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30 MAR 1981

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Medicines Division Market Towers
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Telephone 01-720 2188 Ext

Dr R Lane
Director
Blood Products Laboratory
Dagger Lane
Elstree
Boreham Wood Herts WD6 3BX

Your reference

Our reference

Date
26 March 1981

Dear Dr Lane

MEDICINES ACT - INSPECTION OF 5-6 MARCH 1981

As discussed with you, I enclose a draft copy of my report.

I would stress that this is a draft, and I should appreciate comment upon any factual errors as soon as possible so that I may formally present the report.

In particular, am I correct regarding awarding responsibility for Room 217(a) and onwards to Dr Smith?

Yours sincerely

GRO-C

K J AYDING
Principal Medicines Inspector
(Biologicals)

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Inspection of Blood Products Laboratory
Dagger Lane
Elstree
Herts WD6 3AX

File No IN/400/653/H/05

Date of Inspection 5-6 March 1981

Inspectors K J Ayling
J Flint

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K J AYLING
Principal Medicines Inspector
(Biologicals)

23/3/81.

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1. INTRODUCTION

This inspection was mostly of a general nature to check upon the present conditions at the Laboratory.

eg general conditions of processing areas, standards of housekeeping.

In addition certain specific items were looked at eg Commissioning of autoclaves and ovens, staffing levels and job definitions.

Future inspections will be headed by K J Ayling.

This report does not repeat detailed descriptions of areas which can be found in the previous detailed reports.

2. STAFF

Discussion were held primarily with

Dr R Lane

Dr R Lane	-	Director
Mr D Wesley	-	Head of Large Fractionation
Dr Smith	-	Head of Coagulation Factors
Mr P Leavens	-	Technical Services Manager
Mr G Sharman	-	Head of Filling and Packing
Mr Greulich	-	Head of Chemical Laboratory
Dr Singleton	-	Head of Microbiology

3. INSPECTION

Introductory discussions were held with Dr Lane in order to outline the schedule to be followed and the aims of the visit.

Dr Lane informed us that the autoclaves had not been commissioned using a multi point recorder. This was due to an illness at the contracting company Varley Engineering of Notts.

Attempts to instal the couplings necessary by the BPL engineering staff had not proved successful and the work had therefore been contracted out.

3.1 Large Fractionation (Mr D Wesley)

Associated areas eg immunoglobulins are included for the purpose of this report.

3.1.1 The - 25°C cold store is extremely congested. Rented cold store cccomodation is now available, and this should be utilised forthwith.

Stock from Transfusion Centres is building up in anticipation of returns of finished products "pro rata". Such returns pro rata will not in fact be possible for some time.

3.1.2 Upper Laboratory (Large Fractionation)

Plans to upgrade this area and provide a step over barrier or air lock were said to have been shelved.

Mr Wesley's staff are now doing extensive cleaning.

The Laboratory is now not congested and obviously improved, but

a. Inside a broom cupboard, mould growth is present. There are boarded over parts of the laboratory alongside this cupboard which require checking for similar growth.

b. There is mould growth on the glycerol line serving one of the vessels.

The process vessels are of unusual contruction being of welded pieces of stainless steel.

Environmental monitoring is routinely carried out but results are not apparently available to production.

3.1.3 Lower Laboratory (Large Fractionation) Room 211

This room is at 5°C.

Three rejections of product for pyrogens have occurred over the last two years. Two were thought due to hold ups in production and one due to poor (contaminated) supernatant. Plans to provide air locks, changing facilities etc were again said to have been shelved. An operator entering the adjacent corridor was seen to secure both sets of doors of the air lock open before pushing a vessel through.

The laboratory ceiling is metal clad and poorly insulated pipes were dripping condensate from ice formed on them. Air enters the laboratory through these perforated metal sheets.

Paper is sealed over wooden benches to provide better working surfaces.

The cold store (R 210) has broken down. Removal of condensate and aeration is necessary if microbial growth is not to become a problem.

3.1.4 Room 201

This is used for making up solutions for the fractionation processes. The cold freezer does not have any temperature recording apparatus.

Pooling of single plasma packs for immunoglobulins also takes place here. Such work should be carried out in a dedicated area of a higher standard.

3.1.5 Room 202 - Centritherm room

Cardboard no longer enters this room. Plans for dividing off pumps etc have been discussed.

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3.2.1 (Room 217a) Solution Preparation of Coagulation Factors (Dr Smith)

Plans for providing a lobby/air lock to the final solutions preparations area have been dropped.

There is water dripping onto the overhead perforated metal panels and mould growth has been noticed.

The production room is no longer used for office work also, and a small room has been provided for the 6 technicians involved. -25°C cold store

3.2.2 Room 215 Final Solutions Area — R.217

Asbestos EKS grade filters are still necessary for the initial filtration of bulk solutions, (this helps to remove lipid) but a Pall filter is used to filter the solutions into the aseptic area following this.

This room also has been altered and upgraded. The mobile LAF module appears very small for the area covered.

Flexible tube 2x wrapped product through wall connection made in sterile room

The Pall 0.2 micron filter is however located outside the sterile area, and aseptic connections made under filtered air blowing equipment.

(Filter = Pall NRP 66)

(Filters to certain associated cold processing areas were said to be on the extraction side only. This should be investigated further). Monitoring can be taken Rooms 210 211 206 222 223 224 225

3.2.3 Room ~~217~~ Filling (Aseptic) Suite

This is at present run by Mr Sharman, but plans to hand this over have been made (to Mr Wesley's staff?)

The aseptic area was not entered on this occasion by the Inspectors.

The area appears in good condition, and LAF modules are used over all filling.

repeated on regular basis

Corks are no longer used in cleaning/sterilising bottles. In the changing room the ceiling appears to be breaking up due possibly to the movement of the whole building. Such cracks and resultant breaking off of plaster is evident in many parts.

Monitoring of ovens etc has now taken place.

Inspectorate basis

3.2.4 Cold Room 2

Again this area is improved and less cluttered than previously noted. It is planned in November to shut down and install flush fittings where possible.

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The wooden air ducting in the ceiling is scheduled for upgrading. — replacement in full

This is an incredible overhead system with sliding wooden traps. This has been improved in the ceiling above the processing equipment but the system is virtually uncleanable. Dust was infact found on the inlet ducts (on the far side of the room from the Sharple centrifuges). The trunking above this room should be explored for any signs of an even greater problem.

3.2.5 Room 13

This is used for the initial phase of Factor VIII processing and Factor IX chromatographic work.

Benchcoat wooden benches

Again taped paper is necessary to improve wooden benches. There are severely cracked walls and an air cooling system plus radiators. - all to be replaced.

This is necessary due to temperature fluctuations, and the radiator system is scheduled to be removed.

Openable windows are still present. sealed under fixed cond

Shirtsleeves etc.

3.2.6 Room 16 c

This theoretically should be an aseptic area and is used for filtering and sterilising solutions. The air input is said not to approach BS 5295 Class 1 conditions, but a LAF cabinet is used.

Clothing for these operators is now single piece "coveralls", but one operator who does not go into the filtration room handed equipment to the aseptic area operator. 16-16c

electrum nor haphazard

The aseptic area operator walked out of the aseptic area and re-entered during processing. || no change in air quality ∴ LAF

The argument that it is not worthwhile implementing high standards of operation in these poor areas is not acceptable.

Room 12 has been upgraded and is now used for ~~isotopic labelling~~ of fibrinogen. The further phase of upgrading is scheduled to finish in September. for isotopic labelling in 2CCA.

LAF additions

Plans of the upgradings were briefly viewed. They show staff using the changing room to leave outer garments etc. These staff should not be entering this "clean" area and have no need to do so. A central changing area for putting on clean overalls and taking off "street" outer clothes would be better.

The Travenol system for opening the new polyolefin wedge shaped bags of frozen plasma surprisingly incorporates a hot water system for softening the outer plastic layer before squeezing the plasma wedge out to the plasma pool of Fresh Frozen Plasma.

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Pooling of Time Expired Plasma (5 litre packs) would continue at Regional Transfusion Centres. The new facility will also pool T.E.P for the processing of immunoglobulins.

3.2.7 Freeze Drying Areas

Again these are improved with respect to finishes and general standards.

However no air pressure differentials from "white" to "grey" and appears to exist.

Prefreezing in the Virtis equipment will cease when new systems are implemented.

3.3 Technical Services (Mr Leavens)

3.3.1 Outer Stores for non cleaned items

Washed vials in large plastic bags are stored here also due to the necessity of keeping up with schedules. The area was as tidy as could be expected, and the severe congestion noted here previously was eased.

3.3.2 Preparation Area

A new washing/~~sterilising~~ machine from Hills is proposed.

There is dangerous congestion in the preparation due to trolleys etc and any purposal to decrease machine space is to be welcomed if this relieves congestion.

Traying up of vials for sterilisation was directly under a rack holding upturned bottles. Staff were better dressed than previously noted and well fitting hats were worn. Clothes for aseptic areas are washed before autoclaving, but the high vaccum autoclave was said to make clothes shrink.

3.3.3 Autoclave Area

The autoclaves have not been validated and commissioned using a multi-channel recorder. HTM 10 does set extremely high standards regarding maintenance and commissioning of autoclaves but the commissioning using a multi-channel recorder is an essential.

Couplings for the insertion of the loads were made up by HPL Engineers but these were not thought adequate.

The contracting engineers who carry out planned maintenance, Varley Engineering of Notts apparently are ready to do this work, but staff illness has prevented this.

Daily Bowie-Dick tests are done, indicator tape is used and Mr Leavens does a test involving inserting spore strips at the centre of the Bowie-Dick test.

Such work should be coordinated by the Chief Microbiologist.

3.3.4 Sterile Store

Many items for sterilisation were poorly wrapped and sealed by folding over only once and sticking down with a small piece of tape. It was later elucidated that much of this was not really required for use aseptically. Autoclaving is used to ensure items are freed of any possible hepatitis virus. Such autoclaving should not really be done here.

A pall filter holder (plus filter) was poorly wrapped and found to be wet when opened. This is sterilised by a downward displacement autoclave.

The use of a better autoclave should be investigated and the cycle validated.

Coordination of wrapping of items to be sterilised is necessary, preferably by one set of staff to the same standard.

3.3.5 The Hill bottle wash area previously critised was tidy and free of extraneous objects.

Inspection and Packaging (Mr Sharman)

Very little work was in progress.

Further accomodation to separate inspection from packaging is scheduled.

SOP's for line clearance and other operations have been drawn up and check lists are utilised.

Room 113, due to be altered shortly, shows efflorescence on ceilings following a water leak.

Testing Laboratories and Quality Control

There is no formal Q.C. release of products but Heads of Department ie Mr Wesley and Dr Smith coordinate documents and results for Dr Lane's formal release.

Chemical Laboratories (Mr Greulich)

There is a staff complement of 5 including Mr Grenlich, but 1 post is designated not to be filled at present.

Amongst the work done is

Chemicals
intermediate and final tests for proteins etc
effluent
water

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SOP's for all chemical tests have been written up. The laboratory space available is very small. Work on testing components such as vials and plugs cannot start until calipers and micrometers etc are purchased.

Microbiology Laboratories (Dr Singleton)

New laboratories are scheduled, but it is not definite that these will be able to cope with all necessary testing.

The plant monitoring team has the capability to survey the processing areas and environment, but coordination of results and necessary action should be followed through. Regular reports to nominated managers are necessary.

Some levels of contaminants have dropped progressively eg aseptic filling areas, but others not so, possibly due to the low standard of someareas and lack of buffer air locks etc.

Testing of raw material eg plasma has shown some startlingly bad results.

The supply of non frozen plasma from Belfast is to be discontinued shortly, but previously very high contamination eg 10^6 organisms per ml were obtained for the pooled 5 litre packs.

Some Transfusion Centres also show poor or variable results, and records of these are now circulated to the Centres.

Examples of leaking packs and insufficient samples are also recorded.

4. DISCUSSIONS HELD

Discussions were held with Dr Lane before leaving.

The following points were made.

1. The pressures on staff are understood, and improvements in some areas are apparent, often due to personal initiative by senior staff eg extra cleaning rosters.

2. In some instances, examples of poor procedures or breaking of rules were noted. The fact that the areas themselves are often below standard should not be used as a reason for this.

3. Staff often do not know these responsibilities clearly. Changes in responsibilities were said by Dr Lane to be the cause of this in some cases.

New job descriptions will be finished in March. Division of responsibility must be clearly understood.

4. Commissioning of autoclaves has not been carried out. It was stressed that this should prevent further production if not done forthwith eg early in the week of 9 March.

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5. The absolute necessity of senior staff as

1. Factory Manager (ie Deputy Director, Administration)
2. Quality Controller
3. Chief Engineer

The possibility of a temporary appointment as senior production assistant was discussed as a short term measure until future appointments were made.

5. SUMMARY AND CONCLUSION

The processing areas themselves are instrinsically below acceptable level in many areas.

Staff have made major efforts in many cases, but sometimes the obvious inadequacy of the facility causes them to lower their targets. This is understandable but management must prevent it.

A major effort has been directed to drawing up a large number of SOP's (Standard Operating Procedures) and these must be operated to.

Until staff are appointed to fill the obvious gaps ie

Deputy Director (Admin)
(= Factory Manager)

Quality Controller

Chief Engineer

then this site cannot hope to conform with accepted standards of GMP, even if upgrading of the facilities takes place.

The responsibilities of senior staff in particular must be clearly defined and understood by all staff so that the overall objectives can be achieved.

The non commissioning of the autoclaves is not acceptable and must be remedied immediately.

6. RECOMMENDATIONS DRAFT

The draft report will be sent to Dr Lane as soon as possible so that the matters discussed are confirmed.

It must be re-affirmed that BPL does not conform with accepted standards of GMP and at best will not do so for some time, depending upon appointment of senior staff and upgradings and rebuilding.

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