CONTENTS

DHSC0001362_0001

DHSC0001362_0002

1. INTRODUCTION

Alpha Therapeutic Corporation, a subsidiary of the Japanese Green Cross Corporation, is located on a two level site in the city of Los Angeles, California (see attached site plan). The whole site activities are the preparation of blood products. In addition, there are warehousing, storage and initial sorting of plasma bags at the Temple site, located about 10 miles from the main factory. All plasma collected is in Alpha Therapeutics' own plastic bottles or bags from Contractor Donor Centers (Blood Centers of America). All plasma containers are sampled at source and tested by the Corporate Analytical Laboratories in Memphis, Tenn.

Factor VIII, Profilate, PL4447/005 currently includes a heptane heat treatment virus inactivation stage. The product has heparin added and is named Profilate HP. The site was last inspected in February 1988. Since that date, Alpha have registered and are using a Factor VIII process involving organic solvent and detergent inactivation, followed by a terminal heat pasteurisation stage, for products sold in the USA.

2. SCOPE

The inspection covered the manufacture of bulk Blood Products, the sterilization and filling into dose form containers and the pasteurisation of those finished products.

3. PERSONNEL MET

*Mr Ike Yorihiro	-	Company President
*Mr C Turner	-	Vice President Manufacturing
*Mr L Bown	-	Director Manufacturing
*Dr E Healey	-	Vice President Technical Operations
*Mr J Brady	-	Director Quality Control
*Mr S Jankowski	-	Director Quality Assurance
*Miss M Carr	-	Vice President Regulatory Affairs
*Mr L Bathish	-	Director Regulatory Affairs
*Mr J Guley	-	Director Regulatory Affairs
*Mr J Silvermann	-	New Products Manufacturing Director
*Mr D Dimmick	-	Director Quality Control (Manufacturing)
*Mrs B Monty	-	Senior Quality Engineer
*Mr B Druce	-	Validation Manager
*Mrs S Bain	-	Quality Control Manager
*Mr B Kelly	-	Main Building Filling Suite Manager
*Mr M Truetischler	-	SF&F Albumin Filling Suite Manager

*Present at final discussion.

4. SIGNIFICANT CHANGES

4.1 Personnel

Several managers are now titled Director and Mr Yorihiro is Company President. Mr Silvermann has been appointed from pilot plant operations to be New Products Director.

DHSC0001362_0003

4.2 Premises

4.2.1 The southern filling suite extension has been completed and validated for albumin filling and liquid and freeze-drying operations. In addition, a virus inactivated process area has been created, together with a virus inactivated pilot plant area.

4.2.2 An isolated freeze-drier has been installed to enable bulk intermediate Factor VIII, Factor IX and Fraction II to be dried outside the aseptic areas 102 and 103.

4.2.3 The Chemical Quality Control Laboratory is being rehoused and extended.

4.3 Equipment

Freeze-drying equipment can now be steam sanitized and has been validated for the process.

4.4 Procedures

None.

5. PROGRESS REPORT

A copy of the deficiencies listed following the last inspection is attached. Major items 1-3 have been satisfactorily resolved, together with all other items except item 1, which was not inspected, as the Temple site was not visited.

Major item 4 was unchanged, the heptane treatment room is still connected to the same air handling system as the acetone treatment and drying rooms. The open handling of inactivated Factor VIII powder is still done in an area where in-process albumin powder (not inactivated) is present - see the critical deficiency listed in the Appendix (1989).

6. PRODUCTION PROCEDURES PREMISES & EQUIPMENT

6.1 Raw Material Stores

This building is located on the upper site and a regular shuttle service of a company van transfers materials issued to the main plant on the lower site or to the Temple site for packaging operations. The building is clean, dry and uncongested and has 1509 pallet rack locations (3 high).

6.1.1 Receiving Operation

Copies of the Purchase Order are compared with the materials delivered and the Supplier's delivery note in a segregated area adjacent to the covered vehicle dock (drive on/off), by stores staff. After acceptance, a Receiving Lot Number is logged and each container (a shrouded pallet is considered one container) has the lot number stamped on the surface. The detail is entered on the Departmental computer terminal and a hand copy printed out which indicates Status Code 2 (Quarantine). Three copies are distributed to the Quality Control sample section and the materials are transferred into the locked Quarantine cage. The key to the area is held by the Quality Control Department.

DHSC0001362_0004

6.1.2 Sampling and Release Operations

The sample office in the warehouse holds sampling procedures for all chemical raw materials, packaging components and labels.

Chemicals have every container sampled for an identity test, plus a composite sample for assays. Components are sampled to MIL-STD-105D single sample plan level 1 and are tested to Critical-Major-Minor descriptive defects plus dimension checks on every component sampled.

Upon release, all containers are stamped "release" or "reject". Rejects are retained in the Quarantine area until returned to the Supplier. Computer status changes are made by the Warehouse staff.

6.1.3 Starting Materials Issues

These are transferred in full containers/pallets to the lower site or the Temple site (for packaging) on a transfer note, by stock rotation. No item can be transferred whilst still under computer status 2 (plus they are held in the locked Quarantine cage). All issues are recorded on the computer by lot number.

6.2 IGIV Production (Venoglobulin)

6.2.1 Fraction II Paste Preparation

The area for the bulk manufacture of IGIV, the South Fractionation Room (122), has been operational since October 1988. It has stainless steel-lined walls and is equipped with 4 stainless steel fractionation vessels, 2 x 2600L and 2 x 3100L. The room temperature is variable from +2°C to -5°C, depending on the process stage.

Fraction II + III paste which is re-worked for IGIV production is stored frozen at the Temple Road warehouse. A normal production run starts on Sunday night at 11 pm, according to a pre-programmed production plan. Approximately 250 kg paste are used for a production batch. The specification for accepting Fraction II + III paste for processing is that the ambient microbial level (AML) should not exceed 1000 cfu/g.

Following fractionation, Fraction II paste is harvested in a bank of 9 stainless steel Sharples AS21 centrifuges. The bowls are fitted with teflon liners and both the liners and bowls are scrubbed between use with ethanol and are stored in ethanol. Paste is removed from the bowls, by means of a mechanical bowl-shaker, in the general fractionation room; it is collected into prepared plastic containers lined with polythene and is taken for frozen storage.

Occasionally, Fraction II + III paste is reworked for IGIV production in the North Fractionation Area. This area is in good condition, being only a few years old, and is of larger capacity, being equipped with 5 x 6400L, 3 x 4200L and 1 x 2900L tanks.

6.2.2 IGIV Final Bulk Preparation

Fraction II paste is removed from the cold room; no release criteria are applied at this stage, the policy being merely to take the next lot in line. The batch size is approximately 140 kg paste, with a range of 80-155 kg. Processing takes place in the South Fractionation Room (122).

DHSC0001362_0005

Fraction II paste is reconstituted in WFI, PEG and human serum albumin (HSA). HSA used is 25% Alpha HSA which has been released for clinical use and is added to a final concentration of 0.0086 kg/kg reconstituted Fraction II solution. (The reconstituted solution is usually approximately 1500 kg).

The Fraction II solution is acidified at this stage to pH 3.7 - 3.8, using HCl, and is held for 15-16 hours at 0° - 2°C. The use of HCl is supposedly recorded in a log book but this could not be found; also, each bottle of dilute HCl solution is not identified with the original lot number.

After incubation, the acidified solution is retitrated to pH 6.9 - 7.0, 4% PEG is added and the suspension is filtered through a filter press into a receiving tank. This receiving tank is not dedicated and may have been used in the early (pre-acid treatment) stages. The CIP system for these vessels is not yet functional and has not been validated, so a manual system of cleaning is in use; however, this has not been validated as virucidal. The actual cleaning method varies but the method used is not recorded, the record merely stating "cleaned".

The Filtrate is treated with bentonite, which has been heated at 230°C for 1 hour, before being once more separated and harvested as IGIV paste, which is stored frozen.

6.2.3 Preparation of Sterile Bulk Solution

IGIV paste is redissolved in NaCl, a process which usually takes approximately 12 hours, and then is subjected to DEAE - Sephadex A50 treatment. The gel, packed in a column, is cleaned using 2 hot WFI washes, 2 cold WFI washes and 3 NaCl washes, before being scraped out of the drained column and stored in polythene bags at 0° - 6°C for a maximum of 18 hours. No samples of wash solutions are taken for QC testing.

When the IGIV paste is in solution, the required amount of wet resin is added to the tank and mixed, where it settles and filters through an autoclaved nylon cloth before being pumped into the column, where the resin is retained and the purified IGIV flows through. The silicon tubing is single-use and, at the end of the process, the Sephadex is weighed and discarded.

After a clarifying filtration, the purified bulk IGIV solution is formulated to give the correct pH, protein concentration, albumin and IgG content. Mannitol is added as a stabiliser. Final filtration is through 2 Durapore 0.22 um filters. At present, the sterilising filter and final bulk container are not sterilised as one piece and so an aseptic connection has to be made. This is done under LAF in the AHF level III gowning area. There is no sample taken of the pre-filtered bulk for bioburden testing.

The sterile filtration itself is performed in the IGIV formulation room (105) with the receiving tank (180L) in the adjoining cold room (106). The sterile bulk may be held for up to 2 weeks prior to filling and freeze-drying.

DHSC0001362_0006

6.3 Factor VIII Preparation

There are currently 2 Factor VIII products produced by Alpha Therapeutics, one for USA and one for UK. The USA product is prepared using the organic solvent/detergent viral inactivation procedure, after which it is also pasteurised. In common with other manufacturers using this method, care is taken to avoid re-contamination by handling treated material in a "virally-controlled" area, with its own air supply, dedicated equipment and dedicated staff clothing.

The UK Factor VIII product (Profilate) has a viral-inactivation step involving heat-treatment of a slurry of dried FVIII in heptane. However, the treated product is not protected from possible re-contamination (see Section 6.3.3).

It is planned to submit a UK PL application for solvent/detergent-treated FVIII which omits the pasteurisation step currently used in the US product. (It is also intended to drop the pasteurisation step for the USA.)

6.3.1 Cryoprecipitate Preparation

The steps up to the preparation of cryoprecipitate solution are common to both FVIII products. Plasma is received in plastic bottles which are transported by an automated screw-driven opener which slices through the tops of the bottles, inverts them and drains the plasma slush into a collecting channel. Cryoprecipitate forms in a "fine thaw tank" next to the collecting channel.

Fractionation pools further down the line (in albumin and Fraction II preparation) are sampled and tested for HBsAg and the following day's processing cannot begin until negative results have been received. If the results are positive, all equipment is cleaned with hypochlorite in addition to the normal NaOH treatment.

Cryoprecipitate is harvested in a 2 Westfalia BKA25 centrifuges, up to 5 bowl changes being required. The paste is unloaded in the general fractionation area. The centrifuges are cleaned with NaOH and rinsed with WFI after use. Silicon rinsing tubes were being stored coiled while still containing water.

The cryopaste is re-dissolved in WFI containing heparin, the pH is adjusted and 3.5% PEG is added prior to re-centrifugation. The FVIII-containing supernatant is clarified by filtration (1.2 µm followed by 0.6 µm) to give a final volume of 350-400 kg. This solution may now be processed either by the solvent/detergent method or the heptane slurry heat method.

6.3.2 Solvent/Detergent Method (USA)

All processing following the solvent/detergent treatment is carried out in a dedicated, separate area (the Virus Inactivation (VI) Area), designed to prevent re-contamination of the virally-inactivated bulk. The area has its own, independent HEPA-filtered air-supply and does not draw air from the rest of the factory.

DHSC0001362_0007

Staff entering the VI area put on white gowns (as opposed to the general blue gowns elsewhere) and dedicated footwear. Headcovers, however, are not changed. Staff enter through a change-room which is supposedly at negative pressure to the VI area and at positive pressure to the corridor. However, there are no specifications for the pressure gauges and they are not regularly monitored.

The TNBP/Detergent solution is added to the FVIII solution outside the VI area and mixed for 1 hour before being pumped via a wall-port into the area, where it is mixed for a further 5 hours. The pH and temperature are monitored and adjusted as necessary.

Equipment and chemicals are brought into the VI area through an air-lock. Equipment and containers are double-wrapped, the outer wrapper being removed in the airlock. At the time of inspection, no SOPs were available in the VI area as they are all held in the supervisor's office outside the area.

The FVIII solution is purified by the addition of PEG and centrifugation 4 times in 2 Westfalia BKA 6 centrifuges, the paste being washed each time in glycine solution before being formulated in reconstitution buffer prior to the final sterilising filtration.

The sterile bulk holding tank is prepared and autoclaved outside the VI area, double-wrapped. However, it is brought into the area, via the airlock, on a wheeled base which has passed through other manufacturing areas. Bleach is sprayed on the wheels in the air lock.

The sterilising filter is autoclaved separately and the aseptic connection is made (in the VI area) under LAF. There was no recalibration date sticker on the cabinet. It was said to be done yearly but no records were available. There is no pressure gauge with which to monitor the filter condition and no written cleaning procedure or record of cleaning for the cabinet.

6.3.3 Heptane Slurry Heat Treatment (UK)

For product destined for the UK, the heptane slurry heat-treatment is used. Factor VIII solution is precipitated with PEG and separated in a Westfalia BKA6 centrifuge, followed by a glycine wash. The paste is reconstituted and put into freeze-drying bags (polythene bags with a breather strip) within metal trays.

The FVIII, which at this stage has not been virally inactivated, is freeze-dried in an isolated steam-sanitisable (but not sterilisable) drier which is only used for non-virally inactivated intermediates (FVIII, FIX and Fraction II); this overcomes the major deficieny noted in the previous inspection, whereby virally-inactivated sterile dosage forms were dried in the same drier as these non-treated intermediates.

After lyophilisation, the dried FVIII powder is put into outer bags, heat sealed and stored in drums in a -40°C cold room until it is transferred to the Acetone building for heat treatment.

The method of handling FVIII during and after heat-treatment has not changed since it was raised as a major cause of concern following the previous inspection in February 1988. It is unacceptable in that there is an extremely high probability that heat-treated FVIII will be contaminated with untreated FVIII and/or untreated albumin.

DHSC0001362_0008

The heat treatment is carried out in a small area of the Acetone building, where non-virally activated albumin powder undergoes acetone drying. The air-supply is common throughout the building.

Heptane is drawn into a stainless steel tank and the FVIII powder is poured into through a port at the top. This process generates a dust of (untreated) FVIII powder which settles around the room, including around the mouth of the vessel port. This situation was even worse on this occasion than noted during the previous inspection. The heptane - FVIII slurry is then heated at 61°C for 20 hours to inactivate any viruses that may be present.

At the end of the heating cycle, the slurry is allowed to drain through a mesh plate, which separates the FVIII from the heptane. The vessel port is then opened - allowing untreated FVIII dust to drop into the treated material - and a tube is connected to the port through which HEPA filtered air is blown across the FVIII on the mesh. The air is drawn locally, from the same rooms where untreated albumin and FVIII are handled.

Dried, treated FVIII powder is removed from the heat treatment apparatus in an open vessel, from which it is scooped, in the same room, into plastic bags. Prior to use, the scoop hangs in the room near where the untreated FVIII is poured into the vessel port. Unlike the VI area (see Section 6.3.2), staff working with the treated FVIII do not wear dedicated clothing and footwear. Equipment is not dedicated. The room itself is small and cramped and there is a constant drip of condensation from overhead pipes giving rise to a permanently wet floor.

In the acetone drying room, where untreated albumin is handled, there is a layer of albumin dust along all ledges and projections above eye-level.

When the FVIII bags are filled, they are rolled up, heat-sealed, put into a second bag and sealed again for transfer to the VI area for final formulation and sterilisation. (As this FVIII is possibly virally recontaminated, taking this product into the VI area is likely to compromise the integrity of that area.)

6.4 New Products Manufacturing Area

In addition to the existing manufacturing areas, a new area is being constructed which is planned to be ready early in 1990. It consists of two areas, a Fibronectin primary manufacturing area and a Viral Control Area (VC area).

The Fibronectin primary manufacturing area contains a class 100,000 fractionation room (ambient temperature) containing 2 x 1500L fractionation vessels and 1 Westfalia BKA 35 centrifuge, modified to run air-cooled on refrigerated air. A pasteurising room is attached which abuts the VC area.

Also in the primary manufacturing area are a variable temperature cold room and a -25°C freezer. In addition to primary manufacture of fibrinonectin, some experimental products will be produced here.

The VC area will be used to handle future virally inactivated products, viz liquid IGIV (after solvent/detergent treatment), affinity-chromatography FVIII (also after s/d treatment) and fibronectin (after pasteurisation). The pasteurisation room for fibronectin will be connected via a pass-through, the transfer hose being passed out of the VC area into the pasteurisation room.

DHSC0001362_0009

Air pressure differentials have not been adequately defined and there are insufficient Magnahelic gauges within the area to monitor and indicate the position.

6.5 Water for Injection Production

The whole of the tower site has distilled water provided by two (outdoor) Finaqua 2000 five stage stills fed with deionised water.

6.5.1 Deionised Water

Each of the two deioniser units is monitored by an in-line conductivity meter, which is alarmed at 3 micro siemens, at which level the unit is programmed to shut down.

6.5.2 Distillation System

The Finaqua stills operate in series and the condensate has continuous conductivity monitoring to a chart recorder, which is alarmed at 3 microsiemens with an automatic shutdown. Distilled water feeds through a heat exchanger to a 13,000 gallon hold tank which is held at 80°C. A second 11,000 gallon tank is also fed through a heat exchanger to provide a cold water for injection (WFI) source.

Each tank feeds hot and cold WFI loops to both manufacturing buildings, each with approximately 55 take-off positions which comply with the FDA requirement for "dead legs". All positions are sampled regularly by the Quality Control department to a test programme. Temperature recorders are located on the return sections of the recirculating loops and the cold loops are sanitized every three months using steam. Each hold tank has a vent filter which can be steam sanitized. The microbial count limits are:

Hot Systems	10 CFU/100 ml
Cold Systems	50 CFU/100 ml.

6.6 Sterile Filling

There are two sterile filling areas on site; one, located in the main plant, is called the South Side sterile suite (see attached plan) and is used to fill albumin products, together with any liquid or freeze-dried products post viral inactivation. Routinely however, albumin products are filled in a dedicated sterile filling suite in Building 315 called SF and F. Each area will be considered separately.

6.6.1 Main Building Sterile Filling Suite

The plan for this area is attached and consists of the highlighted rooms numbered 102/103/113/158/160 plus the associated operation change rooms. Each room is fed by a separate independent, balanced, terminally-HEPA-filtered air system. The Fill Room (158) is designed to have 0.05 inches water pressure above the adjacent room 160. Air is recirculated within each room and Room 158 has a 100% laminar air flow ceiling. There is a positive pressure alarm on this area only. Pressure readings are recorded at each fill and records are sent to the Quality Control Department.

DHSC0001362_0010

6.6.2 Equipment and Stopper Preparation

This is carried out in Room 110. Operators change upon entry and the area is provided with hot and cold WFI. Stopper washing, unloading and equipment assembly is carried out under a LAF hood. Each piece of equipment has a temperature indicator and a label which has a seven day expiry date added. Stoppers, after silicone rinsing, are loaded into stainless steel tins prior to sterilization.

6.6.3 Vial and Bottle Preparation & Sterilization

Glassware is unpacked and staged in an outer area before loading on a bottle conveyor in Room 156. The conveyor can accommodate 20 ml - 200 ml containers. A Cozzoli conveyor washer provides six hot WFI washes before feeding to the Fastoria tunnel sterilizer or to stainless steel cans for dry heat oven sterilization. (This process is due to be phased out). Tunnel temperatures are recorded on a Kaye Digistrip using 8 fixed temperature probes inside the oven to provide a cycle with a minimum of 170°C for 140 minutes exposure. The oven cycle is set to give 230/260°C for 45 minutes with a conveyor speed of 20 ft per hour. An alarm is set at 230°/260°C $\pm$ 10°C using visible and audible systems, which are checked and recorded daily. Positive pressure inside two cooling chambers is not measured or alarmed.

6.6.4 Autoclaved Equipment

This double-ended Amsco unit operates on four porous load cycles of 121°C for 20 minutes and includes a vacuum drying cycle (post sterilization). The Standard Operating Procedure lists each load and validation was carried out using maximum load cycles. The autoclave prints out temperatures from 2 wander probes at 2 minute intervals. Exposure time and F_o are both printed out. Filter housings can also be sterilized by a second control autoclave. Clothing (one piece with hoods) for the sterile area is contract sterilized by irradiation.

6.6.5 Solution Preparation

Bulk solutions are prepared in the appropriate manufacturing department specific to each product (viral inactivated areas).

6.6.6 Sterile Filtration, Filling and Freeze-Drying

A mobile vessel containing the bulk solution is located outside the filling room and a sterile connection using a disposable 0.2 micron filter is made to the two-head piston filler inside the 100% LAF filling room, which provides class 100 in all positions. This room has a welded PVC floor coved at walls and corners. Air particle counts are taken continuously during filling. Cleaning equipment is autoclaved into the area and Alpha-employed cleaners clean walls and floors after hours using disinfectants which are changed monthly. A bulk sterility sample is taken during the filling stage.

Partly stoppered vials, after a liquid nitrogen dunk (under LAF), are transferred under LAF onto trays held on a localised LAF-protected cart for transportation to the freeze driers in rooms 101, 102 and 103. These Stokes freeze driers can now be steam sanitized for 30 minutes at 100°C (validated) and have Hepa-filtered air above each door. The freeze driers have five temperature wander probes inside vials, plus shelf probes which feed to a Kaye digistrip temperature recorder. Controls are manual. Vials are closed under full vacuum inside the driers.

DHSC0001362_0011

6.6.7 Vial Cap Sealing

Vials which have been stoppered during filling or freeze drying are fed via the Hepa LAF protected conveyor in room 160 (where the liquid nitrogen dunk tank is located). The conveyor passes to the outside of the Aseptic Area into a Hepa-LAF protected area which has plastic strip walls where the cap seals are added and a batch number is jet sprayed on the unlabelled vials. Completed unlabelled vials are packed into closed labelled shippers for transportation to the Temple site for labelling and packaging.

6.6.8 In-process Control

Vials are sampled, 1 per tray, for in-process weight testing. Air particle counts are taken continuously during filling, plus environmental monitoring for viable organisms. Room air pressures are also recorded during filling.

6.6.9 Operator Changing

Three stage changes take place in rooms equipped with LAF walls. Change procedures are displayed appropriately.

6.7 Albumin Filling Suite (Building 315)

This area is located in Building 315, named SF and F, and the plan is attached, with sterile areas highlighted (1507 & 1518). Each room is fed from the Hepa-filtered main ventilation system with terminal Hepa filters located in the ceilings. The filling room has 100% LAF to provide class 100 in all positions. Air is 80% recirculated. Floors are welded PVC coved at walls and corners. A panel of Magnahelic gauges in the manager's office shows 0.14 inches of water between the fill room and outside. Records are taken daily.

6.7.1 Equipment and Stopper Preparation

This takes place in Room 1516, which is fed with class 100,000 air and requires a clothing change on entry. Hot and cold WFI is provided from the recirculating loops and stopper washing is carried out using the punchcard-controlled Huber washer under a LAF hood, which also provides protection for equipment assembly operations. After labelling and indicator tape addition, autoclave loads are placed into the Amsco double-ended porous load sterilizer, which has been validated for 5 cycles and includes vacuum drying cycles. Autoclave chart record printouts are checked and signed by Quality Control.

6.7.2 Vial and Bottle Preparation and Sterilization

Glassware sized 50 - 500 ml is delivered shrink-wrapped on pallets for unstacking after a visual on-line check, before feeding to the Gillowy washer for 500 ml or Gillowy tunnel washer for smaller vials, both of which use hot WFI and sterile filtered air. The Gillowy Tunnel sterilizer operates at not less than 210°C, not more than 235°C with a sound/light alarm. A Kaye Digistrip prints out temperature probe readings from 8 probes. The process has been validated at the maximum conveyor speed, which is also alarmed and printed out. Air pressure inside the cooling section is monitored as air flow, with a printout plus an alarm set at -0.1 m/sec. The room is provided with air at class 100,000.

DHSC0001362_0012

6.7.3 Solution Preparation, Filtration and Filling

Bulk solution and sterile filtration takes place in the albumin manufacturing area, adjacent to the filling suite. Mobile vessels containing sterile bulk product are placed adjacent to the fill room and aseptic connections made to the needle filter (3-5 head) in the 100% LAF filling room,which has class 100 during operation in all positions. During filling, in-process weight tests are carried out at 30 minute intervals from each filling head. After stoppering, vials pass into the cap sealing room, which is class 100,000 and has LAF above the capping machine. Each container is also jet-coded on the cap. The change area is two stage and includes an air shower cubicle.

6.7.4 Pasteurisation

Containers from cap-sealing are loaded into labelled racks (plus indicator tape) prior to pasteurisation. Pasteurisation was covered during the previous inspection and no deficiencies were noted on this occasion.

6.8 Validation Studies

6.8.1 Tunnel Sterilizer (Main Building)

There is a protocol to revalidate this equipment every 1-2 years with media fills at 6 monthly intervals. A target FH of 170, representing a 12 log spore reduction, is used. Trailing temperature probes (6) in six bottle bundles were run to determine the cold spot. The six lowest positions were used for bio-challenges and endotoxin challenges, all of which produced no growth. Media fills included capped vials and part stoppered vials put through simulated freeze drying operations (including liquid nitrogen dunking). Fills were of 3000 containers plus for each run, except for 500 ml bottles where 1000 containers were filled. Results are 4 failures per 9200 vials (0.025%) for all types of container.

6.8.2 Amsco Autoclave Sterilizer

The protocol calls for revalidation at 1-2 year intervals using 12 temperature probes and a Kaye digistrip recorder. The target Fo is 22. The cold spot was found and a maximum load cycle validated gave a cold spot Fo of 33 with 3 runs. All validation records are approved by Production and Quality Assurance Departments. Biochallenges are used and media control tests carried out.

6.8.3 Freeze-Drier Sanitization

The cycle used was 100°C for up to 50 minutes. 15 temperature probes were used to determine the cold spot for a 30-40 minute cycle. 100% kill was registered on B. subtilis and the local bioburden (0.09 CFU/25 sq cm) of identified organisms (Staph).

The sanitization process is preceded by an alcoholic swab clean down.

6.8.4 Batch Document Review

Manufacturing and Quality Control documents for the aseptic filling of Factor VIII batch UAH9004A for the UK and albumin batch RNE9002 also for the UK were reviewed.

DHSC0001362_0013

7. QUALITY CONTROL

7.1 Environmental Control

Air particle counts were reviewed, from filling positions taken during each filling operation. All recorded less than 10 particles per cu ft (limit 100).

Air particle counts taken monthly in changing rooms recorded less than 10 and in freeze-drying rooms less than 300 particles per cu ft (limit 1000).

7.2 Microbiology

7.2.1 Air Samples for Viable Organisms

A slit sampler is used using 60 cu ft of air. Filling rooms have air alert level of 0.1 CFU/cu ft. Gowning rooms have an alert at 1.0 CFU/cu ft and the freeze-drying room 0.5 CFU/cu ft, monitored twice weekly - all these area usually show zero counts.

7.2.2 Swab Tests

Swab tests are taken at the end of each filling session from fixed and random sites.

Alert levels are greater than zero for filling machines and the Hopper (stoppers); 5 CFU for inside LAF curtains; random position $\geq$50 CFU and $\geq$ 100 for floor samples. Results seen showed zero except on floors, which could rise to 6 CFU on occasion.

Deviations would result in QA and Production investigations and formal reports and the product would be quarantined before a final Quality Assurance decision.

7.2.3 Bioburdens

All albumin solutions have a bioburden sample taken prior to sterile filtration. The results are usually about 100 CFU/ml, with an action level at 1000 CFU/ml.

Factor VIII solutions results were less than 100 CFU/ml with alert and action levels at 100 and 200 CFU/ml respectively.

7.2.4 Sterility Test

The test carried out covers the BP method. Growth promotion records are available for each media batch used. The retest level in the last 12 months is zero in 1200 batches tested.

7.3 Chemistry Laboratories

The Quality Control Chemistry laboratories are currently split into 2 buildings, the North and South facilities. Both are very old buildings with insufficient space. However, a new suite of Quality Control Chemistry laboratories is currently nearing completion. This will replace the existing facilities and provide much improved conditions.

DHSC0001362_0014

The North facility is responsible for traditional "wet" chemistry (coagulation assays, in-process testing for Na^+ etc, acetone and heptane assays). Equipment includes 3 coagulometers (2 x Coagamate and 1 x Hyland Coltech), a flame photometer, a gas chromatograph and a UV spectrophotometer.

Coagulation assays are performed for Factor VIII and Factors IX, II, VII and X. Records of these are excellent, containing all the raw data, reagent batch numbers etc. Factor VIII assays are 2-stage on in-process material, while a 1-stage assay is performed on the finished product.

Unlike coagulation assays, records of other tests are inadequate, consisting only of records of results and not the original raw data. The batch numbers of test solutions are not recorded.

Samples and standards are retained in a series of fridges and freezers in a corridor. The temperatures of these are dutifully but badly recorded. The logs carry the wrong specifications, the temperatures are often wrongly recorded and no action is taken when the temperatures are out of specification.

The South Quality Control Chemistry facility handles chromatography (HPLC) and protein chemistry (Kjeldahl). A number of unofficial, hand-written instructional notes were pinned to the walls. The cold room for sample storage is extremely cluttered, being shared with R and D, but this will be solved when the new laboratories come into use.

8. POST INSPECTION SUMMARY

At the final discussion, it was pointed out that, as a result of the critical defect (see Appendix attached), the inspectors would be recommending to the Licensing Authority that the PL for Profilate PL 0447/0005 (Factor VIII) should be withdrawn until such time as the hazard to virally-inactivated bulk product had been removed, either by isolation or a validated terminal pasteurization stage.

Major and other deficiencies were also listed.

The company response on the critical item was that it had been hoped to have submitted and had approved the new solvent/detergent inactivation process (already used for USA domestic product, i.e. FDA approved). However, because of delays in challenge trials, the submission to the UK authority had been delayed by 18 months and would not be submitted until October 1989.

The cost of redesigning the Heptane equipment to make it virus-free was considered not acceptable in the short-term.

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9. CONCLUSION

No effort has been made to rectify the major deficiency, No. 4 from the last inspection and the situation has actually deteriorated. Consequently this is now considered to be of a critical nature and can no longer be tolerated.

Other deficiencies have mainly been rectified and those others identified during this inspection are not considered to require any Licensing Authority action on other products.

Note Book Ref (DRSW) 1989 Book III pages 28-53.

DHSC0001362_0016

APPENDIX I

DEFICIENCIES FOUND DURING THE INSPECTION OF ALPHA THERAPEUTICS CORP, LOS ANGELES, 6-10 OCTOBER 1989.

A. CRITICAL

Heptane-treated AHF

The procedure is unacceptable in that treated product is handled in a manner likely to lead to re-contamination.

The major concern raised last time has not been addressed - air from the albumin-handling area is drawn in and blown over the Factor VIII Bulk Product after treatment.

In addition, untreated Factor VIII powder is present in the room where the treatment takes place, especially around the lid of the treatment tank, and where the treated powder is unloaded from the open tank.

Personnel, gowns and equipment are shared with an area where unpasteurised albumin is handled; albumin powder is present on ledges and shelves.

In addition, general conditions in the room are not up to standard; condensation is constantly dripping from overhead pipes and the area is far too small.

B. MAJOR

1. The air-pressure differentials in the 2 virus-controlled areas are not properly balanced/specified and measured. Magnahelic gauges are not regularly read and logged against defined specifications. In addition, there are insufficient gauges in the new area to give all the necessary readings.

2. Autoclaved equipment (final bulk tanks) are brought into the viral inactivated areas on wheeled trollies which come in from outside the area.

   There is a need dedicated equipment inside the area.

3. There is no positive air pressure measure or alarm on the cool side of the South side tunnel sterilizer.

4. There is no positive air pressure alarm to the South side sterile filling room.

C. OTHERS

1. The CIP system for Venoglobulin process vessels is not functioning and manual cleaning has not been validated. The method for cleaning varies but is not recorded, other than as "cleaned".

2. The log of Hydrochloric acid usage was not available in the Venoglobulin area.

3. Standard Operating Procedures are often not available in areas where the work is done - in particular, the viral inactivated area, where the staff cannot go out to get them.

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4. There is no bioburden testing of Venoglobulin pre-filtration bulk.

5. In the AHF area, a rinsing line was stored without water being fully drained from it.

6. In the VI Area, the LAF cabinet used for sterile connections had no validation/maintenance sticker and there is no written cleaning procedure or record of same.

7. QUALITY CONTROL CHEMISTRY TESTING

   a) There are inadequate records of tests - only results are recorded; batch numbers or reagents are not recorded.

   b) The procedure for monitoring the temperatures of fridge and freezers (where samples and standards are stored) is in need of review.

8. The Quality Control sampling of chemical raw materials is in an open warehouse.

9. The SF and F Gown Room is at higher air pressure than the Staging area. This was reported by QC but no action had been taken.

10. There is no environmental monitoring of the capping rooms and there is limited unsealed vial protection prior to the capping machine.

11. In SF and F, there is no changing procedure displayed in the Gowning Room.

DHSC0001362_0018

APPENDIX 22

APPENDIX 2

Alpha THERAPEUTIC CORPORATION®
5555 Valley Boulevard, Los Angeles CA 90032
(213) 225-2221 TLX: 4997369

November 2, 1989

Mr. K. J. Ayling
Superintendent Medicines Inspector
Medicines Inspectorate, Room 1804
Department of Health and Social Security
Market Towers
1 Nine Elms Lane
London, SW8 5NQ
England

Reference: Inspection of Alpha Therapeutic Corporation, U.S.A.

Dear Mr. Ayling:

On October 6, 9 and 10, Mr. D. Warburton and Dr. M. Kavanagh conducted an inspection of our biological product manufacturing facilities at 5555 Valley Boulevard, and 2410 Lillyvale Avenue. At the conclusion of the inspection, Mr. Warburton and Dr. Kavanagh discussed with us one critical, three major, and eleven other inspectional observations.

At this time, we wish to respond to these observations, and confirm our commitment to take appropriate corrective action. Enclosed is a listing of each observation followed by our response. We are naturally extremely concerned at the possibility of action being taken against our UK Product License because of our inability to respond as fully as we would like to the critical observation made by the inspectors. Despite our best endeavors to expedite the change to solvent detergent product, we feel that an unfortunate series of technical problems has caused the delay in our submission of the variation to the UK Product License. We wish to emphasize that obtaining data to support the US and UK license variations has been the top priority at Alpha since the last UK inspection in February 1988. In relation to the other points made by the inspectors regarding the n-heptane area, we believe the responses attached exemplify the sincerity and commitment which the company has to satisfying the concerns of the inspectors.

Alpha Therapeutic has always prided itself on the safety and quality of its products. These aspects in particular have contributed to UK

physician's confidence in Profilate Heat-Treated to the extent that we currently supply well in excess of 80% of UK commercial factor VIII requirements. Since the UK inspectors visit in February 1988, we have been working hard to provide as rapidly as possible a quality Factor VIII product improved over the existing product in terms of both its method and manufacture and its viral safety. We fully realize that the shortcomings of the manufacturing facilities for the existing n-heptane product may pose a dilemma for the UK Licensing Authority.

However, we believe we have now taken every feasible step to ensure the current product is as safe as possible. We are convinced that the solvent-detergent product (for which an application has now been submitted) is a superior product and that it has been developed as rapidly as possible. Finally, because of our majority share of the commercial UK Factor VIII market, we consider that the effect of action against our license for the n-heptane Factor VIII product will be a considerable blow to the UK hemophiliac community. We respectfully ask for time to allow the Licensing Authority to process the solvent-detergent variation application.

We take this opportunity to thank Mr. Warburton and Dr. Kavanagh for the highly professional and courteous manner in which they conducted the inspection.

If you have any questions in this regard, please contact me at (213) 225-2221.

Sincerely,

GRO-C

Marietta Carr
Vice President
Regulatory Affairs

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1155R40

Enclosures

cc: Mr. D. Warburton
Dr. M. Kavanagh

Critical Observation

1. The heptane treatment room is connected to the same air handling system as the acetone treatment and drying rooms. The packaging of heat treated Factor VIII powder, and the cleaning of equipment are done in an area where in-process albumin powder which is not inactivated is present.

Response #1

This observation was noted in the previous inspection by the Medicines Inspectorate. Our response to this observation in our letter of July 15, 1988 addressed to Mr. K. J. Ayling, Superintendent Medicines Inspector was as follows:

> "Our Engineering Department investigated the feasibility of providing an independent air handling system, and an isolated area for the handling of the inactivated powder. Due to the explosion proof requirements for such a facility, and the long lead time for building permits in the City of Los Angeles, they estimated that it would take approximately 18 months to modify the facility. For this reason, our effort is now concentrating on expediting the approval of the solvent detergent inactivation process. We anticipate that this new process will be approved by US Food and Drug Administration and the UK Department of Health and Social Security within this period of time."

Even before the UK Medicines Inspectors visit to Alpha in February 1988, the company had attached top priority to registering a solvent-detergent process for Factor VIII. The initial application was made to the FDA on 25th March 1988 and additional supporting evidence was provided on 18th April 1989 (virus inactivation studies) and 5th May 1989 (labelling). The amendment to the US license was approved on 19th July 1989. Certain technical difficulties were encountered in obtaining high titer HIV-1 and then carrying out in vitro virus inactivation studies. This delayed submission of this data to FDA until April 1989. However, the studies then available did not show the kinetics of viral kill - a requirement stipulated as being necessary for Product Licensing by the UK Medicines Control Agency at the time of their approval of CTX 4447/0017A (Letter dated 19th April 1989 from MCA to Mrs. M. W. Tatt of Alpha Therapeutic UK). Such studies had to be contracted out to certain specialist laboratories and the final reports were dated 17th May 1989 and 30th June 1989. The results from these studies enabled a half-life and recovery study on the product to be carried out and the final report of this study was issued on 19th October 1989. The variation to the UK Product License was submitted on 26th October 1989.

From the above you will observe that Alpha has not in any way unnecessarily delayed the registration of the solvent detergent process. Progress on this aspect was provided as requested to Mr. Ayling by monthly report up until May 1989 when he no longer requested to be updated.

In view of the comments made by the inspectors during their visit on 6th, 9th and 10th October 1989, we have instituted the following steps for all future lots:

1. No acetone dried albumin will be harvested in the adjacent Suspension and Filtration room (1413) while the Factor VIII powder is being packaged in Room 1416.

2. Before each packaging of heptane heat-treated powder, the Packaging Room (1416) and Room 1413 which acts as an air barrier between Room 1416 and the Acetone Drying Room (1411) will be thoroughly cleaned.

3. All personnel will be freshly gowned and gloved prior to handling the Factor VIII powder.

4. All utensils and equipment used to handle Factor VIII powder and all portable equipment from Room 1416 will be cleaned and autoclaved prior to use.

5. We will attempt to modify the air handling system so that a positive over pressure will be created in Room 1416 relative to Room 1413. No personnel access to Room 1416 will be permitted during the Factor VIII powder packaging operation.

In addition, we would like to point out that the terminal filter on the air inlet to Room 1416 is a HEPA filter rated at 99.97% efficiency when tested with dioctylpthalate (DOP). The air handling system provides 6 complete air changes per hour. The HEPA filter has been maintained and tested according to the manufacturers instructions. It is our strong contention that the current process, coupled with the additional precautionary steps detailed in this letter will produce a fully satisfactory product.

Major Observations

1. In the South filling area there is no alarm system to monitor the loss of positive pressure in the filling room and the cooling section of the sterilizer tunnel.

Response #1

Please note that this area was remodeled and is not currently in production use pending validation. However, our Facilities Department was requested to locate and install appropriate alarm systems to monitor the positive pressure in the filling room and the cooling section of the sterilizer tunnel in the South Filling area. We estimate that these alarms will be installed and validated by January 1990, and before this facility is put into production use.

2. The wheels which are attached to the sterile bulk tanks are not autoclaved prior to introduction into the AHF-SD Virally Inactivated (V.I.) Processing area.

Response #2

The wheels are presently being sprayed with disinfectant prior to introduction into the Virally - Inactivated (V.I.) Processing area. This procedure will be reviewed and steps will be taken to autoclave the wheels if necessary, and validate the inactivation of the wheel surfaces prior to entry into the V.I. processing area. A team has been appointed to establish a proper transfer system and have it in place by December 1, 1989.

3. In the AHF-SD V.I. Processing area there is no minimum specification for the air pressure differential between various rooms. Also, the new products V.I. Processing area lacks sufficient number of magnahelic guages to monitor the differential pressures.

Response #3

The air pressure differentials between various rooms in the AHF-SD V.I. processing area was validated to achieve the air flows as shown in Attachment #1. The Manufacturing Standard Procedure will be revised to include the monitoring of the pressure differentials to appropriate minimum requirements. Also, additional magnahelic guages will be installed in the new products area prior to operation which is targeted for January 1, 1990.

Other Observations

1. The sampling of chemical raw materials is carried out in an open warehouse which could result in possible microbial contamination of the chemicals and/or samples.

Response #1

A hepa-filter, vertical hood has been ordered and upon receipt will be used to provide controlled environment for the sampling of chemicals.

2. The pressure differential of the gowning room to the hallway in the SF & F building was higher than the pressure differential of the aseptic staging room to the hallway. This was known for several days with no action taken.

Response #2

The gowning room and the aseptic staging rooms are separated by an air shower which blocks air flow from the gowning room to the filling staging area. However, it is our practice to have the air in the gowning room at lower pressure than the aseptic staging area. This situation was

Response #2 (continued)

corrected on October 10, 1989. Additionally, production area managers were instructed to implement corrective action as soon as these deviations in differential air pressure are noted.

3. There is no environmental protection of stoppered, uncapped vials in the capping rooms in the SF & F building and the Main Plant. The quality of air in these rooms is not monitored.

Response #3

Our Facilities Department is currently designing a tunnel-type cover for the conveyer belt which will extend from the filling/stoppering rooms wall to the capping machine. Since the air in the filling/stoppering rooms is positive to the capping room, the tunnel will provide the same quality air over the stoppered vials until they are capped. We estimate that these tunnels will be installed in the main plant and the SF & F building not later than October 27, 1989. Also as of October 19, 1989 our quality control department began monitoring the air quality in both capping rooms.

4. Gowning procedures are not posted in the gowning room of the SF & F building.

Response #4

Gowning instructions were posted in the gowning room of the SF & F building on October 20, 1989. These instructions are similar to the ones currently posted in the gowning room in the South Filling area of the main plant.

5. The Clean In Place (CIP) system in the IGIV processing area is not functioning and a manual system which was not described in an MSP nor validated was used.

Response #5

The Clean-In-Place system in the IGIV area is being repaired and will be operational on November 30, 1989. In the mean time a procedure will be written for the manual cleaning system, and the system will be validated.

6. A chemical usage log for hydrochloric acid used in the IGIV process was not available for the bottle of HCl in use.

Response #6

A chemical usage log for the hydrochloric acid used in the IGIV processing area is used routinely. Information regarding the specific bottle in use during the inspection was entered on the log immediately after this observation was made.

7. Manufacturing Standard Procedures (MSP) were not available in work areas such as the Virally Inactivated (V.I.) processing area.

Response #7

The appropriate MSP's for work done in the V.I. processing area were provided inside the area on October 16, 1989.

8. Bioburden testing of the IGIV bulk is not performed. It was noted that plans are to perform the testing when the procedure is approved.

Response #8

The procedure for the testing of the IGIV bulk solutions was approved on October 2, 1989 and testing of the bulks was implemented on October 23, 1989.

9. The Laminar Air Flow (LAF) unit in the V.I. processing area lacked a record that it was certified. In addition no cleaning record or cleaning procedure was available.

Response #9

The LAF unit in the V.I. area was certified prior to use. However since the certification sticker was misplaced, it will be certified again and certification records will be kept in the appropriate area. Additionally a cleaning log was implemented on October 20, 1989, and a cleaning procedure will be written.

10. Inadequate records of chemical tests in that the lot numbers of reagents were not being recorded.

Response #10

The test records for coagulation products do include the lot numbers of reagents used. This practice was implemented for other products and chemicals on October 23, 1989.

11. The sample storage and test reference material storage (i.e. Factor VIII Mega I) refrigerators and freezers in the QC laboratory did not have adequate temperature control records. Out of temperature conditions lacked notation of corrective action.

Response #11

Appropriate temperature records will be maintained for all refrigerators and freezers used in the Q.C. Laboratory for storage of samples and reference materials. Additionally, the temperature record form is being revised to provide specific space to document temperature deviations and corrective action.

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Attachment 1

V.I. PROCESSING AREA

V88-003

I. Environmental Monitoring

E. Air Flow Verification:

1. Objective: To validate that the air flow is as designed.

2. Acceptance Criteria:

a. Room air differential.

Description				Approx. Differential
1. From	room 148A to		146.	0.10 inches of water.
2. From	room 148A to		121B.	0.05 inches of water.
3. From	room 148A to		130B.	0.05 inches of water.
4. From	room 148A to		121A.	0.05 inches of water.
5. From	room 148B to		148A.	0.05 inches of water.
6. From	room 121B to		146.	0.05 inches of water.
7. From	room 130B to		129.	0.05 inches of water.
8. From	room 130A to		146.	0.05 inches of water.

b. All air flows between rooms must be as shown on attached drawing.

3. Results:

a. All rooms listed in 2a passed.

b. All air flows between rooms are as designed.

4. Conclusion: All rooms met minimum air flow and differential pressure requirements.

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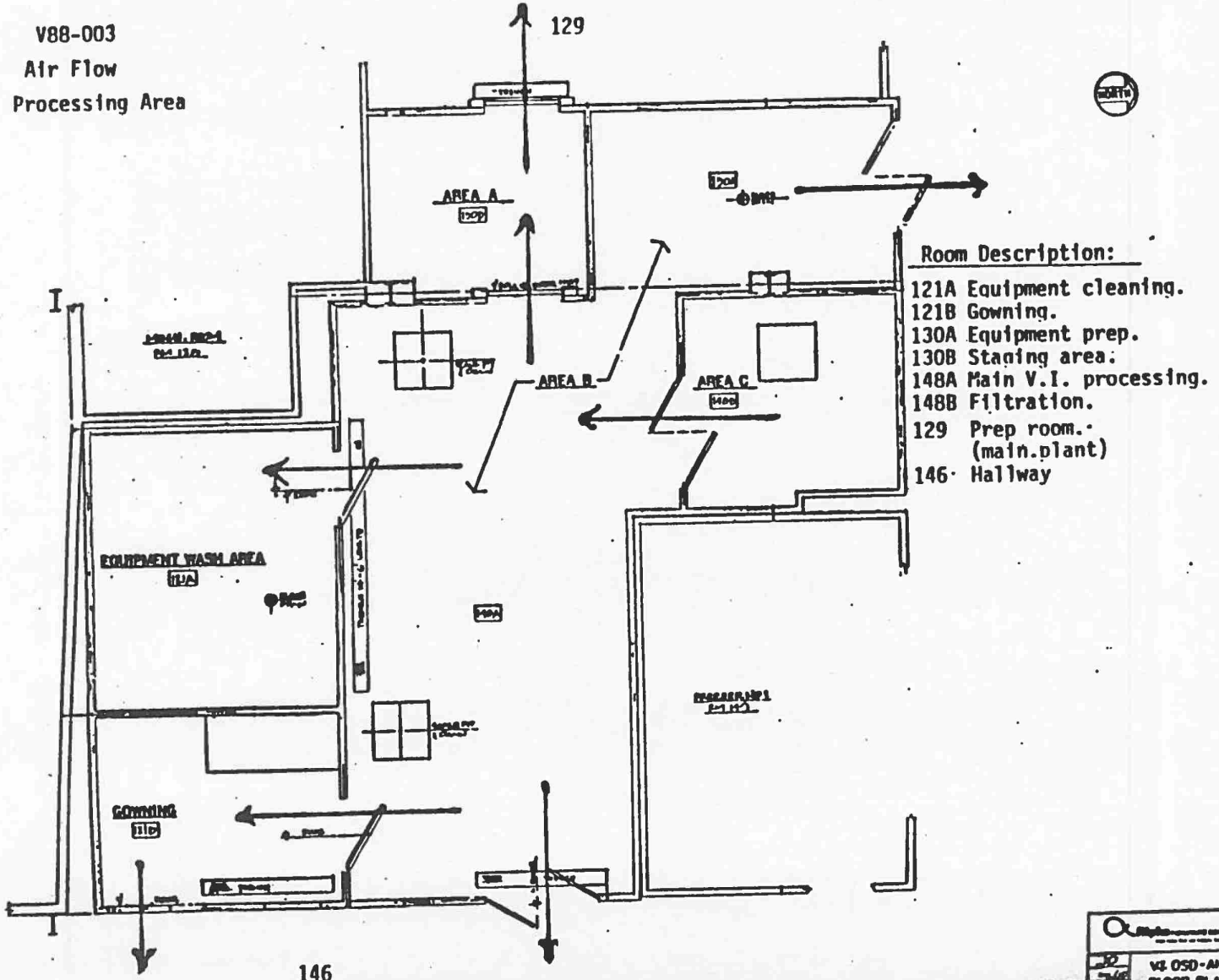
V88-003

Air Flow

V.I. Processing Area



Room Description:

121A Equipment cleaning.
121B Gowning.
130A Equipment prep.
130B Staging area.
148A Main V.I. processing.
148B Filtration.
129 Prep room. (main.plant)
146 Hallway

V8 050-AHF
FLOOR PLAN

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