VISIT TO THE GLASGOW AND WEST OF SCOTLAND BLOOD TRANSFUSION SERVICE, W HOSPITAL, CARLUKE

Dates: 8-9 March 1982 - Inspection

10 March 1982 - Summary

Inspectors: Mr D R S Warburton
Mr D Haythornthwaite

Personnel seen: Dr R Mitchell - Regional Director
Dr R Crawford - Consultant
Dr Hopkins - Consultant
Mr W Muir - PMLSO (Responsible for Manufacturing)
Mr A Barr - SCMLSO (Responsible for Quality Control)
Mr Leitch - SCMLSO (Reagents)

Dr A T B Moir - SHHD (Summary)

A. INTRODUCTION AND BACKGROUND INFORMATION

1. The Manufacturer's Licence for this site expired on 30 June 1981.

2. A previous inspection was carried out on 17 January 1980 by Mr Flint and Dr Purves. The inspection on that date was restricted to the manufacture of Freeze Dried Plasma and the facilities for Rabbit Pyrogen Testing. An informal visit was paid by Mr D Haythornthwaite on 16 July 1981 to discuss standards for facilities.

3. It has to be said that the Preparation Area for bottles and closures which was criticised on the previous informal visit was substantially worse at the time of this inspection. This seems to be due to circumstances beyond the control of the Transfusion Centre Staff and has been caused by the uncertain future of the Freeze Dry facility. It is however understood that the purchase of a new autoclave has gone ahead.

4. This visit was restricted to the manufacturing activities conducted at the Centre along with the Quality Control activities. No donor services were visited and activities at the Glasgow St Vincent Street Donor Centre were also not seen on this occasion.

5. Serious attention was also not given to the Serology Laboratory practices and their reagent preparation (including those from an animal source).

6. Amendments to the list of preparations included the deletion of the manufacture of sorbitol glycerol, sorbitol saline and saline (all obtained from the PFC, Liberton). Additions included leucocyte poor blood and an aseptically prepared solution used for the preparation of the freeze dried cryo precipitate. Laboratory grade saline is also prepared. The capability of producing pyrogen free distilled water is required.

7. With regard to the other deficiencies noted in the previous inspection, staff are to be commended for their efforts in implementing changes where it is under their control. A good start has been made on the production of Standard Operating Procedures.

8. Much of the direct responsibility for the daily success of the Centre falls to Mr Muir and Mr Barr who produce under far from ideal conditions. The question of just what is their responsibility should contaminated material be produced which causes a patient hazard needs considering. For example, whilst they may well have stuck faithfully to a standard operating procedure factors outside their control and due to the poorly controlled environment at the facility may cause unforeseen (and non. detected) contamination.

9. The region is largely self-sufficient in terms of procurement of source material. In addition, they do not supply processed materials to sources outside the region (other than Freeze Dried Plasma).

10. This situation might alter (eg in an emergency) or should strategic supplies be processed here.

11. The method of plasma pooling at this Centre consists of stripping and pooling fresh frozen plasma into polythene bags which are subsequently sealed and held at -30°C until transport is available for shipment to PFC.

12. This method does expose the plasma to an open process which is not normally done in other Centres. However, it is understood that this is the only way in which 22 tons of plasma per year can be processed and in-process monitoring results appear to show no contamination problem of any significance.

13. Whether this has any bearing on the pyrogen test results seen in refrigerator room C is debatable but it would certainly be worthwhile comparing the data generated by the different Centres and the PFC to see if any trends do emerge.

B. FACILITIES FOR THE STORAGE AND PROCESSING OF BLOOD

Basement ambient temperature storage area

14. This area is very overcrowded and contains packaging material as well as finished product (eg stocks of freeze dried plasma).

15. In addition a number of activities occur here including printing, laundry of clean room clothing and the disposal of out of date stock.

16. The area contains extensive electrical switch gear as well as many pipes (some of which drip due to either leaks or condensation). Not only is it therefore hot, dirty and difficult to maintain in a clean manner but the problem of water aggravates the problem.

Remedial action recommended:

17. It was agreed that certain procedural improvements could be made with regard to:-

status labelling of cages containing material (status label more secure within the locked cages);

security and reconciliation of labels could be improved.

18. The Centre needs separate, secure and dry storage areas and activities such as laundering should themselves be housed in a controlled environment. Printing is an important activity and relegating it to the basement may encourage a careless attitude to develop. That is not to imply that staff seen behaved irresponsibly merely an observation of the risks that can result.

[redacted]

Other items discussed in this basement area and vicinity

19. Donor pack preparation is carried out in a corridor as there is insufficient accommodation elsewhere (alternative premises may become available soon).

20. The use of a single standard for determining the appropriate haematocrit of both male and female donors.

21. The use of standard MRC intravenous containers for holding liquids other than those intended for human injection is a potentially hazardous one. For example, solutions containing 95% alcohol and 1% glycerol were seen. It is understood that other solutions or tail ends of processes may be similarly bottled.

22. The disposal of out of date products and used copper sulphate vials containing blood is "down the drain". Perhaps untested materials would be better subjected to sanitation process at the time of discard.

23. Red cells, stored above liquid nitrogen, may be kept for an indefinite period. The need for a definite expiry date was considered unnecessary by Centre Staff.

24. It was noted that supplies of liquid nitrogen were received without an accompanying certificate of analysis. This is probably unimportant for its use as a cryo preservative. White spot nitrogen gas in bottles is used to replace oxygen in the air space above freeze dried products and this should have been certified.

Refrigerated storage

25. Room C, the quarantine room refrigerator, is overcrowded. Whilst it is accepted that it is alarmed and charted where temperature control is concerned such overcrowding can lead to product taking some time to equilibrate as well as leading to incorrect stock rotation. (This applied particularly to stocks of Factor VIII stored here.)

26. It was also noted that one batch of Factor VIII had a pyrogen aggregate of 4.4 on 6 rabbits which is marginally outside the BP 1980 limit. Source plasma used for this product may not have originated in the West of Scotland.

27. Outdated and blood labelled as "contaminated" were seen. It is preferable to store such material in a more secure manner.

Room A, the issue room refrigerator is also overcrowded and contains both quarantined and passed material. The lack of enough +4°C refrigerated storage has led to this poor practice which has been compounded by a type of "negative clearance" on a day's blood packs. That is the technician who physically transfers blood from the quarantine status (on the floor) to the finished product area (on the shelves) does so at a certain time each day and without being notified of a formal clearance from the Hepatitis Testing Laboratory. This procedure should be made more sound by, for example, caging uncleared blood in the refrigerator space which is inadequate at the present time and would require substantial additional space being made available.

29. Stock in this refrigerator was additionally subjected to contradictory labels and it was agreed that this would cease immediately (eg shelves marked O Rh Positive contained AB Rh Positive blood).

30. Cold Room E. The -30°C room refrigerator, was also examined. The desirability of having adequate refrigeration at -40°C (rather than -30°C) was discussed, but no firm conclusion was arrived at.

31. +4 C Zopaz refrigerators. These are housed in the basement and are used for holding single packs of whole blood. These quarantine refrigerators are cleared daily and have chart recorders for temperature attached.

32. Handling of returned blood. This is normally used for plasma processing. Occasionally the blood may be re-issued if appropriate documentation is received indicating the material has been properly stored.

Processing Areas

33. In the time available it was impossible to see all processes carried out. Of those seen no attempt was made to evaluate the activity other than to note which processes were being done in the "aseptic" area and those being done elsewhere. Copies of Standard Operating Procedures have been obtained so a future visit to examine process details would be relatively easier.

34. Processing areas are spread out which means a straightforward flow pattern is unattainable. In addition rooms tend to be off a central corridor usually with direct access to this corridor. This not only allows unrestricted personnel access but means material entry and exit potentially contaminates controlled environments because of the absence of air locks and suitable clean down procedures. Rooms also tend to be multi-purpose in use which is undesirable but unavoidable under the circumstances. The close proximity of rooms containing potential pathogens (eg hepatitis virus and the organisms for nutritive testing of media) and the clean and processing areas might be a hazard if systems break down.

35. Closed system preparations

Platelets
Plasma separation
Buffy coats) in single units
Cryo precipitate)
Cryo free plasma
Red cell concentrates

36. Aseptic preparations

Pools of .... platelets)
..... leucocytes) often considered to be
.... cryo precipitate) a clinical procedure

.... dried plasma
.... dried cryo precipitate

Recovered and washed red cells.

Glycine buffer (used in the preparation of dried cryo precipitate)

Pooling of fresh frozen plasma.

Preparation of transfer factor.

Descriptions and main deficiencies of the Processing Areas visited

37. The Preparation Area (the "kitchen")

38. This was an area given as a priority for upgrading in the previous inspection. Discussions on suitable changes have already been held and it is very surprising to find this area in such a dilapidated condition. /Broken floor tiles, wall cracking, rotting window ledges, opening windows, untreated ceiling, direct access from the corridor, inadequate ventilation, disconnected equipment./

39. It is understood that the reason for the lack of progress has been caused by the uncertainty over the future of the freeze drier activities. However, the Centre will still require a suitable preparation area so it is difficult to understand the absence of any progress.

40. Essentially the area needs urgent upgrading as per the existing agreed plans without further delay.

41. A small number of detailed queries were asked which will no doubt be resolved without difficulty. These include:-

- separate and independent temperature gauge (on the autoclave)
- steam filtration/cleaning (steam to the stills)
- distilled water filtration (to the bottle washing machine)
- need for an air break on the drain of the bottle washing machine.

42. It is understood that a new autoclave (2 cycle ex Dent and Hellyer) will be installed shortly the detailed commissioning and validation would be done by Mr Grant of CSA. The need for planned preventative maintenance according to agreed schedules (eg HTM10) would also be achieved.

43. It was suggested that the routine use of thermo resistant spores on every cycle was unnecessary for the new autoclave providing adequate physical monitoring could be done.

The "Aseptic" Processing Room

44. Two "Aseptic" processing rooms are available separated by a central room which has been turned into a changing lobby. The previous door giving direct access to the uncontrolled environment of the central corridor has been closed off.

45. The rooms themselves fall short of being satisfactory aseptic areas for the following sorts of reasons:-

Absence of terminally fitted HEPA filters.

Uncontrolled access of staff.

Uncontrolled access of materials and absence of appropriate air locks and hatches.

Dust traps (eg hanging lights)

Absence of manometers/alarms on ventilation systems.

Rooms are multi-use (ie different activities are carried out at the same time which means a relatively higher number of staff in the area than may otherwise be necessary).

Staff do not wear full aseptic type clothing.

Changing rooms are inadequate.

Sinks are present (though it is accepted that these are necessary for washing away spillages. However, improvements could be made such as incorporating an air break as well as using heated drain traps).

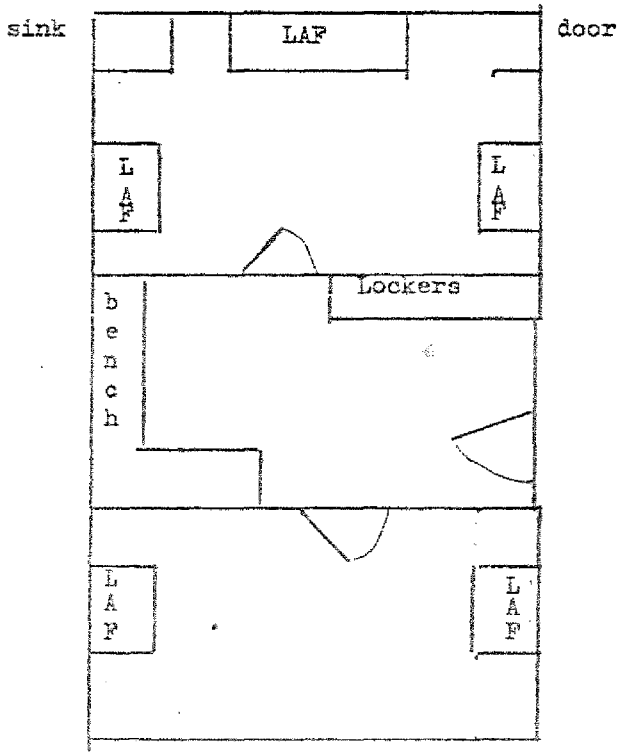
The arrangement of LAF cabinets is also an unusual one and may cause unnecessary turbulence.

The activities done in these areas:

46. Most of the physical volume of work done in the aseptic rooms is pooling of fresh frozen plasma destined for the PFC. The conditions for this activity are probably acceptable . Nevertheless it would still be preferable to sanitise the surface of bags and restrict personnel access.

47. For the aseptic activities, however, the facilities are not up to an appropriate standard. At least as an interim step it is recommended that consideration be given to segregating relatively dirty activities such as plasma pooling from the more critical true aseptic work). Further there are some preparations such as the glycine buffer solution (aseptically prepared) which should not be prepared at all under these conditions.

Schematic of the "Aseptic" area



. The freeze drier area

49. Freeze dried plasma and in future freeze dried cryo precipitate may be done here.

50. Essentially the product is freeze dried in a totally unsuitable environment protected only by a gauze and cotton wool plug. Sterile plasma has to be pooled into containers (in a clean room) which are then removed to a non-sterile area for freeze drying. The containers are then returned to the clean room for capping and sealing.

51. The freeze driers (two primary and two secondary chambers) are housed in an uncontrolled atmosphere with various hoists for the "bells". The room is a through corridor and on the mezzanine level has an opening to an office. The area also contained cardboard and had an opening window (both possible sources of contamination).

52. The oxygen free nitrogen used to refill the chambers at the process end are filtered through MacLay cartridge filters. The grade used was not the finest available but was probably adequate. (Also applicable to the filters on the primary chambers).

Remedial action required:

53. Purchase of a modern freeze drier which could be located with its chamber opening into an aseptic area.

Labelling of blood bags

54. These are labelled in an ambient temperature room reserved for this activity. Segregation of different types of blood is aided by using a colour banded step arrangement. Bags are first separated onto the correct "level" and then the correct labels applied. Various checks are included and labels are reconciled exactly. Perhaps the most important practice involves the double verbal reading out of numbers which is a positive procedure.

55. Some discussions were held on possible future progress with regard to the installation of automated grouping machines linked to a computer which would be capable of scanning and checking labelled blood packs. Such systems are being considered by the Centre but it is understood that no final decisions have been made yet.

C. TESTING FACILITIES AND QUALITY CONTROL

Serology - Blood Grouping and Reagent Preparation

56. The Centre makes most of its own reagents for blood group testing. It was explained that higher titre in itself was not the overriding concern, it was more important to match the reagent to the test system (manual or machine). Donor boosting was not done (except "anti-D").

57. It is understood that reagent "failure" is most uncommon and in most cases would be self-indicating (eg the control would fail too).

58. Reagents were not checked against the British Standard Reference material due to their being unobtainable.

[redacted]. The automatic Technicon BG15 machine used for blood grouping seems not to be under constant surveillance and in view of its reported defects elsewhere the wisdom of such action is questioned. Furthermore, servicing appears to occur only once a year and again it is wondered whether more frequent maintenance might be appropriate.

Hepatitis testing

60. This is carried out in a segregated facility using the Abbot Ausria II system.

61. Every donation is tested. About 1 in 800 new donors are positive to HBsAg. Positive samples are destroyed by autoclaving. All samples are retained for a year for retesting if necessary.

62. The printer which has been implicated in an erroneous negative result previously had now been replaced. In addition a check on the print-out was now done first thing on a daily basis.

63. The high risk laboratory and its immediately adjacent ante-room containing positive controls did not seem to be up to a very high standard. Even if Hepatitis B is downgraded on the "Howie scale" this laboratory must be upgraded to a higher standard.

Quality Control

64. Mr Barr, the nominated Quality Controller, has made excellent progress with regard to the introduction of the concept of Quality Assurance at this Centre.

65. The tests carried out were discussed. Not all tests are as per the Pharmacopoeia but it was felt that this did not represent a particular hazard. Some tests such as platelet count were not done due to difficulties caused by aggregation, at the concentration of the preparation. However, it was pointed out that clinical efficacy could not always be checked by physical or chemical means.

66. Tests used were sensible in that [redacted] things going wrong in the past had been detected and remedied.

Summary of Tests carried out

67. Whole blood

Weight - 548-644 gms

This is done randomly and on samples taken from different donor teams. 10 packs are checked and if 2 of the 10 are outside the range a further 10 are checked.

68. In the past this disclosed a problem with the scales used.

Expired Whole Blood.

69. Sterility test carried out once a fortnight by the Bacteriology Lab on 10 units.

10 mls added to case in digest broth 100 mls
10 mls added to thioglycollate 100 mls
2 x 3 ml in poured blood plates.

[redacted] If no growth the plasma is sent to the PFC.

. . . This differs from the method described in the Pharmacopoeia in terms of frequency of test and volume used (see section A186, BP 1980) though it may be argued that this Monograph was not designed with Blood in mind.

Concentrated red cells.

72. Testing is carried out on expired material.

73. 10 units are tested each morning for:

Haematocrit
pH
Absence of clots

10 units are tested each fortnight for sterility.

74. It was observed that the amount of plasma removed is checked "by eye". Although the Inspectors would have preferred some sort of proportioning device the results seen did indicate staff were achieving a fair degree of consistency (Haematocrits between 65%-75% were seen).

Platelets.

75. In theory these are tested for count, sterility and pH and are on unpooled packs.

76. In practice at 72 hours the count is unreliable becuase of aggregation and it would appear the other tests are not done on pooled platelets because poolimg is done at the Regional Transfusion Centre immediately prior to issue for a named patient and therefore very few packs are returned.

Fresh Frozen Plasma.

77. Two samples are taken daily giving a total of 10 per week.

78. These are tested for Sterility
F VIII
F V (irregularly)

79. Cryoprecipitate.

80. One bag in 24 is taken (24 bags per water bath) for:

Sterility
F VIIIc
F VIII related antigen
Fibrinogen
Volume

81. Pooling is apparently carried out by the user hospital and data is not available on the contamination levels (if any).

82. Buffy Coats and Washed cells.

83. A small volume is taken for sterility.

2 x 3 ml pour plates and 2 x 5 ml into each of 2 x 50 ml broths is carried out.

84. Dried cryoprecipitate (Experimental). See document on file for details of process.

85. The opportunity was taken to talk through the manufacturing process. Each bottle of freeze dried cryoprecipitate comes from a pool of 5 bags. Should the Centre opt for a 30 pool size each pool will produce 6 bottles. The draft monograph for the EP suggested full Pharmacopoeial tests on sizes over 10 pools.

86. The desirability of using "accredited" donors has been discussed on a separate occasion.

87. The use of the 30 pool size allows the sacrifice of a full bottle for complete testing. The alternative (for smaller pools) of taking aliquots from each pool and then sacrificing (say) 2 bottles from each drying batch seemed a possible alternative.

88. The Inspectors did criticize the aseptically prepared buffer solution prepared here and it is understood that dextrose-saline may be a suitable alternative.

89. Testing of freeze dried cryoprecipitate:

Reconstitution
Coagulation
Sterility
Pyrogen
F VIIIc
F VIII related antigen
Fibrinogen

90. Freeze dried plasma

Tests are as per BP

91. Every pool is tested (11 donations = 1 pool) by taking the remnants of the pool.

92. It was noted that every pool is sterility tested but only a small percentage of finished product is so done.

93. A drier run is 200 bottles and 4 random units are selected for:

Reconstitution
Electrolytes
Total protein
Immunoglobulin
Fibrinogen
Moisture

94. The efficiency of the air space replacement with oxygen free nitrogen is not tested.

95. Environmental monitoring

This is limited to settle plates and the use of a slit sampler on a daily basis.

96. In time it is hoped to obtain a Particle Counter in order to able to routinely check HEPA filters (rather than rely on six monthly Microflow checks).

97. Additional checks such as anenometer readings are also useful.

98. In time attention ought to be paid to monitoring of services other than air (eg steam, distilled water).

99. It was noted that Engineers already log refrigerator performance daily. It is recommended that this be extended to cover planned preventative maintenance for the new equipment being processed.

Rabbit Pyrogen Testing

100. This was briefly visited. It is understood that a modified machine for taking temperatures will be available shortly.

Summary of Comments Made

A. COMMENTS ON PRACTICES

101. Infusion bottles should not be used for non injection fluids.

102. The security and reconciliation of labels should be improved.

103. Status labels for cages should be locked inside cages.

104. The presence of considerable quantities of F VIII in Room C implies stock rotation may be difficult.

105. The issue refrigerator (Room A) contains both quarantine and cleared material. The quarantine material is not secure.

106. The contradictory labels here are not good practice.

107. The technician who physically transfers blood bags from "quarantine" to "cleared" should be in possession of a clearance document.

Alternative proposals could be discussed.

108. A trial of an appropriate proportioning device is recommended for the separation of red cells from plasma.

109. The method of plasma pooling by an open method and without being able to sanitise bag surfaces may cause increased contamination.

110. The routine use of thermo resistant spores should be unnecessary as a monitor in the new autoclave providing it can be satisfactorily physically monitored.

111. It is understood that the absence of automatic blood group typing machines linked to a computer which can then confirm the accuracy of labels on blood bags is under active discussion.

112. The presence of pathogens in the room immediately next to the aseptic processing room is questioned.

113. The absence of a particle counter means important monitoring tests cannot be carried out.

114. The preparation of aseptic solutions such as glycine buffer would be better done elsewhere in a higher grade facility.

115. Consideration should be given in the short term to segregating clean room activities so that relatively "dirty" processes do not contaminate more critical activities.

116. Certain modifications are needed on the autoclave, bottle washer and still (see section 4).

117. Formalised training programmes should be introduced for staff.

B. FACILITIES

118. Storage is totally inadequate. This refers to both ambient temperature storage areas as well as refrigerated stores.

119. They are inadequate because existing stores are either overcrowded or of an unsatisfactory nature (eg the basement with its dripping pipework and dusty conditions).

120. Laundry activities should be carried out in a small but clean environment.

121. Preparation of crates for donor sessions should not be carried out in a corridor.

122. The preparation area for containers is appalling. This work needs to be finished without delay.

123. Aseptic areas are not to an adequate standard.

/For the following type of reasons:

Lack of proper change facility

Lack of proper access/air lock for material handling

Inadequate room ventilation

Dust traps in the room

Presence of sinks

Too many activities going on at the same time./

124. Freeze drying is conducted under very poor conditions.

This should be an aseptic operation housed under appropriate conditions.

125. The "high risk" hepatitis facility is not to a very good standard and requires attention.

CONCLUSIONS

126. The staff seen have a good appreciation of GMP and show a high level of awareness.

127. In those areas under their control (eg SoPs, implementation of QA) good progress has occurred.

128. Some practices were discussed which should be improved.

129. Facilities for storage and processing of blood and blood products are either insufficient or inadequate.

130. The most appropriate response from the Scottish BTS would be an entirely new purpose built facility for the processing and quality control of blood at this Centre.

RECOMMENDATIONS

1. The preparation area for bottle preparation must be brought up to standard without delay.

2. A period of 12 months should be sufficient for detailed proposals to be made by the Service (and SEHD). These should rectify the deficiencies in processing facilities and storage areas. /By 11th June 1983/

3. The absence of such proposals should result in a drastic reduction of processing activity at this Centre including the cessation of freeze drying.

4. Other deficiencies and comments may be rectified on an on-going basis.