then placed in lidded polythene buckets and stored at -25°C in a refrigerated room next to the PPF solutioning room.

The former operation is done in a Centritherm Unit which is housed in what appears to be a standard laboratory with a general air supply, not HEPA filtered. The Centritherm evaporator is virtually a closed piece of apparatus which is disinfected, using hot water, before use: the system would be much improved if its component parts were sterilized and the whole operation was carried out in a controlled area. There is no changing room or procedure for entering the laboratory: the ceiling is constructed of perforated tiles, the walls are of painted plaster and the floor of vinyl finish. Laboratory furniture is of wood (some unsealed) and cardboard cartons into which filled bags are put are taken into the area. The door to the area from a common corridor is not always closed during processing and staff do not wear gloves during processing.

19/91

While operators don special clothing in the plasma pooling area on the first floor - trouser suits, wellingtons and masks - to protect the operator from splashes of plasma, no clothing in addition to a standard laboratory coat is worn in this area.

There is no general changing procedure for staff entering the BPL so that they can exchange their outdoor clothes for factory clothes. The operator in the Centritherm room was wearing outside 'running shoes' and a process tube was hanging on the floor near these: this points to another potential source of microbial contamination in addition to that contributed by the general environment of the factory.

Some in-process control work is carried out on the Fraction V paste after centrifugation. The paste is made up into solution in sub-batches (one sub-batch per day). Solutions are filtered. Before evaporation the turbidity is examined (purely visually), electrophoretic tests are done and samples taken for microbial examination. Counts are determined and can lie between 100 and 500 organisms/ml: contaminants are not classified. Poor material is used in production by being mixed with good material to "dilute the bug count out": this type of philosophy is totally unacceptable.

Small scale fractionation of specific immunoglobulins such as anti-bee venom is done in a -10°C room which is part of the suite housing the -5°C and +2°C processing rooms already mentioned: it is equally poor in the fabric of finish and standard of operation carried out therein. However, the environment and procedures used to pool the plasma are more inferior than those cited for large scale fractionation. Plasma is pooled in a general laboratory Appendix 2(b), with perforated ceiling tiles, wooden furniture and rough wooden crates (used for the carriage of bottled chemicals), fibreboard containers of chemicals etc: it is supplied with air the quality of which is probably extremely poor as manifest by black streaks of dirt surrounding the in-put grill. Again, there is no changing room or procedure for entry to this area. 5L bags of selected plasma are thawed out in a sink of hot water drawn from the general factory system.

INTERIM SUMMARY 1

In summary, the general standard of the Fractionation Laboratory operation is extremely poor. Processing involves open procedures at t

beginning and throughout the fractionation operation. Alcoholic fractionation is effected at various pH levels and with appropriate centrifugation plasma fractions are obtained as pastes in the Sharples centrifuges. These pastes are taken up into solution (using cooled distilled water previously stored at 80°C) ~~and filtered (coarse asbestos plus a final 0.22 micron filter~~). Filtrate is then subjected to thin layer vacuum distillation or frozen. Much of the handling of this intermediate product is done in an open manner in the +2°C room which was found to be heavily contaminated with moulds. Plasma fractions are then held frozen or dried, awaiting further processing.

The attitude taken that, as the starting material is contaminated, it is pointless carrying out the rest of the processing under clean conditions is unacceptable, even if the end product has never been shown to elicit pyrogenic reactions. A change in attitude is required to collect the raw material under conditions as hygienic as possible pool it at RTCs under clean room conditions, commensurate with the nature of the operation, to ensure that the microbial load is minimal. All material used in production should be of known microbial load and plasma should be processed in such a way that its microbial load is not contributed to due to inferior premises, procedures and techniques. To achieve this it is imperative that the operation is upgraded,

SHORT TERM: improve handling within the present premises

LONG TERM: upgrade the premises to CLASS 1 or CLASS 2, commensurate with the nature of the operations to be done.

i. Staff training should be implemented/improved.

ii. Documentation should be improved ie. procedures.

iii. Equipment/premises should be improved.

iv. Environmental monitoring should be implemented to at least establish present particulate and microbial loads.

v. Cold storage should be increased to facilitate better segregation and stock rotation.

vi. Staff should wear processing clothing in critical production areas.

Cleaning room change
Settle plates

LF [illegible]
'sporadic [illegible]
sampling'

19/93

vii. Additional key staff is required as present staff are taking the responsibility for too wide a range and extent or production activities and therefore cannot spend the necessary time for supervising immediate production staff who are left too much to use their own initiative (see point i).

Final Solution Preparation

Preparation of the final solutions utilizes frozen Fraction V concentrate - for PPF - frozen albumin concentrate - for salt poor albumin - and freeze dried Fraction II for normal immunoglobulins etc. This activity involves opening bags of frozen material, swabbed with 96% alcohol, in the final solutioning room (see Appendix 2(b)) under vertical LAF and placing in a stainless steel vessel with half of the lid removed. The frozen concentrate is allowed to melt and is taken up into an isotonic solution in the adjacent +2°C room. Water used at this stage has been collected and cooled in another +2°C room, already mentioned which was heavily contaminated with moulds.

Staff working in this area wear ordinary laboratory coats, head covers and sterilized gloves.

The premises are poor. There is no staff changing room. The ceiling and walls have an imperfect painted plaster finish: the floor is of welded vinyl. Wooden furniture and desks are used throughout: they are not easily cleanable: there is a notice board on the wall and the area is used as an office as well as a production area. Air is supplied to the room through high-level wall grills around which is cracked plaster and black streaks, again indicating the poor quality of the air supplied. The vertical laminar flow bench is hung on overhead rails to permit its use over a considerable length of bench. Debris could fall from these rails, and, it is doubtful that this type of distant LAF source would protect the product. There is a great liklihood that it would promote contamination due to turbulence and the proximity of 'shedding' operatives. A fibreboard container of sodium chloride was found in the area: this salt is used to render bulk solution of product isotonic. The fabric of finish of the associated +2°C room is similar to those previously described in the large fractionation suite.

19/94

Non-Sterile

Misrepresented Data.

During the preparation of these solutions samples are taken, using 'sterile' beakers, for protein determinations. This is done using a refractometer. The use of the word 'sterile' for a beaker which has only been washed shows a lax use of the word, indicating a lack of understanding of the true meaning of sterility. This situation occurring so near to the final sterilization by filtration does pose several questions regarding staff training, appreciation of the nature of the work in hand, supervision etc.

Solutions are then filtered through a Carlson Ford asbestos depth filter unit (previously 'sterilized') into a pre-sterilized stainless steel vessel (121°C/1 hr). Because of the tubing (~~non-sterile~~) used post filter this stage of the operation is considered non-sterile. The solution is then filtered through a complicated network of tubes to a PALL filter (0.22 micron), before passing through the wall, in a pre-sterilized piece of tubing, to the 'sterile' filling suite. Procedures used in this area - manipulation of sterilized tubing from a dirty to a clean area - do not lead to good aseptic techniques.

Samples of solutions are taken before and after the penultimate filtration stage for microbial evaluation.

Smaller quantities of Gamma immunoglobulin solutions are pre-sterilized by filtration* into pre-sterilized hermetically sealed cans with filter air bleeds in the solution preparation area and these are taken into the sterile suite for filling, being transferred in the air lock from one wheel base to another which is kept in the clean room.
NOTE: The PALL filter and vessel are sterilized together.

A plan of the 'sterile' filling suite can be seen at Appendix 2(b). This area is cleaned thoroughly once per month. There is no daily or weekly cleaning procedure and this would explain the build up of dust on exhaust grills.

Product and equipment enter the area via an air lock: personnel enter via one of two designated changing rooms. Briefly the changing procedure is as follows: male operatives take off outdoor shoes only (ladies do not), overshoes are put on, hands are washed, head cover

Shoe change + overshoes

*Under LAF in final solutioning room

19/95

(which is too small) is donned, then the mask (hands are not washed again), the operative puts on the one piece trouser suit closing it at ankles (outside overshoes) wrists and neck: sterilized gloves are put on, hair is tucked into hood with gloved hands. The dressed worker then washes the gloved hands with an alcoholic solution on entering the suite.

At the time of inspection the air extract unit in the ceiling, on the dirty side of the male changing room was open with no barrier between it and the outside atmosphere. Cracks were noted in the wall plaster and floor to wall coving was loose. There is an insufficient number of differential pressure manometers to permit the recording of pressures in the various rooms and show a gradation of flow of air from the more to the less critical areas.

Female staff wore the clean room clothing in an inappropriate manner, The hair was not totally covered, make-up was worn, earrings were worn, sleeves of suits were not tucked into gloves: this latter point would probably result in a pumping effect of debris from the sleeve into the critical filling zone.

The vertical LAF is suspended on overhead rails and is directed onto a solid bench which will result in a considerable amount of turbulence around the filling head. It is considered that horizontal LAF would be more appropriate for the type of filling head currently being used.

An alcoholic disinfectant for hand rinsing is not readily available for any operative that may inadvertently touch the face.

There is no LAF facility in the Factor VIII filling room.

Operatives complained that no training had been given for this type of operation but they did realise that specialist information should be sought.

The overwrapping of clothing to be sterilized and taken into this area has not been standardised. Each operative prepares his/her own clothing.

Bottles of diluted and concentrated Chloros in the suite were closed with CORKS.

19/96

In summary, the premises, operations and procedures carried out in the final solution preparation room are inadequate for the types of product being manufactured. There are indications that staff training should be implemented so that some of the potential trouble spots may be identified, and dealt with.

The 'sterile' filling suite should conform and be used as a CLASS 1 area for the aseptic operations being carried out. While the fabric of the premises in general is good, deficiencies have been noted: these should be rectified immediately. One of the major deficiencies exists in the way personnel dress and work in the area: this is highly significant when one notes that the greatest potential source of contamination is the operative. The choice of a vertical LAF has been questioned.

3.2 Dr Ellis' Department : Clotting Factors Laboratory.

Dr Ellis is in overall charge of the Clotting Factor Laboratory. Reporting to him is Mr Petett BSc, the chief technician, who acts as his assistant and deputy: he has worked at BPL for 6 years. A senior technician, a Mr Williams in post for 10 years, is in charge of the day-to-day operations in the Laboratory. Beneath these key people there are technicians, some qualified, others not, and, laboratory assistants.

3.2.1 Products made.

The major products made in this laboratory include:

3.2.1.1. Antihaemophilic Factor (AHF), 50-60,000 (250 in) units/year.

3.2.1.2 Fibrinogen for intravenous use, 100 bottles/week.

3.2.1.3 Fibrinogen for isotope labelling. Highly selected starting material is used to prevent the passing on of hepatitis virus.

3.2.1.4 Fibrin foam (this is freeze dried fibrin which is put into a jar and baked in an oven) 1,000 pieces/year.

19/97

3.2.1.5 Preparation of an intermediate product, Factor IX, which is sent, refrigerated, to the Oxford ≡ PFL 2 x 200L batches/week, and,

3.2.1.6 Thrombin, 1,000 vials per year.

3.2.2. Production Process.

The above range of products are all made in a single suite of laboratories, a plan of which is shown at APPENDIX 2(b).

To illustrate the general types of procedures used the manufacture of AHF only will be considered.

Details of the procedures used in this area are given in a Master Method document which should be referred to, see APPENDIX 3.

3.2.3 Premises, Equipment and Procedures.

This production operation suffers criticisms similar to those already cited for the large scale fractionation unit.

Access of personnel, "tub-trucks" and equipment, from elsewhere in the Laboratory complex to this processing and adjacent areas is too lax.

There are no areas which act as equipment air-locks or changing rooms for personnel to don suitable clothing. There is no standardisation of attire for operatives entering processing room CR2, (i.e no SOP), although in mitigation process workers in close proximity to the process are better covered than others doing less critical operations. This attire consists of coveralls, boots, head cover, mask and gloves and can be used for more than one day. It is stored in metal lockers in the central corridor of the suite between sessions of use. Clothing would be changed at least once per week: it is laundered by a commercial laundry. Hats, masks and gloves are changed daily and boots are washed in Lycolin, infrequently.

19/98

Premises used for the primary preparation of AHF are poor. There is a metal plate ceiling in which there are trap doors; walls are of painted plaster, with cracks and the floor is of quarry tiles. There are numerous service pipes to various pieces of equipment which render the room not easily cleanable.

Air supplied to this room is not filtered it is merely conditioned and recirculated through wooden ducts. There is no forced ventilation of the corridor: any ventilation is merely by air loss from adjacent rooms.

It is in this room that frozen plasma is thawed for the initial stage of Factor VIII production. Melted raw material is then centrifuged (continuous Sharples units) to separate the cryoprecipitate which contains the required fraction. All of the processes undertaken may be described as open.

The aqueous heat exchanger used at 28°C, to aid plasma thawing has been known to leak: this could contaminate the product if it was not adequately maintained and tested.

There are no Standard Operating Procedures (SOPs) for the cleaning and disinfection of the environment or equipment. Disinfection of the cleaned environment is achieved by wiping down surfaces with 1% Hycolin, made up qs, using clean sterilized lint. Floors are cleaned once per week and walls infrequently. Vessels and certain pieces of equipment are steamed out after use (105°C), cleaned with Haemosol solution, then with pyrogen free water and finally with 70% ethanol. They are rewashed immediately before use with sterilized pyrogen free water.

On the completion of each piece of work, floors are mopped with Hycolin.

Laboratories 13 and 16 house further processing steps in Factor VIII production namely centrifugation of precipitate and resuspension of precipitate, and final sterilization by filtration, respectively (see APPENDIX 3 for more detail). The fabric of finish of ceilings and walls is of matt painted plaster, the surface of which is cracked at several locations. The floor is of welded vinyl and the furniture of wood. Laboratory 16 has an [illegible] room in which the [illegible]

19/99

filtration of Factor VIII is done. Access to the latter which has a poor fabric of finish, is gained via a small changing room which is merely an ante-room without the facilities required to permit one to don sterilized clothing in the manner required for an aseptic operation. Work is done under the protection of a LAF bench, which, from appearances, is ill-maintained. In this room the overall pressure relative to ambient is 0.6" water gauge. Neither the room nor the associated equipment looked clean. Clothing used in this area is the same as that used in the processing area but is sterilized and changed on a daily basis.

Windows in laboratories 13 and 16 can be opened and heating of the areas is achieved by enclosed radiators, with top grills, adjacent to the windows.

Factor VIII production is monitored microbiologically. The environment is monitored on a daily basis. There are no seasonal fluctuations in results. Counts of 10 organisms per plate (half an hour exposure) are not uncommon. Samples of solutions are taken immediately prior to sterilization by filtration. This type of control is incomplete in that the quality of aluminium hydroxide gel used in production is not determined.

Filling of Factor VIII into the final vials is always done on the same day that the bulk solution is sterilized by filtration. Consideration should be given to carrying out this filtration stage in the "aseptic filling suite", where the filling operation is done (middle room).

Filled vials with loose fitting bungs are taken in aluminium trays with loose fitting lids from the filling room through the Laboratory to the Freeze Drying Department. Lockable caged trolleys should be used for the product security of unlabelled vials, which are in process: this is not done presently. A reconciliation of vials and bulk product etc. is done after filling but before labelling.

Fibrinogen for aseptic labelling is made on a small scale in laboratory 19. This is a standard laboratory with no filtered air supply, associated changing room etc. therefore the premises are not [illegible] for the type of operation undertaken. It is of a similar standard to laboratories 13 and 16. Filling of the product is done in the aseptic filling suite.

19/100

Documentation presently available covers Manufacturing Records, Apparatus Lists, AHF Filling Record, Residues and Rejects Disposal Record, Pyrogen Free Solutions and "Ambient Air Sterility", the title of the last document poorly describes collected settle plate data!

Staff training is merely by exposure to current manufacturing situations.

Dr Ellis recognises that the unit is suffering from chronic staff shortages and extremely poor facilities.

This situation has worsened over recent years owing to increased production and the constraints placed upon the operation by the premises, both in design and lack of appropriate facilities. He would like to totally separate the production of prothrombin and factor VIII, but again this cannot be done owing to the lack of space.

INTERIM SUMMARY 3

In summary, the premises, facilities and operations carried out in this area are inadequate for the aseptic preparation of any product. Immediate action should be taken to initiate steps to rectify these deficiencies. These should be short term to update and create new documentation, procedures etc to cover all procedures used in and associated with production. Steps (longer term) should also concurrently be taken to rectify the deficiencies in the premises. These it is considered could only be achieved by the erection of a purpose built factory complex, since the limitation of the present laboratory complex are blatantly apparent, both to the inspectors and scientists on site alike.

3.3. Dr Singleton's Department : Filling of Plasma for Freeze Drying

Dr Singleton is in charge of the microbiological testing laboratory and the manufacture of one product namely freeze dried plasma.

3.3.1 . Production Process in brief.

2L pools of plasma, (10 donor pools), in glass Winchester bottles

19/10!

are supplied by two Regional Transfusion Centres. The outsides of the Winchesters are washed prior to storage at 4°C. These pools may be stored for up to 4 months before use. All containers have samples removed on which RI assays and sterility tests are executed. About 30 of these are used for each filling session. Aliquots are "aseptically" filled into British Standard Transfusion bottles which are then closed with perforated plastic plugs and dust covers. The contents of these bottles are then spun and frozen to form a shell to aid the subsequent freeze drying operation, which is carried out in the freeze drying department. Following this bottles are labelled, inspected etc: these aspects will be examined at the follow up inspection which will take place during the week beginning 16 July 1979.

3.3.2 Premises, Procedures and Equipment.

Plasma for production runs is stored in the +4°C cold room in Dr Singleton's department. "Aseptic" filling is done in the innermost of twin rooms (see APPENDIX 2(b)). The door between these rooms is suspended and sliding in nature. The premises are of painted plaster walls and ceilings with old wooden laboratory type benching on which cardboard boxes were lying. The floor was of stone, terrazzo type finish. Air drawn from the corridor, where filthy aluminium crates were being stored, is filtered and supplied at high level at one end of the room and extracted at low level at the other end where a horizontal LAF bench is sited (see 3.5 for quality of air filters).

The floor is cleaned weekly with a machine used elsewhere in the WBI: there is no SOP for the cleaning/disinfection of these rooms.

Operatives clothing is re-sterilized without first being cleaned. Persons undertaking aseptic filling enter via the adjacent room, as does equipment, product etc, and don wellingtons, masks, headcovers and surgeon's type gowns. The sleeves of these gowns are not elasticated and gloves are not worn. Wooden trolleys used elsewhere are wheeled into this area.

Filling of plasma is not done under LAF protection but [illegible] the air-input which supplies air of doubtful quality. The LAF is used during the sterility testing of in-process and finished products.

19/102

Production and testing activities such as these should not be carried out in the same laboratory.

Materials supplied for each run consist of tested plasma in 2 litre Winchesters (30), sterilized filling heads, one for each Winchester - these are sterilized in bulk in one pack - sterilized freeze-drying caps and sterilized transfusion bottles capped with cotton wool/Gauze plugs, with paper dust covers. All of these enter the filling room through the ante-room area which is used as a storage/changing area where gowns are donned over outside clothing e.g. woollen jumpers etc. The filling operation is carried out around a bunsen burner, using "no touch" technique: it is not done under the protection of the LAF.

INTERIM SUMMARY 4

For a filling operation such as this, true aseptic facilities and procedures, with currently accepted techniques, are required, but are not being used. This is due to severe deficiencies in the premises, general facilities and procedures being used. Prompt action should be taken to initiate the steps required to rectify the failings and introduce quality assurance into the process.

3.4 Freeze Drying Department.

At the time of this inspection Mr Kinnarney was in charge of the unit in the absence of his immediate boss who was on sick leave.

Products supplied to this department for further processing, that is freeze drying, are as follows :

3.4.1 Fraction II and Specific Fraction II material from Mr Wesley's unit.

3.4.2 Factor VIII, Fibrinogen and Thrombin from Dr Ellis' unit, and,

3.4.3 Plasma from Dr Singleton's unit.

Plasma for freeze drying are held in cold storage awaiting [illegible]

19/103

availability of the appropriate freeze drying units.

A plan of the department can be seen at APPENDIX 2(b). Vertical freeze drying units, used for albumin and large bottles of fibrinogen and plasma, are housed in the main laboratory; the horizontal Edwards units (K2) are in an adjacent, recently upgraded area, which is supplied with air filtered down to 5 microns. This air is lost via the air-lock. The air lock and another adjacent room have also been upgraded to provide smooth, impervious, easily cleanable surfaces. The latter is to be used to house a small portable freeze dryer not yet on site; in the future fraction II will be dried there, while the former is used for equipment/product and personnel entrance; it is also used to store clothing for use in the area. Clothing used consists of a suitable hood, one piece suit, overshoes, mask and disposable gloves; it is donned in this area, but there are no handwashing facilities. Product taken in through this personnel changing area is poorly protected against potential contamination since vials are not sealed and they are held in trays which have only loose fitting lids.

Cleaning and sterilization procedures undertaken in this area are carried out but the details are not recorded. The Edwards units are sterilized by ethylene oxide using water and ethylene oxide (12% in halocarbon) at ambient temperature; the efficacy of this as a sterilization procedure has not been adequately validated, nor does there seem to be any logic in the choice in frequency of sterilizing the chamber.

Within the main freeze-drying laboratory, a small room designated as the Needling Room, has been built. This is where bottle caps used in freeze-drying are exchanged aseptically for sterilized caps with inserted needles and plugged with cotton wool, to permit nitrogen charging of the head space. On completion of the charging process, done in the vertical freeze-drying units, bottles are returned to the Needling Room where the needles are removed.

Air is supplied to this room from the freeze-drier room via 5 micron filters, only around the time that the room is to be in use. The use of vertical LAF units in this situation as far away from the aseptic manipulation is questionable as there is a high probability of turbulence occurring at bench level and consequent contamination from operators. Clothing used in this area is donned in the freeze-drying room.

19/104

The premises used for loading vials into freeze-driers are not totally satisfactory for aseptic procedures e.g. entry of product and personnel. Adequate validation studies have not been undertaken to verify the adequacy and required frequency of the sterilization procedure currently used on freeze-drying chambers.

Premises, facilities and procedures used for the Needling Operation are totally unsatisfactory.

3.5 Washing and Sterilization of Equipment.

When Mr Smith left the BPL, no person was made responsible for the washing-up and sterilization of equipment, Mr Sharman, Mr Smith's deputy, is temporarily in charge.

Bottles, vials and bungs are washed in rooms 229 and 228, the latter of which adjoins the "sterile filling suite".

Vials are washed and dried in an ACIC machine to a programmed cycle after which they are packed under LAF into trays in which they are sterilized in one of the two hot air sterilizing ovens. These ovens have forced air circulation and at the end of the sterilization cycle cooling air is drawn in through HEPA (0.2 mincron) filter banks. They have been tested to ensure that sterilization temperatures are achieved uniformly throughout the load. Sterilizer charts form part of the production records.

Bungs are washed in a Schuco machine and then transferred into stainless steel baskets in which they are dried in the ACIC machine. Subsequently, they are put into nylon bags - with cotton bungs at their closures - and sterilized by steam. The sterilization procedure has <u>not</u> been validated.

Bottles are transferred in crates from the ante room to 229 to room 228 where they are washed in a Miller-Hydro machine. The washing cycle is as follows, boiling water, hot soda solution, two hot rinses and one cold - all mains - and a final rinse of distilled water. All bottles, vials and bungs have this final distilled water rinse.

19/105

Other components and items of equipment used in production are washed by hand in a general wash-up area, tubing is done in a second ACIC machine. The walls and ceiling of this area are of painted plaster and the floor is of quarry tiles. Ventilation of the area is natural, through open windows.

Assembly and wrapping of items for sterilzation is done in an adjoining room, the fabric finish of which is poor.

Three Manlove autoclaves are used for sterilization procedures, two are of the downward displacement type and one of the high vacuum type. Commissioning of these was done in 1973 and periodically they are challenged with spore strips. Sterilization cycles are normally 20lb./sq" (126°C) for 30 minutes or 60 minutes for the former units, and 134°C for 3 minutes for the latter. The downward displacement units have the facility to pull vacuums at the beginning and end of cycles and these cycles are used to sterilize nylon wrapped items. It has <u>not</u> been shown that items so wrapped have had adequate steam penetration to achieve sterilization.

Sterilized equipment found in a "clean" store designated for this purpose was found to be inadequately wrapped, that is <u>not</u> double wrapped.

INTERIM SUMMARY 6

The fabric of the premises which house the bottle/vial washing operation are reasonably good, with a filtered air supply and LAF cabinet, but the layout could be improved.

The processing and assembly of rubber bungs and cap bodies could be changed to minimise handling.

Hot air sterilizing ovens should have data books in which use and maintenance information can be recorded. One temperature chart should be used per cycle. The Gallenkamp hot air sterilizing oven has no record of commissioning. Suits used during aseptic filling operations are wrapped in this area, but, they are not washed prior to sterilization.

The premises of the general wash-up area are acceptable but those for the wrapping of equipment should be improved. The sterilization efficacy of item

19/10.6

which are wrapped in nylon should be validated. The double wrapping technique for sterilized components and equipment should be adopted.

3.6 Engineering aspects of plant and equipment.

Mr Montgomery, the chief engineer, has working for him one assistant engineer (previously a fitter), 1.5 electricians and one process fitter. He stated that his present staff allocation is totally inadequate.

The general air filtration system in the factory utilizes Microflow GA filters (95% efficient at 5 microns). Brief details of the systems used in different areas follows:

3.6.1 Fractionation Laboratory and Associated Areas.

The upper large scale fractionation room, centritherm room and adjacent areas are supplied with terminally filtered air (95% efficient at 5 microns). However, the ground floor part of the fractionation suite does not have a filtered air supply. Its air is in a total recirculation system without make-up. This situation was difficult to appreciate since some air is lost through extract grills which are fitted with filter material. When the unit is formalized once per year, or, periodically (unspecified) the 5μ filtered air is supplied to the unit to flush out traces of formalin. When this has been completed the inlet is blanked off and the system returned to total recirculation.

3.6.2 Room 207: Wash up area for large pieces of equipment.

This area has a separate heated and filtered air supply (total loss) with pre-filters and terminal GA filters.

3.6.3 Room 230: Initial wash up area and assembly zone for the wrapping of items to be autoclaved.

This area is supplied with air that has been pre-filtered only.

3.6.4 Rooms 228/229: Bottle and vial washing area.

This system supplies air that is pre-filtered at the plant room and is passed through terminal GA filters into the area.

19.1.07

3.6.5 Clean side of Double-Ended Autoclaves.

Air filtration here is through both pre-filters and terminal GAs and is a total loss system.

3.6.6 Final Solution Preparation Room.

Air supplied to this room is both pre-filtered and passed through GA filters.

3.6.7 The Sterile Filling Suite.

The system used in this area was designed by Mr J Furman. Air supplied to the suite is passed through pre-filters, GA filters and finally terminal GAA filters (99.997% efficient at 0.5 microns). Air is ducted back to the plant room via GAA filters placed at extract grills. Blanking off plates used on vents to atmosphere post formalisation of the room are not always adequately sealed.

No tests have been done to validate the effectiveness of the seal between terminal filters and trunking using dioctylphthalate, as evidenced by black streaks at the perimeter of filter housings. No other tests e.g. anemometer or microbiological have been done. Some smoke tests have been performed to determine air flow patterns.

3.6.8 Dr Singleton's Filling Room.

Air supplied to this room is drawn from the general microbiology corridor where filthy aluminium crates were being stored: it is passed through GA filters in the terminal position. The air flow rate from these is $\langle$ 25 cu/ft/min. There is no air supply to the air lock other than that lost naturally from the filling room.

3.6.9 Dr Ellis' Laboratories.

Room CR2 has only partial air filtration which is afforded by the scavenging effect of a Microflow unit (GA) left running in the room. Air within the room is recirculated and conditioned: it is drawn up from the side of the room where the Sharples centrifuges stand and is cooled by passing over cold glycol coils, in wooden ducting, in the

ceiling void and passed back in at the other end of the room. The ducting has never been cleaned out.

The aseptic filling room in laboratory 16 has air supplied through a GA filter: the source of this may be corridor or roof air: apparently little is known of this system.

Laboratory 19 where albumin for the Radiochemical Centre is prepared has no filtered air supply; air is only conditioned.

3.6.10 Edwards Area Air Supply.

This is a separate system used purely to supply this area. Again the air is pre-filtered before passing through GA filters in the duct about 10' removed from the inlets to the room. Feed air is drawn from the corridor adjacent to the changing room.

3.6.11 Needling Room.

The quality of air filtered into this room was not known but was considered to be probably no better than 5 micron: feed air is drawn from the main freeze drying room.

Smoke tests are not routinely carried out to determine the general air flow within rooms: the only exception is the sterile filling suite where these tests were carried out at commissioning of the unit. Settle plates are used to determine microbial levels but a standard procedure applicable throughout BPL did not appear to be applied.

Control and maintenance of LAF work stations is exceptionally weak: that done will not give any assurance that the units are working as designed. Work stations are not on contract maintenance. Particle counts within the units are not determined. Air-flow rate determinations are undertaken, but readings are not taken at discrete points on the filter face, and, no action points have been defined. Mr Montgomery was not sure which class of filters were used in some of the older Microflow units (LAFs) but considered they could have an average porosity of 5μ.

The control exercised over air supply plants, filters etc and LAF units, and, the maintenance of these is totally inadequate for the types of operations carried out at BPL.

The responsibility for autoclave control and maintenance appears to have fallen between two stools. Control tests are not done by the engineers, they are organised by Mr Sharman. Methods used include the Bowie Dick Test, Brown's tubes and spore strips. Validation studies of the effectiveness of these units as sterilizers is ill-defined. Maintenance is breakdown in nature. Although a Planned Preventive Maintenance scheme is being prepared, Mr Montgomery does not have the staff to institute it, therefore maintenance of autoclaves is inadequate.

Hot air sterilizing ovens are multipoint thermo-couple tested by Mr Sharman's staff.

There are no routine inspections of equipment by autoclave and hot air oven manufacturers.

Similarly, control and maintenance over the freeze driers is the responsibility of staff in that department, and not that of the engineers. Mr Montgomery presumed that this was breakdown in nature.

Mistral centrifuges in Dr Ellis' department are in a maintenance contract.

Responsibility for ensuring the satisfactory operation of the Sharples Centrifuges was only recently taken over by Mr Montgomery, after Mr Smith left.

Maintenance and the control of equipment is inadequate and ill-defined. This is a severe deficiency.

14/11D

4. SUMMARY SESSION OF THE VISIT OF 23 - 27 APRIL

A summary session was held at which Dr Lane was the sole representative of the BPL. It was intimated to him that the inspection was carried out along the same lines as those used in pharmaceutical industry. Production only had been examined during this 5 day period of inspection and that a follow-up inspection would be required to cover documentation and laboratories.

Our disagreement with the attitude taken, in certain parts of the laboratory, that as the starting material is contaminated there is little point in the rest of the processing being done under clean conditions, was given. The type of sterile products made on this site should be produced to proven and accepted Good Manufacturing Practices.

In general our findings were that the operations carried out on this site were unsatisfactory from the following points of view:

4.1 Premises.

4.2 Procedures - lack of standardisation and those available incompletely cover operations.

4.3 Equipment and Plant - inadequate control and maintenance.

4.4 Lack of adequate documentation to control the production operation as per the Guide to Good Manufacturing Practice.

4.5 Inadequate Environmental Control - both particulate and microbial.

4.6 Staff Training - none at present.

Examples of these were given to Dr Lane to justify the statements: details of these may be found in the body of this report.

19/11

5. PASTEURISATION OF PPF; INSPECTION AND PACKAGING - MR. SHARMAN

Part of Mr. Sharman's duties include pasteurisation of Plasma Protein Fraction (PPF) and the packaging and despatch of this and all other products manufactured in the Blood Products Laboratory.

5.1 Pasteurisation of PPF

Plasma Protein Fraction is pasteurised by heating for a minimum period of 10 hours at a temperature of $60^{\circ} \pm 0.5^{\circ}C$ in order to inactivate hepatitis virus. The process is carried out in two large, floor mounted, hot air ovens in room 220 which is adjacent to the sterile filling room. The ovens are equipped with circulating fans and were manufactured specially by Westwood Major Ltd.

One batch of PPF occupies both ovens as sub-batches A and B.

There are three compartments in the body of the ovens, each of which takes two stacks of filled bottles in metal crates. Hot air from the fan compartment circulates via the airduct in the base of the oven and is forced upwards by baffles into the bottle compartments.

Temperatures are monitored by six probes and recorded on Cambridge temperature chart recorders. The probes are situated:-

in a bottle in the lower airduct
in the free air space in the lower airduct
left, front, top of the load
left rear top of the load
right front top of the load
right rear top of the load

The ovens were said to be commissioned in 1974 by Mr. Vallet and Mr. Montgomery and that temperatures at all points were within $\pm 0.5^{\circ}C$. They have not been re-commissioned since then but the probes are checked every month against a National Physical Laboratory (NPL) certified thermometer in a thermostatically controlled water bath.

Maximum reading thermometers are also placed in the front, top, left and right positions during each production load and the temperatures are noted on the Cambridge charts.

The door seal gaskets were in an extremely poor condition and the inspectors were worried that cold air could be sucked in and lower the oven temperature. This was said not to occur as the temperature throughout was maintained at $\pm$ 0.5°C. Inspectors were also worried that the temperature might be affected by a reduction in air velocity through failure of the fan but if this did happen then the heating up period would be unduly long and would be seen by Mr. Sharman when checking the records.

The ovens were not maintained on a planned preventive basis but the Cambridge recorders were serviced every two months by the supplier. Consideration should be given to servicing the ovens on a regular basis and at least twice yearly. More documented control is also needed over this critical stage of manufacture where hepatitis virus is inactivated.

5.2 PPF Incubation

After pasteurisation the bottles are transferred to the Incubation Room (1.07) and stored at a temperature of 32° $\pm$ 2°C for from 10 to 14 days. This room is heated by two fan heaters, placed high up on opposite walls; and circulation of the air is assisted by an auxiliary fan on the floor. The fan heaters are controlled by thermostats and the room temperature sensed from a point near the door and recorded on a chart.

From the positioning of the fan heaters there is a good possibility of localised overheating on some stacks of bottles and airflow patterns could fluctuate according to the number and positioning of the stacks and positioning of the floor fan.

As the room is completely full with one week's production additional space is required

19/113

After the requisite storage period at 32°C the bottles. which have been inverted during this period, are inspected for leakage and bacterial growth, and acceptable bottles are then transferred next door for a further three weeks storage at ambient temperature.

Each bottle is labelled with a batch number and whether pasteurised in the A or B oven.

As with the 32°C quarantine store extra space is likewise needed in the ambient store.

From the ambient store the P.P.F is removed to room 1.11 for inspection and packaging.

5.3 Inspection and Packaging

Inspection and packaging of all products is carried out in room 1.11. This is a T-shaped room with laboratory benches along the walls in the leg of the T, a bench along the end wall of one arm to serve as a despatch area, and in the opposite arm two labelling machines and a cartonning machine.

The room is well lighted with natural and artificial light but is an open-plan area which is not segregated or partitioned in any way for the various packaging operations.

Only one product at a time was said to be dealt with in the room, but two products were on the benches at the time of our visit although this was probably due to Mr Sharman being called away to assist us in the inspection. In any case it is standard procedure to inspect and package part of a batch of P.P.F in the morning, switch to a different product in the afternoon, and then subsequently to continue with the batch of P.P.F! This was said to reduce fatigue and improve inspection efficiency. Staff employed on inspection are not given eye sight tests including those for colour blindness.

P.P.F is inspected under polarised light (ALLAN viewers) for fibres, and for precipitation and other particles by swirling the bottles, shining a

19/114

light upwards through the base and viewing against a black background. Defects are classified and recorded but the operators do not have check lists of defects for specific products to which they can refer.

P.P.F is labelled on an EEC Autolabeller which is continuously set up for this product with the labels in position. The rationale for this was that no other product would be labelled on the machine. Inspectors pointed out, however, the problem of labels not being controlled in a secure manner and the possibility of bottles being coded with labels from previous batch runs.

The second labelling machine was a 'WHITEHALL MACHINERY LABELLER' which was also set up but for labelling anti-D Gammaglobulin. A fault had developed and the firm's engineer had been called for to examine it, but the labels had been left on the machine. This indicates a lack of discipline and inadequate control of the labelling operation.

The Vial cartonner was a BOSCH, HOFLIGER and KARG machine.

Inspection and labelling of P.P.F constitutes the major workload but the area was not laid out to facilitate a continuous flow of work or to prevent a crossover of product at the various stages. Other smaller product batches were inspected and labelled on the static benches.

The packaging operation for P.P.F was inspected as being representative of the handling of products generally. Although there was a packaging record it was insufficiently detailed and omitted some important aspects of the packaging operation, e.g line clearance checks prior to starting the operation.

Dried Human Plasma was being labelled during the afternoon of our visit and the labels were being batch coded in manuscript from a production record sheet. There were no written procedures for the operation and although there was said to be a system of cross checking it was not apparent to us and checks were not recorded.

Opening from the packaging room were ancillary rooms for the storage of transit cartons, storage of labels and printed packaging materials, finished goods and despatch.

19/115

5.4 Transit Cartons Store (room 1.13) and Labels Store

This room is used for storing and making up cardboard transit cartons, but, due to severe shortage of space in the packaging area generally, was also used for storage of packed stock, inspected stocks and non-inspected material. In fact it appeared to be a general storeroom. Drains run through the room at ceiling level and up to two months ago had been troublesome due to leaking but have now been repaired.

One corner of the room is caged off to provide a secure, locked area for printed labels printed cartons and leaflets. There were no written specifications for any of these materials and the only quality control checks were those carried out infrequently by Mr Sharman.

5.5 Final Products Ambient Store (Room 1.12)

This room has a floor area of approximately 144 sq feet and is totally inadequate for the purpose as only remnants of packed stocks are generally held here for supplying small orders on demand. P.P.F and Freeze Dried Plasma are stored in the D.H.S.S Store at Bristol and the packed product is despatched from Elstree weekly. Packaged stocks, prior to despatch to Bristol, are stored mainly in the corridors for lack of other storage space.

South East London and Wessex Regional Transfusion Centres take 200 and 100 bottles respectively of P.P.F per month made up from all batches produced in that period and these are used routinely on patients to test for any adverse reactions. These consignments are made up prior to despatch of the remainder to Bristol and are held in the Final Products Store.

Although it is an 'approved products' store it also contained :

Fibrinogen labelled as "not checked"
Fibrinogen labelled as "checked and sorted" and hence visually inspected only.
Time - expired albumin
Time - expired serum
Time - expired P.P.F.

19/116

Appropriate storage, other than in an approved products store, is needed for such materials.

5.6 Quarantine Stores (Rooms 1.09 and 1.10)

These two rooms, immediately outside the entrance to the packaging room, are in fact one room which has been divided almost to ceiling height by a wire grid. The rooms are maintained at +4°C and the temperature recorded on a CAMBRIDGE chart recorder which is checked daily and the chart changed weekly.

Normal and convalescent gamma globulins are quarantined in wooden trays with metal lids secured by crimped metal tags. Each tray is tag labelled with the contents and batch number and whether inspected or not. Inspected material is sealed again in the same way as non-inspected material until it is labelled. After labelling, the product is packed in fibreboard transit cartons and banded with plastic strapping.

Room 1.09 is the quarantine store and room 1.10 the released materials store, but material is only released against specific batch numbers so it is not possible to issue non-released material.

Rejected material was found in the quarantine store, and should either be returned direct to the production departments or held in a secure box labelled "REJECTED" until the entire consignment has been inspected.

As with other rooms there is a serious shortage of storage space.

5.7 Small Orders Despatch Section

Small orders are made up for despatch on a bench at one end of the packaging room (1.11).

There is a record book for each product which shows quantities produced and issued on specific dates, with a batch reconciliation carried out when batches are expended. The only exception to this was for Fibrin which is stored in a refrigerator in room 1.13 and which is not reconciled on a batch basis.

5.8 Complaints

Mr Sharman said that complaints were never received but if there were any that required recall then this could be undertaken immediately as the destinations of all batches were recorded. It was later suggested to us that complaints would be dealt with by Dr Lane but we did not have a chance to question him on this.

INTERIM SUMMARY 9

A better documented control is required over the pasteurisation process which is a critical stage of manufacture in which hepatitis virus is inactivated. Planned preventive maintenance of the operation is also required instead of breakdown maintenance.

It was very apparent that quarantine storage and despatch areas were far too small for the volume of production and this resulted in some otherareas being used for purposes for which they were not intended and for corridors to be used for storage.

The temperature distribution in quarantine areas was suspect due to the positioning of fan heaters, variable stacking within the rooms and variations in the airflow patterns.

Printed packaging materials i.e labels, cartons and leaflets were not defined in written specifications and were not quarantined on receipt or adequately quality controlled.

Packaging operations were not defined by written procedures, were not organised in such a way as to prevent cross flow of products and various key procedures in the operations were not recorded.

Labels were left on machines in a non-secure manner.

All packaged stocks were not held in a quarantine store until the documents and records were checked and the products released by an appropriate person delegated for the task.

19/11/8

6. ANALYTICAL LABORATORIES

The analytical laboratories are in charge of Mr Greulich who in turn reports to Mr Vallet.

Staffing of the laboratories is as follows:

6.1 Quality Control Chemist:
Mr Greulich, B.Sc (Chemistry), M.Sc (Analytical Chemistry)

He has been with the Blood Products Laboratory for about ten years, having started as a junior technician.

6.2. Deputy Quality Control Chemist.
Mr R Brunsden, H.N.C (Chemistry), L.R.I.C (Analytical Chemistry)

Has been with the Laboratory since January 1979 and was previously at Bedford College, University of London.

6.3 Mr N Croad, H.N.C. (applied biology)

Responsible for elemental analysis of intermediate and finished products

6.4 Mr D Morris, Medical Laboratory Technician.

Seconded from production on a temporary basis to assist Mr Brunsden on gel filtration assays, electrophoresis, nephelometry, ethanol determinations and testing of raw materials.

There is a complement for a junior technician but there has been no success in filling the post.

Laboratory staff are responsible for taking their own samples of in-coming raw materials which are quarantined in the stores and notification of their receipt is by telephone. Analytical staff do not receive copies of purchase orders or delivery notes so do not know what consignments to expect.

The laboratory staff apply the quarantine labels to the containers.

Samples are taken into washed 50 ml. plastics universal containers for solids and glass screw-capped production bottles for liquids.

The sampling equipment is kept in the laboratory.

All containers are sampled and the contents identified and a full analysis done on a blended sample of up to five containers.

Consignments are sampled in the stores, which are overcrowded; methanol is sampled in the inflammables store and ethanol from tanker deliveries is sampled by the worker who supervises the delivery.

There are only about 18 chemical raw materials and these are purchased from approved suppliers on the basis of satisfactory performance over the years. The main suppliers are British Drug Houses and Hopkin Williams.

All chemicals have recently been given an expiry date of one or two years before re-testing. Most chemicals have written specifications prepared by Mr Greulich, but they were not dated or signed as being approved. All these specifications are to be re-written as time permits and they will then be dated and include analytical procedures.

Packaging components i.e. bottles, vials, closures, labels, cartons etc. are purchased either from D.H.S.S or from industry but in either case there are no specifications. no sampling and no testing.

Mr Greulich has recently started to date stamp outer containers of packaging components for stock rotation purposes. Printed cartons are given a life of one year 400 ml P.P.F bottles three years and 540 ml plasma bottles five years. There is no scientific basis for the periods chosen which corresponded only with the stock holdings at that time. In any case, bottles received from D.H.S.S. could already have been in store for an indeterminate period of time.

19/12

Analytical work is shared between two sections responsible for physical and biochemical testing respectively. Each laboratory maintains a register for booking in samples and progressing the tests. The test results are checked in one laboratory by Mr Brunsden or Mr Greulich and in the other by Mr Croad and then transcribed on to analytical data sheets. The sheets are checked and signed by Mr Greulich, who also comments on the results, approved and initialled by Mr Vallet and then submitted to the production departments.

Mr Greulich has no involvement in microbiology and the production departments collate all their own test results.

Analytical calculations are worked out on pieces of paper which are subsequently destroyed when the results are transcribed into record books for each test procedure. We suggested the use of personal laboratory note books and for all calculations to be seen and checked by Mr Greulich at regular intervals and the books signed and dated by him.

On checking through the raw materials specifications we discovered that those for aluminium hydroxide, water, ethanol and methanol have still to be written up.

Analytical results were invariably recorded by means of ticks as an indication of compliance whereas it would be more meaningful to record actual results. An analytical result for TRIS was reported as >99.8% against a required standard of 99.8% ; this again was unsatisfactory and the actual result should have been recorded.

The analytical suite comprises four separate laboratories in rooms 6, 6A, 5 and 1B.

Room 6 is the general laboratory which is used also for gel filtration determinations using three U.V Absorptiometers and associated columns manufactured by L.K.B.

Standard solutions were said to be made up freshly as required except those in regular use which would be used up within one week of preparation. Some solutions which should have been discarded had been retained and were undated. It was agreed that such solutions would either be dated with a shelf life or discarded after use.

Standard solutions made up from commercial concentrates are checked approximately every three weeks against other standard solutions for correctness of factorisation.

Room 6A - Instrumental Laboratory.

The instruments included the following:
Zone Electrophoresis by SHANDON
PYE UNICAM SP 1800 U.V. SPECTROPHOTOMETER
Water Bath.
AMINCO NEPHELOMETER
HILGER and WATTS U.V. Spectrophotometer for protein determinations.
RELEAS-O-MATIC Single Pan Balance.
Refrigerator.
METTLER Top Pan Balance.
GELMAN Electrophoresis Scanner for Slider.
JOYCE LOBEL Electrophoresis Scanner for Slider.
Moving boundary electrophoresis apparatus.

All equipment is serviced on twice yearly contracts with the manufacturers. Details are retained by the administrator Mr Bailey.

Volumetric glassware is washed in the laboratory, dried in a drying cabinet and stored in a cupboard.

Room 5 - Biochemistry Laboratory.

Equipment included:
KJELTEC System 1003 Distilling Unit.
TECHNICON, Heating Block, 40 unit.
BAIRD Atomic Absorption Spectrophotometer, A 3600.
pH Meter.
EIL 705 S pH Meter.

Room 1b

Contained:
PERKIN ELMER F17 Gas Chromatograph.
M.S.E Superspeed 75 Centrifuge
M.S.E Highspeed 18 Centrifuge
Melting Point Apparatus.

19/122

INTERIM SUMMARY 10

Not all chemical raw materials were defined in written specifications and some were insufficiently detailed.

There were no specifications for packaging components and the laboratory staff were not involved in quality controlling such materials.

Analytical calculations should be made in personal laboratory work books and not on pieces of paper which are destroyed. Work books should be checked regularly and signed by Mr Greulich.

It was apparent that the laboratory was inadequately staffed to undertake all the necessary analytical work, staff were transient and there was much dissatisfaction due to a lack of definition from top mangement of their job responsibilities.

The laboratories provide a service on demand from production departments but are insufficiently involved in the initiation of a comprehensive quality assurance system.

Some improvement in the recording of test results, e.g by giving the actual results, and improvement in the format of test reports, e.g by noting acceptable tolerance limits on reports is needed.

19/1.23

7. DOCUMENTATION AND FINAL PRODUCT RELEASE

Analytical and production records were examined for the three main production departments, i.e. Large Fractionation and Final Solutions Laboratories, Coagulation Factors Laboratory and Freeze-Dried Plasma Laboratory. The heads of these departments are Mr. Wesley, Dr. Ellis and Dr. Singleton respectively. As Dr. Ellis and his chief technician were attending a symposium we discussed the documents with Mr. Williams the senior technician.

To evaluate the systems in the three departments we examined the records of one batch each of Plasma Protein Fraction, Freeze-dried Antihaemaphilic Fraction (Factor VIII) and Freeze-dried Small (10 donor) Pool Plasma.

7.1 Plasma Protein Fraction Documentation - Mr. Wesley

As there is no single plasma pool throughout the operation we had to check the fractionation records of all those plasma pools taken to produce a specific batch of PPF (Fraction V).

The following points were noted and discussed:-

7.1.1 Quantities were in litres and although this was obvious to the staff the denomination was not shown on the production record.

7.1.2 Details crossed out and amended were not signed by the operators or any reason given for the amendments.

7.1.3 Plasma volumes in the production vessels are measured by hydrostatic pressure but this was not obvious from the records.

7.1.4 The 5-litre packs of frozen time-expired plasma are tested at the Regional Transfusion Centres and supplied as hepatitis negative. Except for supplies from North London (Edgware) and Brentwood Regional Transfusion Centres all other material is re-tested for Australian antigen at the Blood Products Laboratory by Mr. Combridge.

7.1.5 Packs reported as hepatitis negative by the Regional Centres could be found subsequently to be hepatitis positive.

7.1.6 In some cases a sample sachet is not supplied with the bulk material or else the sample is not available for Mr. Combridge to carry out an Australian antigen test. In such a case the plasma is used as part of the plasma pool on the argument that the PPF solution is pasteurised to inactivate any hepatitis virus that might be present.

7.1.7 Sterility testing of time-expired plasma, when first introduced, was not to protect the patient but to provide an indication of the quality of material supplied from the Transfusion Centres. The policy was to test 1 in 10 packs only.

Now all plasma is tested for the presence of micro-organisms except where there is insufficient sample in the sachet or the sachet is missing.

[5-litre packs of fresh frozen plasma for factor VIII are not tested for the presence of micro-organisms.]

7.1.8 The production records showed that about 3 out of 40 packs were infected and not used, 16 out of 40 batches had no samples for testing and hence could have been infected but were used in the pool.

7.1.9 It is not possible to achieve proper stock rotation of the frozen plasma because the -25°C cold rooms are severely congested and it is thus impossible to use the oldest plasma first. Some plasma is also stored in commercial cold stores under contract and there is no indication of when it will be returned for processing.

There is no upper limit for the storage of this plasma and we were told that it has been successfully fractionated up to five years old.

19/125

7.1.10 Part of the plasma pool is made up of factor VIII supernatant from Dr. Ellis's laboratory and from the Fractionation Laboratory at Oxford.

7.1.11 Mr. Wesley takes a sample of plasma from the bulk pool for a microbiological count but the result is known only in retrospect after the pool has been fractionated.

Although the material initially brought from Oxford was highly contaminated its quality is now much improved.

7.1.12 The 5-litre packs of plasma used in the Coagulation Factors pools are often not tested for micro-organisms as Dr. Singleton cannot cope with the work load. However, all this material is tested for Australian antigen either by Mr. Combridge or the North London and Brentwood Regional Transfusion Centres.

7.1.13 In-process testing comprises:-

7.1.13.1 Pool from 5-litre packs of time-expired plasma is sampled for microbial counts.

7.1.13.2 Pool of supernatant plasma from Dr. Ellis is sampled for microbial counts.

7.1.13.3 The combined plasma pool is sampled for microbial counts but the organisms are not typed.

7.1.13.4 The combined plasma pool is sampled and tested for Australian antigen.

7.1.13.5 Retention samples of the plasma pool are taken and kept at $-35^{\circ}C$.

7.1.14 Results of calculations are recorded on the production sheets but not the actual calculations. These should be shown together with an indication that they have been checked and by whom.

19/126

7.1.15 Alcohol used in production is not tested for micro-organisms and neither are any of the reagents.

7.1.16 There is no routine maintenance of production equipment such as stirrers and centritherms.

7.1.17 From the analytical records it was difficult to decide whether Mr. Vallet or Mr. Greulich was in charge of the analytical laboratory as some test certificates were signed by one and some by the other. Staff were also uncertain of this point and had some difficulty in knowing with whom to deal.

7.1.18 Tolerance limits for e.g. pH ranges are not stated.

7.1.19 Solutions for concentration in the Centritherm could have microbial counts of 50 per ml prior to concentration and the same count after concentration. This appeared to be somewhat odd as higher counts would be expected on the concentrate.

7.1.20 Diluted solutions for bottling can also have microbial counts of 50 per ml and more. There is no upper acceptable limit and levels as high as 10^4 per ml are known; even at this level the final product was said not to be pyrogenic.

7.1.21 Batch numbers of the reagents used in production were not recorded on the batch production records.

7.1.22 Material rejected for particulate contamination was re-claimed by including in subsequent plasma pools.

7.1.23 Sterilised equipment used in the production process e.g. tubing, filters, vessels, caps etc is autoclaved as mixed loads which may be used in different production batches. It is therefore not possible to provide a temperature recorder chart with each production record and so pieces of sterilisation tape from the sterilised packs were attached to the records. As this is not necessarily indicative of a satisfactory sterilisation cycle either

photocopies of the charts should be attached or a statement included on the production record that the chart has been examined by a nominated person and is satisfactory.

7.1.24 Where repeat testing is carried out the reason for so doing should be stated on the records.

Before a batch of P.P.F is released, Mr Wesley collates the various production and test records and prepares a summary of the important parameters which he signs and submits to Dr Lane for his approval and signature of release. This is a good system.

The production documentation for P.P.F Solution was comprehensive and could with some relatively easy modifications be regarded as satisfactory. Shortcomings were the lack of adequate packaging information as mentioned previously under that section and inadequate environmental monitoring.

The preparation of a batch summary sheet is to be commended and likewise the fact that Dr Lane acts as quality controller in releasing the product.

We did not have time to examine other products for which Mr Wesley is responsible but we trust that the documentation for P.P.F is typical of his entire range.

7.2 Freeze-Dried Antihaemaphilic Fraction (Factor VIII) - Mr Williams.

The starting material is fresh frozen plasma supplied in 5-litre plastic packs.

When a delivery arrives at the Blood Products Laboratory the stores staff notify production by telephone and within half an hour the consignment is stored in the $-25^{\circ}C$ cold room.

Consignments are checked against the delivery sheets for damaged packs and correct labelling of packs and outer protective cartons. However, when damage occurs, the damaged packs are not always segregated from good stock.

There is no uniformity in the supply of sample sachets as some Regional Transfusion Centres leave them attached to the main packs, others separate them from the packs but supply them in the cartons with the packs, others pack the sachets all together in a separate container. Some Transfusion Centres have a higher damage rate of sample sachets than others and this often accounts for insufficient samples for testing. Standardisation of the method of supplying sample sachets should be considered.

The packs and sample sachets are labelled with specific batch numbers which are also imprinted into the plastics material. These details are transcribed from the consignment sheet into receipt books for each Regional Transfusion Centre. The reason for individual books was said to be to enable material from individual Regional Transfusion Centres to be processed separately, but this could also be achieved by recording the details on production record sheets.

Mr Combridge notifies the results of hepatitis testing by means of a hand written list and occasionally reports the absence of samples for testing. As batches are checked before sending to the hepatitis testing laboratory it is odd that some samples are missing. Mr Williams explained this by saying that he could not rely on his staff to do the job properly. The samples are occasionally found subsequently, but if not then a core sample is taken from the main pack. This is done in the open laboratory using a separate sterile sampling tool for each pack; there is a possibility though of contaminating the pack.

Material from Regional Transfusion Centres North London and Brentwood is hepatitis tested at these Centres and not re-tested at Elstree. All other fresh frozen plasma for Factor VIII is tested at Elstree by Mr Combridge who uses a modified method of the ABBOTT radio-immunoassay test.

No microbial counts are made on the samples except those from Regional Transfusion Centres Cardiff and Cambridge. The aim originally was to test material from all Centres but Dr Singleton could not cope with the work-load under nine weeks and storage of 5-litre packs then became a problem. As the Cardiff and Cambridge plasma was contaminated with large numbers of G negative organisms it was decided to keep a check on material from these two Centres. The quality is now said to have improved.

19,129

The manufacturing record sheets need to be revised as follows:

7.2.1 To provide space for recording the checking of batches on selection in the cold room and again when used in production.

7.2.2 The manufacturing record could with advantage be standardised with that for Large Fractionation material.

7.2.3 The pH of the cryo-supernatant is currently recorded in a laboratory notebook whereas this and other manufacturing parameters should be recorded on the manufacturing record.

7.2.4 Sterilising filters are not pressure tested as there is no convenient pressure lines, although this matter is being considered.

7.2.5 All sterilised equipment used in processing must be proved as such by a copy of the temperature chart record or by a statement in the production record that the process was checked and correct.

7.2.6 Positive action is not taken on settle plate results which indicate high numbers of micro-organisms.

7.2.7 When an analytical result is out of specification it is repeated once only even if the two results are widely different, e.g solution times of AHF were 36 minutes and 12.5 minutes. Duplicate results should not be relied on but done in triplicate.

7.2.8 The manufacturing record has been condensed into too small a space; procedures should be more specific e.g equipment such as stirrers should be clearly defined and quantities which are estimated should be clearly recorded as such.

7.2.9 There should be space on the record to show that it has been checked, and by whom, as the record goes from Mr Williams via Mr Pettet to Dr Ellis and is not signed by any of them until the batch us released by Dr Ellis.

7.2.10 Mr Pettet checks the test results and transcribes them into a book in order to compare trends but there should also be a summary sheet showing results against specification limits. There would be merit in having a standardised procedure on the format developed by Mr Wesley for P.P.F.

19/130

7.2.11 Responsibility for final release of products from the Clotting Factors Laboratory should also be standardised in line with Large Fractionation material.

7.3 Freeze-Dried Small Pool Plasma - Dr Singleton.

Documentation for this product was again different from that in the other two manufacturing departments. Being one of the oldest established products the documentation has developed in an ad-hoc fashion over the years and no thought appears to have been given to changing the system. In fact there was resistance to change from some of the staff.

Processing and testing details are recorded mainly in a series of production books but also on official record sheets and odd pieces of paper.

Much important information vital to an aseptic manufacturing procedure e.g. the cleaning of processing areas, environmental monitoring, medical checks on staff (known carriers have been used in production), records of sterilisation of equipment, was absent or the data not even collected.

After the freeze drying stage the bottles are released to Mr Sharman for packaging and Dr Singleton does not see the packaging record and has no say in the operation. Dr Singleton said there was no signed release of the product or scrutiny of the entire documentation but that batches "just left the building".

INTERIM SUMMARY 11

Documentation and records in use in the three major manufacturing areas were all different in format and comprehensiveness; and if any thought had been given to standardisation it was not apparent.

The records in the Large Fractionation Laboratory are the best and with minor modifications would result in an acceptable system whereas the records for Freeze Dried Plasma are totally inadequate.

19/121

The the three manufacturing departments appear to operate as entirely separate units with little interchange between them and no overall management at top level.

There is no standardised system for the appraisal of manufacturing and testing records or for the final release of products; Dr Lane releases products from the Large Fractionation Laboratory and Dr Ellis from the Clotting Factors Laboratory, but the release of Freeze Dried Plasma is a grey area in which no one person has overall responsibility for release.

GRO-C

DR. J PURVES
Medicines Inspector

MR. J FLINT
Principal Medicines Inspector

25 JULY 1979

19/132