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GRC Consultants

19882

166 p.
diagrams

GMP AUDIT REPORT

AND

RECOMMENDATIONS FOR IMPROVEMENTS

TO

HUMAN INTERFERON PLANT

FOR

TRIGON, BUDAPEST

UNIDO CONTRACT 92/100P

G E GUIDOBONI
SEPTEMBER 1992

This report has been prepared for the United Nations Industrial Development Organisation (UNIDO) for the project TF/HUN/90/911 "Advisory Services to TRIGON on the Manufacture of Diagnostics and Registration of Interferon"

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SYNOPSIS

An audit of the existing facilities of Trigon for the production of human interferon (EGIFERON) has shown that the Trigon staff have an understanding of the requirements for compliance with Good Manufacturing Practice (GMP) for a biologically produced pharmaceutical.

However, the audit has also shown that certain key aspects of the facility could not be considered adequate or appropriate for a modern biotechnology unit in which a sterile injectible product is made, and which requires approval and licencing by the US FDA authorities.

Recommendations are made for upgrading and rehabilitating the existing facilities, but the extent of the required modifications suggests that it might be more appropriate to consider the production of Egiferon in a new purpose-built facility.

Guidelines are included on key aspects of clean room design, clean room clothing and clean room operation, as well as particular aspects of HVAC design, especially the integrity testing of the HEPA filters and associated fittings.

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SECTION 1

INTRODUCTION

1 INTRODUCTION

Towards the end of 1989, the Government of the United Kingdom announced that it was to establish a Know-How Fund (UK/KHF) for Hungary to assist selected major production companies in the preparation of short to medium term programmes for upgrading and expanding research and development as well as improving the existing production facilities, first of all in the pharmaceutical, fine chemical, food and biotechnology sector of the industry. To this end the UK/KHF commissioned GRC Consultants, under bilateral arrangement with the Hungarian Government and industrial counterparts, to conduct a general review study of the pharmaceutical industry which formed the basis for this project.

Many opportunities for follow up activities were identified in the study (1). The Hungarian Government assigned priority to the Trigon project and requested financial support from the UK/KHF through UNIDO.

In May 1992, GRC Consultants was awarded a contract to carry out this project and work began at the end of May 1992.

The original Terms of Reference for this project included a Concept Design Study for the rehabilitation of the Trigon diagnostics production unit in Budapest and an advisors report on the requirements for registration of human interferon.

However, at the project kick-off meeting (2) it was agreed that Trigon wished to change the Terms of Reference basically from a diagnostics to an interferon production Concept Design Study but the registration requirements report was to remain. It was explained that diagnostics now form a small and decreasing part of Trigon's operations, especially since the reorganisation and privatisation of the company and its separation from its parent company Egis.

The change in Terms of Reference from diagnostics production to interferon production was significant in that the diagnostics production unit was not an FDA approvable or validated facility whereas clearly the interferon project is certainly subject to authority approval and validation of equipment and techniques. The preparation of a Concept Design Study for interferon production, together with the audit of the existing interferon facility, could therefore require an increase in effort by GRC Consultants and an increase in programme length.

This was accepted by all parties present at the kick-off meeting and GRC Consultants began the modified project (emphasis on the audit and recommendations for improvements where necessary) with an audit of the existing interferon production facilities.

This report contains the results of the audit, together with the recommendations for upgrading, which are presented in a number of self evident sections as shown in the Contents list.

It is appropriate to record that GRC Consultants and Trigon have signed a Secrecy Agreement which enables technical, scientific, commercial and other sensitive information to be transferred between, and used by, both parties in strict confidence.

Furthermore, because of the fact that the technical and scientific data and registration information received from Trigon remain the property of Trigon, all the reports prepared for this project are marked 'Confidential' and are restricted for the use only of project personnel.

SECTION 2

OVERALL PROJECT AIM AND SCOPE OF REPORT

2 OVERALL PROJECT AIM AND SCOPE OF REPORT

The original primary aims of the project were twofold. The first aim was to conduct a Good Manufacturing Practices (GMP) audit to define what actions might be needed to upgrade the existing Trigon facilities for the production of diagnostics.

The second aim was to advise Trigon on what steps have to be taken in order to carry out a product registration application for the interferon product EGIFERON. This advice is the subject of a totally separate report. (3)

However, as mentioned in the Introduction, the Terms of Reference for the project were agreed to be changed, at the kick-off meeting (2), with the most significant point being that the GMP audit was to be concerned with the facilities for the production of EGIFERON, not diagnostics. The actual audit was carried out during the course of two visits to Trigon (2, 4) and the results of the audit of the existing facilities are given, basically, in Section 4 of this report.

As a result of the survey and audit, various recommendations are made for the rehabilitation of the existing facilities to the condition which GRC Consultants believes, but in no way can guarantee, should be acceptable to EC and FDA inspectors (as part of the Facilities or Establishment Licence application - see (3) "Report on Work Required to Gain US Regulatory Approval for EGIFERON" which is the second report produced for this project).

Within the Terms of Reference, timescale and budget allowed for this project, the recommendations for improvements, etc, concentrate on those aspects which, in GRC Consultants opinion, require the most attention and which are concerned mainly with the quality, design, construction, maintenance and operation of the interferon production unit.

These recommendations, etc, are presented basically in Section 5 and include the key topics of heating, ventilation and air conditioning (HVAC), materials and personnel flows, clean room clothing and changing protocols.

The Appendix to this report contains further information on key topics covered in Section 5 and includes details of procedures for the integrity testing of HEPA filters, seals and housings, since HVAC is considered to be one of the most important features of the existing interferon facility which need improving.

SECTION 3

PROCESS DESCRIPTION

3 PROCESS DESCRIPTION

The description which follows should be read in conjunction with the process block diagram included at the end of this section. The description is intended to give an overall appreciation of the processing steps involved in the current Trigon process for the production of EGIFERON. Because of the sensitive scientific and commercial nature of the process (and product) no specific details are given in this section.

The process includes the preparation of the activating virus at the microbiology laboratory of the Medical University of Szeged but these facilities are not included in the scope of this report.

The process consists of a number of discrete stages as summarised below.

Sendai Virus Preparation

This step is carried out at Szeged and consists essentially of the inoculation and incubation of prepared eggs. After incubation the eggs are broken and the virus fraction recovered by centrifugation. The purified virus fraction is frozen in ampoules and sent by car from Szeged to Budapest. After receipt in Budapest the virus is allowed to warm up to ambient temperature and is used to inoculate the interferon process (see further details later).

Plasma Preparation

This involves the preparation of a human blood plasma fraction which is an essential component of the subsequent incubation. The processing involves mixing with appropriate salts, followed by dialysis and finally sterile filtration. The prepared plasma is then held for QC check before use.

Buffy Coat Cell Preparation

Buffy coat cells (leukocyte rich layer of human blood) is received from the National Institute of Haemotology and Blood Transfusion and is prepared essentially by lysis in the appropriate salt solutions followed by centrifugation. The collected cell culture is then inoculated with the sendai virus preparation as described above, in the presence also of the blood plasma fraction.

Incubation

The buffy coat cells inoculated with the sendai virus are incubated to induce the production of interferon. After incubation the mother liquor is diluted and deactivated. The solution is then centrifuged, pH adjusted and filtered.

Fractionation and Dialysis

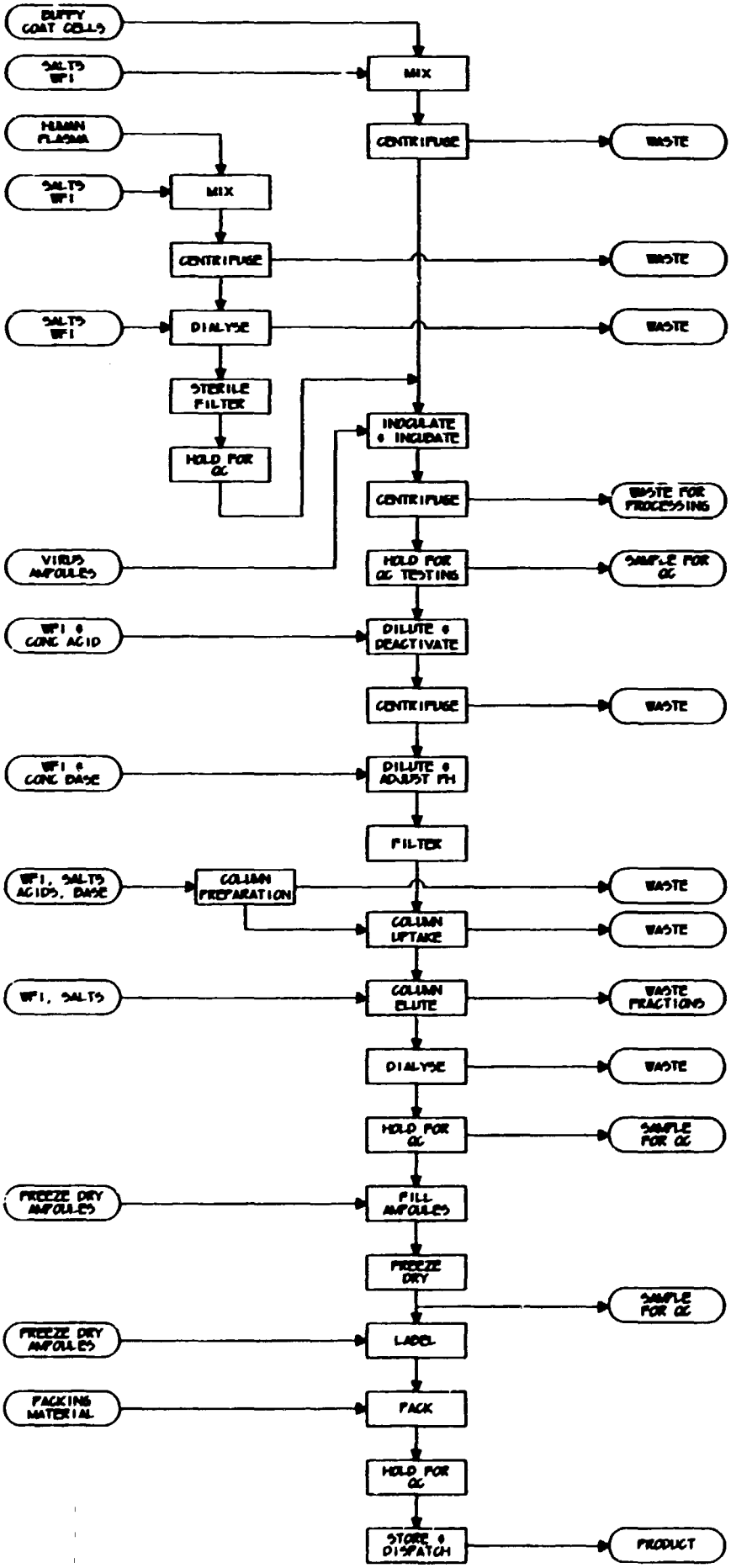
The filtered mother liquor is then fractionated into approximately 20 components by column chromatography over glass beads. The interferons are held on the column and progressively eluted with various eluate solutions which dispose various fractions. Fractions which are selected for further processing are then dialysed to remove ionic impurities.

Freezing and Packaging

The liquor containing the active component from the previous stage is prepared for freeze drying by filling into ampoules. The ampoules are then frozen and the material then freeze dried. After freeze drying the ampoule bottles are labelled and the products held for QC. On release from QC the ampoules are packed as appropriate and made ready for dispatch.

Clearly the above abbreviated processing scheme only gives a brief outline of the steps involved in the production of interferon. It may be observed here that the whole of the interferon production process is carried out essentially in laboratory scale glassware and laboratory scale processing

equipment. There is no processing step (other than the preparation of components and utilities, etc) which in any way resembles medium or large scale biotechnology processing as per the traditional fermentation based industries. It has to be appreciated that the scale of operation is essentially laboratory scale with the inevitable large amount of manual handling and manual movement of bottles, centrifuge tubes, etc, from one location to another. This point is explained in a little more detail in the section dealing with layout.



KEY

WFI - WATER FOR INJECTION

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PROJECT
TRIGON

DRAWING TITLE
HUMAN INTEFERON
PROCESS BLOCK DIAGRAM

DRAWING NUMBER	REV
92/012/201	D

SECTION 4

GMP AUDIT

4 GMP AUDIT

The existing interferon production facilities at Trigon have been examined and audited during two visits (2, 4) primarily for their compliance with US FDA requirements as given in regulations for drug products (Title 21 Code of Federal Regulations, Parts 210 and 211). In particular, the requirements of sections 211.42 (design and construction features) and 211.46 (ventilation, air filtration, etc) were uppermost during the audits and examinations. Attention was paid also to the "critical areas", that is those areas in which the sterilized dosage form, containers and closers are exposed to the immediate environment.

Special attention was also paid to the clothes changing practices, from personnel entry from the street into the facility, right through to the use of "sterile" clean room clothing.

It is appropriate to note here that for the purposes of this project, GRC Consultants has assumed that the handling of the Sendai virus (on receipt from Szeged) and the subsequent process operations which involve 'live' microorganisms, are carried out from the point of view of Biological Hazard Containment Level 1, at laboratory scale. Reference may be made to Appendix I which gives the essential requirements for Level 1 work, as defined by the UK Health & Safety Executive (HSE) Advisory Committee on Dangerous Pathogens (ACDP) guidelines 1990.

4.1 GMP AND VALIDATION IN GENERAL

It is appreciated that the main purpose of the audit, as noted above, is to assess the existing facilities for their compliance with GMP (as would be required by FDA) with a view, eventually, to obtaining an "Establishment Licence", see the other report (3). However, GMP is only one part of a total Quality Assurance (QA) system, and VALIDATION is another topic which must be fully understood in the context of an "approved and validated" facility. Hence the concepts of GMP and validation have significant implications and it is therefore appropriate to review, in this section, key aspects of GMP and validation as they affect the Trigon interferon plant.

4.1.1 Good Manufacturing Practice (GMP)

Good Manufacturing Practice, GMP, is that part of a total Quality Assurance (QA) system which is aimed at ensuring that products are consistently manufactured to a quality appropriate to their intended use. Hence GMP is concerned with manufacture and Quality Control.

It cannot be over emphasized that GMP's are a series of GUIDELINES for the design, validation and operation of a pharmaceutical manufacturing facility. They state WHAT has to be achieved but they are not DESIGN PRACTICES which tell a designer, engineer or manufacturer HOW to achieve the objectives. The translation of the design intent into real life equipment and facilities which satisfy the GMP requirements is the responsibility of the designer, manufacturer, constructor, installer (the contractor) who must demonstrate proven expertise and capability in all of these activities.

The basic principles of GMP require that plant and buildings, such as the development unit, must be located, designed, constructed, installed, adapted and maintained so as to suit the operations, processes and products carried out in them. For the purposes of this project, the interferons made in the unit are regarded as biological products as far as the requirements for GMP are concerned.

The notes which follow reflect GRC Consultants understanding of the up-to-date 'thinking' of US, UK and EC inspectors and are intended to give Trigor some idea of the levels to which design, installation and operation may have to be taken to secure regulatory authority approval.

(i) Current GMP Regulations

Various USA, UK and EC regulations require that all biological pharmaceutical chemicals be manufactured, processed, packed, and held in accordance with current good manufacturing practice. No distinction is made between medicinal chemicals and finished pharmaceuticals, and failure of either to comply with current good manufacturing practice constitutes a failure to comply with the requirements of the various Acts.

(ii) Requirements for GMP

Since the products which are made in the Trigon unit are destined eventually for approval and sale in the EC and USA, the plant will be required to meet the requirements of all relevant national and local authorities. These are as follows:

(a) The process plant and associated areas must meet the requirements typically of the inspectorate of the Food and Drug Administration of the USA (FDA), the Medicines Control Agency (MSC) of the UK and the appropriate EC authorities.

(b) The areas in which the finished or intermediate product is exposed to the atmosphere must be designed to meet good manufacturing standards as specified typically by the "Orange Guide", published in the "Guide to Good Pharmaceutical Manufacturing Practice", published by HMSO.

(c) Local Hungarian planning permission.

(d) Hungarian Building Regulations.

(e) Local Bye-Laws.

The basic principles of GMP which apply to the plant require that buildings should be located, design, constructed, adapted and maintained to suit the operations carried out in them. They also require that equipment should be designed, constructed, adapted, located and maintained to suit the processes and products for which it is used. Building construction and equipment layout should ensure protection of the product from contamination, permit efficient cleaning, and avoid the accumulation of dust and dirt.

Many of the notes which follow are concerned with the process operations as well as the equipment design. A full understanding and appreciation of the production/process requirements is needed if the plant and equipment are to perform as required.

(iii) General Concepts and Guidance

Assurance of product quality is derived from careful attention to a number of factors including selection of quality parts and materials, adequate product and process design, control of the process, and in-process and end-product testing. Due to the complexity of today's medical products, routine end-product testing alone usually is not sufficient to ensure product quality for several reasons.

The basic principles of quality assurance have as their goal the production of articles that are fit for their intended use. These principles may be stated as follows:

(i) quality, safety, and effectiveness must be designed and built into the product;

(ii) quality cannot be inspected or tested into the finished product; and

(iii) each step of the manufacturing process must be controlled to maximise the probability that the finished product meets all quality and design specifications.

Although strict observance of high standards of GMP, approaching or equalling those expected for finished drug products, may be expected in some types of medicinal chemical processes, in many others it is neither feasible nor required to apply rigid controls during the early processing steps. In all processes of this type, however, the requirements should be increasingly tightened according to some reasonable rationale. At some logical processing step, usually well before the final finishing operation, appropriate GMP requirements should be imposed and maintained throughout the remainder of the process.

Good judgement and a thorough knowledge of the process are required to permit sound evaluation of the processing step at which imposition of GMP requirements should take place.

As noted above it will often not be feasible to apply full GMP concepts to the entire process. However, Trigon should be encouraged to apply those concepts to the maximum extent as far backward in the processing chain as feasible.

(iv) Summary for GMP Requirements

It is not possible, or appropriate, to detail in this section how and where all the implications of the above statements may be incorporated into the design of the plant. However, it can be stated that at all stages of the detailed design development, for process design, equipment definition, plant layout, building layout, materials flow, personnel flow, etc, the requirements for GMP and validation should be recognised and incorporated as appropriate. Furthermore, if rehabilitation of the existing facility moves into the detailed design stage, the requirements will continue to influence design activities. Refinements to the design are expected to be made as a better and clearer understanding of the precise equipment items and building/plant layout is gained.

This process of refinement of detail to ensure compliance with the regulations should also continue through procurement, construction and installation to mechanical completion in preparation for the formal validation procedures (see later).

4.1.2 Validation

Validation is a system for establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes.

Validation is also a perception of Quality Assurance which is particular to the pharmaceutical industry. It is based on the premise that it is impossible to conduct Quality Control, or analytical tests, on each and every individual dose of medicine to confirm its purity and efficacy. The approach is therefore taken that the manufacturing process must be demonstrably capable of producing precisely what it is intended to, in terms of both quality and quantity.

(i) Overview

Typically in the EC, UK or USA, a manufacturer starts to prepare the Validation Master Plan at the concept stage of a project, shortly after the product licence has been granted by the authorities and a decision has been made to proceed with commercial manufacture.

The Master Plan encompasses all aspects of the manufacturing process, including facility design, raw materials used, process descriptions, details of manufacturing locations and environmental conditions, utilities, process equipment, automated systems, construction documentation and testing, standard operating procedures, production documentation, on-going monitoring and preventive maintenance programme for the operating environment and equipment, operator qualifications and experience required, staff training, analytical testing programme, equipment calibration (both production and analytical) and many more.

The key to validation is documentation. This provides a record to show, amongst other things, that the facility is what the user specification called for, that the equipment does what it was designed to, that the appropriate processing stages have been faithfully and correctly carried out, and that the operating personnel are appropriate to the tasks demanded of them and properly trained.

With regard to the possible rehabilitation of the interferon plant for Trigon, this means that each aspect of any contractor's scope of works which might directly or indirectly have an effect on product quality must be as follows:-

- Fully and accurately specified.

- This specification to be agreed in writing by the Client.

- Designed in detail so that it is clear what is intended, and demonstrable that the design meets the specification (e.g. by drawings, calculations, etc).

- Manufactured and installed in strict compliance with the design.

- Tested in order to demonstrate that the original specification is reliably and repeatedly met, including under conditions of challenge when a deviation is introduced into one or more parameters (e.g. change of cooling water supply pressure, change of ambient temperature).

It will be seen therefore that:

- Comprehensive documentation must be generated at each stage.

- The requirements are not dissimilar to those of Quality Assurance, with which Trigon are already familiar.

It is essential that all of this documentation is compiled as it becomes available into a separate Validation File - a fully comprehensive dossier which allows a complete verification of a particular feature of the completed facility back through design to the original design intent.

Thus all aspects of the contractor's design must be documented - client's brief, assumptions, calculations, drawings.

Equally, vendors/sub-contractors must supply full design/installation information. This must be requested at tender stage in any enquiry specification, otherwise additional costs will be incurred at a later stage and some information, e.g. materials mill certificates, may no longer be traceable. It is worth considering making a stage payment conditional on the prior receipt of full documentation.

The contractor's Validation File should typically contain the following:

- Scope of Work document
- Definition Brief
- Calculations - by discipline
- Room Data Sheets
- Packages
  For each package the following should be included:
  - order specification
  - vendor design information
  - vendor design drawings
  - vendor as-built information/drawings
  - pre-validation testing details and results
  - operational qualification testing and results
  - construction documentation
- Building layouts

It should be made clear in any enquiry specification what degree of inspection will be involved, who will carry it out, and what documentation is required from the sub-contractor. This must be followed through at the appropriate time to ensure that all the documentation is made available, either from the sub-contractor or from the main contractor's site supervision team.

The document gathering exercise should not be a diffuse uncontrolled exercise. An individual should be nominated from within the permanent project team at an early stage to be responsible for the Validation File. The mechanics of document gathering could then be delegated to others.

(ii) Validation Planning

Whilst the concept of formal validation was introduced for the production of sterile dosage forms only., it is now required for most stages in biological pharmaceutical and medicinal chemicals production.

Validation of the design, installation and operation of the facility is critical to the project. Planning for validation must be considered and undertaken at every stage of the project. Key to successful facility validation is the development of a validation plan. Such a plan will firmly establish the responsibilities for executing each stage of validation.

The validation plan includes the following stages:-

- Prepare outline validation philosophy and scope
- Consult with regulatory authorities to confirm philosophy and scope
- Set up system for collecting and collating records generated during the validation process

- Set criteria for documenting records from outside suppliers
- Develop acceptance criteria for installation qualification (IQ)
- Develop acceptance criteria for operational qualification (OQ)
- Develop protocols for IQ and OQ
- Develop Standard Operating Procedures (SOPs) for each validation test
- Execute IQ, either using contractor's teams, in-house teams or validation consultants.
- Execute OQ using in-house teams
- Prepare the complete validation dossiers for the facility
- Set up a system for auditing and recording design changes which occur during the project up to handover from the contractor.

(iii) Requirements for Validation

(Note: in the context of this study, the Purchaser may be Trigon and the Supplier normally is the equipment supplier or engineering contractor.)

The design, installation and operation of the complete system must be validated to the satisfaction of the Purchaser and the regulatory authorities. The requirements for project validation fall into three areas: Design Validation, Installation Validation and Commissioning Validation.

The Supplier shall provide a copy of the index of his validation manual, for review by the Purchaser, on contract signature or within an agreed period.

Validation and commissioning records will be recorded by the Supplier on forms supplied by the Purchaser. The Supplier is expected to comment on standard or draft forms prepared for this purposes by the Purchaser.

(a) Design Validation

The Supplier must supply copies of all design calculations, drawings and specifications which will be used to demonstrate that the plant as designed is capable of meeting the process design intent, and that the operation of the system can be controlled and monitored so that the design intent can be met consistently and that appropriate operational records can be obtained automatically.

All equipment items, instruments, piping items, valves, etc, are to be uniquely identified, using the Purchaser's numbering system on ELD's/P&ID's, layout drawings and piping isometrics to enable the installation to be validated against the design.

Following approval of drawings and design information, any deviation or change from the design proposed by the Supplier must be approved by the Purchaser in writing before the change is actioned. In addition requests to change from the approved design made by the Purchaser, must not be actioned unless approved in writing by the Purchaser.

(b) Installation Validation

The Supplier must initiate and operate a system of recording the installation activities and checking the installation details against the design. (Of particular importance is the completeness of the documentation associated with welding of sterile service pipework). The Supplier will be responsible for providing pro formas for installation checking, to the satisfaction of the Purchaser.

(c) Commissioning Validation

A validation team will be set up which will comprise personnel from the Purchaser and the Supplier. This team will be led by the Purchaser.

The commissioning validation will comprise two phases. Once the system is running satisfactorily, all the controls and instruments will be validated for accuracy and operation to design. This phase will involve the Purchaser's personnel operating the plant and the Supplier and Consultant advising on test procedures.

The second phase will be the operational validation. In this phase the system will be operated in the intended manner and the performance of the system recorded and compared to the requirements and guarantees. Again, the Purchaser's staff or agents will be available to carry out sampling and the chemical and microbiological tests required. The Supplier will be expected to be involved in these phases.

Items (a) and (b) will form part of the Supplier's scope of work before take over of the plant. Item (c) will be carried out following take over of the plant.

4.2 FACILITIES DESCRIPTION

The existing interferon production unit is located in Budapest at Hogyes Endre U4, H1092 Budapest, not far from the centre of the Pest side of Budapest. GRC Consultants understands that the building, which forms part of a much larger block of buildings included mainly apartments, was constructed in the mid 1930's. The main entrance is at street level, directly off the street into a large security controlled lobby/corridor.

The original building was extensively modified in 1981 to accommodate the production of human interferon as well as a range of biologically based diagnostics in separate facilities. The basic construction of the building consists of conventional brick foundations, brick walls, reinforced concrete ceilings, steel and aluminium cover, aluminium opening frames and heat and light insulating glass in the main production areas. The main roof beams are in the original timber.

The building is located on four levels;

- the basement (below street level)
- the ground floor (at street level)
- 1st and 2nd floors

There is also the ceiling/roof void above.

The building is formed in the shape of a horseshoe with part of the "courtyard" covered to provide storage accommodation at the ground floor level.

The current general arrangement of the Trigon facility is shown in drgs. 92/012/111 - 92/012/114 (in Section 4.4) (based on Trigon drawings) and contains the following:-

(i) Basement

Much of the basement is occupied by toilet and changing facilities, the kitchen and dining room, and other services and utilities facilities. A significant portion of the changing facilities are dedicated to those workers who work in the interferon production areas and the changing facilities as such are classified as clean facilities.

(ii) Ground Floor

There is a mixture of facilities on the ground floor and these include general offices and secretarial rooms, obviously not in the clean area. There are also the main stores which are partly under the covered courtyard and partly in the main block of the building. This floor also contains most of the solution and component preparation ares for the interferon production unit.

(iii) First Floor

The bulk of the rooms at this level are concerned with interferon production and packaging, etc. This floor also contains various laboratories and offices associated with diagnostics and non-interferon work. The interferon and diagnostics facilities are effectively separated.

(iv) Second Floor

A very limited amount of accommodation is available on the second floor and consists mainly of the QC office and QC laboratories for interferon production. Access is also available at this level to the ceiling void and the air handling units in the air conditioning room.

GRC Consultants understands that there is a limited number of stores across the road from the main unit housed in another apartment block. These have not been inspected in the course of this current project.

4.3 GENERAL IMPRESSIONS

The general impressions which follow are based on observations made by GRC Consultants during the two visits of 29th May and 30th July 1992.

The general impression of the overall building is as one would expect from a 1930's construction in a relatively quiet street of Budapest. It is not possible to guess that a biological production facility is accommodated within the building from observations from outside.

The entrance doors are heavy and imposing and the inner lobby/corridor is relatively neat and tidy and is observed by a security man from a security room at one end of the entrance lobby. Access to most areas is controlled from this point and it is difficult to imagine any unauthorised person proceeding any further than the lobby without being challenged.

The stairway from the lobby, either down to the basement or up to the first floor mezzanine office is, as one would expect from this style of building, somewhat enclosed, reasonably tidy but shows the signs of some lack of maintenance.

The general offices, meeting rooms, secretarial and other facilities appear adequate for their purposes.

In the basement area are to be found the main changing rooms both for interferon and diagnostics production although these are separate facilities. The overall appearance of these changing facilities is adequate but their relationship to the toilets and meeting areas is questionable and this point is dealt with further in the sections dealing with layout and materials/personnel flow. The general impression is one of adequate neatness and tidiness but with some now dated fittings, fixtures and facilities (but this is entirely understandable).

At the ground floor level are to be found a range of facilities separated into their various functions. The covered courtyard which acts mainly as a general storage and warehouse area provides weather protection for packaged goods-in materials which themselves are arranged in bays delineated by simple screens. The overall impression, however, is one of a certain degree of untidiness but more obvious is the complete mixture of products, components, raw materials, bits of machinery, etc, all together in the one main storage area. There is no evidence of any strict quarantine (maybe not needed in this area). Access from this covered courtyard is possible to a room which contains various chest freezers which GRC Consultants understands are used for storage of the frozen Sendai virus on its receipt from Szeged. These freezers appear to be locked but the storage room itself is open to the main warehousing area so that in the event of, for example, an accidental spillage or droppage and breakage of Sendai virus vials, the material could be released into the general ambience of the whole warehouse.

Also off this covered area is the general plant room in which is contained the steam raising plant, demineralising water plant and the air handling units for some of the laboratories. This room is rather tightly packed with equipment and access for maintenance work appears to be rather restrictive.

The open part of the courtyard contains various bits of spare equipment and miscellaneous materials stored in a rather haphazard fashion giving a general appearance of untidiness.

Also at the ground floor level are the raw materials preparation and component preparation areas. The immediate general impression in these areas is favourable with neat, tidy, uncluttered corridors, acceptable temperature, with clear evidence of the general avoidance of horizontal ledges, protrusions, etc, thus giving a relatively clean, neat overall appearance.

Within the prep and storage rooms, materials are housed on shelving which is neat, tidy and the materials are in orderly rows giving an overall impression of efficiency and attention to good manufacturing practice detail.

The first floor level contains the bulk of the interferon manufacturing facilities and the overall immediate impression is one of a clean, neat, tidy and workmanlike facility. It is clear that attention has been paid to trying to satisfy the general requirements for GMP but there are examples of possibly poor finish and practice which will be discussed in the appropriate sections which follow.

An impression is formed of a lot of small rooms connected by a relatively few number of corridors and this could lead to considerable movement and interaction of people from various areas. Also materials and products at various times are moved through these corridors and the principles of personnel and materials segregation are reviewed elsewhere. Within the main interferon production area itself, the general appearance is bright and airy and clearly the Trigon staff have tried to satisfy the requirements for GMP as they understand them. However, there are points of detail which may be considered unsatisfactory and these will be dealt with in the appropriate section.

During the first visit in May GRC Consultants had the opportunity to enter the sterile processing suite via the changing areas, etc, and an impression was gained of the approach to the use, maintenance and care of sterile clothing worn in the sterile areas. The general impression was gained that the clothing and facilities reflected Western European practice of some years ago and certain features would be considered inappropriate these days. This is dealt with in a later section.

On reviewing the actual operations which are carried out in the processing area, it became evident that there is considerable movement of materials and people between basically the preparation and incubation area in one room and the centrifuge room alongside. Materials are constantly being moved from one room to the other for processing with the accompanying movement of people.

On the second visit in July GRC Consultants was able to see the roof void space above the interferon production suites and the air handling unit room which serves this area. The general impression in the roof space was generally very unsatisfactory with an obvious lack of maintenance and housekeeping, exemplified by the extensive and persistent areas of pigeon droppings throughout the ceiling void above the interferon production room. This situation would be totally unacceptable in a modern facility.

In conclusion to this section, the overall impression may be summarised as being at first glance reasonable but on detailed examination, and especially when looking at the HVAC arrangements and "behind the scenes", a rather disappointing impression is formed of a lack of attention to maintenance, cleanliness, etc, in those areas which are not immediately obvious to the eye. This aspect is highly unsatisfactory and is totally inappropriate for a modern biotechnology facility producing biological pharmaceuticals.

4.4 LAYOUT

The room layout of the four floors of the Trigon building is given in drgs 92/012/111 - 92/012/114. The building incorporates a central covered courtyard and has several flights of stairs for moving between levels.

In subsequent sets of drawings of the building layout illustrating such things as raw materials flow, only floors which are pertinent to the discussion are reproduced.

Process workers enter the basement changing rooms in street clothes before proceeding in greywear to the process rooms located on the ground and first floors. QR Quality Control and chemical analysis is performed on the second floor.

There are local change areas close to the process rooms where workers change into whitewear.]

The building inherently does not lend itself to incorporating neat layouts which lead to logical and linear personnel and materials flow. There are a variety of small staircases which mean that personnel traffic routes are not readily clear from the drawings alone. The staircases result in alternative routes being available for entry into various parts of the facility. For instance the first floor process corridor may be accessed via the porter's lodge (room 202) or via the basement change area.

The materials flow into the building stores is not centralised and this could lead to problems in raw materials control and Quality Control raw material authorisation. The subject will be dealt with in greater detail in the next section since clear and logical personnel and material flows are essential for the correct operation of a GMP plant.

Some rooms in the building are not used for interferon production. This becomes a problem where these areas, such as the Isotope labs (rooms 301-304) on the 1st floor, share common facilities with the GMP suite. In the case of the Isotope labs they share a common corridor and lift with the GMP suite. Means must be sought to isolate these non-process areas from the GMP areas.

There is no overall facility pressure specification within rooms. This must be introduced as room pressure differentials are essential to maintain contaminants in areas such as the packing room.

The facility contains a large number of toilets which are accessed by personnel in greywear. This is not good practice and toilets should only be available in black areas, accessed by staff in street clothes.

The basement contains a dining room which is used by staff in greywear. This is not good practice and must be modified so that this area is used by staff in black street clothes only.

The laundry which is located in the basement must operate under conditions which are at least as clean as the process areas in which the garments will be worn. Procedures should be in place to verify the cleanliness of the garments after washing. It is understood that the garments are transferred to the ground floor for sterilizing prior to use in the process areas. Under ideal conditions the garments would leave the laundry in a finished state to ensure good quality control and reproducibility. Many Western companies find it cost effective to contract out to an external company the cleaning of clean room garments.

The changing rooms in the basement are located on a different level to the main plant but this is not ideal as it means stairs are required. Stairs are difficult to construct in a crevice free manner and are difficult to clean. Stairs also prevent material being transferred in trolleys and often mean a lift is required for material transfer. Lifts cause additional problems from a cleanliness point of view, as by the nature of their operation they must contain voids and pulley mechanism which can harbour contaminants.

The stairs leading to the basement from the ground floor inner courtyard and the spiral staircase from the basement to the first floor process areas appear to have no doors to prevent gross movement of air into and out of the basement area.

The white coat changing room (room 29) is also open to the spiral stairwell. Doors should be provided at all points in the plant to prevent draughts conveying contaminants to clean areas.

The ground floor has a roofed courtyard area used for storing some raw materials. The method of construction of this roofed courtyard makes it difficult to sanitise effectively. Some raw materials are stored near the engine room and, in the absence of room pressure control, these raw materials may be exposed to migrating vapours, such as oil mist originating from the engine room.

The grey to white changing room for the ground floor media preparation area is room 214. Raw materials from the cold room (room 217) and the weigh room (room 216) must also pass through this change lobby, a situation which is not ideal. It also appears that personnel entering the sterilizing room (room 213) must get changed in room 214 and then walk through the grey corridor to this room. It is not good practice for personnel in different grades of clothing to share the same corridor.

Sterile freeze dry ampoule preparation occurs in the dish washing room (room 211). This operation is carried out close to the waste materials store (room 212) which may contain quanti ies of live virus. The mode of operation of these two rooms should be examined to minimise the likelihood of contamination of the freeze drier ampoules with any virus material. This is particularly important as the waste materials store (room 212) is accessed through the dish washing room (room 211). It is therefore conceivable that

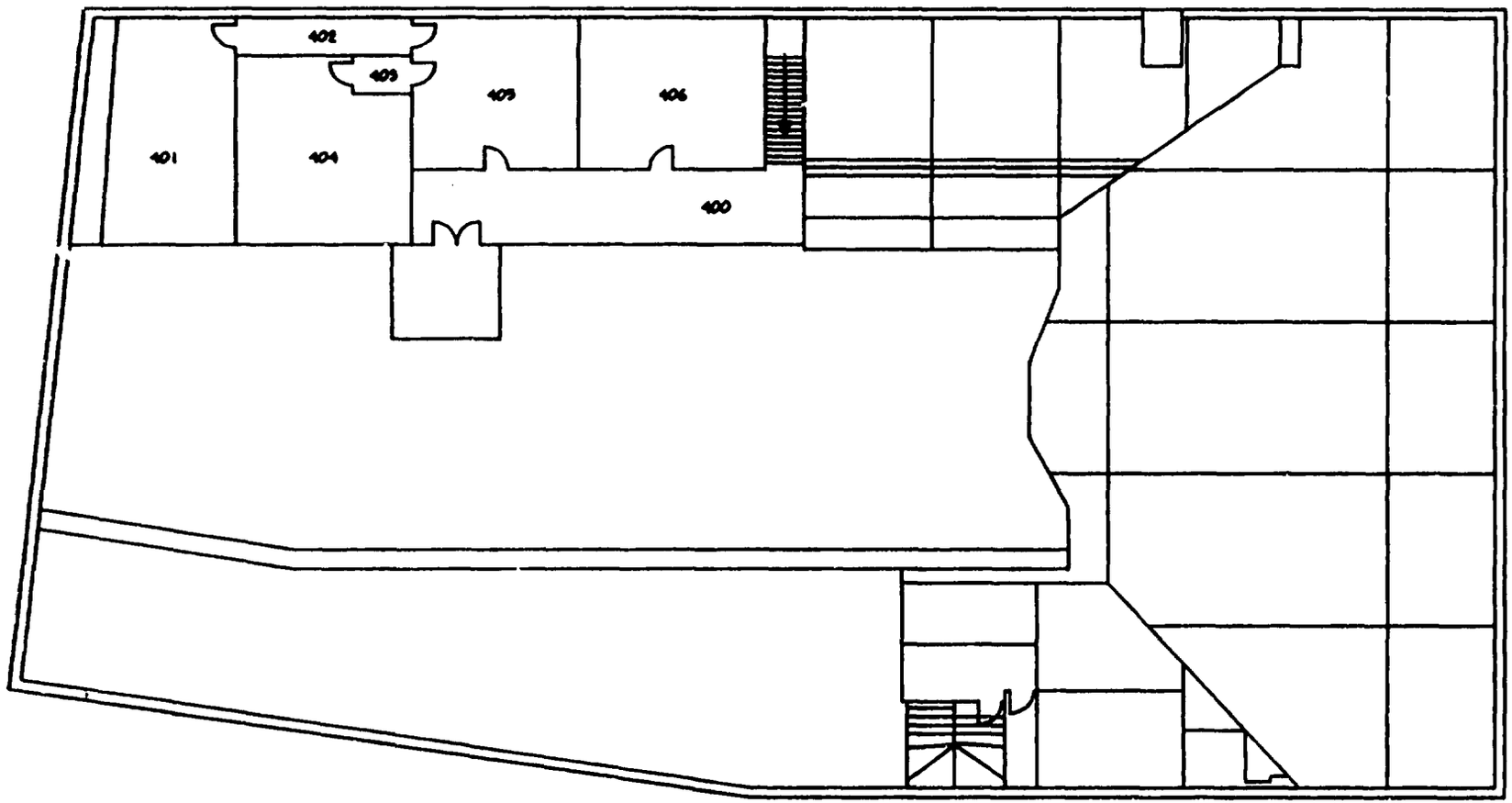
soiled personnel from the waste materials store (room 212) passing through the dish washing (room 211) may produce an aerosol of virus material which the absolute filters on the laminar air flow cabinets will not stop, causing potential contamination of the freeze dry ampoules (or stoppers) if they are exposed under the laminar flow cabinets.

A 'sterile' lift is used for transfer from the ground to the first floor. Because of the nature of lift construction, this lift is best considered grey and all materials carried by the lift should be suitably protected from contamination, for instance by double wrapping.

Storage areas within the building are dispersed and it is believed that some raw materials such as salts are stored across the road from this building. Raw material storage should be centralised for greater control.

The sterile lift transfers materials from room 212 on the ground floor to the sterile solution store (room 325) on the 1st floor. The sterile material is then transferred in a trolley to the sterile suite without passing through a grey corridor. This situation is not recommended and could be improved. The ideal solution would utilise a pass through autoclave between the solution make-up area and the sterile suite, both on the same level.

Room 312 is a lobby which is used for the transfer of personnel and many types of materials into and out of the sterile suite and the packing area. Room 315 is a lobby which is used for the cleaning of materials being transferred and also as a sterile change area. Both these areas appear to be congested and this part of the plant needs modification to give more space for these operations and improve the logical flow of raw materials and personnel.



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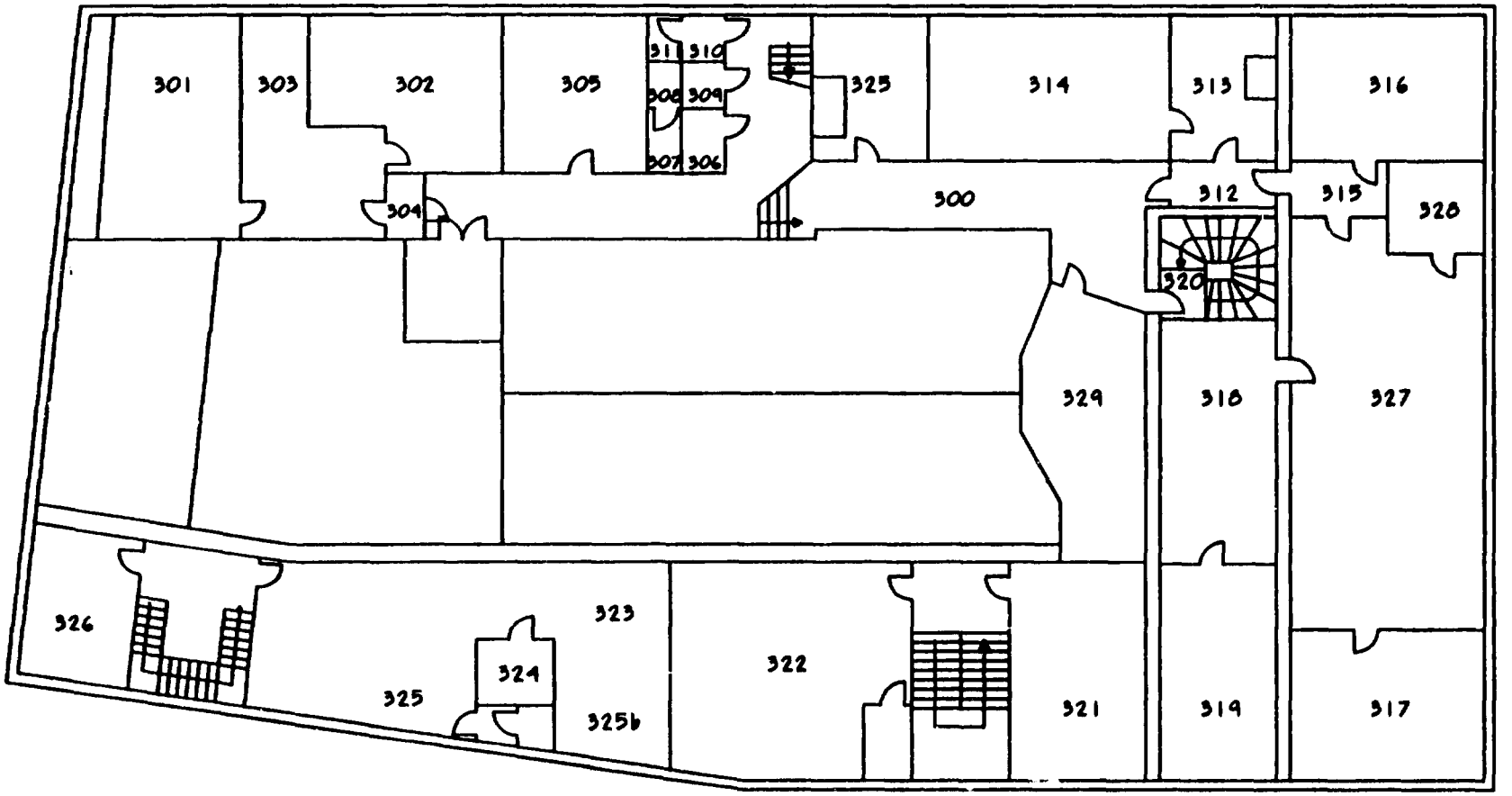
			DRAWING NUMBER 92/012/111	REV A



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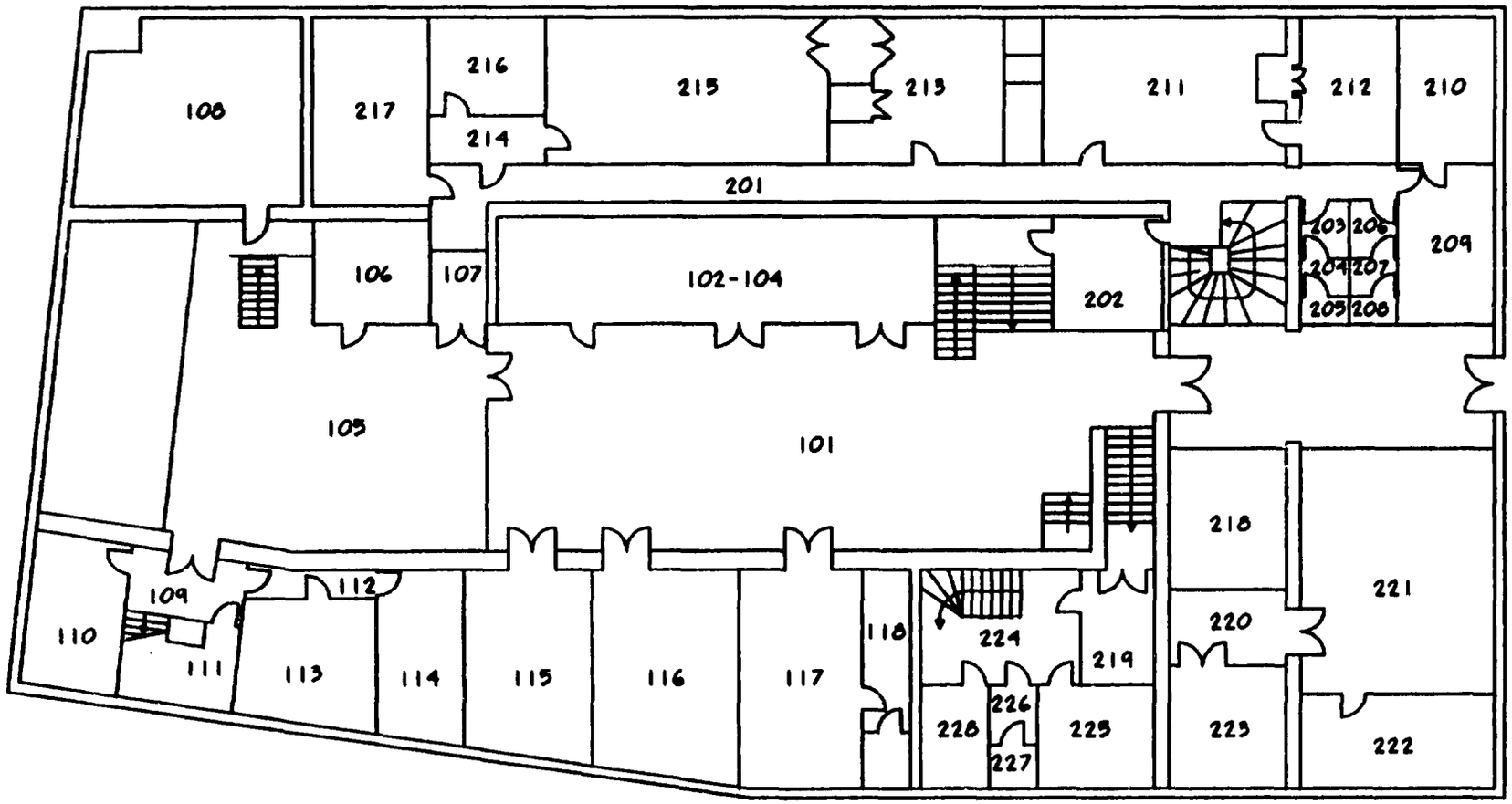
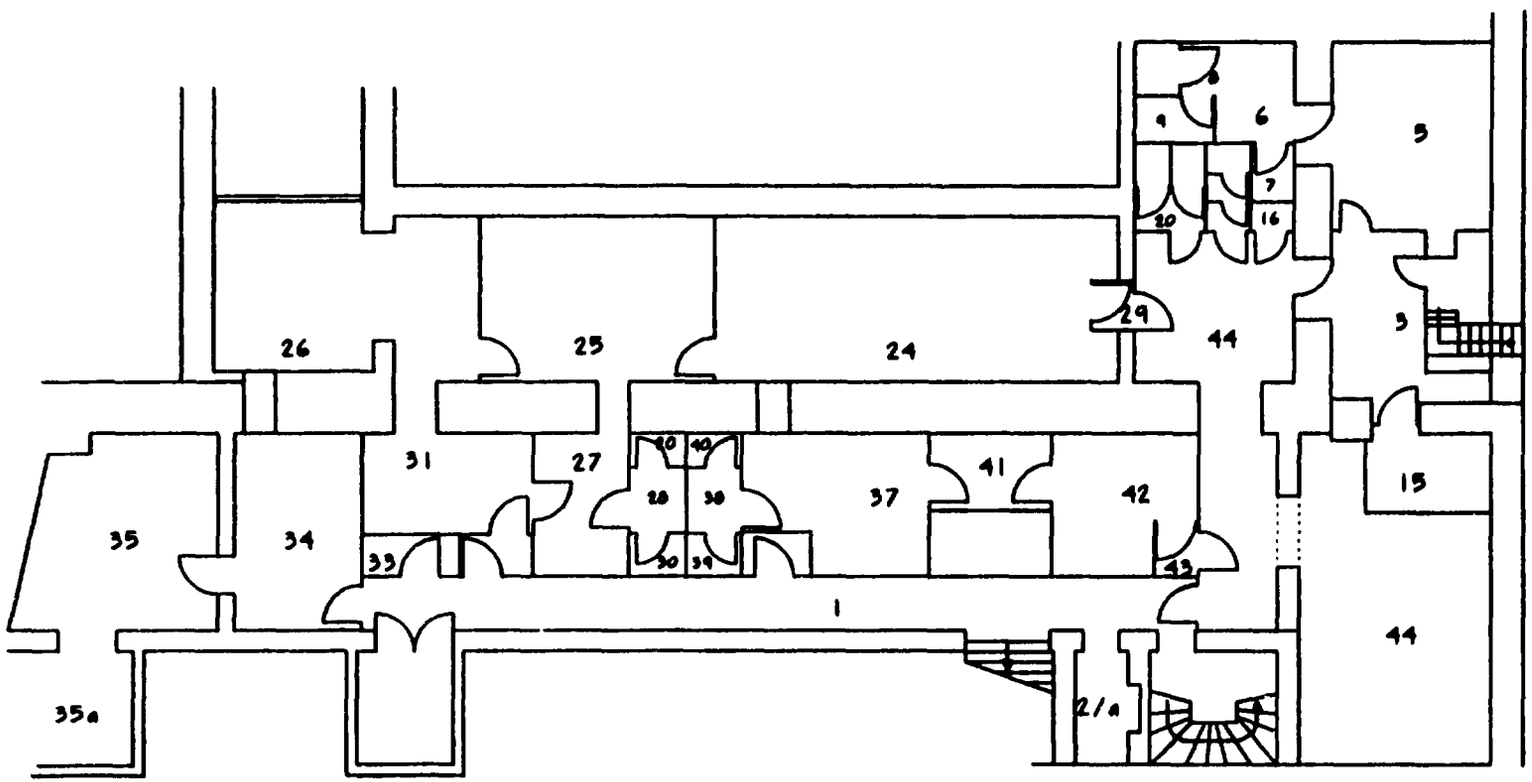
			DRAWING NUMBER 92/012/112 — REV A



GRC CONSULTANTS WESTBROOKE HOUSE 78 HIGH STREET ALTON. HANTS GU34 1EN TEL: 0420 88847 FAX: 0420 88427	CLIENT UNIDO	PROJECT TRIGON TF/HUN/90/911	DRAWING TITLE PRESENT LAYOUT GROUND FLOOR DRAWING NUMBER: 92/012/113 — REV: A



GRC CONSULTANTS WESTBROOKE HOUSE 78 HIGH STREET ALTON. HANTS GU34 1EN TEL: 0420 88847 FAX: 0420 88127	CLIENT UNIDO	PROJECT TRIGON TF/HUN/90/911	DRAWING TITLE PRESENT LAYOUT BASEMENT DRAWING NUMBER 92/012/114 — REV A

Rooms 301-305 on the 1st floor are used for research which is not connected with human interferon production. Attention should be paid to the segregation or relocation of these rooms away from the human interferon plant.

Most of the rooms in the sterile suite on the 1st floor perform different functions at various stages of the process. This leads to many room to room transfers and does not give a logical linear flow of materials through these rooms. The movement of materials through these rooms and the layout of these rooms should be examined to improve material flow through them.

4.5 MATERIALS AND PERSONNEL FLOW

4.5.1 Material Flow

The raw materials used in this facility are split into categories and their movement is shown in drgs 92/012/115 and 92/012/116.

Buffy coat cells and human plasma are used straight away and so are transferred directly to the sterile suite on arrival.

It is understood that salts and some other materials are kept in stores across the road from the man facility. This practice should be reviewed and an alternative method of storage found.

Packing materials are carried through a frequently used grey corridor. Ideally packing material which may well be particle shedding should be transferred to the packing room in a way which minimises the exposure of the grey area to the packing material and the packing material should be sealed in a non shedding cover.

It is clear from the drawing, and the example raw materials receipt presented at the end of this section, that there are a variety of methods and routes used in the receipt of raw materials. These procedures must be simplified in order to tighten controls on materials movement and stock management. Presently there is no central check-in point for raw materials, this must be introduced to enable consistent QC checks of raw materials. The procedures introduced for stock control will be followed by all materials, including those which will be used immediately.

From the raw materials flow and output materials flow drgs 92/012/115, 92/012/116, 92/012/122 and 92/012/123 it can be seen that the corridor (300) and the lobby (312) are widely used for materials transfer in both directions, and there are no distinct routes for materials into and out of the facility. The area around the corridor (300) and lobby (312) is also widely used for personnel traffic. This area needs to be modified to reduce congestion and improve both material and personnel flows.

The sterilizing room (room 213) on the ground floor contains a pass through autoclave and heat sterilizer. Ideally the sterile side of this autoclave should open into the sterile process area. However in this case the sterile goods are transferred via a lift and a grey corridor (300) through a change area (315) to the sterile area. This procedure is complex and hence increases the chances of problems occurring in what should be a simple transfer.

From the output materials flow drgs 92/012/122 and 92/012/123 it can be seen that the packing room (room 314) is accessed through the waste materials transfer room (room 313) on the 1st floor. There appears to be no logical reason for this apart from chance location of the rooms. It is not good practice to use one process room to access another for reasons other than following a logical processing sequence. This is a

particular problem in this case since the waste transfer room will be handling a variety of waste including some which may contain small quantities of live virus.

It is believed that the product is stored with some raw materials in room 114, this is not good practice and some method of segregation should be used.

On the ground floor, weighed raw materials appear to be transferred via the change room (214) to the make-up room (215). This constitutes a problem and the use of a pass through hatch should be investigated.

The process material flow in the sterile area involves many room to room transfers at various stages of production. Investigations to minimise the number of transfers should be carried out.

Some raw materials are stored in the covered courtyard. This courtyard is widely accessed by facility personnel and is used as a general thoroughfare. The raw materials here are therefore open to abuse by passers-by and need to be moved to a secure location or access to the courtyard must be restricted. The security of the whole facility with regard to unauthorised personnel movement should be considered.

Protocol 4.5.1 lists the actions followed by Trigon following the receipt of buffy coat cells and lists the subsequent cleaning procedure. Bottles of buffy coat cells are cleaned in room 315 on the 1st floor, which is also used as a changing area and materials transfer path. As noted previously there is a problem of congestion here. Protocol 4.5.2 lists the movement of virus ampoules. These materials are received, stored, cleaned and transferred to the sterile suite. The ampoules are contained in a plastic bag in a -70°C fridge prior to transfer to the sterile area. If the material was double bagged on delivery, instead of a single bag as at

present, the outer bag would protect the inner bag from potential contamination from the freezer and the journey to the lift across the yard. The outer bag could be left in the lift before removing the ampoules in the inner bag on the 1st floor.

Protocol 4.5.3 detailed the movement of packing materials in the plant.

Protocol 4.5.1

Buffy Coat Cells Movement

Arrival by car

Carry through main door to courtyard

Wipe with cloth outside lift

Put boxes in lift and send to 1st floor

On 1st floor lift bottles of buffy coat cells out of box, leaving box in lift

Carry bottles through to 315

Wipe with cloth and disinfectant

Carry through to 327

Wash with cloth and disinfectant

Wash with alcohol

Place in laminar flow to dry prior to use

Protocol 4.5.2

Virus Ampoule Movement

Arrival by car (the virus samples are packed in bags stored in a cool box with liquid nitrogen)

Take cool box through to store 114 via the lobby 112

Lift bags into -70°C freezer

Store until needed

Lift out ampoules in plastic bag

Carry through to lift

Place in lift and send lift to 1st floor

Remove from lift and carry to 312

Wash outside of bag with water

Carry through to 315

Clean outside of bag with disinfectant

Clean outside of bag with ethanol

Carry through to 317 via 327

Place in laminar flow cabinet prior to use

Protocol 4.5.3

Packaging and Label Movement

Arrival by van

Carry through to lift

Place in lift and send lift to 1st floor

Remove from lift

Carry through to the packing area, room 314, via rooms 312 and 313

4.5.2 Personnel Flow

Personnel entering the facility proceed to the processing areas via the basement black to grey change area and finally change into process sterile wear in a room local to the process area.

The process rooms may be split into the following areas.

1. Ground floor Media Preparation Suite
2. 1st floor Sterile Solution Store (room 325)
3. 1st floor packing and dirty material dispatch (rooms 314, 313)
4. 1st floor sterile processing suite

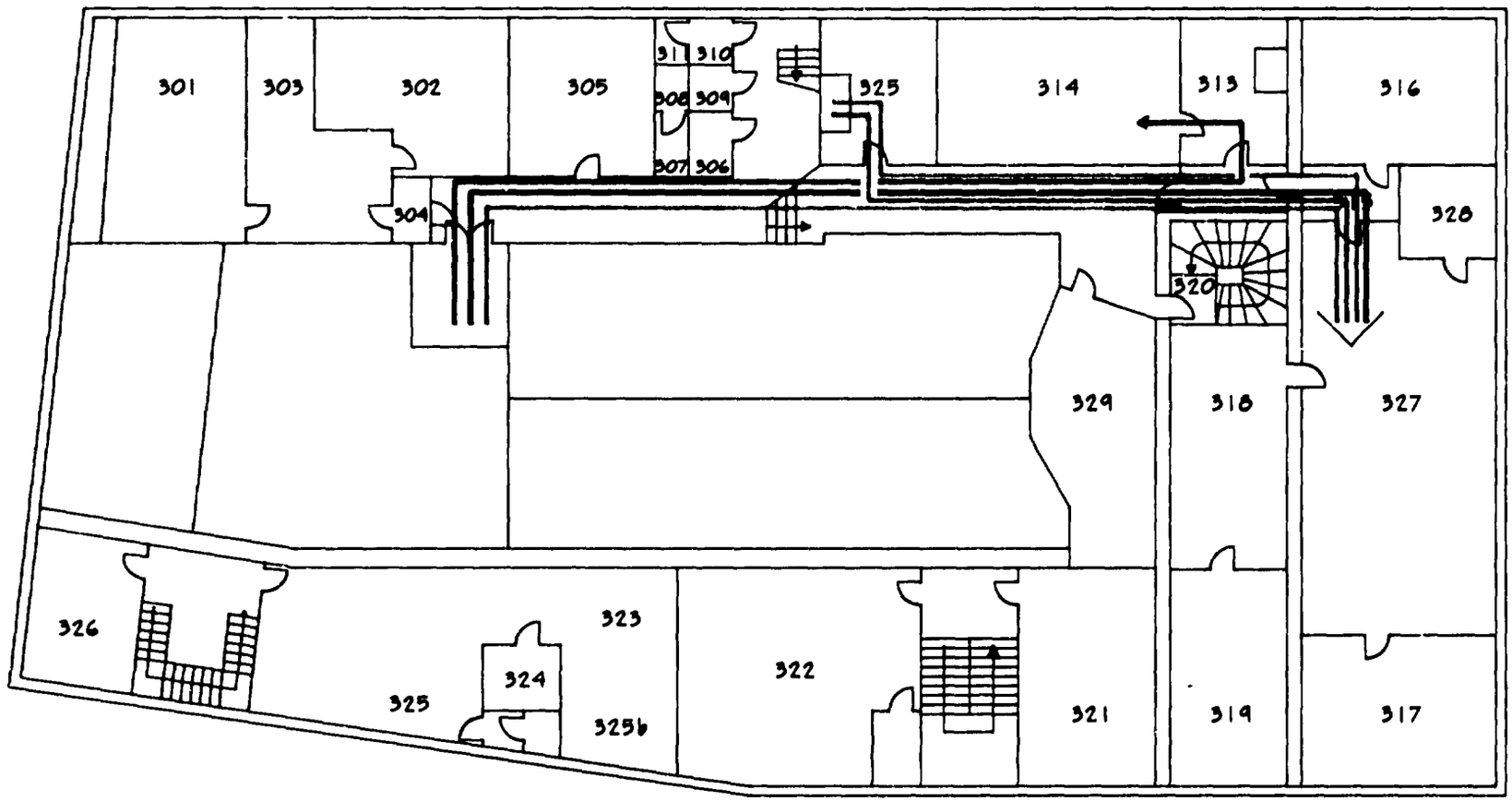
These areas are shown in drg 92/012/120 and 92/012/121.

Areas 1, 3 and 4 above contain a local white change lobby. Area 2, the 1st floor sterile solution store, has no white change lobby and changing into whitewear is done in the room itself.

Drgs 92/012/117 - 92/012/119 show the personnel flow to each of these areas.

The table overleaf shows the changing room used for each of the process areas above. The local grey to sterile change rooms are small and this could lead to problems of physical contact between personnel and clothing contained within these rooms. The operation of these rooms should be assessed under operation to determine whether changing can be reliably achieved without the danger of contamination.

The personnel flows to other areas of the facility part from the process areas is confused by the multitude of stairwells, and as mentioned previously many parts of the facility can be reached by more than one route. The flow of personnel through



DUFFY COAT CELLS
HUMAN PLASMA ——————

SALTS ETC ——————

PACKAGING/LABELS ——————

FREEZE DRIER AMPOULES/
STOPPERS ——————

VIRUS AMPOULES ——————

GRC CONSULTANTS VESTBROOKE HOUSE 78 HIGH STREET ALTON. HANTS GU34 1EN TEL: 0420 88847 FAX: 0420 88427	CLIENT UNIDO	PROJECT TRIGON TF/HUN/90/911	DRAWING TITLE PRESENT MATERIALS FLOW 1st FLOOR
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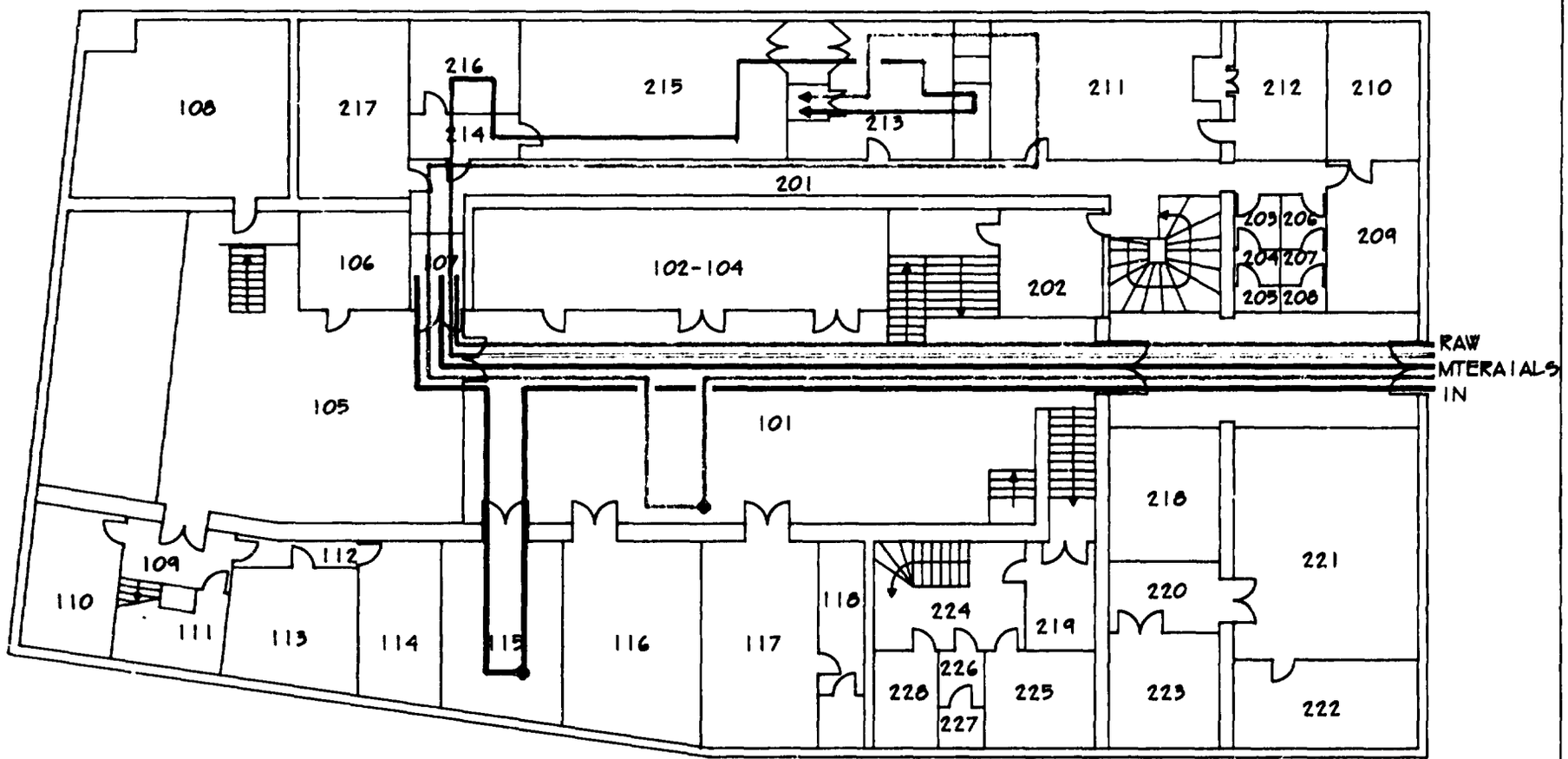


BUFFY COAT CELLS
HUMAN PLASMA

SALTS ETC

PACKAGING/LABELS

FREEZE DRIER AMPOULES/
STOPPERS

VIRUS AMPOULES

GRC CONSULTANTS
WESTBROOKE HOUSE 78 HIGH STREET
ALTON. HANTS GU34 1EN
TEL: 0420 89847 FAX: 0420 89427

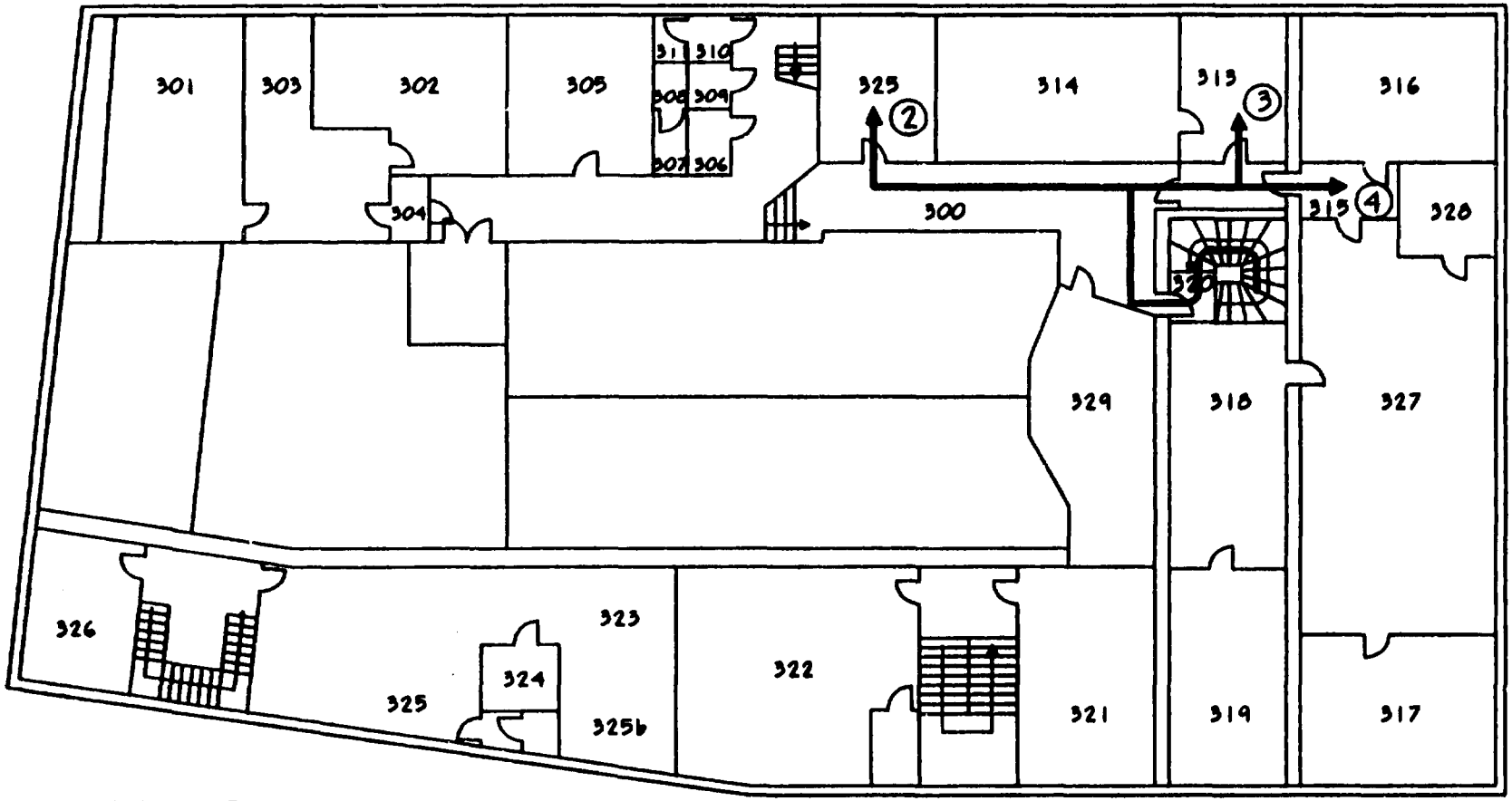
CLIENT
UNIDO

PROJECT
TRIGON
TF/HUN/90/911

DRAWING TITLE
PRESENT MATERIALS FLOW
GROUND FLOOR

DRAWING NUMBER
92/012/116

REV
A



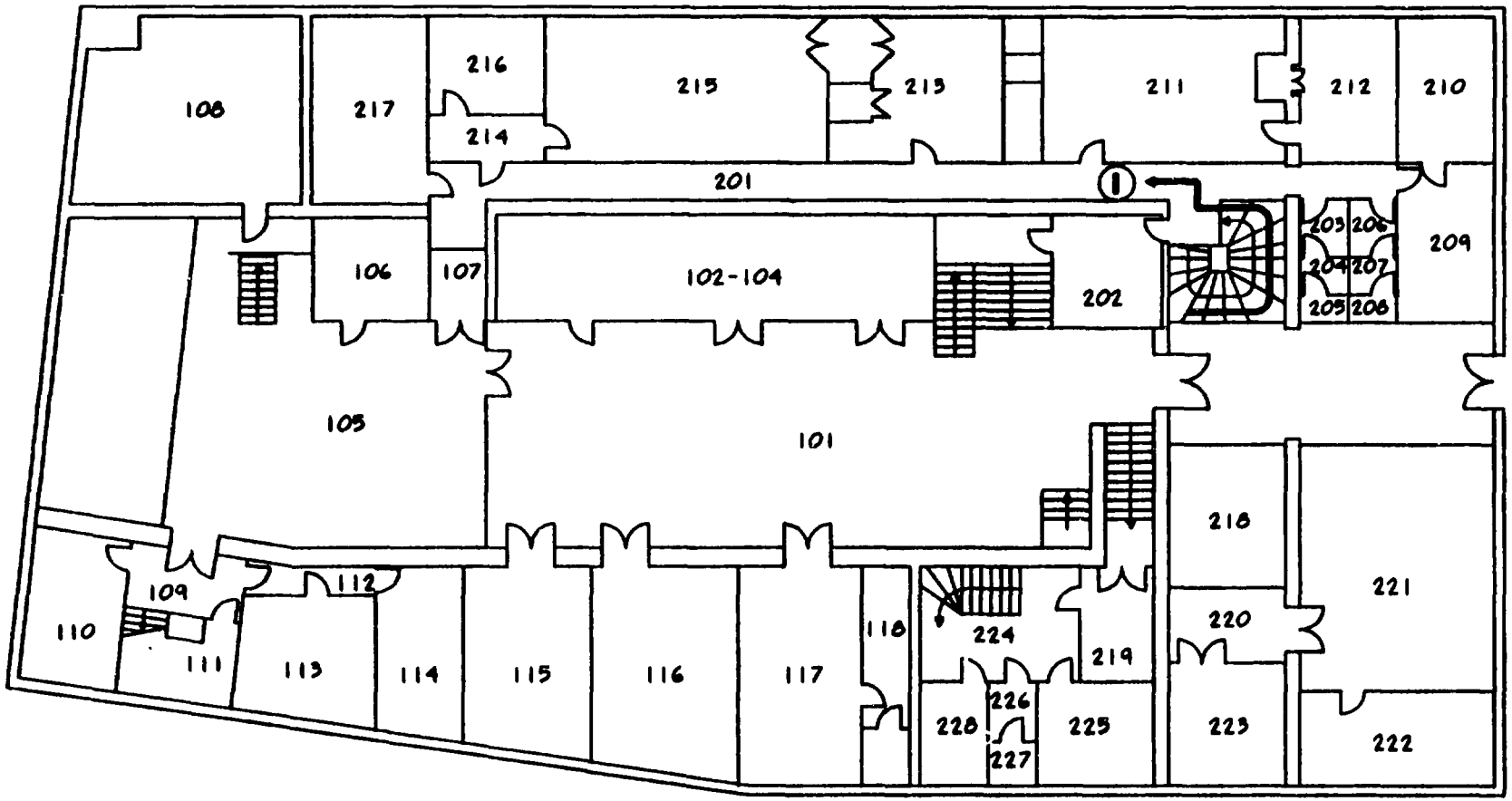
FEMALE PROCESS PERSONNEL

MALE PROCESS PERSONNEL

ALL PROCESS PERSONNEL

THE CIRCLED NUMBERS REFER TO PROCESSING AREAS

GRC CONSULTANTS WESTBROOKE HOUSE 78 HIGH STREET ALTON, HANTS GU34 1EN TEL: 0420 88847 FAX: 0420 88417	CLIENT UNIDO	PROJECT TRIGON TF/HUN/90/911	DRAWING TITLE PRESENT PERSONNEL FLOW 1st FLOOR DRAWING NUMBER 92/012/117 REV A



FEMALE PROCESS PERSONNEL

MALE PROCESS PERSONNEL

ALL PROCESS PERSONNEL

THE CIRCLED NUMBERS REFER TO PROCESSING AREAS

GRC CONSULTANTS
WESTBROOKE HOUSE 76 HIGH STREET
ALTON. HANTS GU34 1EN
TEL: 0420 88847 FAX: 0420 88427

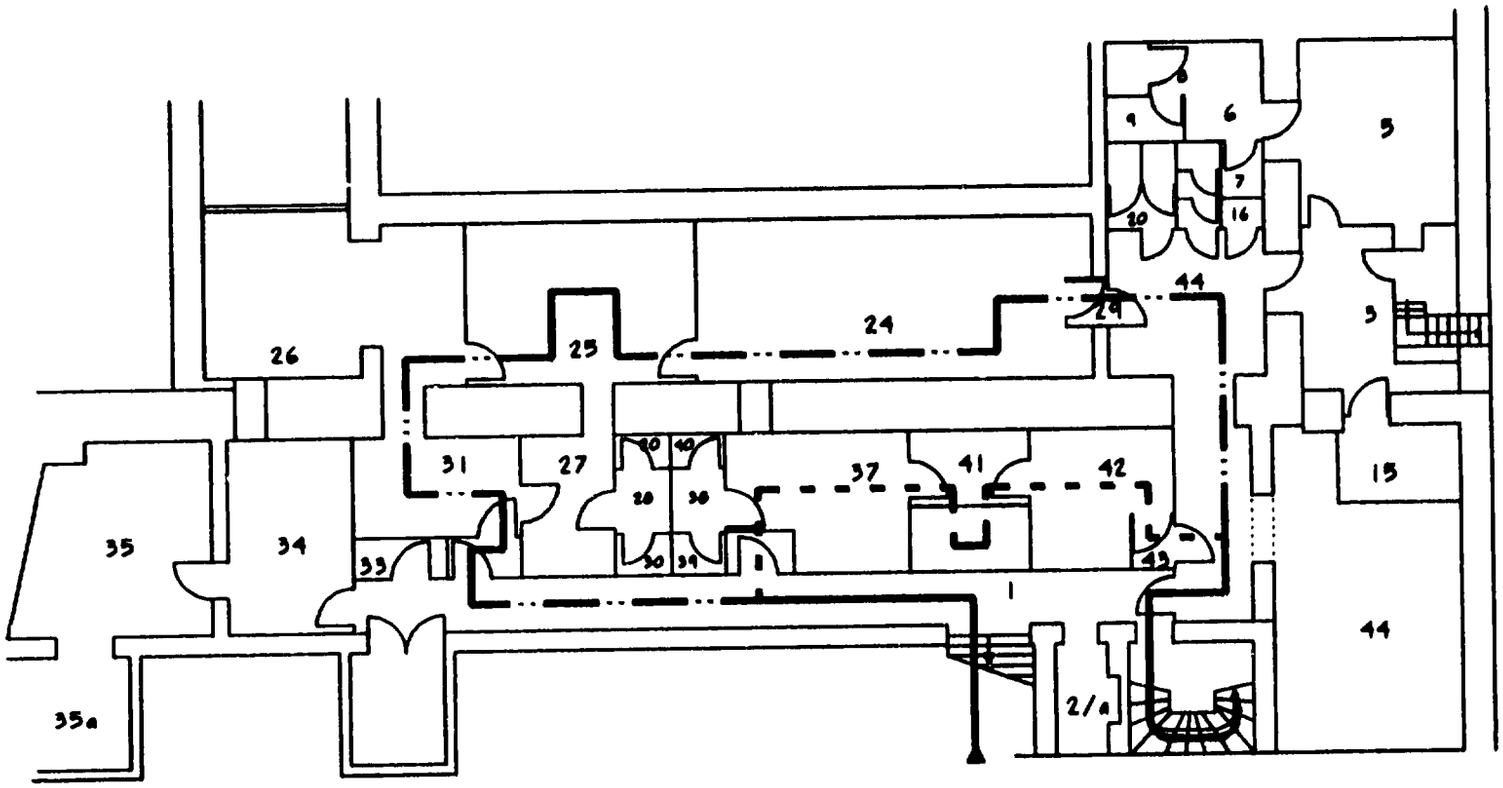
CLIENT: UNIDO

PROJECT: TRIGON TF/HUN/90/911

DRAWING TITLE: PRESENT PERSONNEL FLOW GROUND FLOOR

DRAWING NUMBER: 92/012/118

REV: A

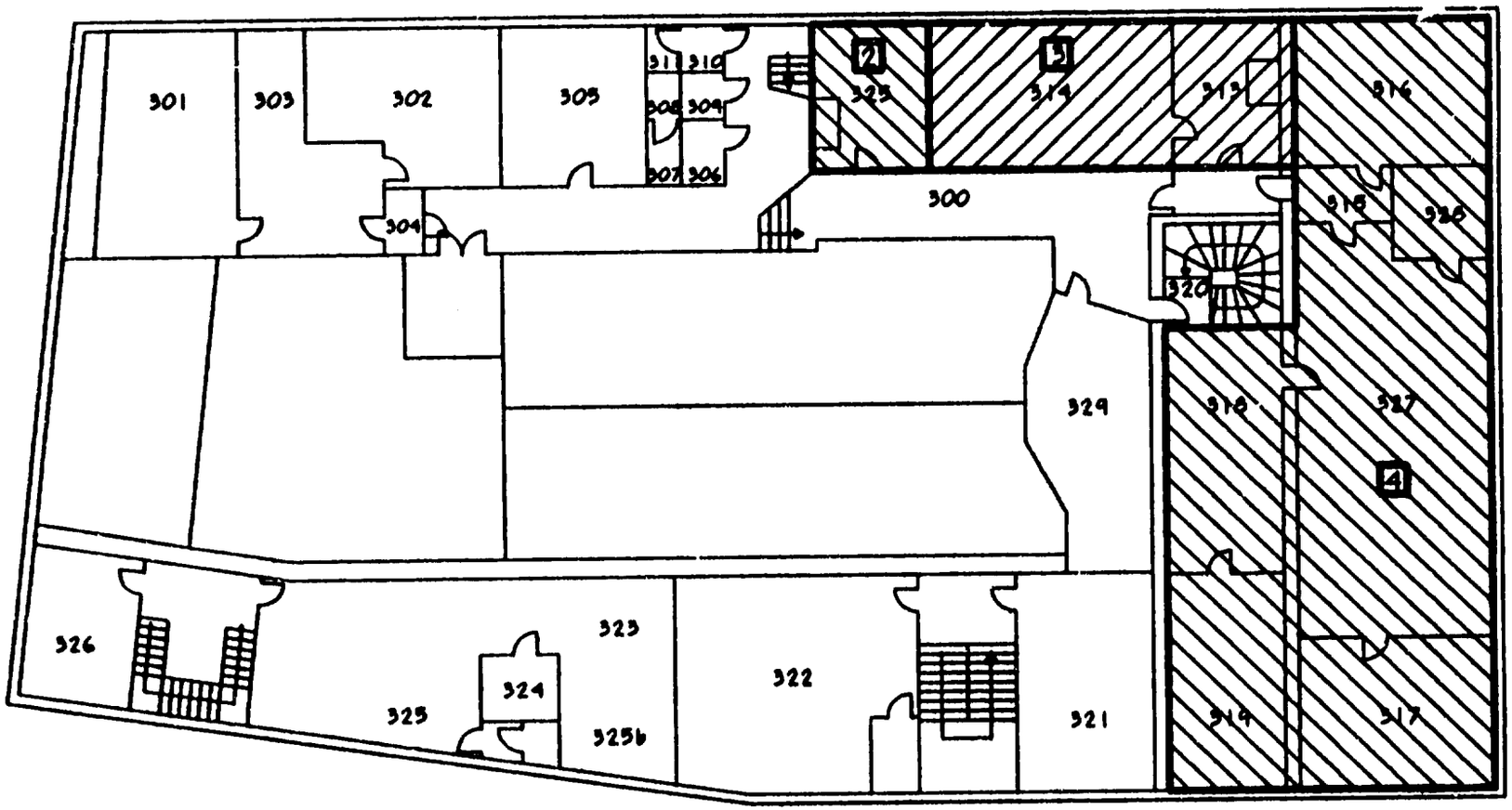


FEMALE PROCESS PERSONNEL

MALE PROCESS PERSONNEL

ALL PROCESS PERSONNEL

GRC CONSULTANTS WESTBROOKE HOUSE 78 HIGH STREET ALTON. HANTS GU34 1EN TEL: 0420 88847 FAX: 0420 88427	CLIENT UNIDO	PROJECT TRIGON TF/HUN/90/911	DRAWING TITLE PRESENT PERSONNEL FLOW BASEMENT
			DRAWING NUMBER 92/012/119
			REV A



PROCESS AREAS

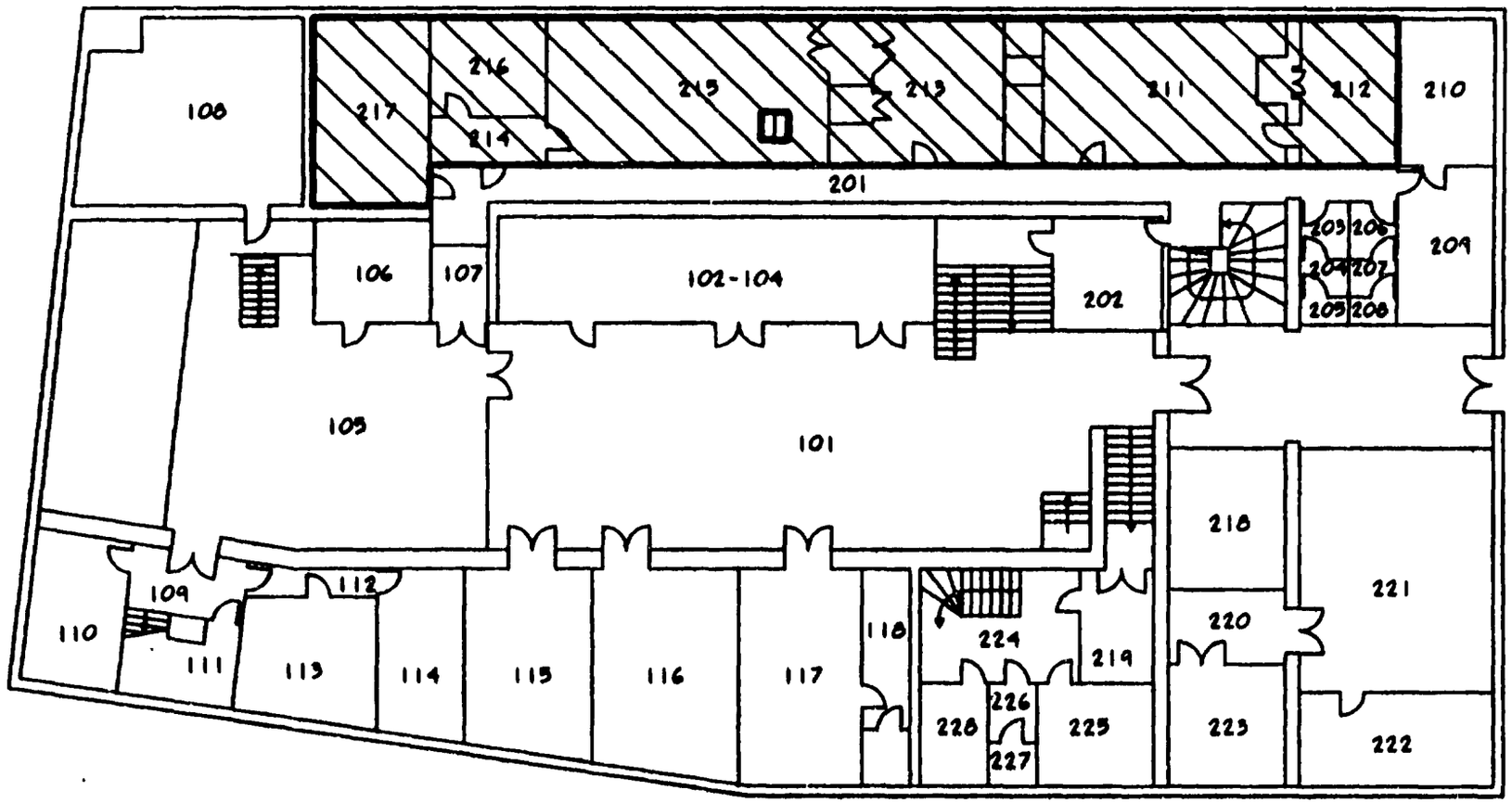
1 - MEDIA PREPARATION SUITE

2 - STERILE SOLUTION STORE

3 - PACKING AND WASTE DISPATCH

4 - STERILE SUITE

GRC CONSULTANTS WESTBROOKE HOUSE 70 HIGH STREET ALTON, HANTS GU34 1EN TEL: 0420 88847 FAX: 0420 88427	CLIENT UNIDO	PROJECT TRIGON TF/HUN/90/911	DRAWING TITLE PRESENT PROCESS AREAS 1st FLOOR
			DRAWING NUMBER 92/012/120
			REV A



PROCESS AREAS

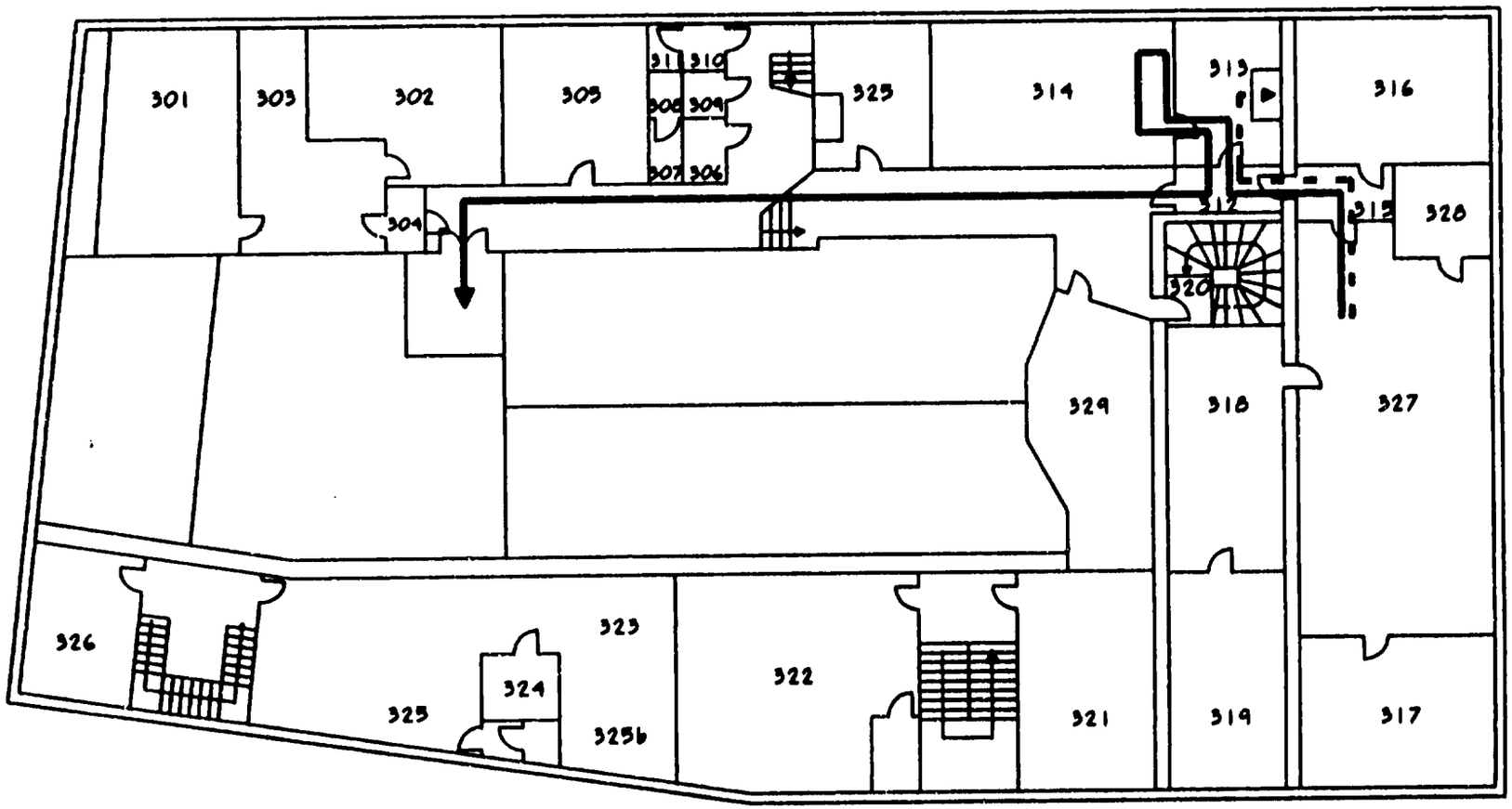
1 - MEDIA PREPARATION SUITE

2 - STERILE SOLUTION STORE

3 - PACKING AND WASTE DISPATCH

4 - STERILE SUITE

GRC CONSULTANTS WESTBROOKE HOUSE 70 HIGH STREET ALTON. HANTS GU34 1EN TEL: 0420 88847 FAX: 0420 88427	CLIENT UNIDO	PROJECT TRIGON TF/HUN/90/911	DRAWING TITLE PRESENT PROCESS AREAS GROUND FLOOR
			DRAWING NUMBER 92/012/121
			REV A



PRODUCT ——————

WASTE - - - - -

GRC CONSULTANTS WESTBROOKE HOUSE 78 HIGH STREET ALTON. HANTS GU34 1EN TEL: 0420 88847 FAX: 0420 88427	CLIENT UNIDO	PROJECT TRIGON TF/HUN/90/911	DRAWING TITLE PRESENT MATERIAL OUTPUT FLOWS 1st FLOOR
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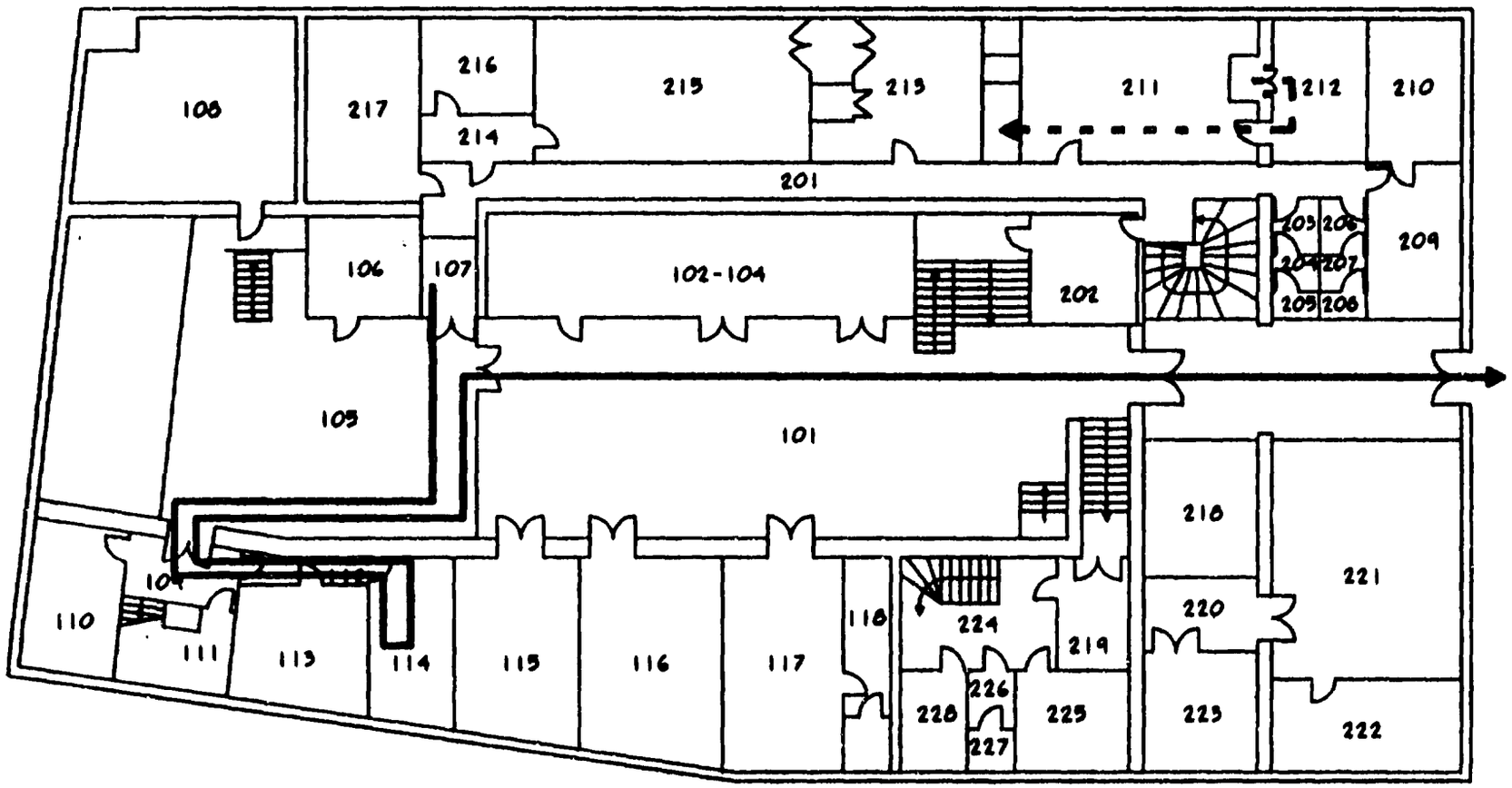
			REV A



PRODUCT ——————

WASTE - - - - -

GRC CONSULTANTS WESTBROOKE HOUSE 78 HIGH STREET ALTON. HANTS GU34 1EN TEL: 0420 88847 FAX: 0420 88427	CLIENT UNIDO	PROJECT TRIGON TF/HUN/90/911	DRAWING TITLE PRESENT MATERIAL OUTPUT FLOW GROUND FLOOR
			DRAWING NUMBER 92/012/123 — REV A

the facility should be rationalised where possible to develop a logical and linear flow. This may involve the merging of some or all of the change areas.

4.6 CHANGING PROCEDURES

The personnel flow description, Section 4.5, identifies the changing areas on the plant. It can be seen that personnel entering the plant first change into greywear which consists of trousers, T-shirt, slippers, underwear and socks. They then proceed to their respective process area and change further in a local changing room.

Protocol 4.6.1 specifies the Black to Grey change procedure. A process worker disrobes in the Black change area and carries his underwear and socks with him to the shower. He showers and collects and puts on his greywear int he Grey change area.

Note that this protocol states that he wears his own socks and underwear in the Grey area. The workers slippers do not cover the socks fully and this exposes the workplace to the linting fabric material of the socks. Workers should be supplied with socks of a non-linting nature. The reuse of workers personal underwear is not ideal but is less of a problem as they are covered by the greywear and hence do not pose a direct hazard to the workplace.

The use of T-shirts as greywear is not ideal as the arms are fully exposed and form a large particle shedding area. However, given the working conditions, T-shirts may be acceptable for reasons of operator comfort.

Protocols for the changing room prior to entering three of the process areas are presented (protocols 4.6.2, 4.6.3 and 4.6.4).

Note that the ground floor media preparation suite and the 1st floor sterile suite change includes the use of hoods and hand cleaning regimes. However, the change procedure for the sterile lift lobby on the 1st floor does not. This could be seen as an inconsistency so a full change procedure should be used.

Slippers with personal socks exposed are used in the sterile area. This is not acceptable, overboots secured against the trouser legs should be used.

The sterile suite protocol (protocol 4.6.4) does not mention the use of masks. It is recommended that the lower face be covered with a mask or an appropriate hood in the sterile suite.

It is understood that gloves are put on in the sterile suite immediately prior to any operations in the laminar flow cabinets. It is recommended that gloves should be put on as part of the change procedure, and are cleaned at appropriate times prior to operating within the laminar flow cabinet.

The changing rooms do not contain stepover benches which separate areas of differing cleanliness. Stepover benches are important as they reduce the contamination of shoes and provide a psychological reminder to staff of the need for stricter cleanliness procedures. Any redevelopment of the changing areas should include provision for stepover benches.

Protocol 4.6.1

Black to Grey Change

Streetwear

Go downstairs to basement

Enter Black Change Area

Remove clothes, place in locker and carry underwear and socks to shower room

Hang underwear and socks on hook

Shower

Dry and put on underwear

Enter Grey Change Area

Remove greywear from locker

Put on greywear (trousers, T-shirt, slippers) and socks

Go out of basement and enter Process Change Area

Protocol 4.6.2

Grey to Sterile - Ground Floor Media Preparation Suite

Enter change lobby (room 214)

Wash hands with disinfectant

Take out green sterile gown from sterile box and put on

Wash hands with disinfectant

Change slippers

Wash hands with disinfectant

Take out hood from sterile box and put on

Enter Media Preparation Suite

Protocol 4.6.3

Grey to Grey/Sterile - Sterile Lift Lobby

Enter 326

Put on green sterile gown in the sterile lift lobby

Go about work

Protocol 4.6.4

Grey to Sterile - 1st Floor Sterile Suite

Enter 312

Wash hands in sink

Enter 315

Wash hands with disinfectant

Take out green sterile gown from sterile box and put on

Wash hands with disinfectant

Change slippers

Wash hands with disinfectant

Take out hood from sterile box and put on

Enter sterile suite

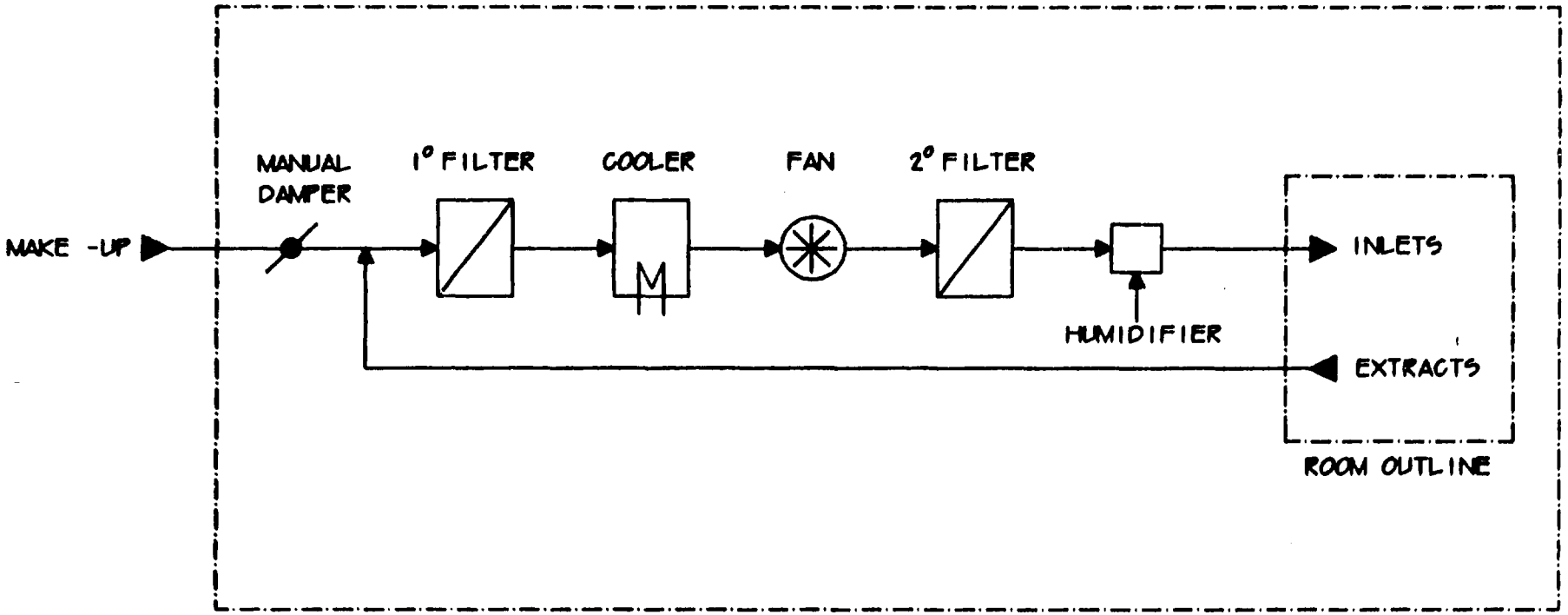
4.7 HVAC

Since HVAC is one of the more important aspects of design for a GMP facility, attention has been paid to the arrangements at Trigon for the HVAC of the interferon production area. Detailed drawings of the original installations were made available and examined in detail at both of the visits in May and July.

GRC Consultants understands that the design and installation of the HVAC system was carried out by an Austrian company during the refit in 1981. The only plans and drawings available date from this time and Trigon are confident that no changes whatsoever have been made to the HVAC layout since its installation in 1981. The system consists basically of a recycle system, see sketch overleaf, with make-up from atmosphere only to compensate for losses of air from the system via doors and other openings. This represents a fairly high percentage recycle rate. Fresh make-up air to the system is taken from the courtyard area via a simple inlet grill (which was seen to be heavily coated with dirt and bird droppings).

Trigon do not normally test the inlet air for quality and there is no pretreatment of the inlet air other than filtration within the unit itself.

The ducting is constructed from aluminium (surface totally untreated) and joints are sealed with conventional "klingerit". GRC Consultants understands that there is no provision for the internal inspection of the main ductwork and this was confirmed during the inspection of the ceiling/service void.



GRC CONSULTANTS WESTBROOKE HOUSE 70 HIGH STREET ALTON, HANTS GU34 1EN TEL: 0420 88847 FAX: 0420 89427	CLIENT UNIDO	PROJECT TRIGON TF/HUN/90/911	DRAWING TITLE HVAC: OVERALL SCHEMATIC DRAWING NUMBER 92/012/202 REV D

Within the interferon production area the air inlet and air extract points are all at ceiling level. There is no attempt at high level in, low level extract in any of the processing rooms.

Within the air handling unit there are primary and secondary filters, details currently unknown but are being sought. The terminal sterilizing filters into most of the process rooms are by ATEX filter and have 99.97% efficiency rating. The main sterile room inlet air filters have 99.99% filtration efficiency. All the filter housings are the originals as installed in 1981 but over the years the filter elements have been repeatedly changed and have been supplied from a number of different sources. Details of the existing filter elements, their type, specification, integrity testing, etc, are being sought.

The air handling system feeding the interferon production suite also feeds some of the laboratories and rooms on this first floor level alongside the interferon production facilities. This means that air from laboratories and other rooms is extracted and fed into the system for input into the interferon production suites on a virtual total recycle basis. The HVAC system was originally fitted with a humidifier based on the injection of ordinary boiler steam. This system is no longer in use and there is effectively no humidity control of the HVAC other than by cooling.

In terms of air flow control, there is a limited measure of manual adjustment on the extract grills by which the air from a room may be effectively prevented from being extracted when the room is not in use.

GRC Consultants understands that Trigon do not currently have the means for measuring or monitoring either the pressure in rooms or the differential pressure between any of the rooms. Furthermore it is understood that no pressure measurements

have ever been made in the facility to determine the pressure gradients within the rooms in order to comply with GMP requirements for cleanliness. Where a room is required to be kept under negative pressure relative to an adjacent room, this is achieved simply by having 'extract only' from that room.

The overall impression of the HVAC system serving the interferon production area is that of a system designed and built to a standard which would not be acceptable today from EC, USA authorities GMP points of view. GRC Consultants has not been able to review any basic design specifications or documentation from which the original system was built and installed. GRC Consultants understands that in 1980-81, Trigon (whilst still a part of EGIS) asked an Austrian company, Weiss Technik GmbH, to design and install an HVAC system "suitable for interferon production" but no basis of design or firm specification for the function and duty of the HVAC system was issued by Trigon.

It is understood that Trigon do commission a Hungarian company to carry out particle analysis of the air at different locations in different rooms in order to determine the "classification" of that room. Some of these results have been reviewed by GRC Consultants and they do show, <u>at the time of testing, at certain specific points in the rooms</u>, that the air particle counts generally indicate compliance with PIC Class D (US equivalent 100,000). This class of air cleanliness would probably not be acceptable today by US and Western European standards for facilities producing sterile injectibles, even though key operations, where active material is exposed to the environment, take place in laminar air flow cabinets which have demonstrably much cleaner air in them.

One of the most serious deficiencies regarding the current HVAC system concerns the apparent lack of proper design data, construction, installation and detailed specification

documentation which is needed to support any application for an Establishment Licence. Reference should be made to report (3) which contains details of the type of information which is needed to support the application for an Establishment Licence and includes reference to system validation. It is GRC Consultants opinion that Trigon would have considerable difficulty in preparing the basic technical information on the HVAC system needed to support an application for an Establishment Licence. Retrospective validation of the HVAC system design, construction, installation and operation would be extremely difficult in view of the apparent lack of the basic design documentation, etc.

4.8 EQUIPMENT

The remarks made in this section relate to the equipment which GRC Consultants was able to observe during the two visits. It is noted that on neither visit was equipment seen in use, for understandable organisational and operational reasons. However it is emphasized from the outset that the "equipment" used by Trigon for interferon production is generally small scale (large laboratory) glassware and, as such, is adequate and fit for the purpose of producing interferon.

The centrifuges are typical of those used in similar biotechnology/pharmaceutical operations and appeared to be in good condition and well maintained. The various laminar air flow cabinets (sometimes called laminar flow hoods) are by now becoming slightly aged but appeared to be well maintained and in good working order. GRC Consultants has been able to review some air quality measurement tests made in the various laminar flow cabinets and the results appeared satisfactory. However, the results only relate to air conditions on a certain day, at a certain time and do not show whether the air quality is maintained consistently over continued periods of operation. It is becoming common practice in the USA, EC to

monitor the air quality in laminar flow hoods in which sterile injectibles are prepared/handled, etc, on a CONTINUOUS basis with a particle counter in use during operation. This practice is also extending to the rooms themselves, not just the laminar flow cabinets.

The freeze drying equipment (freezer and lyophiliser) appeared to be in good condition but it was not possible to examine the interiors of either.

The chromatography purification/fractionating column (PHAST system) is relatively new and appeared to be in good condition. Such units are widely used in similar biological/pharmaceutical applications and are generally approved for such use.

The ampoule filling machine/dispenser is small and operated totally within a laminar flow cabinet. It appeared well maintained and adequate for its purpose.

Regarding equipment in general, the point is made here again, that if Trigon intend to prepare documentation in support of an Establishment Licence, then all the technical, specification and design details of all the equipment used for interferon processing will have to be available and collated. GRC Consultants does not know if all this information exists or can be obtained.

4.9 UTILITIES AND SERVICES

In comparison to more conventional fine chemical and pharmaceutical production plants, the Trigon interferon plant is a relatively small consumer of utilities and services. The following services are generally identified in a typical

pharmaceutical facility but only those marked * are considered as important in the context of this report on the Trigon interferon unit.

* Heating, Ventilation and Air Conditioning (HVAC)
  Hot and Cold Water
  Chiller Package
* Effluent Treatment
* Steam
  Electrical Services
  Compressed Air

  Vacuum Systems
  Dust Collection

In addition, because the interferon products are "sterile injectibles", the following specialist services are required and are all considered important in the context of this audit:

  Water for Injection (WFI)
  Purified Water (PW)
  Clean Steam

4.9.1 HVAC

This is considered to be a subject of such significance that it is treated in some detail in its own right in Sections 4.7 and 5.6

4.9.2 Hot and Cold Water

These services are available for general use at Trigon. Provided they are not used in the context of "sterile injectibles" production (either in contact with the active materials or components such as bottles, ampoules, stoppers,

caps, etc, which may come into contact with the active material), the generation and use of these two services is considered adequate, as far as GRC Consultants has been able to ascertain during the two visits.

4.9.3 Chiller Package (Chilled Water)

Chiller packages are used to generate chilled brine, at around 0°C, for general cooling duties. The system used generally appeared satisfactory. Special refrigerated rooms have their own integral chillers which appeared adequate.

4.9.4 Effluent Treatment

The interferon facility, in fact, produces very little effluent as such. The effluents from the personnel washing and changing areas pass to the general foul sewer within the building and then to the municipal drain.

Effluents, mainly supernatants and residues from centrifuging operations in the interferon production unit, are generally collected in aspirators in the washing area and are deactivated by a validated procedure before final discharge to the municipal drain. This appears to be adequate at present, but for the future, more attention may have to be paid to segregation and treatment of "process" drains if viral material, other than the Sendai virus, is contemplated or anticipated.

4.9.5 Steam

General process heating steam is obtained from the central boiler and is adequate. However, where steam is used for sterilization purposes, it is obtained separately as clean

steam in a dedicated unit fed with demineralised water. Again, this appeared adequate according to this audit (within the given time and budget constraints).

4.9.6 Electrical Services

These appeared totally adequate for the purposes required. The question of interruptable supply and the possible need for automatic emergency back-up (via batteries or diesel generator) should be addressed in the future.

4.9.7 Compressed Air

Relatively little compressed air used in the facility. Where it is used in the interferon production areas, or in media/components preparation, it is generally sterile filtered before use (as it should be).

4.9.8 Vacuum Systems

Relatively very little used and the local systems, used as needed, appear adequate.

4.9.9 Dust Collection

This is inextricably linked to the HVAC system, see 4.9.1 above. In fact, no conventional "dust extraction" systems are needed for interferon production and this topic is adequately covered in 4.9.1 above.

4.9.10 Specialist Services

Trigon recognise the need for high quality purified water and water for injection in the production of interferon and have a well established process and procedure for preparing "High cleanliness sterile and pyrogen free water, produced with ion exchange and reverse osmosis (RO)" in accordance with the summary given in the following pages.

GRC Consultants has also received sketches of the process and equipment used by Trigon for the preparation, handling and distribution of the purified water and WFI.

The overall impression gained of the system and its operation was satisfactory but it must be noted that the design, operation and validation of purified and WFI systems is continually under review by the authorities and the standards required are becoming ever tighter. The authorities are reviewing with increasingly greater attention the treatment and handling of water used for washing, rinsing and product formulation in all segments of the pharmaceutical industry.

Recently, in the USA, new standards have been proposed for pharmaceutical grades of water. The Water Quality Committee of the Pharmaceutical Manufacturers Association (PMA) has proposed an update to the United States Pharmacopoeia (USP) standards relating to water for pharmaceutical uses, including Purified Water and Water for Injection. In an article published in the November/December 1991 issue of 'Pharmacopoeia Forum', the PMA suggested using a conductivity measurement as an alternative to the current USP tests for the ionic purity of water.

The current USP standards for chloride, sulfate, calcium, ammonia and carbon dioxide levels in water are based on wet chemical test methods that were introduced into the USP in 1890 or earlier. While these tests are inexpensive and

name of product:
factory (in house) name:
High cleanliness sterile and pyrogenfree water, produced with ion exchange and RO

PRESCRIPTION OF PRODUCTION

1. The name of the product:
factory name:
High cleanliness sterile and pyrogenfree water, produced with ion exchange and RO

2. The prescription of the product:
colourless transparent liquid, filled in well closed flasks (500 ml - 100,000 ml)

3. Of use time: keeping in sterilized well closed flasks
on room temperature: 4 hours
on + 4 degree C 72 hours

4. Quality requirements of the product
4.1 Organoleptic examinations:
colour: colourless
odour: odourless
flavour: flavourless
4.2 Physical, chemical features:
The colour of the liquid must not change within the of use time. Mechanical contamination not allowed.
4.3 Examination methods
4.3.1 Analytical: per charge
according to Ph Hg VII.
4.3.2 In-production examination: per charge
pH: 4,5-6,5
conductivity: 0,1 · µs - 2 µs
4.3.3 Harmlessness examination: monthly
according to USP XXI
4.3.4 Pyrogenity examination: vitro LAL test; monthly
according to Ph.Hg VII.
4.3.5 Sterility test: monthly
according to Ph.Hg. VII.

5. Stability test: physical features must not change

6. Used material
6.1 Deionizated water
Produced from good quality tap water, filtered with sand-bed from coarse particles. Cations and anions of the soluble salt are replaced with hydrogen and hydroxil ions by anion/kation exchanger resins.
pH 4,0-6,8
conductivity: 1,0 - 15 µS

6.2 Milli RO filtered water
The Milli RO equipment is supplied with deionizated water, and produces pyrogenfree filtered water. Super Q equipment is supplied with this RO water.
pH: 4,5-6,5
conductivity: 1-5 µS

6.3 Super Q filtered water
Pyrogenfree and sterile filtered water, injection purity
pH: 4,5-6,5
conductivity: 10,0 megaohm/cm

7. Quality requirements:
Quality: according to the Ph.Hg VII. meets the requirements of Aqua destillata

7.1 With the application of the system described above the quality of the water meets the requirements of the injection purity water, accordingly USP. XX.

8. Equipment used for production

8.1 Ion exchanger
Type: DH-80 HOH 1 ½" twin columns manually operated
manufacturer: Aprilis 4 Gépgyár Nagykanizsa
flow rate: 1800 l/h

8.2 Water filter
type: Milli RO-120
manufacturer: Millipore
flow rate: 120 l/h

8.3 Water filter
type: Super Q
manufacturer: Millipore
flow rate: 1,3 - 11,3 l/min

8.4 Filter elements

8.4.1 Rogard prefilter 31" CDPR 031 F3

8.4.2 Rogard prefilter 12" CDPR 012 F4

8.4.3 Durapore sterile filter
0,22 µ CVGL 01 TP 1 hydrophil

8.4.4 Durapore sterile filter 0,22 µ CVGB 01 TP 1 hydrophobic

8.4.5 RO reverse osmose filter element CDRO 025 SO

8.4.6 Carbon filter CDFC 022 03

8.4.7 Ion ex filter CDBM 022 02

8.4.8 Ultrafilter MU 60 CD UF 022 02

8.4.9 Millipore sterile filter 0,22 µ MP GL 20 CA 1

8.4.10 Conductivity cell Type: OK 102 1

8.4.11 pH probe Type: OP-208

8.4.12 Sterile workbench Type: ASSAB H 4

8.4.13 Glass vessels: 40 l
80 l
5-10 l
glass beaker
graduated jar

9. Sterilization, cleaning and disinfection of the water purification system carried out according to the prescription of the operation manual.

9.1 General disinfection of Milli-RO water filter: with 1 % formal solution in each 3rd month.

Disinfection of Milli-RO filter elements: with chlorine pills: Cat Nr iZWC1 00 F 50 2 pills/week

9.2 Super Q, general disinfection: with 1 % formal solution in each 2nd month.
Disinfection of UF with 1 % Sodium hypochlorite solution every week
Sterilization of sterile filter elements
Durapore
Milli pack
in autoclave 121 degree C 30 min monthly

10. Description of production:

10.1 Size of charge: 1,300 l; 12 hours/day operation

10.2 Scope of usage:
for preparatory steps
dish washing - rinsing
solvent/dilution production
for preparation production
The purified water is continuously circulated.

10.3 Storage: in sterilized well closed flasks under the conditions written in 3.
Storage in accordance with GMP requirements

11. We regularly inspect the safety of the operation and the microbiological cleanliness of the water purification system. The results of the regular checks-up are documented.

12. Prescriptions, instructions for personnel.
The person who involved with the production must be trained for this task, and must have the due ability experience and qualification.

13. Safety regulations
Materials used for regeneration - 30-32 % HCl; NaOH - are poisonous, aggressive and corrosive.
Sodium hypochlorite, 37-38 % solution of formal are aggressive, corrosive poison.
These materials have harmful effect either through direct contact, or in airborne form.
These materials must be handled in a very careful way, following the safety regulations.

18. June 1987

compiled by: .....

checked by: Mr. Zsolt Pallai
Ms. Klára Onodi

approved by: .....
director

relatively easy to perform, the results are subjective and qualitative, as either a colorimeter or turbidimetric endpoint is used.

The PMA proposes that these tests be replaced with a single conductivity measurement based on the lowest possible conductivity of water that would still meet the existing USP specifications. The proposed conductivity specification was chosen based on a chloride concentration of 0.47 ppm (the theoretical endpoints of the USP test) with an equivalent amount of sodium as the counter ion. This concentration would result in a solution conductivity of 1.25 umho/cm at 25°C.

The PMA method proposes that the conductivity be measured off-line in a beaker because of concerns that on-line conductivity instruments cannot be accurately calibrated for this application. One concern with off-line conductivity measurement is that pure water exposed to the atmosphere will pick up carbon dioxide from the air, which will increase the solution conductivity. A more stringent conductivity specification of 1.25 umho/cm may be used instead, to avoid the need for carbon dioxide equilibration and pH measurement. This approach would be more convenient for users whose water systems produce water that is purer than the USP standards.

The impact on the pharmaceutical industry if this change is accepted will be to simplify the water testing protocols by replacing five highly variable, subjective tests with a single, reliable measurement. In the future, it will also simplify water system operation, because systems that are designed to operate with significantly lower conductivity are certain to meet the USP specification for ionic purity; thus, system validation and monitoring will be streamlined. Some firms, however, may have systems that meet the existing standards but their water does not meet the proposed conductivity specification. In this case, the system would have to be upgraded.

4.10 CONTROL MATTERS

In the context of this report, 'control; is taken to be process control, both in the interferon manufacturing process and in the preparation of medium and components. However, the interferon process, in comparison to the more conventional pharmaceutical processes, does not have an extensive or integrated process control system applicable across the whole process. Rather, control is exercised generally by manual operations carried out by the operators in well-defined small scale individual activities which themselves take place in laminar flow cabinets.

In terms of more conventional 'control' the operations which employ 'controllers' basically are those of centrifuging, freezing, freeze drying and sterilization of media and components, etc.

These units generally use local electronic or programmable logic controllers which are operated to validated protocols and produce records of their operations. During the relatively limited time available to examine those operations (including the fact that the units themselves were not actually in operation during the visits) GRC Consultants concluded that the level of control has been adequate.

In the more general sense, 'control' of the interferon process is exercised by Trigon by means of conventional "paper documentation" and computerised batch records and these appeared adequate. However, it is recognised that the whole approach to both process and quality control is becoming increasingly tighter and subject to close attention by the various authorities.

SECTION 5

RECOMMENDATIONS FOR UPGRADE

5 RECOMMENDATIONS FOR UPGRADE

There are essentially two elements to most of the topics covered in this section. As a result of the audit visits and the identification of possible deficiencies in the existing interferon facilities, GRC Consultants makes recommendations for upgrading in two elements. The first element concerns concepts for layout and movements, etc, on the ASSUMPTION that this is what we would aim for 'WITH NO CONSTRAINTS ON GEOMETRY OR SIZE OF FACILITY'. The second element concerns GRC Consultants preliminary attempts (within the time and budget constraints of this project) to accommodate as far as possible the upgrading 'WITHIN THE BASIC FABRIC AND OUTLINE OF THE EXISTING BUILDING'. This inevitably involves some compromise and the preliminary designs are obviously subject to discussion and development as and when the project moves to the next phase (not part of this current assignment).

5.1 LAYOUT

5.1.1 Concept

Conceptual layouts are presented as 'best case' solutions. The present plant layout will be modified as far as is considered practical to resemble these conceptual layouts.

Drg. 92/012/102 shows the conceptual overall layout. Note that areas are shown which may contain serval rooms. In developing this layout a number of general principles were followed. Personnel flows are linear and a perimeter corridor is provided mainly for personnel traffic. Material flows are linear and where possible pass through devices are included for transfer between different grades of area. The crossing of materials in differing stages of the process and waste

materials is minimised. The distance travelled by in-process materials is minimised by careful room layout and again the use of pass through hatches.

Note that the overall layout has four grades of area. Black, Grey, Grey+ and White. The Grey+ class is between the Grey and the White class and the change protocol strictness will be somewhere between the two. The Grey+ wear is used in the raw material preparation suite where cleanliness but not absolute sterility will be required.

The kitchen and dining room are located outside the main plant area and are not shown on the conceptual layout.

Conceptual layouts are given for the goods storage areas and changing areas identified in the overall layout. These layouts are again conceptual only and do not necessarily have a similar orientation or shape shown in the overall layout.

The conceptual change area is given as drg. 92/012/103. Note that use of benches which show the start of the Grey and White areas. A shower by-pass is provided for use at breaktimes for personnel access to the dining room in the Black area without the need to shower. It is not considered practical for all staff to shower before re-entering the facility after breaktimes.

The conceptual goods out area and packing layout is shown in the goods stores layout drg. 92/012/104. The packing room and product quarantine room are shown as part of the Grey area with a pass through hatch to the Black product dispatch area.

The conceptual goods in area is also shown in the goods stores layout drg. 92/012/104. A Black cleaning area is shown for primary cleaning of goods before transfer via a pass through hatch to the Grey goods in quarantine area. Quality control personnel inspect the goods in the quarantine area using the

laminar flow cabinet where necessary. Quality Control authorised goods are then transferred to the released goods store. Materials from the released goods store are then transferred to the Grey process area or the White process area via an intermediate White goods cleaning area. Note that although the White goods cleaning area is shown adjacent to the released goods store in the drawing, this does not necessarily have to be the case in the final layout as the White goods in are still classed as Grey at the released goods storage stage, and may thus be transported across Grey areas.

5.1.2 Change to Existing Layout

In order to improve personnel and material flows a number of changes are proposed here. These improvements represent initial ideas and require further development and discussion before implementation can be considered. The practicalities of altering some potentially load bearing walls needs investigation.

Drgs. 92/012/124 - 92/012/126 show the proposed new layout and the changes are discussed below.

Basement

The whole area has been modified so that the dining area and WC may only be accessed in Black clothing. Note that there is now only one entrance to the basement and one exit via the spiral stairwell. The stairs formerly used by process workers to access the basement will now be used for emergency exit only.

Ground Floor

In order to simplify materials movement into and out of the facility, raw materials enter at one point only and products similarly leave at one point only.

A goods in store is provided which includes a goods cleaning lobby. Here materials receive a primary clean before being transferred via a pass through hatch to the Grey quarantine area. On receiving QC approval the goods are transferred out of the quarantine cage into the general store area.

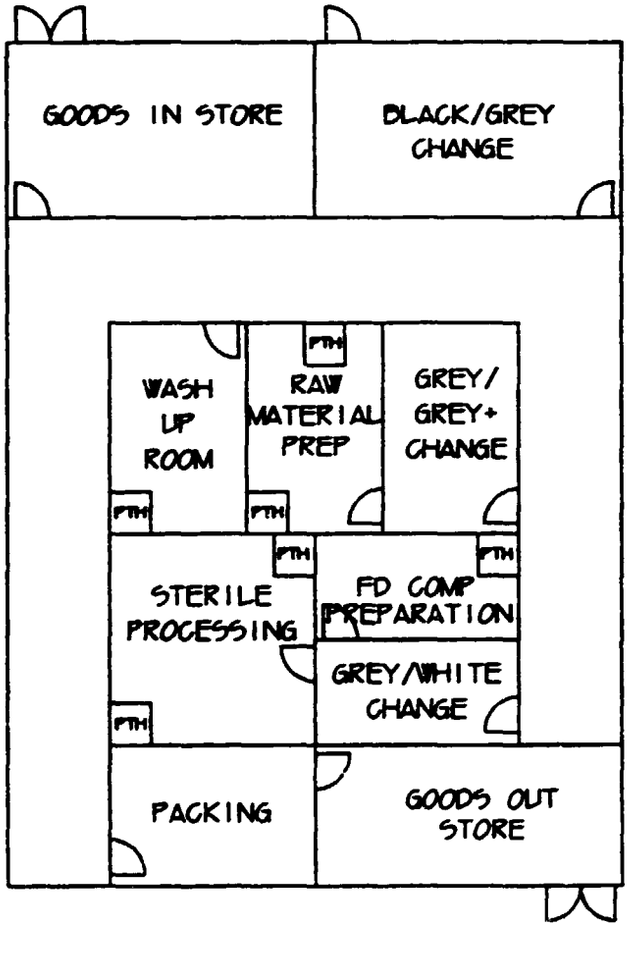
The goods out store has a similar quarantine cage and also a goods awaiting dispatch area. In the layout both these areas are classed as Black.

1st Floor

The area around the sterile change room (room 315 in original layout) has been completely rearranged to ease congestion and help produce a more logical and linear materials and personnel flow.

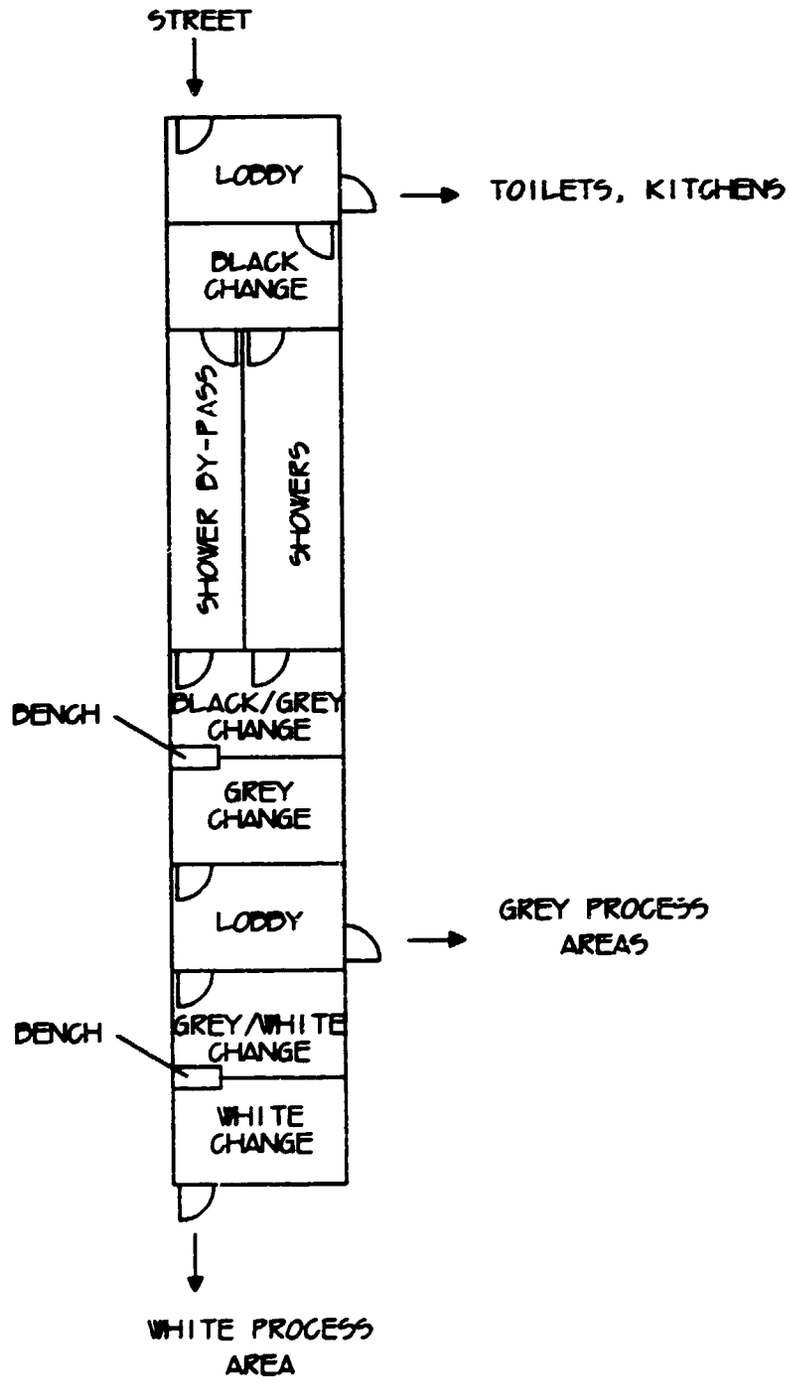
Separate changing rooms for Grey/White change and waste treatment room change are provided. It is proposed that waste will be substantially inactivated in this room before transfer to the ground floor, perhaps for a final autoclave step. This room may be split into 2 areas, a deactivated and a live side. The waste is transferred by the lift to the ground floor as before.

A pass through hatch is specified between the process area on the right of the 1st floor and the general laboratories on the left. The mechanism of what is packed and where this is done should be examined since the product must pass through a Black area before reaching the stores on the ground floor.



PTH - PASS THROUGH HATCH
FD COMP - FREEZE DRYING COMPONENTS

GRC CONSULTANTS WESTBROOKE HOUSE 76 HIGH STREET ALTON. HANTS GU34 1EN TEL: 0420 89847 FAX: 0420 89427	CLIENT UNIDO	PROJECT TRIGON TF/HUN/90/911	TITLE CONCEPTUAL OVERALL LAYOUT
	DATE: AUG '92 SCALE: N/A DIMENSIONS IN:	DRAWING NUMBER 92/012/102	REV D



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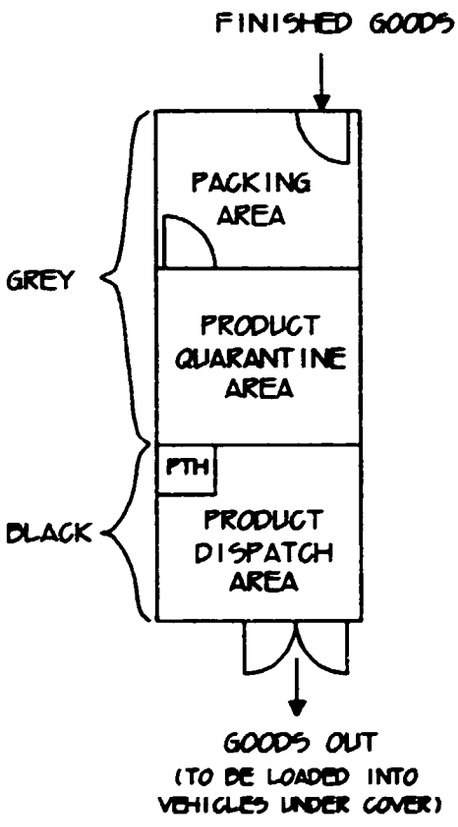
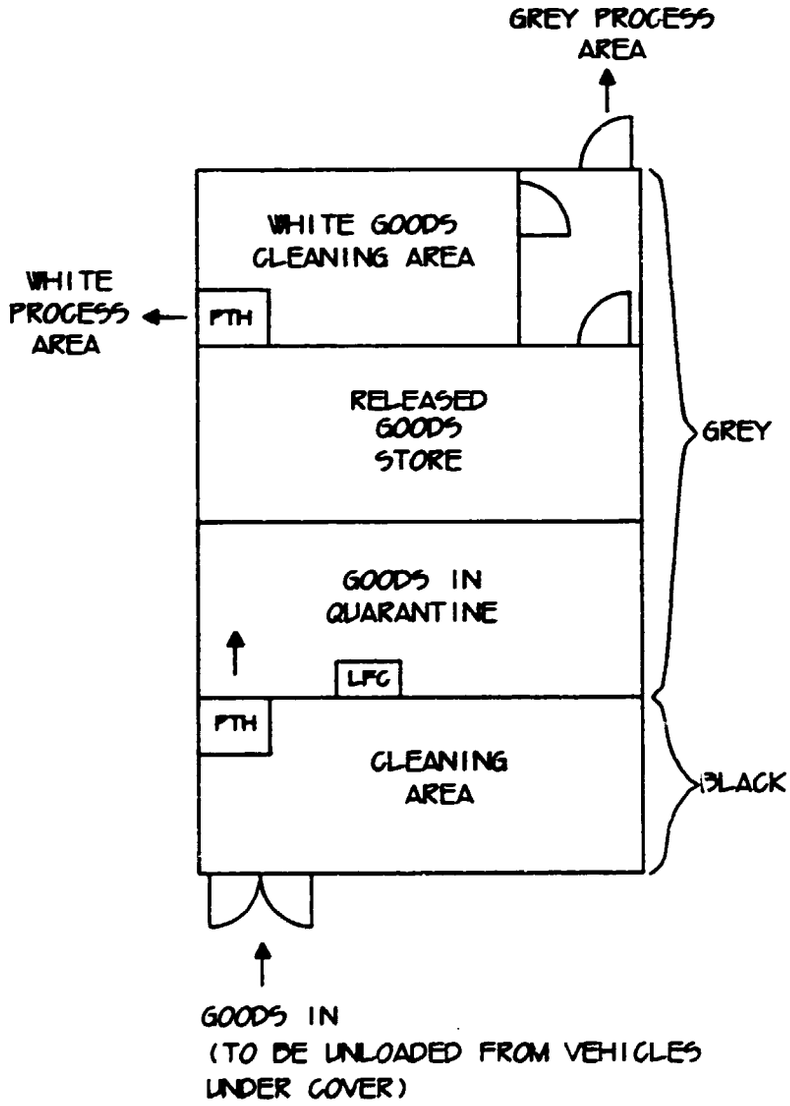
ALTON. HANTS GU34 1EN
TEL: 0420 88847 FAX: 0420 88427

CLIENT	UNIDO
PROJECT	TRIGON TF/HUN/90/911
TITLE	CONCEPTUAL CHANGE AREA LAYOUT
DATE:	AUG '92
SCALE:	N/A
DIMENSIONS IN:	
DRAWING NUMBER	92/012/103
REV	D

CONCEPTUAL GOODS OUT AREA AND PACKING LAYOUT

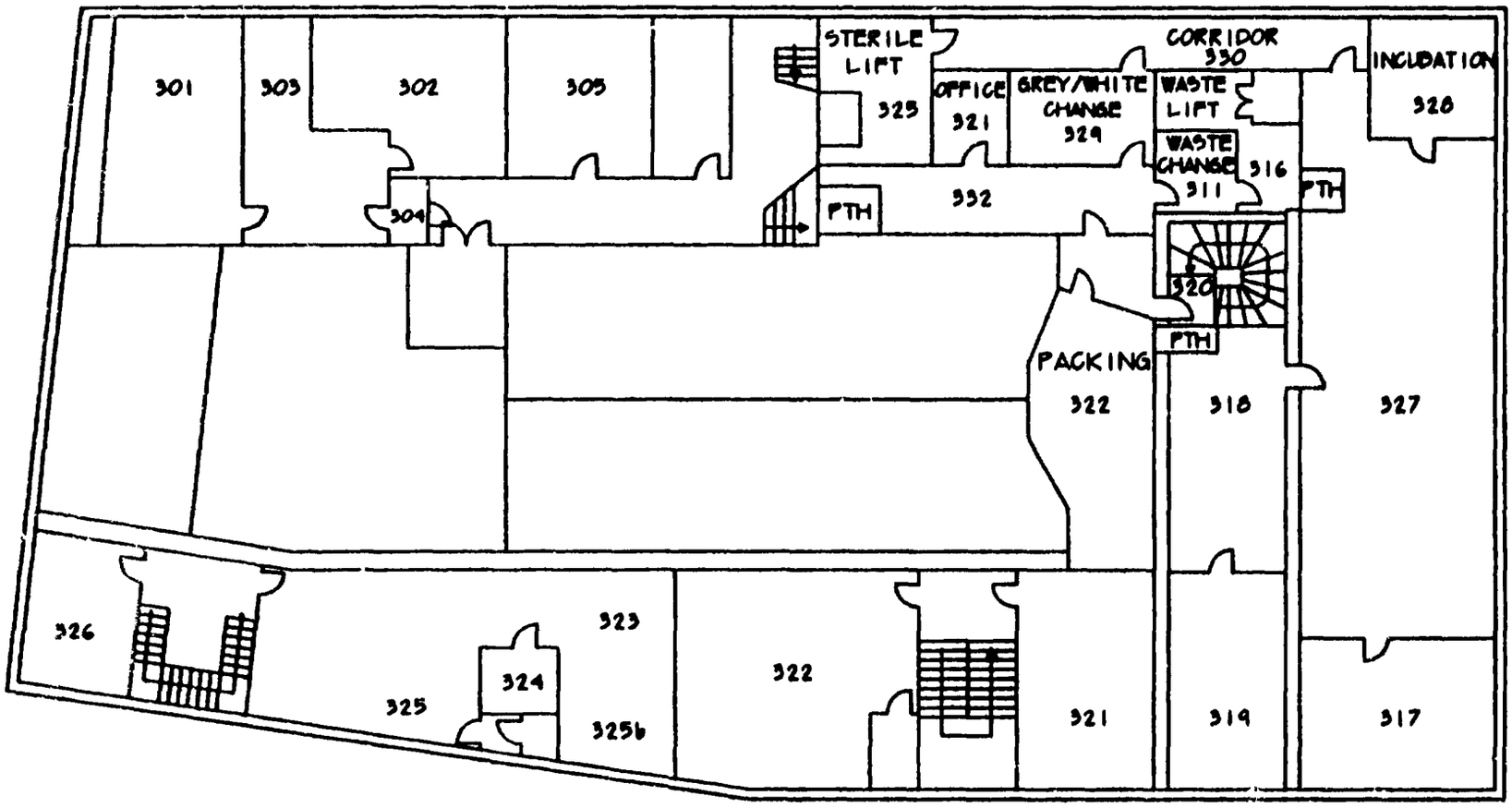


CONCEPTUAL GOODS IN AREA LAYOUT

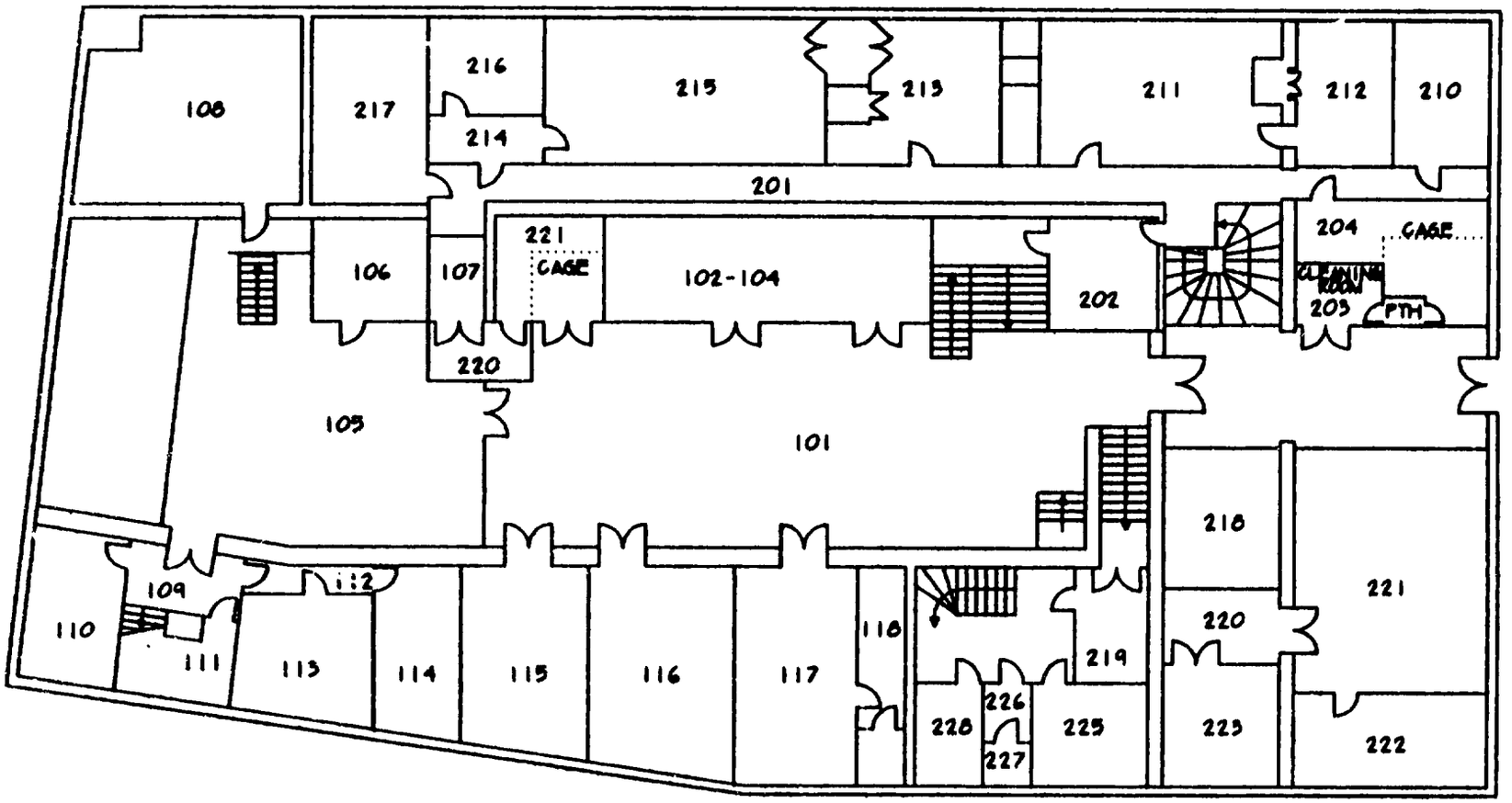


PTH - PASS THROUGH HATCH
LFC - LAMINAR FLOW CABINET

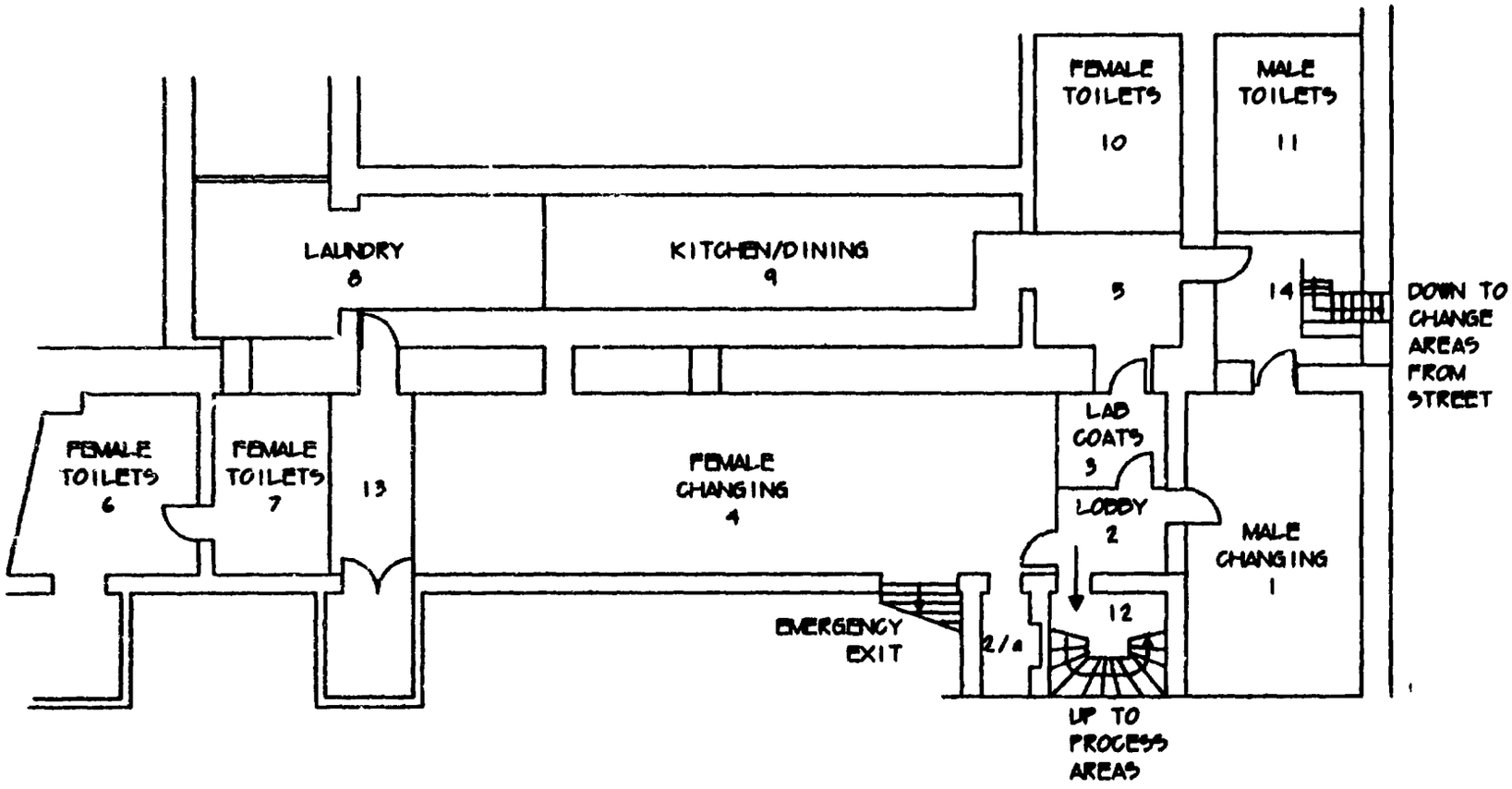
GRC CONSULTANTS WESTBROOKE HOUSE 78 HIGH STREET ALTON. HANTS GU34 1EN TEL: 0420 89847 FAX: 0420 89427	CLIENT UNIDO	PROJECT TRIGON TF/HUN/90/911	TITLE GOODS STORES LAYOUT
	DATE: AUG '92 SCALE: N/A DIMENSIONS IN:	DRAWING NUMBER 92/012/104	REV D



GRC CONSULTANTS WESTBROOKE HOUSE 78 HIGH STREET ALTON. HANTS GU34 1EN TEL: 0420 88847 FAX: 0420 88427	CLIENT UNIDO	PROJECT TRIGON TF/HUN/90/911	DRAWING TITLE PROPOSED IMPROVED LAYOUT 1st FLOOR
			DRAWING NUMBER 92/012/124 — REV A



GRC CONSULTANTS WESTBROOKE HOUSE 78 HIGH STREET ALTON. HANTS GU34 1EN TEL: 0420 88847 FAX: 0420 88427	CLIENT UNIDO	PROJECT TRIGON TF/HUN/90/911	DRAWING TITLE PROPOSED IMPROVED LAYOUT GROUND FLOOR
			DRAWING NUMBER 92/012/125
			REV A



GRC CONSULTANTS WESTBROOKE HOUSE 78 HIGH STREET ALTON. HANTS GU34 1EN TEL: 0420 88847 FAX: 0420 89427	CLIENT UNIDO	PROJECT TRIGON TF/HUN/90/911	DRAWING TITLE PROPOSED IMPROVED LAYOUT BASEMENT
			DRAWING NUMBER: 92/012/126 — REV: A

Depending on the volume of products involved it may be possible to install a small store near this pass through hatch as an alternative to the ground floor stores.

The process room (327) has become larger as a result of the changes in layout. It may be possible to build sub-rooms in the room for particular process steps, such as buffy coat cell preparation.

2nd Floor

The 2nd floor QC suite is supplied with sealed samples via the 1st floor Black/Grey transfer hatch located in the middle of the floor. The QC area is now classified as a Black area in the new layout and is provided with its own independent change facilities.

5.2 MATERIAL AND PERSONNEL FLOW

5.2.1 Idealised

Drg. 92/012/110 shows the material flow through the goods stores. It can be seen that the flow is linear and the materials go through a pass through hatch when transferring between the Black and Grey areas.

The material flow through the overall layout is given in drg. 92/012/105. The materials flow is split into two in the central part of the plant, with the resulting two parts representing process flow and freeze drier components (such as ampoules and stoppers) respectively. Note that raw materials such as buffy coat cells may well follow the process flow line through the raw materials preparation area, which may contain

the White goods cleaning room shown on the goods stores layout drg. 92/012/104. The details of individual rooms within the area will be specified at the next stage of the design.

Drg. 92/012/107 shows the personnel flow through the change area from the Black street area to the White process area. The return flow may utilise the shower by-bass corridor.

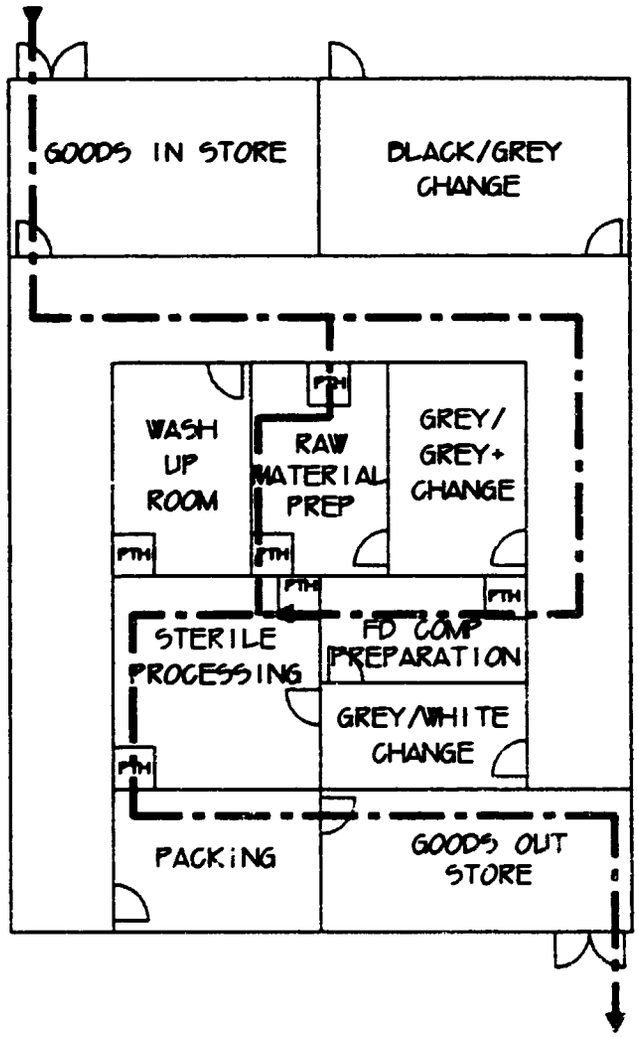
The personnel flow through the overall plant layout is given in drg. 92/012/106. The central Grey plant corridor is used to distribute personnel to the process areas directly or via change areas to access the higher class areas.

5.2.2 Materials and Personnel Flow in the Proposed New Layout

The materials flow in the proposed new layout is given in drgs. 92/012/127 and 92/012/128. All raw materials of any kind which are used in the Human Interferon Process Facility enter through the goods in store shown on the ground floor. All product leaving the facility does so via the pass through hatch in the middle of the 1st floor and goes down the product lift to the goods out store, for QC approval notification and finally dispatch. In the proposed new layout product is not transferred through the open courtyard (105) but through an enclosed lobby.

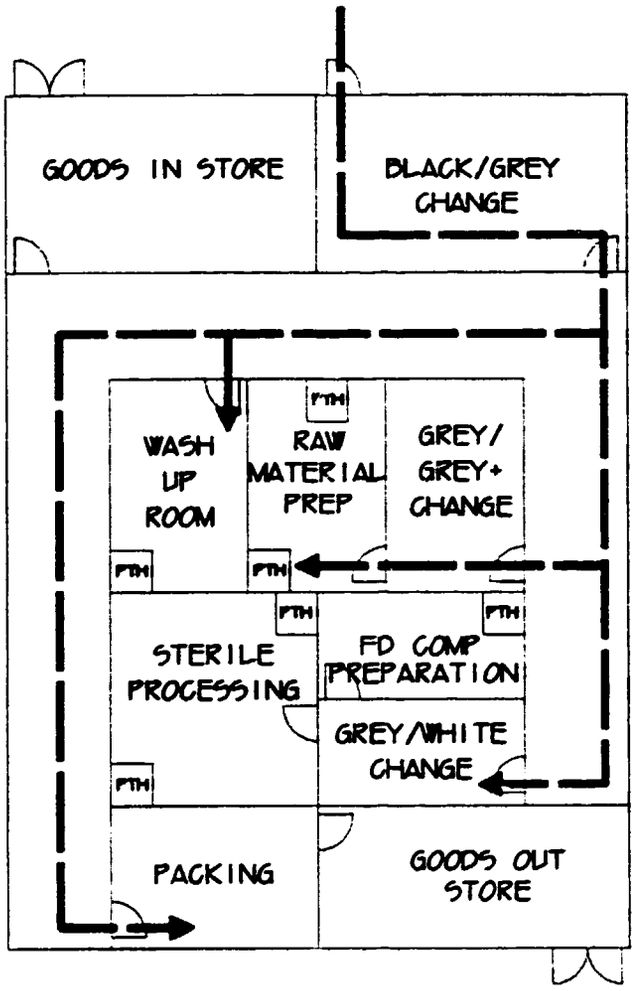
All material, buffer solutions and biological materials enters the sterile suite via the sterile lift and are transferred down the transfer corridor (room 330) which is now part of the sterile area.

Waste materials leave the sterile suite via a hatch in the main laboratory (room 327). The material is substantially deactivated (probably chemically) before transfer to the ground floor via the waste lift.



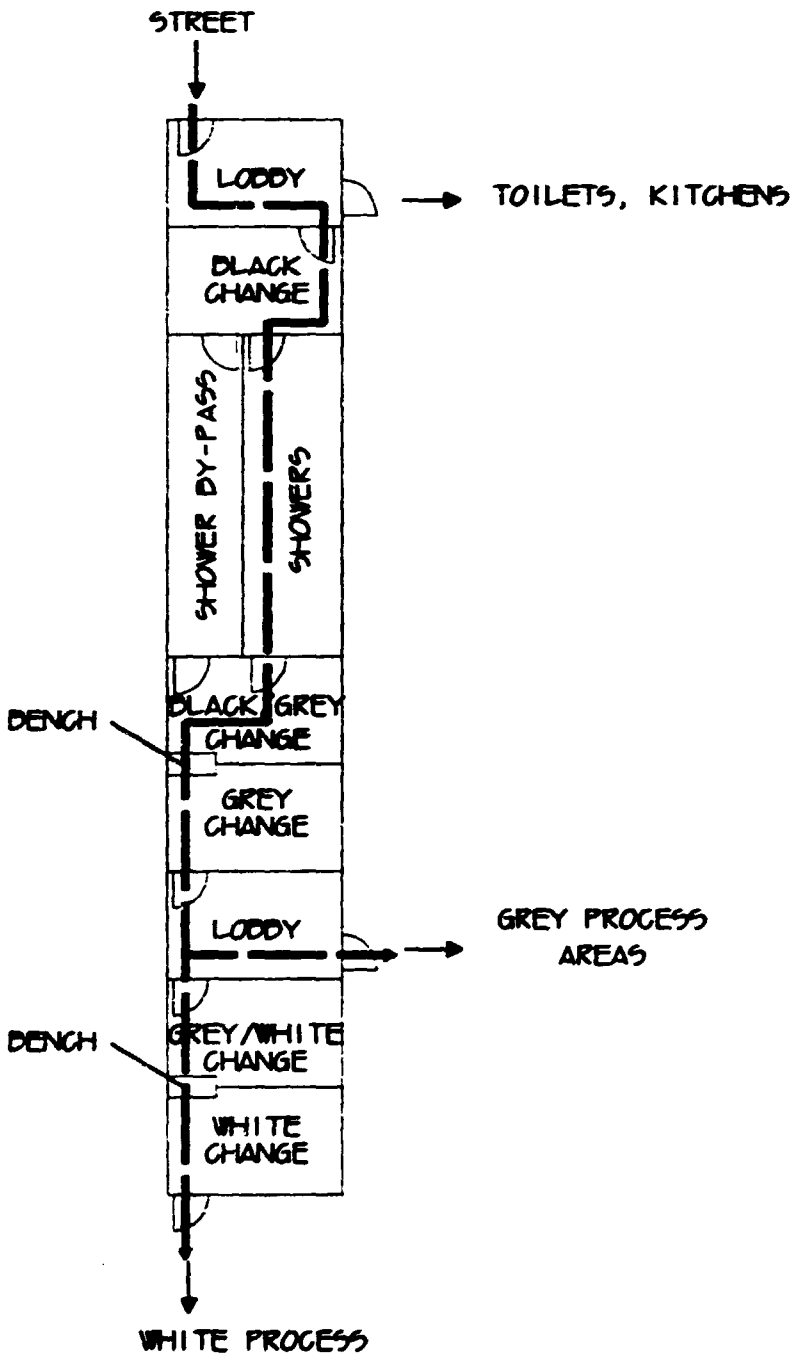
PTH - PASS THROUGH HATCH
FD COMP - FREEZE DRYING COMPONENTS

GRC CONSULTANTS WESTBROOKE HOUSE 78 HIGH STREET ALTON. HANTS GU34 1EN TEL: 0420 89847 FAX: 0420 89427	CLIENT UNIDO	PROJECT TRIGON TF/HUN/90/911	TITLE IDEALISED OVERALL MATERIALS FLOW
	DATE: AUG '92 SCALE: N/A DIMENSIONS IN:	DRAWING NUMBER 92/012/105	REV A



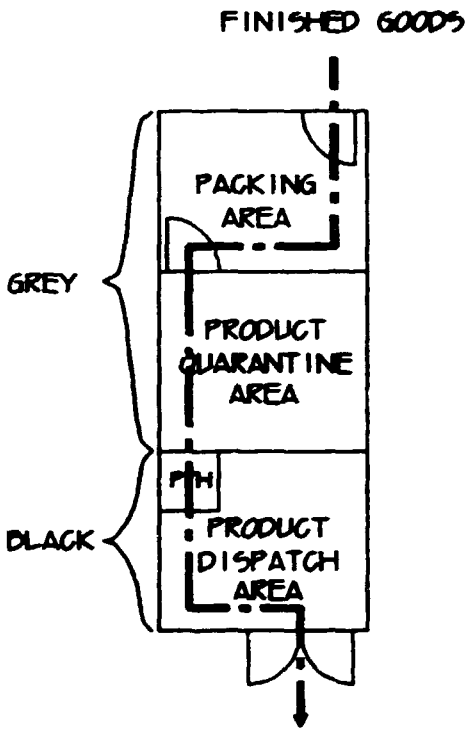
PTH - PASS THROUGH HATCH
FD COMP - FREEZE DRYING COMPONENTS

GRC CONSULTANTS WESTBROOKE HOUSE 76 HIGH STREET ALTON. HANTS GU34 1EN TEL: 0420 89847 FAX: 0420 89427	CLIENT UNIDO	PROJECT TRIGON TF/HUN/90/911	TITLE IDEALISED OVERALL PERSONNEL FLOW
	DATE: AUG '92 SCALE: N/A DIMENSIONS IN:	DRAWING NUMBER 92/012/106	REV A

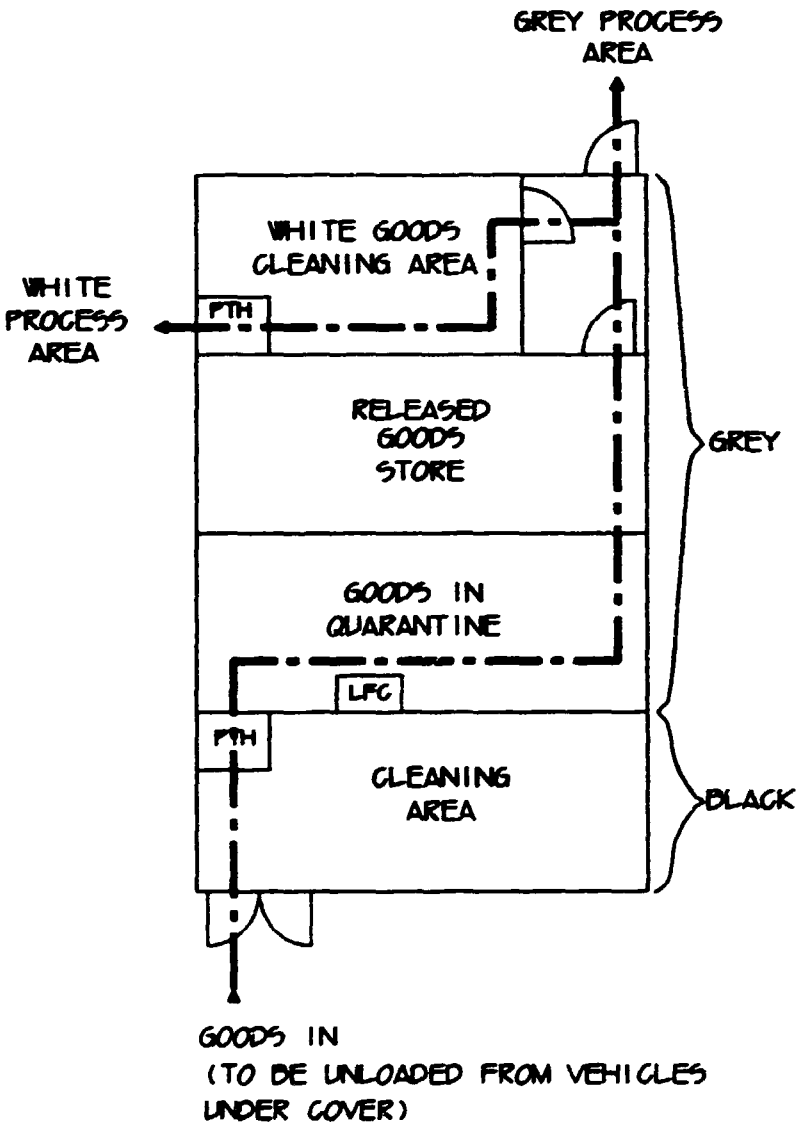


GRC CONSULTANTS WESTBROOKE HOUSE 78 HIGH STREET ALTON. HANTS GU34 1EN TEL: 0420 88847 FAX: 0420 88427	CLIENT AREA UNIDO	PROJECT TRIGON TF/HUN/90/911	TITLE IDEALISED CHANGE AREA PERSONNEL FLOW
	DATE: AUG '92 SCALE: N/A DIMENSIONS IN:	DRAWING NUMBER 92/012/107	REV A

CONCEPTUAL GOODS OUT AREA AND PACKING LAYOUT

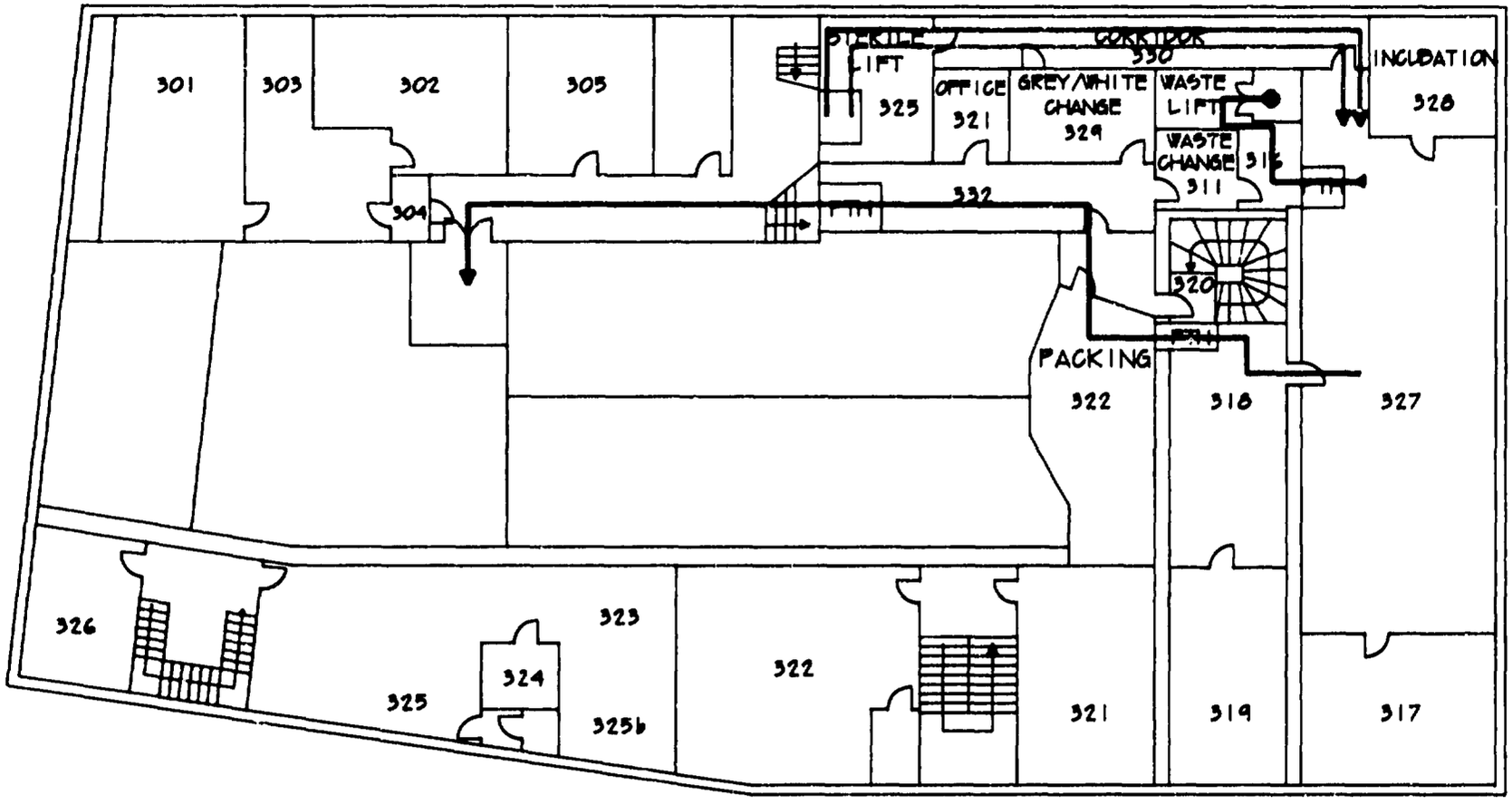


CONCEPTUAL GOODS IN AREA LAYOUT



PTH - PASS THROUGH HATCH
LFC - LAMINAR FLOW CABINET

GRC CONSULTANTS WESTBROOKE HOUSE 78 HIGH STREET ALTON. HANTS GU34 1EN TEL: 0420 88847 FAX: 0420 88427	CLIENT UNIDO	PROJECT TRIGON TF/HLN/90/911	TITLE IDEALISED. MATERIALS FLOW IN GOODS STORES
	DATE: AUG '92 SCALE: N/A DIMENSIONS IN:	DRAWING NUMBER 92/012/110	REV A



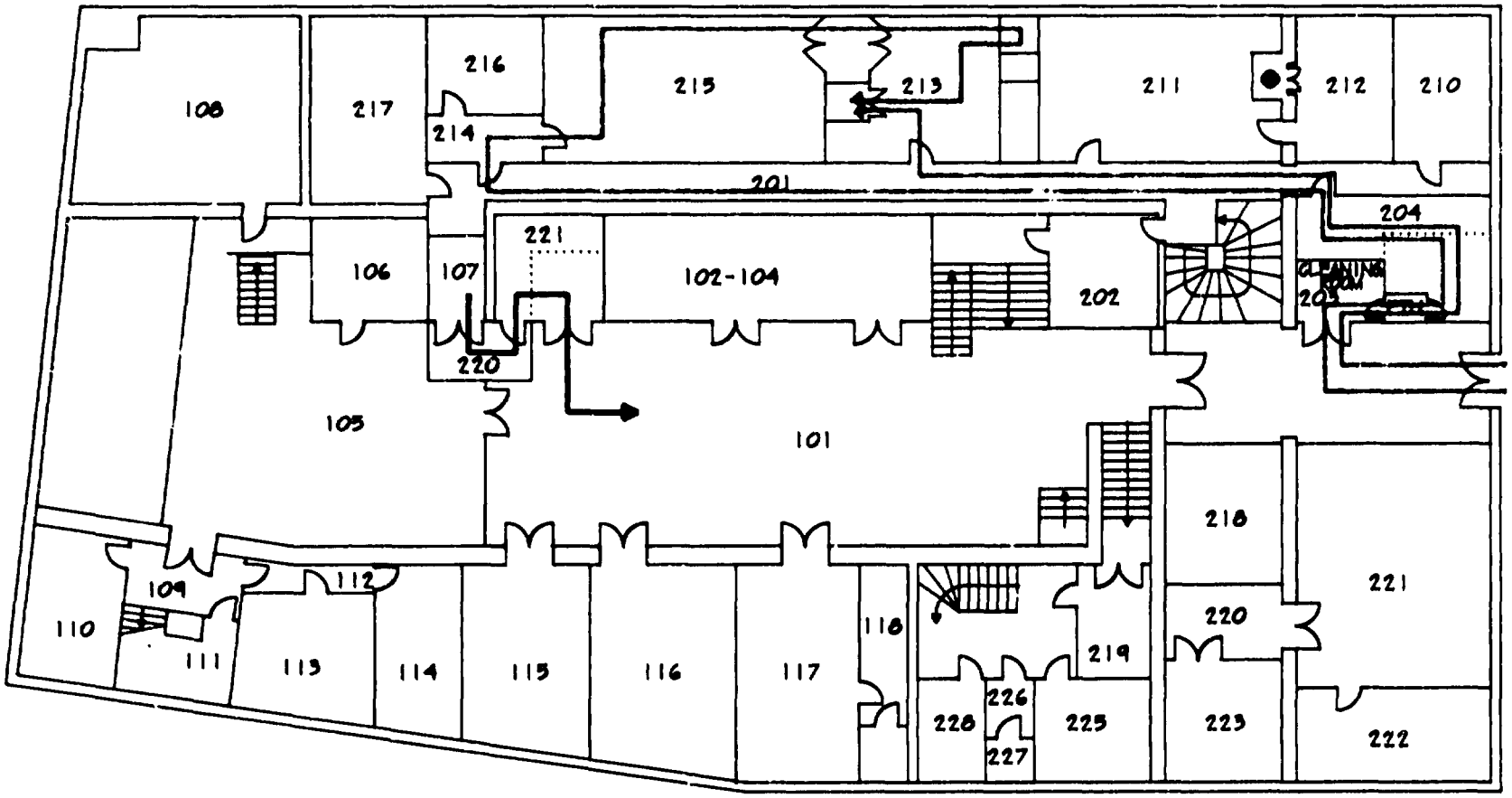
BUFFY COAT CELLS
VIRUS AMPOULES

SALTS ETC

PRODUCT

WASTE

GRC CONSULTANTS WESTBROOKE HOUSE 78 HIGH STREET ALTON, HANTS GU34 1EN TEL: 0420 88847 FAX: 0420 88427	CLIENT UNIDO	PROJECT TRIGON TF/HUN/90/911	DRAWING TITLE PROPOSED MATERIALS FLOW 1st FLOOR
			DRAWING NUMBER 92/012/127
			REV A



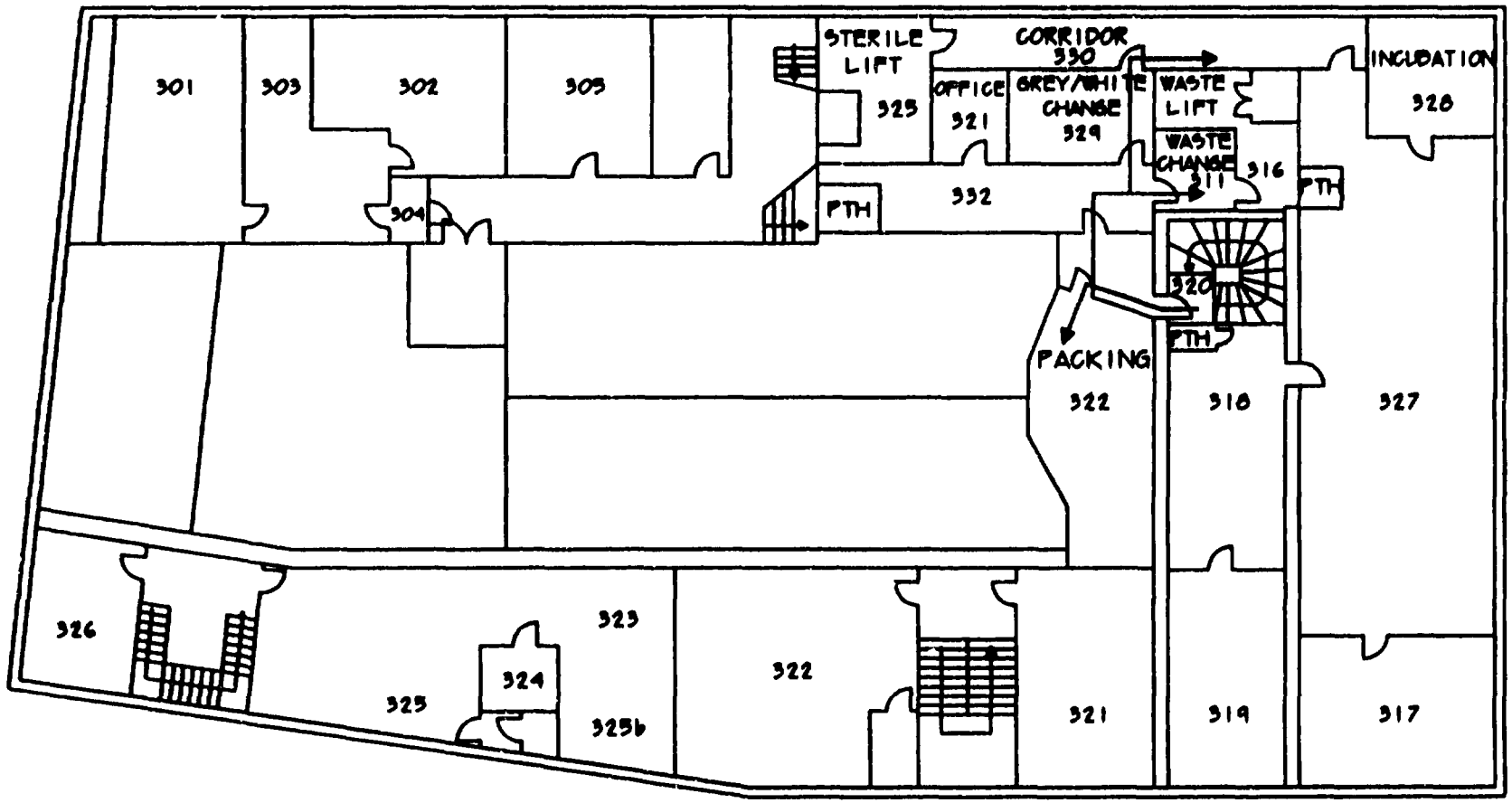
DUFFY COAT CELLS
VIRUS AMPOULES

SALTS ETC

PRODUCT

WASTE

GRC CONSULTANTS VESTBROOKE HOUSE 70 HIGH STREET ALTON, HANTS GU34 1EN TEL: 0420 88847 FAX: 0420 88427	CLIENT UNIDO	PROJECT TRIGON TF/HUN/90/911	DRAWING TITLE PROPOSED MATERIALS FLOW GROUND FLOOR DRAWING NUMBER: 92/012/128 REV: A

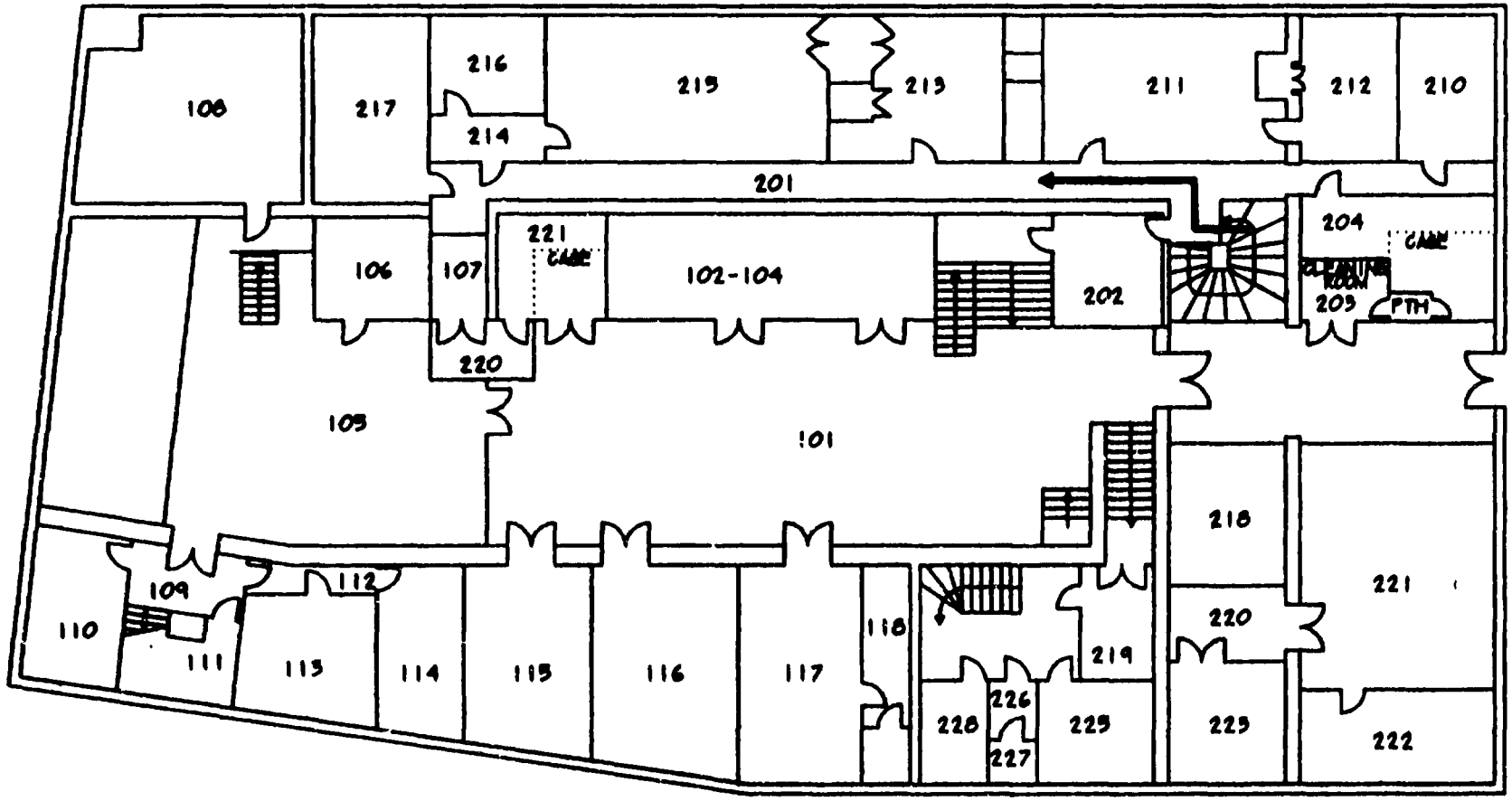


FEMALE PROCESS PERSONNEL — · · —

MALE PROCESS PERSONNEL — — —

ALL PROCESS PERSONNEL ———

GRC CONSULTANTS WESTBROOKE HOUSE 78 HIGH STREET ALTON, HANTS GU34 1EN TEL: 0420 88847 FAX: 0420 88427	CLIENT UNIDO	PROJECT TRIGON TF/HUN/90/911	DRAWING TITLE PROPOSED PERSONNEL FLOW 1st FLOOR DRAWING NUMBER 92/012/129 REV A

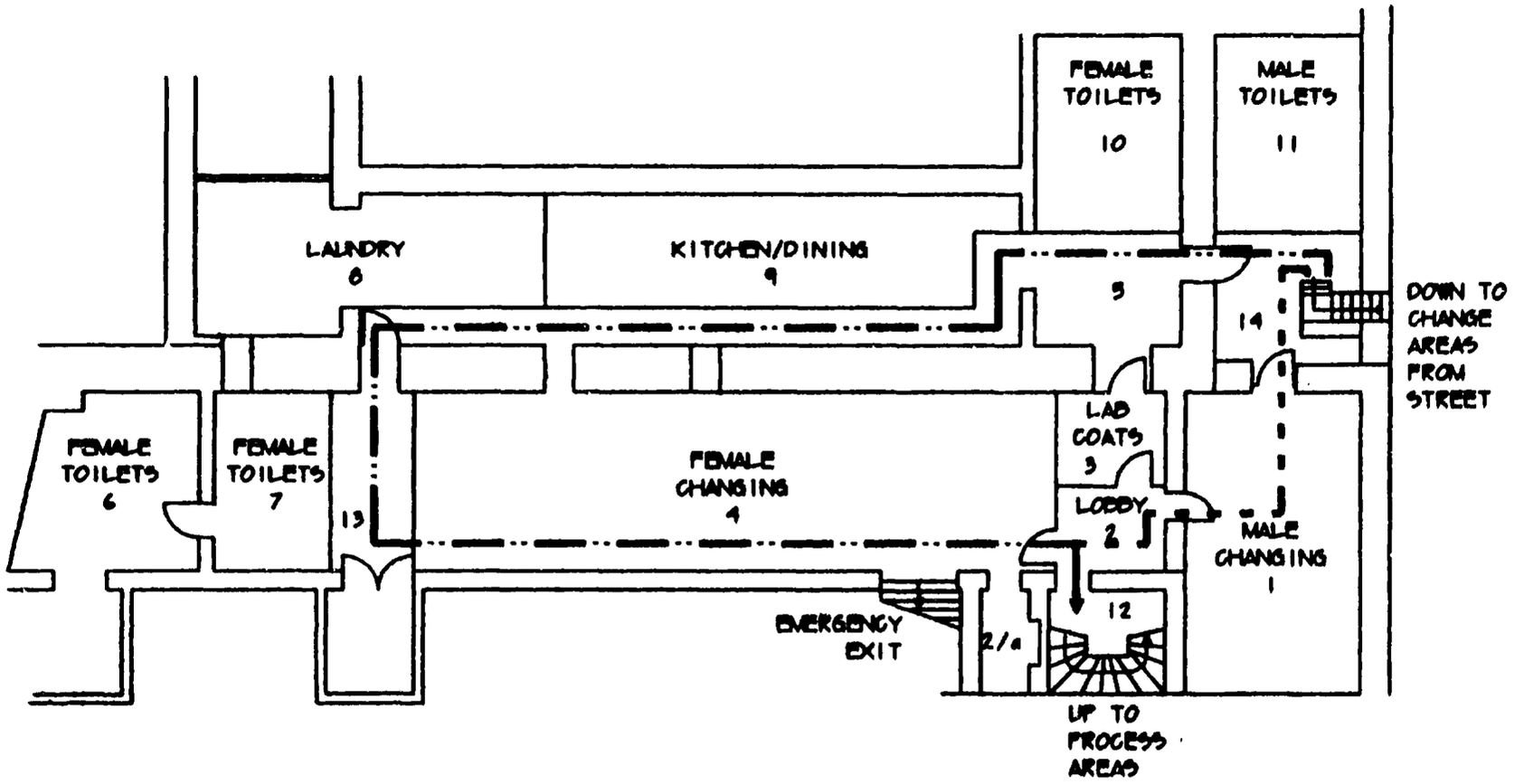


FEMALE PROCESS PERSONNEL

MALE PROCESS PERSONNEL

ALL PROCESS PERSONNEL

GRC CONSULTANTS WESTBROOKE HOUSE 70 HIGH STREET ALTON, HANTS GU34 1EN TEL: 0420 88447 FAX: 0420 88427	CLIENT UNIDO	PROJECT TRIGON TF/HUN/90/911	DRAWING TITLE PROPOSED PERSONNEL FLOW GROUND FLOOR
			DRAWING NUMBER 92/012/130
			REV A

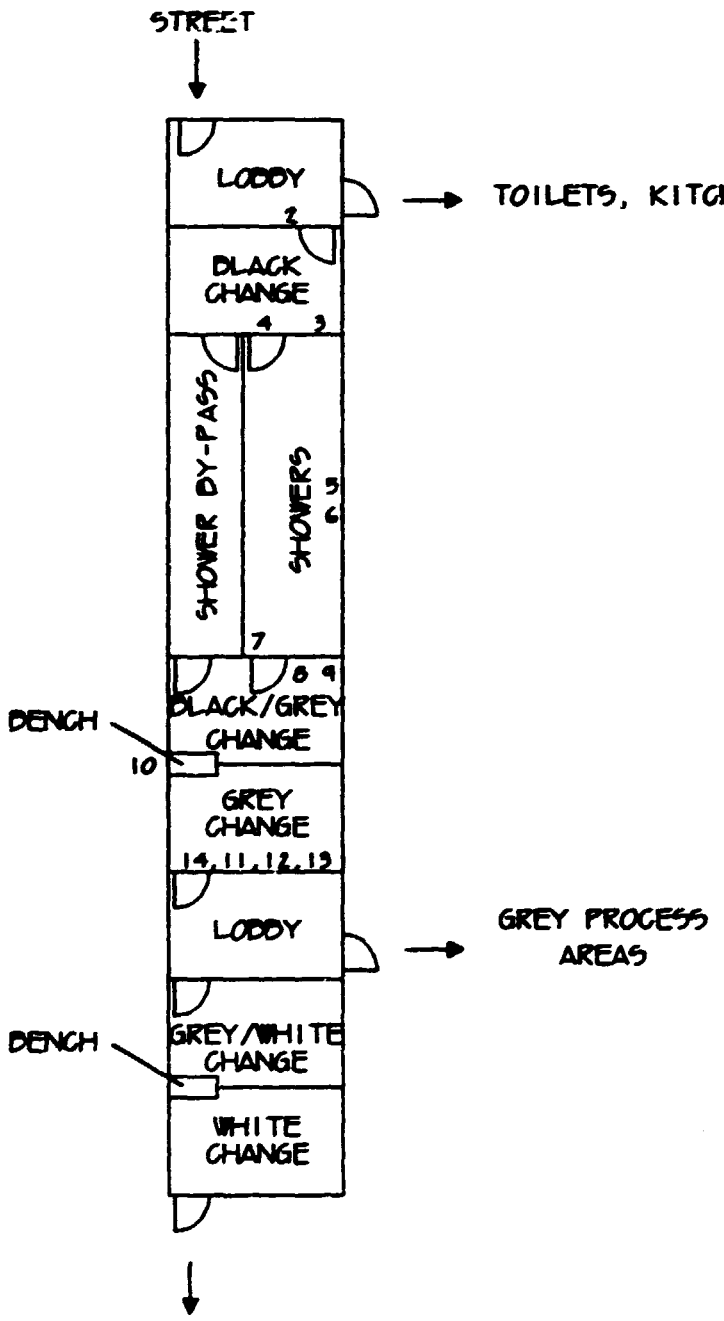


FEMALE PROCESS PERSONNEL

MALE PROCESS PERSONNEL

ALL PROCESS PERSONNEL

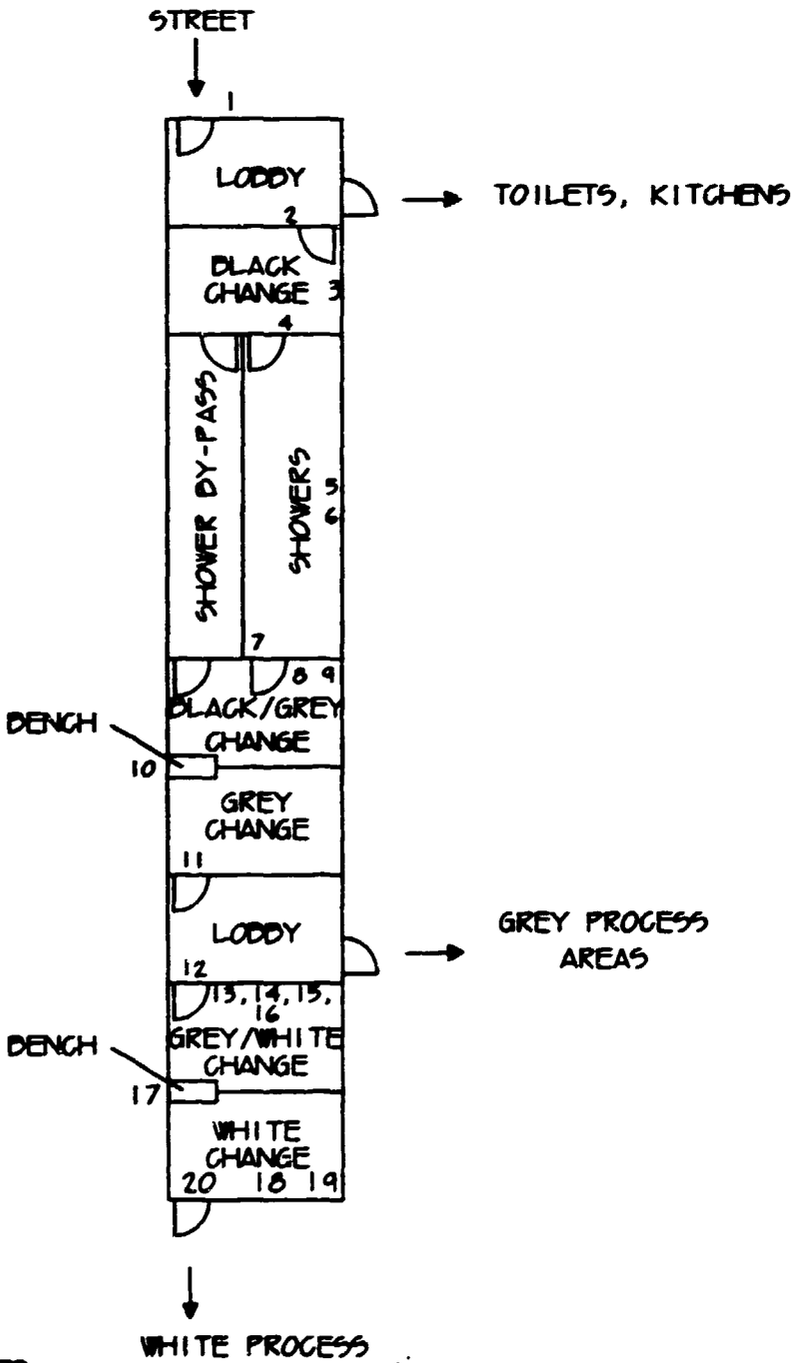
GRC CONSULTANTS WESTBROOKE HOUSE 76 HIGH STREET ALTON, HANTS GU34 1EN TEL: 0420 88847 FAX: 0420 88437	CLIENT UNIDO	PROJECT TRIGON TF/HUN/90/911	DRAWING TITLE PROPOSED PERSONNEL FLOW BASEMENT DRAWING NUMBER 92/012/131 — REV A



THE NUMBERS REFER TO OPERATIONS DETAILED IN PROTOCOL 5.3.2

GRC CONSULTANTS
WESTBROOKE HOUSE 78 HIGH STREET
ALTON. HANTS GU34 1EN
TEL: 0420 88847 FAX: 0420 88427

CLIENT AREA	PROJECT	TITLE
UNIDO	TRIGON TF/HUN/90/911	BLACK TO GREY CHANGE OPERATIONS
DATE: AUG '92	DRAWING NUMBER	REV
SCALE: N/A	92/012/108	A
DIMENSIONS IN:		



THE NUMBERS REFER TO OPERATIONS DETAILED IN PROTOCOL 5.3.2

GRC CONSULTANTS
VESTBROOKE HOUSE 78 HIGH STREET
ALTON. HANTS GU34 1EN
TEL: 0420 89847 FAX: 0420 89427

CLIENT AREA	PROJECT	TITLE
UNIDO	TRIGON TF/HUN/90/911	BLACK TO WHITE CHANGE OPERATIONS
DATE: AUG '92	DRAWING NUMBER	REV
SCALE: N/A	92/012/109	A
DIMENSIONS IN:		

The personnel flow through the proposed new layout is given in drgs. 92/012/129 - 92/012/131. The two stage change procedure of Black/Grey, Grey/White or Grey+ is retained. However, more space has been allocated for changing, in particular the Grey/White area used to access the sterile suite on the 1st floor is much larger.

A small Grey office is retained on the 1st floor for administration duties.

5.3 CHANGING PROTOCOLS

Protocols are presented for Black to White change (protocol 5.3.1) and Black to Grey change procedures (protocol 5.3.2). These are accompanied by change operation drgs. 92/012/109 and 92/012/108 which detail diagrammatically where the operations take place, corresponding to the numbers given in the protocols.

The Black to White protocol uses shoes, disposable overshoes and overboots. The overshoes protect the garments being put on from contamination originating from Grey area shoes before the White area overboots are put on. It should be noted that gloves are put on and disinfected before entering the White area.

The Black to Grey change is essentially a shortened version of the Black to White change. Hair protection is worn instead of hoods and masks and gloves are not considered necessary.

In summary, the Grey area clothing is underwear, socks, shoes, trousers, jacket and hair protection.

The White area clothing is underwear, socks, shoes, overshoes and overboots, trousers, jacket, hood, masks and gloves.

Protocol 5.3.1

Black to White Change

Location	Operation	Instruction No.
Black Area	Go to toilet if required before entering	1
Lobby	Through door to	2
Black Change	Remove all clothes, jewellery and make-up, place in lockers provided	3
	Through door to	4
Shower Room	Rinse body thoroughly with soap provided	5
	Take towel provided and dry excess water off	6
	Through door to	7
Black/Grey Change	Completely dry body, dispose of towel in bin provided	8
	Put on underwear from locker provided	
	Put on jacket	9
	Put on trousers	
	Sit on bench and put on socks and shoes, step over bench to	10
Grey Change	Through door to	11
Lobby	Put on disposable overshoes stepping into	12
Grey/White Change	Disinfect hands with alcohol based disinfectant. Rub well and allow to air dry	13
	Open bag containing sterile suit. Put on hood touching the outside as little as possible and making sure all hair is tucked in. Put on face mask making sure that the nose strip is shaped securely around the bridge of the nose.	14

	Treat hands once more with disinfectant	15
	Put on jacket, touching the outside as little as possible and ensuring that the hood yolk is tucked inside the jacket.	16
	Put on sterile gloves, touching the outside as little as possible and ensuring the gloves overlap the cuffs of the jacket sleeves.	
	Put on suit trousers, touching the outside as little as possible and preventing the trouser legs from coming into contact with the floor	
	Sit on bench between and put on overboots stepping through to	17
White Change	Disinfect gloves thoroughly with an alcohol based disinfectant	18
	Check all suit fastenings are secure	19
	Enter aseptic area, opening the changing room door by pushing with elbows	20

Protocol 5.3.2

Black to Grey Change

Location	Operation	Instruction No.
Black Area	Go to toilet if required before entering	1
Lobby	Through door to	2
Black Change	Remove all clothes, jewellery and make-up, place in lockers provided	3
	Through door to	4
Shower Room	Rinse body thoroughly using soap provided	5
	Take towel provided and dry excess water off before entering	6 7
Black/Grey Change	Completely dry body, dispose of towel in bin provided	8
	Put on underwear from locker provided	9
	Put on jacket	
	Put on trousers	
	Sit on bench and put on socks and shoes, step over bench to	10
Grey Change	Disinfect hands with alcohol based disinfectant. Rub well and allow to air dry	11
	Put on hair protection and beard snoots if necessary	12
	Disinfect hands with alcohol based disinfectant. Rinse well and allow to air dry	13
	Check all fastenings secure	14
	Go through door to	
Grey Area		

5.4 CLEAN ROOMS AND CLOTHING

5.4.1 Basic Principles of Clean Room Design

The basic principles of clean room design can be applied to all rooms in varying degrees and further details are given in Appendix II.

The room structure is designed and constructed carefully and in such a way as to allow the attainment of surfaces around walls, windows, doorways, air entry and exit points, service penetrations and equipment interfaces which have the minimum of crevices and uncleanable recesses. (There must be provision for the incorporation perhaps at some future date of additional services that may not be foreseen at the outset.)

The room surface finishes must be sealed, non-shedding, non-reactive to a range of disinfectants and must be capable of continuing maintenance and repair should damage occur. The ideal finish is entirely joint free. Particular attention should be paid to the connection point of the surface finish to construction features such as doors and windows.

Specialist equipment can sometimes be supplied with control or indicator panel which may be flush mounted or sealed into the clean room wall.

Where piped services penetrate the clean room finish, they must be carefully designed with closing plates and sealed using an elastomer such that allowance is made for expansion and contraction whilst maintaining an unbroken seal.

Items of equipment sited centrally in clean room can be serviced by a pendant protruding down from the ceiling carrying the necessary mechanical and electrical service outlets and connections. These must be integrated in terms of finished sealing and cleanability.

The attention to detail cannot be overemphasized. The use of experienced site construction technicians who appreciate the demanding requirements of a clean room structure is essential. All people who work on the construction of the site must be fully aware of the standards required and be capable of achieving them.

5.4.2 Clean Room Clothing

General Considerations

People are the dirtiest objects ever to enter a clean room accounting for 80% of particle contamination. Clean room clothing thus has the completely opposite function to normal clothing and is designed to protect the environment from the person.

Typically in a sterile clean room environment personnel will wear three layers of clothing. Normal underclothes will be worn plus a second layer of greywear. This grey wear consists of a lightweight top and trousers which may be made of poly/cotton for operator comfort. Poly/cotton socks and clean grey shoes will be worn.

The operator dressed in greywear will now be totally covered in a layer of whitewear which forms the 'person filter' protecting the environment from the person. A small area around the operative's eyes is usually left exposed.

The whitewear consists of a coverall (or jacket and trousers), overboots and a hood. These are initially sterile and are worn in conjunction with sterile gloves and a mask.

Greywear may be used on its own in controlled but not sterile areas but discretion is required in specifying a mixed grey and white personnel grey change area. Much depends on the type of processing undertaken in the grey area.

This section will be concerned with this third set of clothing, whitewear.

Requirements of Clean Room Clothing

There is no doubt that the most effective clothing for clean room operatives is one which is totally sealed with a zero air permeability, however such a garment would be uncomfortable and impractical for prolonged wear. The materials used for clean room clothing are nearly all made from 100% polyester continuous filament fibres which is tight weaved. These filaments are strong enough to minimise abrasion and shear. The fabric also reduces the generation of static electricity which could cause a pick up of dust.

The garments are non-linting and of a suitable tight fabric construction to minimise the passage of dust and lint from the wearers body and inner clothing. The garments are moderately loose fitting to reduce abrasion against inner clothing and contain a minimum number of enveloped and possibly heat sealed seams.

Garments are made without pockets, belts, pleats and elasticated areas as these all form dust traps.

Care is taken to ensure a good fit around various cuffs to prevent the release of particles, which is exacerbated by the 'bellows effect' caused by operative movement. The garments should be well cut to prevent large areas of excess cloth forming bellows.

Sewing threads must also be made from non-linting fibres.

The design of the overboot takes into account the work performed by the clean room operative and the floor characteristics.

Attention is paid to the quality of clothing ties and clothing design to ease dressing.

Service Methods

Clean room garments are typically washed and then sterilized. The processing is done in an environment similar to that in which it is worn.

Washing is achieved by laundering or dry cleaning. Laundering is a hot aqueous process which has good soil and human residue removal properties. Dry cleaning utilises a solvent such as Perchloroethylene in a cold process for dirt removal. Laundering is probably the best of the two washing methods due to its capacity to remove water solubles such as sweat, odour and sugars.

Sterilization may be achieved by autoclaving, ethylene oxide or gamma irradiation. Autoclaving can cause shrinkage which can significantly shorten the useful life of a fabric. Ethylene oxide treatment achieves sterilization without fibre deterioration but is becoming increasingly unacceptable as a means of sterilization. Gamma irradiation is probably the best sterilization method for clean room clothing and has the advantage that sterilization may be achieved after packing.

The washing of clean room garments may be successfully achieved on site, but many smaller operations find the high cost of installing washing clean rooms and special machinery means that it is cost effective to contract out cleaning to specialist companies.

Further details of clean room clothing are given in Appendix II and outline guidance notes for operations in clean rooms are given in Appendix IV.

5.5 BUILDING DESIGN AND FINISHES

This section gives preliminary outline details of the finish, quality, etc, which are appropriate for a modern biopharmaceutical unit for the production of sterile injectible products to US and EC authority standards.

5.5.1 Room List

The list given overleaf shows the key rooms identified by reference number, description and "standard" to which GRC Consultants would expect these rooms to be finished. Only those rooms which are involved with interferon processsing, in any way, are given in the list.

5.5.2 Room Standards

Basically, five room standards are proposed as summarised below:

GRC Room Standard	Standard Description	Clean Room Standards		
		USA	EC	UK
C5	Basic Industrial Standard	N/A	N/A	N/A
C4	Hygienic Standard	N/A	N/A	N/A
C3	Low Controlled Class	100,000	D	K
C2	Intermediate Controlled Class	10,000	C	J
C1	High Controlled Class	100	AB	CF

N/A Not Applicable
USA Standard is 209D (1988)
EC Standard is GGMP (1992)
UK Standard is BS5295 (1989)

Room No.	Description	GRC Standard
Basement		
1	Male Changing Room	C4
2	Lobby	C4
3	Laboratory Coats Lobby	C4
4	Female Fermenter Changing Room	C4
5	Corridor	C4
6	Female WC	C4
7	Male WC	C4
8	Laundry	C4
9	Kitchen - Dining Rooms	C4
10	Female WC	C4
11	Male WC	C4
12	Stairway	C4
13	Corridor	C4
14	Lobby	C4
Ground Floor		
101	Covered Courtyard	C5
102-104	Plant Room	C5
105	Outside Courtyard	-

107	Elevator	-
108	Air Conditioning Room	C5
112	Lobby	C4
114	4°C Cold Store (Interferon product)	C4
115	Store Room (contains Sendai virus in freezers)	C4
201	Corridor	C3
202	Porter/Security Lodge	C5
203	Goods-in Clearing	C4
204	Goods in quarantine and cleared stores	C4
210	Office	C4
211	Dish Washing	C4
212	Dirty Materials Store	C4
213	Sterilization Room	C3
214	Lobby	C3
215	Solutions Preparation Room	C3
216	Dispensary	C3
217	Cold Room (4°C)	C4
220	Goods Out Lobby	C4
221	Goods Out Store	C4

1st Floor

301	Air Conditioning Room	C5
311	Waste Transfer Room Change	C4
316	Waste Preparation Room	C4
317	Freeze Drying Room	C2
318	Centrifuge Room	C3
319	Cold Room	C4
320	Stairwell	C4
321	Air Conditioning Room	C5
322	Packing	C4
327	Main Production Room	C2
328	Incubation Room	C3
329	Grey/White Change	C3
330	Corridor	C3
331	Office	C4
332	Corridor	C4

Second Floor

400	Corridor and Stairs	C4
401	Tissue Culture Laboratory	C3
402	Air Lock	C3
403	Air Lock	C3
404	Viral/Microbiology Laboratory	C3
405	Preparations Room	C4
406	Office	C5

The details of each of the C1 - C5 standards are given in the sheets which follow. They are generally applicable and would need to be modified eventually to Trigon's particular requirements.

C5 BASIC INDUSTRIAL STANDARD

This standard applies to all general offices, changing rooms, amenities, corridors, control rooms, etc, except where otherwise indicated on the individual Room Specifications.

Steam is available for either direct or indirect heating.

Adequate protection is to be provided to changing and toilet areas.

Fire Protection

Detection: Smoke and rise of heat detection.
Fighting: Local hand-held extinguishers.

Access

Normal: Authorised personnel via reception/entrance lobby.
Maintenance: As above and based on permit to work.

C4 HYGIENIC STANDARD

HVAC Services

Temp: Heated to legal minimum by steam radiant panels or with HV system.
Humidity: Not controlled
Air changes: 5 per hour
Forced/natural: Forced
Pattern: High level in, low level extract
Pressure: Atmospheric
Filtration: Min 96% efficiency to BS2831 No. 2 test dust
Recirculation: Not more than 80%
Heat recovery: None

Electrical Services

Power outlet type: Flush, sealed
Phone outlet type: Flush, sealed
Lighting level: 500 lux
Lighting type: Twin fluorescent tube with diffusers, readily cleanable

Finishes

Floor: Smooth, hard, non-dusting surface, acid/alkali resistant, washable, e.g. 'Ucrete' or equivalent

Walls*: Smooth, hard, non-shedding, washable. Preferred finish: 2 coat epoxy sealed 'plaster pac' with suitable corner/edge protection. Alternatively concrete blocks or similar may be used instead of 'plaster pac'.

Ceilings*: Smooth, non-shedding, cleanable, sealed with epoxy paint, e.g. sealed plasterboard or painted.

Skirting: Wall to floor finish in floor finish material.

Coving: Not required.

Doors*: Generally to industry standard, flush, gloss painted, self closing, with SAA furniture and vision panels glazed to fire protection requirements.

Windows: Flush, sealed, non opening, ledge free. Glazing to fire protection requirements.

* Detailed design to incorporate fire protection requirements.

Drainage

Drains: No floor drains/gulleys
Spills and wash down: By squeegee and liquid vacuum cleaner
Process drains piped above floor level
Sinks: Stainless steel, wall mounted

Fire Protection

Detection: Smoke and rise of heat detection
Fighting: Local hand-held extinguishers

Access

Normal: Authorised personnel by management via change area
Maintenance: As above and based on permit to work
Emergency escape: Doors and break out panels as per layout drawings
Clothing: Working clothes as defined by Trigon management

C3 LOW CONTROLLED CLASS

This class is equivalent to USA Class 100,000 (209D, 1988), EEC Class D (GGMP, 1992), UK Class K (BS5295, 1989).

HVAC Services

Generally to BS5295 or other suitable standard.
Temp: 20°C ± 2°C by steam heating/chilled water in HVAC system
Humidity: Generally not controlled
Air changes: To meet BS5295 but not less than 10 per hour
Forced/Natural: Forced
Pattern: High level in, low level extract
Pressure: + Positive (min 15 Pa gauge, max at least 15 Pa below Class 2 pressure). Low room pressure alarms to be installed with timed delay.
Filtration: Inlet; coarse prefilter and final HEPA filter to BS5295
Outlet; not required
Recirculation: Not more than 80%
Heat recovery: None

Electrical Services

Power outlet type: Flush, sealed
Phone outlet type: Flush, sealed
Lighting level: 500 lux
Lighting type: Twin fluorescent tube with diffusers, sealed flush into ceiling

Finishes

Floor: Smooth, hard, non-dusting surface, washable, with proprietary epoxy finish

Walls*: Smooth, hard, non-shedding, washable, 2 coat epoxy paint on plastered board or 'plaster pac'.

Ceilings*: Smooth, non-shedding, cleanable, sealed with epoxy paint, suspended false ceiling, integral light fittings and air diffusers. Where possible air filters and lighting tubes should be changeable from outside room area.

Skirting: Sealed wall to floor in floor finish material.

Coving: Sealed wall to ceiling in wall finish material.

Doors*: Generally to industry standard, self closing, sealing, flush, gloss painted, with SAA furniture and vision panels glazed to fire protection requirements.

* Detailed design to incorporate fire protection requirements.

Drainage

Drains: No floor drains/gulleys
Spills and wash down: By squeegee and liquid vacuum cleaner
Process drains piped above floor level
Sinks: Stainless steel, wall mounted

Fire Protection

Detection: Smoke and rise of heat detection
Fighting: Local hand-held extinguishers

Access

Normal: Authorised personnel by management via change area
Maintenance: As above and based on permit to work
Emergency escape: Doors and break out panels as per layout drawings
Clothing: Working clothes as defined by Trigon management

C2 INTERMEDIATE CONTROLLED CLASS

This class is equivalent to USA Class 10,000 (209D, 1988), EEC Class C (GGMP, 1992), UK Class J (BS5295, 1989).

HVAC Services

Generally to BS5295 or other suitable standard.
Temp: 20°C ± 2°C by steam heating/chilled water in HVAC system
Humidity: Not controlled
Air changes: To meet BS5295 but not less than 20 per hour
Forced/Natural: Forced
Pattern: High level in, low level extract
Pressure: ++ Positive (min 15 Pa above Class 2 pressure, max at least 15 Pa below Class 1 pressure). Low room pressure alarms to be installed with timed delay.
Filtration: Inlet; coarse prefilter and final HEPA filter to BS5295 terminally located
Outlet; not required
Recirculation: Not more than 80%
Heat recovery: None

Electrical Services

Power outlet type: Flush, sealed
Phone outlet type: Flush, sealed
Lighting level: 500 lux
Lighting type: Twin fluorescent tube with diffusers, flush sealed into ceiling

Finishes

Floor: Smooth, hard, non-dusting surface, washable, e.g. proprietary epoxy finish, or welded PVC.

Walls*: Smooth, hard, non-shedding, washable, e.g. 2 coat epoxy paint or welded PVC lining on plastered block or 'plaster pac'.

Ceilings*: Smooth, non-shedding, cleanable, sealed with epoxy paint, suspended false ceiling, integral light fittings and air diffusers. Where possible air filters and lighting tubes should be changeable from outside room area.

Skirting: Sealed wall to floor in floor finish material.

Coving: Sealed wall to ceiling in wall finish material.

Doors*: Self closing, sealing, flush, gloss painted, with SAA furniture and vision panels glazed to fire protection requirements. Generally to industry standard.

* Detailed design to incorporate fire protection requirements.

Drainage

Drains: No floor drains/gulleys
Spills and wash down: By squeegee and liquid vacuum cleaner
Process drains piped above floor level
Sinks: Stainless steel, wall mounted

Fire Protection

Detection: Smoke and rise of heat detection
Fighting: Local hand-held extinguishers

Access

Normal: Only permitted via clean change
Maintenance: Permit to work via clean change except during shutdown
Emergency escape: Doors and break out panels as per layout drawings
Clothing: Working clothes as defined by Trigon management

C1 HIGH CONTROLLED CLASS

This class is equivalent to USA Class 100 (209D, 1988), EEC Class AB (GGMP, 1992), UK Class EF (BS5295, 1989).

HVAC Services

Generally to BS5295 or other suitable standard.
Temp: 20°C ± 1°C by steam heating/chilled water in HVAC system
Humidity: Not controlled
Air changes: To meet BS5295 but not less than 20 per hour
Forced/Natural: Forced
Pattern: High level in, low level extract conventional flow (local laminar flow cabinets)
Pressure: +++ Positive (min 15 Pa above Class 2 pressure).
Low room pressure alarms to be installed with timed delay.
Filtration: Inlet; coarse prefilter and final HEPA filter to BS5295 terminally located
Outlet; not required
Recirculation: Not more than 80%
Heat recovery: None

Electrical Services

Power outlet type: Flush, sealed
Phone outlet type: Flush, sealed
Lighting level: 500 lux
Lighting type: Twin fluorescent tube with diffusers, flush sealed into ceiling. Resistant to gas sterilization.

Finishes

Floor: Welded vinyl, resistant to gas sterilization and swabbing, laid on flat prepared surface.

Walls*: Lined with vinyl, GRP or similar, smooth, washable, ledge free and resistant to gas sterilization and swabbing.

Ceilings*: Suspended type, sealed with impervious, non-shedding finish, e.g. epoxy paint or welded vinyl sheet, resistant to gas sterilization. Integral sealed light fittings. Air filters and lighting tubes to be changeable from outside the room area.

Skirting: Sealed wall to floor in floor finish material.

Coving: Sealed wall to ceiling in wall finish material.

Doors*: Self closing, sealing, flush, gloss painted, with SAA furniture and vision panels glazed to fire protection requirements. Generally to industry standard.

* Detailed design to incorporate fire protection requirements.

Drainage

Drains: No floor drains/gulleys
Spills and wash down: By squeegee and liquid vacuum cleaner
Process drains piped above floor level
Sinks: Stainless steel, wall mounted

Fire Protection

Detection: Smoke and rise of heat detection
Fighting: None

Access

Normal: Only permitted via clean change
Maintenance: Permit to work via clean change except during shutdown
Emergency escape: Doors and break out panels as per layout drawings
Clothing: Working clothes as defined by Trigon management

5.6 HVAC ESSENTIALS

5.6.1 General Considerations

The detailed design and installation of a pharmaceutical heating, ventilation, and air conditioning system is a specialised task which must be undertaken by an experienced company. The company must integrate and co-ordinate all aspects of the facility design which influence HVAC efficiency. Factors to be considered include the following:-

- Room finish, e.g. welded vinyl
- All materials used in facility construction
- Room fittings, e.g. doors, windows, etc
- Fittings furniture, e.g. door handles, etc
- Integration of pipework into rooms
- Integration of equipment into rooms
- Control of room pressure
- Control of room temperature
- Control of room humidity
- Specification of flush light fittings if necessary and specification of lighting levels
- Control of direction and rate of air flow
- Control of HVAC noise level where practical and worthwhile
- Accessibility of HVAC, lighting and other equipment

All aspects of clean room design are best considered together and most successfully handled by one specialist company. This company would perform the detailed design and the installation of the clean room facility.

5.6.2 Detailed Considerations

The system heating capacity is capable of raising the building temperature to its design requirement within 2-3 hours, assuming a shutdown of 2 days. (The fitting of heat recovery systems may be considered if any economic advantage is possible).

The specified temperatures is maintained taking into account:-

- Minimum number of air changes
- Heat gain from plant operation

It is normal to design for an air temperature 18-22°C ± 2. Ventilation in process areas and such similar spaces is based on 'uni-directional' air flow principles. This means that all extract will, as far as practicable, occur at low level in the vertical plane representing the wall surface faced by the plant operator(s) when operating the plant. All supply air is delivered within the zone which is opposite to this plane. Air is supplied at sufficiently low linear momentum to ensure that the only air movement perceived at the operating positions is that due to the general drift of air towards the exhaust plane. The above requirement can, of course, only be attained under ideal isothermal conditions.

All safe areas adjacent to hazardous areas have their air supply/extract set to provide a higher pressure than that in the adjacent hazardous area.

The air handling plant contains filters heaters/coolers to maintain the conditions as selected, together with controls to maintain design air flow over the clean to dirty filter condition.

The requirement for humidity control for process and other resources is examined and agreed with Trigon with respect to the operations carried out in the plant and the degree of product exposure.

Illumination is provided at 500 lux with 1000 lux in inspection areas. Care must be taken to avoid glare from white surfaces where applicable.

Noise levels are kept in the range 50-60 dBA, but lower levels should be used in areas with no production machinery.

5.6.3 HVAC GMP Considerations

To ensure compliance with the required quality considerations within the guides to GMP, it is essential to validate the working rooms and determine the environmental conditions which exist in the room during actual production with an acceptable and predetermined level of contamination. The determination of these conditions is then be used during subsequent re-testing during production such that the quality of the environment can be measured particularly if there are failures or problems in production.

Prior to the validation being carried out, all air moving and service systems will have been commissioned and will have received operational qualification to assure that the installed systems are working to the design intent. These tests will include some or all of the following.

1. Room temperature tests
2. Room humidity tests
3. Calibration of all monitoring equipment on parameters such as flow rates, pressure and temperature
4. HEPA filter integrity tests

5. Airborne particulate counts which may be carried out in the as built, at rest or operational conditions
6. Pressure differential tests throughout all zones
7. Air visualisation tests with doors closed and open
8. Air pattern visualisation within individual rooms
9. Room recovery to indicate the "clean up rate" within individual rooms.

All of the above tests will be carried out and carefully recorded to an agreed and approved standard such as the American IES-RP-CC-006-84-T recommended practice for testing of clean rooms.

Detailed protocols for the sterilization and/or cleaning of the facilities must be developed since these are essential in support of the achievement of GMP.

SECTION 6

OVERALL CONCLUSIONS AND RECOMMENDATIONS

6 OVERALL CONCLUSIONS AND RECOMMENDATIONS

On the basis of the two audit visits made in May and July 1992, GRC Consultants conclusions are as follows:-

- The first impression of the interferon production facility, especially in the "sterile" processing areas, is one of a facility which is well cared for by the Trigon staff.

- The staff show a good understanding of the general requirements for GMP as exemplified by the attention which has been paid to the neatness and tidiness requirements particularly in the "sterile" processing areas.

- In general, and as far as can be ascertained within the constraints of the project, the processing equipment appears adequate but is clearly showing signs of age.

- Within the "sterile processing" areas a number of minor design deficiencies are identified and these could be put right relatively easily.

- The HVAC system which serves the interferon production area is considered to be significantly below the standard expected for a modern facility for sterile injectibles production and the whole system requires extensive upgrading.

- The air quality within the laminar flow cabinets, where product is exposed to the environment, is shown by particle count measurements carried out on an annual basis to satisfactory AT THE TIME OF THE TEST - but its quality on a day to day basis is unknown.

- The air quality in the main sterile processing rooms appears to be Class D (PIC basis) and this is considered to be unsatisfactory by modern standards (Class C at least is expected).

- The quality and type of garments worn in the sterile areas (Trigon green) would be considered unsatisfactory by modern standards for a facility producing sterile injectibles in so far as the garments are clearly showing signs of age and wear.

- The protocols for changing into 'sterile wear' before entering the main interferon production suite probably would not be considered strict enough by modern standards and need updating.

- Many aspects of layout and personnel/materials flow and movement would not be considereed appropriate for a modern sterile injectibles production unit.

- Overall, it is concluded that in its present state and with some of the existing operating practices, it is unlikely that Trigon would be successful in applying for an Establishment Licence for the facility from the FDA.

In the light of the audit carried out, the following general recommendations are made:-

- Trigon should seek to establish, in the light of the recommendations for upgrading, the cost of modifying the existing buildings in Hogyes Endre u.

- Trigon should also investigate the opportunities for, and the costs of, establishing an Egiferon production unit in a purpose-built building, or in an existing modern facility which could be adapted/modified to accommodate te Egiferon process.

APPENDICES

APPENDIX I

EXTRACT FROM:-

"Categorisation of Pathogens According to Hazard and Categories of Containment" 1990

Containment Level 1

39 Containment Level 1 is suitable for work with organisms in Hazard Group 1. Laboratory personnel must receive instruction in the procedures conducted in the laboratory.

1 The laboratory should be easy to clean. Bench surfaces should be impervious to water and resistant to acids, alkalis, solvents and disinfectants.

2 If the laboratory is mechanically ventilated, it is preferable to maintain an inward airflow into the laboratory by extracting room air to atmosphere.

3 The laboratory must contain a wash-basin or sink that can be used for hand washing.

4 The laboratory door should be closed when work is in progress.

5 Laboratory coats or gowns should be worn in the laboratory and removed when leaving the laboratory suite.

6 Eating, chewing, drinking, smoking, storing of food and applying cosmetics must not take place in the laboratory.

7 Mouth pipetting must not take place.

8 Hands must be disinfected or washed immediately when contamination is suspected, after handling viable materials and also before leaving the laboratory.

9 All procedures must be performed so as to minimise the production of aerosols.

10 Effective disinfectants must be available for immediate use in the event of spillage.

11 Bench tops should be cleaned after use.

12 Used laboratory glassware and other materials awaiting disinfection must be stored in a safe manner. Pipettes, if placed in disinfectant, must be totally immersed.

13 All waste material which is not to be incinerated should be rendered non-viable before disposal.

14 Materials for disposal must be transported in robust containers without spillage.

15 All accidents and incidents must be recorded.

APPENDIX II

ASPECTS OF GOOD MANUFACTURING PRACTICE

APPENDIX II

ASPECTS OF GOOD MANUFACTURING PRACTICE (GMP)

1 INTRODUCTION

As noted in section 4.1 of the main report, GMP is concerned with manufacture and quality control. Also the principles of GMP require that the facilities must be designed to suit the operations carried out in them and it is appropriate that, for the purposes of this report, two key features should be examined in some detail. The two features chosen each demonstrate a different aspect of GMP but both are related to "cleanliness" as it applies to biological pharmaceuticals production.

The first topic is the design and construction of CLEAN ROOMS and the second topic is concerned with CLEAN ROOM CLOTHING. Clearly there are many other aspects of GMP but these two topics are chosen since they involve facilities and operations at the point where the product is most vulnerable to contamination and/or infection, i.e. where the product is, or potentially is, exposed to the environment and to the worst source of contamination, the human being.

2 CLEAN ROOM DESIGN

One of the most important aspects of GMP is the creation and maintenance of a 'clean' environment in which key pharmaceutical processes take place. This section is concerned with the design and construction of clean room facilities and key aspects of clean room design are summarised below.

2.1 The Clean Room

A clean room is any room or area in which an attempt is made to limit and control the amount of airborne dust (particulate matter). Contamination is considered to be any foreign substance that will have a detrimental effect on the mechanism or process in question.

The control of airborne particulate matter is accomplished by 5 means:

1. Preventing entry of the particulate matter
   This is accomplished by filtration of the air entering the clean room.

2. Purging of particulate matter
   The air handling system changes the air in the room and this removes particulate matter generated within the room.

3. Prohibiting the generation of particulate matter
   Clean room clothing is made of "limiting linting" fabric which will not produce excessive quantities of lint as it is flexed. Similarly room appointments, floors, etc, are chosen for this resistance to particle generation.

4. Protecting the product from impact and settling of particulate matter. The low level of particulate matter in clean rooms contains a majority of the smaller size particles which settle out very slowly. These smaller particles have a very long "life".

5. Providing an area for the cleaning of parts and personnel. Everything entering the clean room is cleaned so that as little contamination as possible is added to the room atmosphere by transfer from dirty objects.

2.2 Particulate Matter

Particulate matter takes on all shapes. It can be any material, organic or inorganic, of miniature dimensions.

Particulate matter may be categorised by physical characteristics such as shape, size and hardness. The amount of control necessary within any room depends upon the product being produced.

When particulate matter is suspended in gas (such as air) it is called airborne particulate matter. The same material suspended in a liquid is called fluid contaminant, whereas the same material settled in liquid is referred to as silt.

2.3 Sterile or Aseptic Areas

The main consideration is that of excluding microbial contamination in addition to the solid particulate matter. The construction of the facility will include the use of similar, if not identical, materials to that of a clean room, but generally more stringent rules apply to personnel hygiene and cleaning of work surfaces will take place regularly using an bactericidal solution.

Periodic gas cleaning should be built into a planned maintenance shut down by the use of formalin heated to produce formaldehyde which will permeate the entire area and machines for anything up to 6-8 hours.

Equipment such as autoclaves, hot air ovens, etc, with front and rear entries should be built into the walls of the sterile area making sure that the bulk of the unit is outside the room. Ideally the equipment should be flush fitting on the inside.

Terminal HEPA filtration should be used in the design of sterile facilities and 20 air changes per hour minimum calculated for in the air system to the room. An over-pressure should be maintained in the main production areas with 'bleed off' grilles to change rooms and air locks.

2.4 Laminar Flow Theory

Essentially, laminar flow is produced when air is introduced uniformly at low velocities into a space confined on four sides and through an opening equal to the cross-sectional area of the confined space.

Laminar flow stratifies the air so that minimum cross-stream contamination occurs. There is little or no transfer of energy from one streamline to another. Suspended particulate matter on one streamline will tend to stay in that particular streamline until captured.

HEPA filters produce a uniform distribution of air when a pressure differential is applied across them; they are also the most efficient filters presently available.

A room with HEPA filters at one end or in the ceiling and an exit equal in area directly opposite will have a very low contamination level, with laminar flow proceeding from entrance to exit.

2.5 Clean Room/Sterile Area Specifications

2.5.1 Classification of environmental cleanliness

Environmental cleanliness is stated in terms of size and maximum permitted number of airborne particles and is designated class 1, 2, 3 and 4 environments.

Class 1 - The particle count shall not exceed a total of 3000 particles/m^3 of a size of 0.5 micron or greater. The greatest particle present in any sample shall not exceed 5 micron.

Class 2 - The particle count shall not exceed a total of 300,000 particles/m^3 of a size of 0.5 micron or greater.

2000 particles/m^3 of a size 5 micron or greater.

30 particles/m^3 of a size 10 micron or greater.

Class 3 - The particle count shall not exceed a total of 1,000,000 particles/m^3 of a size of 1 micron or greater.

20,000 particles/m^3 of a size 5 micron or greater.

4000 particles/m^3 of a size 10 micron or greater.

300 particles/m^3 of a size 25 micron or greater.

Class 4 - The particle count shall not exceed a total of 200,000 particles/m^3 of a size 5 micron or greater.

40,000 particles/m^3 of a size 10 micron or greater.

4,000 particles/m^3 of a size 25 micron or greater.

2.5.2 Containment Surfaces

Side panels, tops and work surfaces should be such that they will provide a cross-section area equal to the filter face. In normal circumstances, these containment surfaces will be perpendicular to the filter face.

2.5.3 Final Filters

All final filters are of the HEPA type, which make up either the rear or top surface of the enclosure and should cover the entire area of that surface.

2.5.4 Prefilters

Prefilters should be used to prolong the life of the HEPA filters. The efficiency of the prefilters should be tailored to the anticipated contamination load and the desired life of the HEPA filters.

2.5.5 Airflow Patterns

Airflow patterns should be uniform with a minimum turbulent pattern in the unobstructed areas of the enclosure.

A magnehelic gauge or similar device should be fitted to indicate pressure differences across the filter banks.

2.5.6 General

The design of all rooms, whatever airflow techniques are used, should take into account the following requirements:

Provision of services and facilities necessary to carry out the planned function of the room.

The prevention of contamination being introduced by the entry of circulating air, and entry or exit of personnel and material.

Elimination of dead spots in air circulation and built-in traps where contamination can accumulate.

Arrangements for the removal of contamination generated within the area.

Provision of air conditioning facilities.

2.5.7 Construction

The construction of the clean room should take the following into account:

The construction should prevent leakage of air (in order to enable a positive pressure to be maintained). All internal surfaces are to be smooth and free from dust, crevices, crack ledges.

All internal corners should be 'coved' or radiused to provide a smooth easy clean surface.

Construction materials should be non-particle generating and also possess no electrostatic properties.

The colour scheme is optional, but the chosen colour should show any dusty deposited on the surface.

The floor is to be covered in a material which will not generate contamination particles under the proposed traffic load. Special consideration must be given to abnormal requirements such as anti-acid or anti-corrosive properties, high floor loads or anti-static and conducting properties.

The floor coverings should be continuous and where a sheet material is used all butt joints should be welded or otherwise suitably joined.

Doors are to be closed fitted and equipped with seals to prevent loss of pressure. All conventional rooms should be provided with an airlock facility to ensure no loss of room pressure. The airlock doors should be equipped with an interlock system to prevent both doors being opened at the same time.

2.6 Environmental Specification

Room Pressure

All clean rooms shall maintain a pressure above that of surrounding and/or adjacent areas to ensure that any leakage will be outward.

Unless the required process conditions are different, the following temperature and relative humidity conditions are applicable.

Temperature Range

The room temperature should be maintained at 20 ± 2° for general application.

Relative Humidity

The maximum relative humidity shall be between 35% to 50%. Humidity controls shall be capable of holding the specified relative humidity within ±10% for general application.

Laminar Airflow Velocity

All horizontal laminar airflow systems should have an airflow velocity of 90 feet per minute (fpm) within ± 20 fpm.

Vertical flow devices can have the velocity reduced to 60 fpm ± 10 fpm.

Air Changes

Conventional clean rooms shall have a minimum of 20 air changes per hour.

3 CLEAN ROOM CLOTHING

Clean rooms are locations where the ultimate in cleanliness and hygiene are required. When people enter a clean room, contamination rises sharply so clean room clothing is designed to protect the environment in the clean room from the people working in it. Hence the clothing is, in fact, a filter which is just as important as any other filter in the clean room.

The importance of clean room clothing, as part of GMP, is illustrated in the key points which are summarised below.

Clean room clothing is designed to protect the product from the human being. A properly constructed and operated clean room will have a certain level of contamination, of which people account for about 80%. The clothing people wear must therefore act as a barrier to particles being shed by both the body and undergarments and, equally important, must not shed particles from the fabric itself.

Clean room clothing, therefore, must act as a filter and be made from fibres which do not shed particles and lint.

3.1 Garment comfort

The comfort and wearability of clothing arises not only from its weight and "feel" but also its ability to remove moisture rapidly, such as sweat, and to allow it to be dispersed over the greatest area of fabric rather than to remain localised and thus to give the feeling of dampness.

Fibre technology has developed to the point where modern fabrics can be made from 100% polyester and be capable of carrying moisture across the fabric, thus making it more comfortable to wear.

3.2 The garments

It cannot be repeated too often that people represent 80% of the contamination in a working clean room. The garments are therefore primarily "a people filter system" and must be designed using the appropriate fabrics to prevent contaminants from either the body or the work clothing interfering with the manufacturing and/or performance of a product.

The overriding features of the specification for a clean room garment are as follows:

- Non-linting fibres.

- Tight fabric construction to minimise passage of dust and lint from wearer's body and inner clothing.

- Individual filaments of the fabrics must be as strong as possible in order to reduce abrasion and shear.

- A minimum of seams and those which do exist must envelope firmly the raw edge of the material. Raw edges should be heat sealed.

- Garments to be loose fitting to reduce abrasion against inner clothing.

- Garments to be made without pockets, belts and pleated or tucked areas.

- Sewing threads to be made from non-linting fibres.

- The fabric should reduce the generation of static electricity as much as possible as is compatible with its ability to remain non-linting.

- Fabrics should have good sweat dispersal characteristics for personnel comfort.

3.3 Processing and Service

The first consideration in the technology of clean room clothing is the design of fibre, fabric and garment to meet the standards of clean room use.

The seccnd consideration is the means by which those garments may be used on a continuing basis. This is called processing and service.

It is worth noting that the normal criteria for cleansing clothing, namely that it be both clean and aesthetically pleasing, are of almost secondary importance to the need for it to be particle or contamination free.

The criteria to be met when processing garments are identified as:-

- To wet out the load.
- To remove soiling from the load.
- To hold that soil in suspension.

- To remove the suspended soil from the machine used for processing.
- To remove the residue of soap or detergent from the load at the end of the cycle.

There are two methods of cleansing fabrics:

Laundering, or wet washing, and dry cleaning, or solvent washing.

Wet Washing:
A washing machine uses water, which has a low cost, and which is dumped to waste after each cycle.

Dry Cleaning:
A dry cleaning machine uses an expensive solvent.

In terms of clean room clothing processing it is generally held that fluorocarbon is the more acceptable spirit largely as the latest generation of machines using this solvent are totally enclosed which is a positive benefit for this application.

3.4 Sterilization of Garments

One of the key aspects of clean room clothing, particularly to the pharmaceutical and medical products industries, is the need to destroy viable organisms and sterilization is needed to destroy all viable organisms.

The three methods available are:

- Autoclaving
- Ethylene Oxide
- Gamma Irradiation

(i) Autoclaving is clearly effective and is both cheap and easy to use but, as far as synthetic fibre clothing is concerned, it is by far the worst method to be used. The heat will create considerable shrinkage, the fibres are very likely to be severely damaged in a very short time and thus a very short life may be expected.

As a clean room garment process, autoclaving is very unsatisfactory.

(ii) Ethylene Oxide is increasingly unacceptable as a means of sterilization because of its explosion potential. In clean room clothing terms it is outstanding in doing the job without any known deterioration of the fibres.

(iii) Gamma Irradiation - As far as clean room clothing is concerned this is probably the best compromise solution as at the approved radiation does there is not only an effective kill of viable organisms but the fabric has reasonable resistance to the cumulative degradation that is inevitable with irradiation.

Sterilization is achieved by passing the product to be treated before the irradiation source on a conveyor. Products to be irradiated are separated, physically, from those already treated and administrative controls and records on dosages given are stringently enforced.

APPENDIX III

PROCEDURE FOR THE INTEGRITY TESTING OF

HEPA FILTERS, SEALS & HOUSING

APPENDIX III

PROCEDURE FOR THE INTEGRITY TESTING OF HEPA FILTERS, SEALS & HOUSING

1 INTRODUCTION

The following procedure is to be read in conjunction with the latest version of the British Standard for Environmental Cleanliness in Enclosed Spaces BS5295 Parts 0-4: 1989. This procedure is to be adopted whether the room is designed in accordance with BS5295, or United States Federal Standard Clean Room and Work Station Requirements Controlled Environment FED-STD-209D dated 15 June 1988.

2 PREPARATORY MEASUREMENTS

2.1 Room Pressures

2.1.1 Prior to commencing any leakage detection tests, the difference in air pressure between the controlled space under test and any adjacent areas of lower classification, including void spaces, shall be undertaken in accordance with BS5295: Part 1: 1989 Appendix B.

2.1.2 The results of the pressure tests shall be recorded and comparison made with the specification for the room. If any deviation of greater than or equal to $\pm$ 5 Pa is detected the room shall be rebalanced and the test for air pressure repeated.

2.2 Air Power Velocity Measurement

2.2.1 Air flow velocities through the HEPA filters or workstations being tested should be measured using a calibrated hot wire or vane-type anemometer accurate to within ± 3% of full scale.

2.2.2 The air flow velocity through each filter should be no greater than + 5% above the manufacturers recommended maximum air flow velocities and no greater than - 5% below the manufacturers recommended lower air flow velocity limit.

2.2.3 All air flow velocities should be recorded and a review of the overall results undertaken to confirm uniformity of velocity for the filters in each room.

3 INTRODUCTION OF AEROSOLS

3.1 Where possible aerosols should be introduced upstream of individual filters in such a manner as not to effect other filters on the air distribution system.

3.2 Where it is not possible to introduce an aerosol in accordance with item 3.1, it shall be introduced in the air handling unit fan section preferably immediately in front of the fan to ensure adequate mixing of the aerosol with the air stream.

3.3 Aerosol concentrations shall be in accordance with BS5295, Part 1, 1989 Appendix C2 and C3.

4 PROCEDURE

4.1 The procedure for testing leaks shall be in accordance with BS5295, Part 1, 1989 Appendix C5, and as clarified below.

4.2 For all measurements the photometer shall be set to use the logarithmic scale in order to minimise background or extraneous effects.

4.3 All readings shall be based on the calibration chart for the photometer being used for the test.

4.4 Once aerosol has been introduced into the upstream air flow the upstream aerosol concentration shall be measured and the photometer set to read 100% in accordance with BS5295: Part 1, 1989 Appendix C5.

4.5 Unless specifically agreed by the client's Head of Quality Control Department or nominee, a reduction in the upstream aerosol concentration will not be permitted.

4.6 Prior to scanning and introduction of aerosol a flexible shroud made of plastic sheet should be positioned around the filter to be tested in order that no extraneous factors should effect the readings. Care must be taken to ensure that the movement of the photometer when scanning will not be impaired and that all parts of the filter, filter assembly and seals can be adequately accessed.

4.7 The overall procedure for the scanning of filters shall be in accordance with BS5295: Part 1: 1989 subject to the following clarifications:-

4.7.1 Once the upstream concentration has been established and the photometer set, the filter should be scanned at a rate of not greater than 0.05 m/s moving at a steady speed at all times. During the initial scan the photometer should not at any time be stationary.

4.7.2 If a concentration of aerosol is detected above the permissible limit, see Table 3, BS5295: Part 1: 1989 Appendix C, the scan will not be stopped but will continue until the complete filter and filter assembly has been scanned. A note will be taken of the approximate position of the concentration.

4.7.3 Where an unacceptable concentration is detected, the filter including all recesses and the surrounding area inside the shroud (as described in 4.6) shall be cleared of aerosol using a vacuum cleaner. A narrow nozzle shall be used in order that aerosols which may have collected in stagnant or inaccessible points around the filter assembly can be adequately cleared.

Note: Subject to inspection it may be necessary to wipe the surfaces of the filter assembly with a non shedding cloth.

4.7.4 The scanning procedure will be repeated in accordance with 4.7.1 after a period of 30 seconds has elapsed after cleaning the filter in accordance with 4.7.3.

(a) If no concentrations above the permissible level are detected the filter will be deemed to be acceptable.

(b) If an aerosol concentration above the permissible level is detected the actions stated in 4.7.2 and 4.7.3 are to be repeated.

Note: The change in location of the aerosol concentration may mean a change in tracking of the aerosol and therefore is to be treated as a potential repeatable leak.

4.7.5 If after repeating the above procedures 3 times an unacceptable aerosol concentration is still detected its position (or positions) are to be noted in order that remedial action as detailed in Section 5 can be carried out.

4.7.6 Prior to further investigation being carried out the remaining filters and filter assemblies are to be tested before detailed actions taken to pinpoint a leak.

4.8 Leak Location

4.8.1 If the primary scans of a suspect filter indicate a failure of the media the filter shall be rescanned. If a point failure is found, the upstream concentration shall be checked for conformance with BS5729: Part 1: 1989 and if the challenge is within limits then the filter is deemed to have failed and must be replaced with a new filter.

4.8.2 If a failure is located at the edge of the filter a small diameter nozzle shall be used to detect the exact position of the leak. Static or slow scanning less than 0.01 m/s are acceptable.

Once the position of the leak is detected the upstream aerosol concentration shall be checked for conformance and a report issued in accordance with BS5927: Part 1: 1989 Appendix C8.

5 REMEDIAL ACTIONS

5.1 Adjustment of filter retaining screws is acceptable provided the filter has not been installed using unreasonably high force. If adjustment to the retaining screws is to be made this shall be done by turning the screw by no more than a 1/2 turn before retesting.

Note:

1. Unreasonably high force may distort the filter assembly, knife edges or landing bars.

2. It is preferable to use a manual screwdriver or a device which includes an accurately controlled torque limiter with an indicator.

3. Under no circumstances should a mechanical or electrically drive screwdriver be used for fitting or adjusting retaining screws.

5.2 If after adjustment of the retaining screws aerosols are detected within acceptable limits then the filter will be deemed to be accepted.

If the filter fails after retesting further adjustment may be undertaken provided the retaining screws are not overtightened. If after tightening the screws the filter continues to fail then the air conditioning system is to be switched off and the filter removed.

5.3 After the filter is removed inspection of the following is to take place:-

5.3.1 Knife Edges:

Inspect knife edges for the following:-

(a) notches
(b) distortion
(c) non linearity
(d) parallelism

A straight edge and engineers level should be used.

5.3.2 Filter:

(i) Inspect the filter gaskets for the following:-

(a) Adhesion of butt joints
(b) Adhesion to filter body
(c) Distortion
(d) Splits and air paths

(ii) If any of the above indicate the potential for a serious leakage the filter should be replaced and the filter returned to the manufacturer for regasketing.

(iii) If no physical damage is noted the filter shall be reinstalled at 180° from its original position. The filter will then be retested.

(a) If a leak is detected in the same position as first reported it may be inferred that there is a failure in the filter assembly.

(b) If a leak is detected in a position at the opposite side of the filter to that originally reported it may be inferred that there is a failure in the filter or filter gasket, in which case the filter is to be replaced.

(iv) In the case of a filter assembly failing, silicon may be applied to effect a seal to the knife edge or landing assembly. Only silicon of the type specified by the filter assembly manufacturer is to be used.

If silicon is to be used it can only be applied to the high pressure side of the knife edge or landing.

Once the silicon has been applied, the filter is to be retested using the above procedure.

(v) Silicon is not permitted on the low pressure side of the knife edges, landings or gaskets.

(vi) Silicon grease is not permitted on the knife edges of new installations without the prior permission of the Head of the QC Department or his nominee.

5.4 If after the above procedures have been carried out a repeatable leak is still located the filter assembly is to be removed and replaced with a new unit.

6 REPORTING

In all cases the actions taken throughout the testing period including remedial actions are to be recorded and the results kept on file for inspection.

APPENDIX IV

CLEAN ROOM OPERATIONAL RULES

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HOUSEKEEPING, PERSONAL HYGIENE AND OPERATOR DISCIPLINE

General Housekeeping

1. Visitors are not permitted to enter the clean room except with supervisory authorisation.

2. All entry and exit to the clean room will be via the airlock except in the case of emergencies.

3. Movement should be restricted to the minimum in order to prevent stir-up of settled particulate matter on clean room floor or furniture.

4. Use intercom whenever possible.

5. Lockers should be kept clean and neat inside and should be inspected regularly.

6. Locker tops should be kept clean and clear of clothing and other materials.

7. Never leave exposed parts or materials on the work bench.

8. Always enter and leave the clean room at a slow pace.

9. There will be no smoking in the clean room at any time.

10. No food may be taken into or consumed in the clean room at any time.

11. Pass through hatches should never be used for communication.

12. Operators should consider everything but their own immediate work area to be contaminated.

13. Operators should recognise the common forms of contamination and report occurrences when seen.

14. No wood is permitted in the clean room.

15. No pencils or rubber erasers may be used. Non-retracting ballpoint pens should be used at all times.

16. No paper should be taken into the clean room unless specific types have been cleared for use.

17. No abrasive cloths or files will be used.

18. Hand tools should be cleaned prior to entry into clean room.

19. Only test fixtures, tools, jigs, assembly fixtures or other items needed to perform the work required will be provided.

20. Tool boxes will not be permitted in the clean room.

21. Surplus materials should be stored in containers provided.

22. All tools or other items which have been dropped should be considered to be contaminated.

23. All tools or work which operators believe to be contaminated should be reported.

24. Assemblies or other work pieces should be covered during non-working shifts.

25. All employees should be responsible for a high degree of cleanliness and neatness at his or her workstation.

26. All visitors to the clean room must observe all the rules which clean room operators are required to observe. This rule includes top management as well as line supervisors.

Personal Hygiene

27. Bathe or shower frequently.

28. Shampoo hair at least weekly and take action against dandruff.

29. Always wear clean under-clothing.

30. Always wear clean outer clothing.

31. Avoid rubbing or scratching exposed parts of the body.

32. Always wear gloves especially if hands are severely chapped.

33. Hair should be cut as short as is socially tolerable.

34. Never comb hair in the clean room.

35. Do not wear nail polish.

36. Never wear or apply cosmetics in the clean room although lipsticks may be worn with approval.

37. Personal items such as keys, coins, cigarettes, matches, handkerchiefs, watches, tissues and combs should not be carried into the clean room.

38. The wearing of jewellery such as large rings, necklaces, earrings, lockets and bracelets should not be permitted.

39. Valuables such as wallets may be carried but worn under protective clothing and not removed in the clean room.

40. Male operators should shave daily.

41. Male operators with beards or moustaches should wear protective masks.

42. Always wash hands and scrub fingernails thoroughly. Hand lotions, creams or soaps containing lanolin which tighten the skin should be used.

43. Always dry hands by non-linting method such as warm air driers preferably with filtered air.

44. Operators with colds or who are developing a skin condition or who have sunburn should notify their supervisors.

Clothing Rules

46. Specialist protective clothing is to be worn at all times by all individuals entering the clean room.

47. The full specified garment outfit for each clean room must be worn.

48. Clothing must be changed for clean items at the prescribed frequency and times for each clean room. This may be specified as each entry into the clean room, daily or at any other frequency specified for a particular location.

49. All clean room clothing items should be checked at each change for raveled or frayed edges. No clean room clothing should be worn outside the clean area.

50. Boots, hoods, coats, caps or other items of clothing must be thoroughly secured by the method provided at all times when in the clean room.

51. Protective hand or finger coverings should be used as instructed.

52. When not in use, clean room clothing should not be allowed to come into contact with any possible contamination. Garments should be kept, by the prescribed method, in a closed compartment located in an uncontaminated location.

53. Hair should always be confined under a protective covering. The hair at the nape of the neck which cannot be covered by a conventional cap or snood may be acceptable providing the head covering is properly worn.

54. Hair that is uncovered at the front of the head on the foreline may not be acceptable and an alternative head covering should be adopted.

55. Personal clothing to be worn under the special clean room items should be chosen carefully so as to exclude items which are lint producing such as angora, fluffy pullovers or other such items.

56. Do not wear soiled or sweaty street clothes in the clean room.

Clean Room Clothing

57. A high standard of housekeeping practice is essential in maintaining a clean room. When cleaning such a room it must be kept in mind that the mere addition of personnel to the

environment will increase the contamination level in the room. It follows, therefore, that the times at which the room is to be cleaned should be chosen with care.

58. The clean room should be cleaned when no production or research work is being performed in the room. It should be remembered that it will take some time for the increased contamination level, caused by the cleaning activity, to decrease. It follows that the higher the air change rate the lower the disturbance to operational standards of a particulate count.

59. It is recommended, therefore, that cleaning should be scheduled for the period immediately following the end of a working shift.

60. Room cleaning should be undertaken daily and a full cleaning specification produced and implemented.

61. Minor dry floor and bench vacuuming can be performed during room operation, if necessary, provided that both the equipment and procedures used will ensure a minimum of disturbance to settled particulate matter.

62. The following considerations concerning clean room clothing are relevant:

- Cellulose mops and sponges can be used with water. It is suggested that the water used should have a particle count of not more than 100,000 particles per cubic foot of particles greater than 0.5 microns.

- High grade plastic buckets may be used providing that they are not subject to flaking.

- Anodized aluminium ladders only are recommended where necessary.

- Detergents, where necessary, should be selected carefully in order to ensure that a low residue producing type is used.

- Vacuum cleaning should ideally be done with a central vacuum system or failing that with a carefully selected portable machine.

- All housekeeping equipment is a potential source of contamination and movement of these items in and out of the clean room should be carefully planned.

- Each operator should be responsible for cleaning his or her workstation at periodic intervals during the work shift. This assists in the proper management of the clean room and prevents mishandling of the workpiece by clean room maintenance personnel.

  Cleaning materials for this purpose should be positioned permanently at various points throughout the clean room.

REFERENCES

(1) Report on Upgrading and Expansion of the Pharmaceutical, Fine Chemical, Biochemical and Food Industries - Phase 1 - Exploratory Mission, October 1990

(2) UNIDO Contract 92/100P, Project Trigon, Notes of Visits/Meetings 29 May 1992

(3) UNIDO Contract 92/100P, Project Trigon, "Report on Work Required to Gain US Regulatory Aprpvoal for EGIFERON", August 1992

(4) UNIDO Contract 92/100P, Project Trigon, Notes of Visits/Meeting 31 July 1992