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GOOD MANUFACTURING PRACTICE AUDIT

OF

BIOTECHNOLOGY PILOT PLANTS

OF

THE BIOGAL PHARMACEUTICAL COMPANY

DEBRECEN

UNIDO CONTRACT 92/030

G E GUIDOBONI
SEPTEMBER 1992

This report has been prepared for the United Nations Industrial Development Organisation (UNIDO) for the project TF/HUN/90/906 "Technical Assistance for the Fermentation and Downstream Processing Pilot Plants of Biogal"

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SYNOPSIS

This report presents the results of a Good Manufacturing Practice (GMP) and Sterile Engineering audit of the fermentation and downstream processing pilot plants of the Biogal Pharmaceutical Company at Debrecen.

It is concluded that in several respects, the facilities and equipment require considerable upgrading and improving if they are to satisfy the requirements of GMP and sterile engineering of a modern biotechnology pilot plant, especially if processes are to be developed which are different from Biogal's current range.

CONTENTS

SECTION 1

INTRODUCTION

1 INTRODUCTION

During 1990, GRC Consultants carried out, for the Hungarian Government, a survey of the Hungarian fine chemical, pharmaceutical and biotechnology industries with a view to identifying the needs for upgrading these facilities to current USA, Western European GMP standards. As part of the study a number of projects were identified for support under a further round of funding from the UK Government (administered by UNIDO).

One of these projects was identified for Biogal at Debrecen and involved, initially, a GMP audit of the existing fermentation and downstream processing pilot plant, together with a Front End Design (FED) study for the upgrading of the same facilities.

In February 1992, GRC Consultants was awarded a contract to carry out this project and work began at the end of February 1992, with a visit to Debrecen to carry out a GMP and sterile engineering audit of the pilot plants. It was also agreed with Biogal that a visit should be made to the UK by two key Biogal staff to receive lectures in GMP and aspects of sterile engineering so that they would more fully appreciate the relevance and implications of the comments made in the audit report and the FED study.

This report contains the results of the audit presented in self evident sections.

Section 2 contains background information which is necessary to understand fully the context of the audit, particularly as it has implications for the future possible use of the biotechnology pilot plants for processes which may be quite different from those currently in development (based on penicillin type antibiotics).

Section 3 deals with topics and design aspects which are applicable to the two fermentation pilot plants and the downstream processing areas, whereas Section 5 deals with overall general impressions of the whole pilot plant.

Section 6 deals in detail with the fermentation pilot plant, the downstream processing area and the broad subject of utilities and services in so far as they affect the pilot plants.

Some of the topics covered in this report are developed in the final FED study report which contains sufficient equipment, mechanical and layout information, together with appropriate outline engineering standards/specifications, to invite contractors to bid for the detailed design, construction and installation of a completely new development pilot plant facility on a site yet to be identified.

SECTION 2

BACKGROUND

2 BACKGROUND

The following notes are intended to set the background against which the GMP audit was carried out. It is appropriate to comment here on certain key aspects of Biogal's short to medium term policies, in so far as they are known to GRC Consultants, for the development facilities.

It is appreciated that for various sound commercial/technical reasons, certain aspects of Biogal's policies and research/development targets and plans have not been made known to GRC Consultants. This is entirely understandable and it does not detract from the value of the GMP audit. However, the following points are made and were discussed openly with Biogal staff during the audit.

- For the short term (2-3 years) it is highly likely that the existing pilot plant facilities will share the building with a certain amount of chemical production and cosmetics production. The consequences of shared facilities are briefly mentioned elsewhere in this report.

- Regarding Biogal's proposed research/development plans as they affect the pilot plant for the next 3-5 years, it is understood that the majority of the work will be concerned with Biogal's core business of antibiotics, although mention was made of cholesterol reducing, and similar, agents. It is also possible that some enzymatic penicillin processing may be carried out.

- Biogal do not intend to carry out any tissue or mammalian cell culture within the next 3-5 years.

- From a management and organisation point of view, the fermentation pilot plants have been separate from the downstream processing (DSP) pilot plant. GRC Consultants

understands that there are plans for reorganisation within the Research and Development Department which could result in a clear integration of these two pilot plant areas.

- The most important aspect of Biogal's short to medium term plans is the fact that they do not intend to use their pilot scale facilities to prepare materials for direct clinical trials, hence in the short term, the facilities do not require formal regulatory authority inspection and approval. Furthermore, Biogal state that in the short term, they do not intend to use genetically manipulated organisms in the pilot plant facilities.

- However, since the whole purpose of the GMP audit was to assess the quality and operation of the pilot plants from the current Western Europe, EC and North American points of view of Good Laboratory, and Good Manufacture Practices, it was agreed that the audit must take into consideration the implications of the Practices if Biogal are serious in their intentions to enter the Western European, EC, and USA markets in the future. Hence all the comments in the bulk of this report are made in the light of the notes above and from the point of view of what Western European, EC and North American companies, and authorities, would expect to see in modern biotechnology based development facilities.

It is appropriate to mention here that since the visits by GRC Consultants to the Biogal pilot plants in 1990, a number of changes, modifications and improvements have taken place. These are noted in the appropriate section of the audit report.

Throughout this report, GRC Consultants makes a number of recommendations for improvements and modifications for upgrading equipment, layout and services in order to satisfy, more closely, the requirements of current GMP in the EC. These observations and recommendations are made in good faith

but GRC Consultants recognises and fully appreciates the fact that Biogal do not necessarily always have the funds available to carry out recommended improvements, even when the need for the improvements is acknowledged.

SECTION 3

GENERAL TOPICS

3 GENERAL TOPICS

The following notes apply to topics of a general nature in all areas of the pilot plants.

3.1 PROCEDURES

A wide range of standard operating procedures (SOP's) are in use throughout the pilot plant. From the ones seen by GRC Consultants, the impression was formed that the procedures were somewhat variable in both quantity and quality. There did not appear to be a co-ordinated volume of all procedures kept as a master set with an obvious approving authority.

It is acknowledged that a strict regime for SOP's is not required for laboratories and pilot plants to the same extent as required in production facilities, but a more obvious/demonstrable organisation of procedures should be in place. It is especially important to keep such procedures up-to-date, since by the very nature of a development facility, equipment and process may be changed at intervals and accidents can and do happen if detailed operating instructions are not available, up-to-date and approved.

If clinical trials material is ever made in the facility, then not only will SOP's have to be strictly observed but they will also have to be validated and subject to regulatory authority inspection.

3.2 DOCUMENTATION

The technical documentation associated with the design and installation of equipment and pipework systems is generally very poor. In particular there are virtually no detailed general arrangement or piping installation drawings (certainly

no pipework isometrics) and this restricted the auditing of key aspects of GMP and sterile engineering design. It was therefore necessary to rely almost exclusively on observations "in the field" and of the externals of operating equipment.

However, it is noted that documentation of instrumentation and circuit wiring was reasonably extensive, and this is encouraging.

Nonetheless, as a minimum, detailed operating and maintenance manuals from equipment suppliers would be expected to be readily available for virtually every piece of equipment.

With regard to the apparent lack of readily available technical documentation on most of the fermentation and DSP equipment, the most serious consequence would follow if clinical trials material were ever to be made in the facility. It would be extremely difficult to validate the design and construction of the majority of the facilities.

The remarks made above do not, as such, apply to the computer control and data logging systems for the fermenters. These are clearly in place and adequate for the bulk of the work carried out.

Overall, however, much more attention has to be paid to the generation, collation, and maintenance of technical documentation associated with virtually every aspect of the operation of the pilot plants.

3.3 SAFETY

Overall the general level of safety throughout the pilot plants is reasonable, except in two general areas.

- In the small pilot plant area, most fermenter agitator drive belts are totally unguarded and constitute a serious hazard to operators.

- In the DSP pilot plant there are serious concerns over the generation of static electricity charges on glass and plastic ware handling highly flammable solvents. [Information has previously been supplied to Biogal on methods of dealing with electrostatics.]

Whilst carrying out the GMP audit, a number of minor safety points were observed and are noted below.

- Particularly in the small fermenter pilot plant, there are several examples of bottles of liquids on small shelves immediately above unprotected electric power sockets. Many of these bottles are connected by plastic tubing to peristaltic pumps. Leakage from the pipe, or fracture of the glass bottles, could lead to liquids in the electric sockets with consequent problems. Such bottles and shelves should be resited away from electric sockets.

- Also in the small fermenter pilot plant, several trailing electric sockets and plugs were observed on the floor close to pools of water. Apart from the obvious electric hazard, these trailing leads are a trip hazard and should be properly routed or guarded.

- In the DSP pilot plant there are many examples of glassware components in very vulnerable positions. In particular, the offtake nozzles and taps on the bottom of the glass ion exchange columns are unguarded and extremely vulnerable to being knocked or broken off by a passing operator. Since these columns routinely contain highly flammable solvents, the risks of breakage and spillage of solvents are considered unacceptably high.

- Most of the simple glass taps in the glass ion exchange columns show evidence of being secured in place with adhesive tape, presumably to stop the taps from working loose and falling out in use.

- Most of the glassware columns appear to be assembled from conventional laboratory style column sections and components. They do not appear to have any protective overwrapping film to prevent shattering in the event of a crack or breakage. Overwrapping with an appropriate self adhesive tape is strongly recommended.

- Some of the glassware components appear to be inadequately supported or protected against strain, either from handling or from the weight of a full column. GRC Consultants would expect to see significantly more structural support steelwork and clamps, etc, particularly for the glass ion exchange columns. It is noted that the distillation rigs are significantly better protected and supported.

In subsequent visits to the pilot plants, GRC Consultants noted that most of the 'obvious' danagerous safety features had been corrected satisfactorily by Biogal staff.

3.4 BUILDING CONTAMINATION

It is obvious that Biogal carry out fermentations based on penicillin in the main factory facilities. The problems fo cross contamination with penicillin are well known and are the subject of specific requirements in the various guides to GMP. The fact that penicillin fermentations are carried out on the site apparently without significant consideration to containment of the organism, causes some concern when reviewing the possibility of the use of the pilot plant facility to produce other non-penicillanic materials. It could present Biogal with serious problems if the company

wishes to undertake fermentations and other downstream processing activities using non-penicillanic materials, because of the fear of cross contamination. In particular, if the facility is likely to be used to produce non-penicillanic clinical trial material, GRC Consultants considers it doubtful that products of this nature would be acceptable to international regulatory authorities.

It is also understood from discussions with the research staff in 1990 that when materials have been sent abroad for analysis by major Western European companies, contamination has been detected, thus making the sample of little value and undermining the general credibility of Biogal to produce high quality material.

3.5 AMENITIES

For their current purposes, the amenities are generally adequate but with some poor features in key areas.

- In the second floor mens toilet room, only one of the urinals was flushable, the ventilation was totally inadequate, and there was neither soap available nor hand drying facilities. These deficiencies must be rectified as a matter of urgency since they could reflect badly on the whole approach to general good hygienic practice in the whole of the pilot plant.

- The arrangements for changing are basic but adequate at present. However, significant upgrading of changing facilities are recommended, even for compliance with current large scale laboratory practice with biological materials. Details of improved arrangements will be included in the Front End Design Study as part of this overall project.

- It is considered highly inappropriate these days to have eating facilities, for operators, within a laboratory or pilot plant building, unless there is a very clear and significant separation of eating facilities from work areas. The present location of the "mess room" is considered unsatisfactory and the facility should be relocated or closed.

SECTION 4

OVERALL LAYOUT

4 OVERALL LAYOUT

The existing pilot plant facilities are located on three floors of an existing building at the site in Debrecen. The general arrangement of the existing layout is shown GRC Consultants Drg Nos:

92/004/001 Ground Floor Layout
90/004/002 First Floor Layout
90/004/003 Second Floor Layout

which are included at the end of this section for reference.

The ground floor of the facility contains the downstream processing area, basically between grids A-D and 1-5. It is noted that this ground floor is shared with a chemical production department and, in consequence, the whole of the ground floor is not available to the Research and Development group.

The first floor of the building contains the fermentation pilot plant storage area located between grids A-B and 1-3. In addition, a small dining area is located off the storage area for use by the pilot plant staff. There is also a sterile room in which culture and inoculum are prepared. Between grids C-D and 1-3 is a plant room area which contains some of the services which support the fermentation activities. These include water chillers, formaldehyde generator, etc.

There is an access from an adjacent building which enters the main spine corridor on gridline 1 between grids B and C.

The fermentation pilot plants nos. 1 and 2 and located on the second floor of the building (see drg. no. 003A) in an area which includes a series of laboratories and offices. The second floor is accessed via lifts and stairs which are

located between grids 9 and 10 and a stairwell which is located in the large scale fermentation area (Pilot Plant No. 2).

SECTION 5

GENERAL IMPRESSIONS

5.1 OVERALL IMPRESSION OF FACILITIES

5.2 PERSONNEL AND MATERIAL MOVEMENTS

5 OVERALL IMPRESSIONS

5.1 OVERALL IMPRESSION OF FACILITIES

The overall appearance of the facility gives the impression of being uncoordinated and having been underfunded for some time. The interrelationship between downstream processing and fermentation areas is poor, mainly because of the separation of the second floor and ground floor areas. However, the general arrangement of the building appears to be appropriate for pilot plant purposes.

The layout of the central spine corridor with service and storage facilities located in cupboards/ducts on either side of the corridor provides a very flexible arrangement. In addition, the building is well served with passenger and goods lifts, with adequate access to all floors. However, the access and escape routes provided in the region of gridline 1 are inadequate and need improvement.

Each floor has its own amenity/WC facilities and the location of these facilities appears to be good (see, however, Section 3.5).

The building is currently shared between the R&D group and a chemical production group and this causes some problems to pilot plant operations. If Biogal are to establish a properly organised pilot facility with adequate services which could meet GMP requirements, then the whole of the building needs to be given over to R&D activities. This will be particularly necessary as space will be required for the general improvement of environmental services, particularly heating and ventilating which at present are of a very poor standard.

The building finishes applied throughout the pilot plant are again inadequate in comparison with those required in Western Europe and the USA. Virtually no attempt has been made to provide cleanable wall, ceiling and floor finishes which would minimise cross contamination.

The quantity of basic services appears adequate but the quality of these services needs careful review in the light of GMP requirements. In particular, the provision of adequate quality air, process water, and clean steam needs further review, see also Section 7.

The general condition of the DSP area on the ground floor is relatively poor from a GMP point of view. It is acknowledged that Biogal are in the process of improving the wall finishes in this area and the electrics have recently been overhauled and new flameproof light fittings installed.

The DSP area is still relatively congested even though some redundant equipment items have been removed from DSP Area No. 2.

The general condition of the first floor is very poor and requires considerable upgrading and reorganisation. In particular, the environment in the "sterile room" is inadequate for a modern biotechnology/pharmaceutical development facility.

The storage area is not well organised and is not acceptable from a GMP point of view. The 'housekeeping' in this area is also relatively poor and there is evidence of continuing infestation.

The plant room area is still untidy and in need of renovation and improvement.

On the second floor, the general condition is significantly better than on the other two floors, notwithstanding the general remarks made above regarding wall and ceiling finishes, especially in the pilot plant areas. The laboratories, control room, computer room and offices appear to be entirely adequate and with only minor improvements would satisfy GMP requirements.

5.2 PERSONNEL AND MATERIAL MOVEMENTS

Materials

The movement of material and chemicals into the facility appears to occur in a somewhat haphazard manner. If the facility is to approach the standards currently adopted in Western Europe, then greater attention must be paid to material control, quarantine and in-process stores.

There appears to be no specific quality control applied to incoming materials and, once released for processing, they are dispensed in an apparently random manner. Procedures for material receipt, checking and dispensing require considerable revision.

Personnel

The control of personnel movement throughout the facility is relatively poor. It is quite normal for modern pharmaceutical and biotechnology facilities to have restricted access, particularly if the company is working on novel products. At present, there is no obvious restriction on the access of personnel to the facility, and unauthorised staff appear to be able to enter the plant without passing through any form of security door.

The current arrangement of the building, and the fact that it is shared with another operating group, makes restricted access difficult. In the event that the pilot facility is ever required to make clinical trial material to GMP standards, much greater attention must be paid to the movement of material and personnel to minimise cross contamination and to ensure control at all times.

Aspects of material and personnel flow are developed further in the Front End Design Study.

SECTION 6

PILOT PLANT OPERATIONS

6.1 STORES AND DISPENSING

6.2 SMALL FERMENTER PILOT PLANT

- 6.2.1 Equipment
- 6.2.2 Mechanical Design Features
- 6.2.3 Fermenters and Associated Fittings
- 6.2.4 Pipework Systems
- 6.2.5 Building Services/Finishes
- 6.2.6 Procedures
- 6.2.7 Miscellaneous Topics

6.3 LARGE FERMENTER PILOT PLANT

- 6.3.1 Equipment
- 6.3.2 Fermenters and Associated Fittings
- 6.3.3 Pipework Systems
- 6.3.4 Miscellaneous Topics

6.4 DOWNSTREAM PROCESSING

6 PILOT PLANT OPERATIONS

This section contains the results of the GMP audit together with some outline suggestions for improvement. However, it is recognised that Biogal have chosen the Front End Design Study to be based on a new, and as yet unidentified, site rather than a significant upgrading of the existing facilities. Hence this section of the GMP audit report concentrates on the facilities as they exist now, not on what they would be if significantly and extensively upgraded.

6.1 STORES AND DISPENSING

The present storage and dispensing area is relatively poorly organised and still shows evidence of infestation. There is no obvious system of quarantine for raw materials nor is there any obvious arrangement for the secure/separated storage of in-process materials and finished product. To satisfy even the basic requirements of GMP, it is important to have a system in place for ensuring that materials entering the plant can be properly traced and securely quarantined, usually by means of a caged and locked compound.

In the current arrangement, there is evidence of the stores/dispensing area being used as a general throughway for various staff (some not necessarily connected with the pilot plant). This situation is highly undesirable and should be put right as a matter of priority.

The whole area is extremely congested with little free floor space for the easy handling and weighing out of raw materials from sacks or kegs.

6.2 SMALL FERMENTER PILOT PLANT (AREA No. 1)

The notes in this section concern aspects both of GMP and Sterile Engineering. It is acknowledged that the contamination record of penicillin type fermentation in the small pilot plant is relatively good. However, if Biogal are to carry out non-penicillanic fermentations, then aspects of sterile engineering design and operation, as noted in this review, could adversely affect the ability to achieve consistently contamination free fermentations.

It is also recognised that some of the points made in this section have been made previously to Biogal in 1990 and, where possible, certain improvements have been made, particularly in the large pilot plant - see Section 6.3 Throughout this section frequent use is made of the abbreviations

(GL/MP)
(SE)

where (GL/MP) means that a particular aspect, feature or detail is concerned with Good Laboratory and/or Manufacturing Practice in general, and

where (SE) means that a particular feature is concerned especially with some aspect of sterile engineering design.

6.2.1 Equipment

The equipment in this area consists basically of the following:-

- 4 x 300 litre stainless steel fermenters fitted with computer controlled instrumentation

- 4 x 60 litre stainless steel fermenters fitted with basic local only instrumentation

- Various 30 and 110 litre stainless steel media holding and feeding vessels

- Feeding system consisting of a mixture of automatic and manually controlled valves and peristaltic pumps

- A computer for process control and data logging/acquisition

Both the 60 and 300 litre fermenters may be used either for seed culture or production.

The 300 litre fermenters computer system controls a range of operations such as:-

- fermentation (batch, fed batch, repeated fed batch)
- washing in place
- filling
- sterilisation
- inoculation
- transfers (limited)
- sampling (part of a cycle)

6.2.2 Mechanical Design Features

The following general mechanical design features are noted for improvement.

(i) The head plates of the 300l fermenters are based on a novel bayonet fixing which has certain poor design features. The two main problems with this type of design are, first, the inability to apply an even pressure from the top plate onto the main body of the fermenter, and, second, it is necessary to use a

flogging hammer to remove the top plate. The action of hammering the top plate to open it means that severe shock is sent through the system onto the load cells and the mass flow meter with a possible consequent loss of use and accuracy. It is recommended that the head plates are replaced with standard ring clamp type arrangements.

It is also noted that internal webs have been added to the head plates to strengthen them for steam pressure containment. These webs are relatively poorly welded and finished and could be a source of residual contamination. They also prevent the free flow of sterilising medium over the underside of the head plate, and the sterilising of this part of the fermenter could be compromised.

(ii) The design of the agitator system has a number of poor features. The agitator shaft runs between ball bearings rather than conventional thrust bearings and it is understood that there is a limitation on the speed of the agitator because of this lack of rigidity. As and when possible this system should be replaced with appropriate bearings and seal system to ensure that there are no undue vibrations or whipping of the agitator shaft. It is noted that there is no bottom steady bearing and this could cause 'run out' on the shaft during operation. This will inevitably cause a deterioration of the gland packing during periods of prolonged operation.

6.2.3 Fermenters and Associated Fittings

The following points are identified for improvement but the order of listing does not imply any priority of importance.

(i) The 300l fermenters do not have jackets which cover the total vertical surface of the fermenters. This lack of total cover could compromise the ability to sterilise the whole of the internal surface of the fermenters. (SE)

(ii) The agitators on the fermenters generally are fitted with single mechanical seals. Double mechanical seals with sterile purge are virtually standard on modern fermenters and are strongly recommended. (SE)

(iii) The surface finishes within the fermenters and on external finishes appear to be adequate. However, it is understood that on certain flanges a gramophone finish has been employed. This is normally considered bad practice and should be avoided in the future. (SE)

(iv) The baffle plates inside the fermenter are held in place by a housing ring which itself sits within the fermenter. This ring cannot easily be cleaned during the cleaning in place procedure, and ideally the baffle plates should be located onto lugs welded directly onto the fermenter wall. It is recognised that this would be a significant modification, unlikely even to be carried out on the existing fermenters. This feature would be avoided in future new fermenters. (SE)

(v) Sterilised fermentation air is supplied to each fermenter from a common manifold. Modern practice dictates that each fermenter should have its own independent sterilising filter to prevent any possible cross contamination (from a common manifold). (SE)

(vi) For similar reasons, modern practice dictates that each fermenter has its own off-gas sterilising filter. This is an absolute requirement where pathogens or containment are concerned. (SE) (GL/MP)

(vii) The general arrangement of the fermenters is such that for GMP purposes it would only be possible to undertake one type of fermentation in the room at a time. In the future event that two different processes were to be undertaken, some form of segregation between the fermenters would be necessary. (SE)

(viii) Extensive use is noted of screwed fittings and ball valves in process lines. All pipework handling process fluids should be in 316L stainless steel, welded to the appropriate standard. Valves should be of the diaphragm type. Further details of recommended pipework and valve systems will be given in the Front End Design Study. (SE)

See also Addendum at the end of this report.

6.2.4 Pipework Systems

(i) The observed standard of pipework welding is generally relatively poor and needs to be improved. This may be achieved by the appropriate training of Biogal's own welders or by insisting on an improvement of the supplier/installers welding techniques. (SE)

(ii) 'Deadlegs' are noted in various sections of pipework. These deadlegs could cause problems with incomplete sterilisation of containment and much more attention must be paid, at the pipework design and installation stage, to the elimination of these deadlegs. (SE)

(iii) Most of the process lines do not appear to slope either to high point vents or low point drains. This is very poor sterile engineering practice and should be rectified in the future. (SE)

(iv) Use is made of wooden block to support and secure process pipes. The use of wood is abolished in biotechnology facilities in the USA and EC mainly because of its ability to harbour contamination. (GL/MP)

(v) It is noted that most diaphragm valves are not installed in the correct self-draining free flowing orientation. Incorrect installation of these valves can lead to non-draining of liquids and the sterilisation of the pipework systems in which the valves are installed can be compromised. (SE)

6.2.5 Building Services/Finishes

The following features are identified as falling far short of GMP requirements for a modern biotechnology facility.

(i) The ceiling system used in the plant is generally inadequate in that it does not seal the room from the service void above, and it is extremely difficult to decontaminate or clean. (GL/MP)

The ceiling should be constructed either of individual washable tiles which are clipped and sealed in place or a single monolithic ceiling in plaster or equivalent. (GL/MP)

(ii) The floors generally are in good condition and adequate for a research/GMP pilot plant area. Further attention to detail on the walls is required,

particularly with the interface between the walls and floor, and walls and ceiling. Where possible these should be coved to ease the cleaning down and decontamination. (GL/MP)

(iii) The use of windows which open direct to the outside atmosphere is noted. These are not considered appropriate for GMP and should be sealed closed, with no horizontal ledges on which dirt or contamination can accumulate. It is recognised that the windows are opened for ventilation and humidity control purposes. This practice is contrary to GMP and must be changed. (GL/MP)

The whole question of appropriate ventilation is addressed in the Front End Design Study.

6.2.6 Procedures

(i) The existing cleaning-in-place (CIP) procedure is appropriate for the current types of fermentations being carried out. However, for the future it is anticipated that a much more rigorous CIP system is installed, based on the use of dilute caustic solution, detergents and hot/cold clean water, injected in an appropriate sequence via a sprayball or equivalent device.

It is noted that for the pilot plant to comply with GMP it would be necessary to establish a validated cleaning procedure. This would mean developing an appropriate protocol which would include the taking of samples as part of a validation procedure to ensure that no living organism is left within the fermenter after the cleaning and sterilising cycles have been completed. (GL/MP) (SE)

(ii) Currently, most of the fermenter products are sent to drain at the end of the fermentation batch. The broth may, or may not, be deactivated by heat/chemicals before being sent to the common drainage system for the whole building. For the future, the whole procedure for the deactivation and disposal of fermenter broth must be addressed since the current practice of passing 'live' broth to the drain is generally unacceptable from a GMP point of view. (GL/MP)

(iii) The current techniques for sampling are appropriate for the current types of fermentation, but for the future, especially if pathogens or containment are involved, a much more stringent sampling method will be required. This could involve the use of specially designed "contained" sampling valves/bottles and details will be included in the FED study.

(iv) Currently the seed fermenters are inoculated by pouring the inoculum from a shake flask into the fermenter via an 'Ingold' type port in the top plate. This may be appropriate for the current type of fermentation development work but is wholly inappropriate in a modern biotechnology pilot plant. Live culture should be transferred in a closed system involving demountable couplings and sterile air pressure transfer from culture bottle to fermenter. (GL/MP) (SE)

6.2.7 Miscellaneous Topics

(i) During the audit, live infestation (cockroaches) was observed on two occasions in the small fermenter pilot plant area. This is most inappropriate in a modern biotechnology facility and must be eradicated as a matter of urgency.

(ii) There are two cable/pipe ducts in the floor of the pilot plant, beneath and to the rear of the large fermenters. The ducts are partially covered by floor plates but it is highly likely that these ducts are extremely difficult to clean and keep free from gross dirt accumulation and/or contamination. It is clear that liquids can easily spill into these ducts which constitute a breeding ground for all manner of contamination. This is a very poor feature of the design and construction of this part of the small fermenter pilot plant and improvements should be made as a matter of urgency. These types of partially closed floor ducts are totally inappropriate in a modern biotechnology facility. (GL/MP)

(iii) Pools of stagnant water were noted in several places. This indicates both relatively poor floor drainage and general housekeeping. These stagnant pools are potential sources of contamination and constitute an environmental risk to the operators. (GL/MP)

(iv) Open topped waste bins are noted in the pilot plant area. These are unacceptable and should be removed. Much more attention has to be paid to the control, handling and disposal of wastes from any source in a biotechnology development facility. (GL/MP)

6.3 LARGE FERMENTER PILOT PLANT

As in Section 6.2, the notes made here concern aspects both of GMP and Sterile Engineering design as they affect a modern biotechnology pilot plant.

6.3.1 Equipment

The equipment in the large pilot plant is generally as follows:-

- 4 x 1000 litre stainless steel fermenters, relatively new (made by Vegyepszer) and fitted with computer controlled instrumentation

- 4 x 600 litre stainless steel fermenter, relatively old and fitted only with basic local instrumentation

- 6 x 200 litre stainless steel holding tanks, on weigh cells, capable of in situ sterilisation

- Autoclave, old, for the preparation of sample bottles for use throughout the pilot plant

- Modern feed system using computer controlled peristaltic pumps

- Computer system for process control of fermentation, and data acquisition and logging

The 600 and 1000l fermenters may be used both for seed culture and production. The computer system is capable of controlling a range of process parameters (temperature, pH, dissolved oxygen) and is used to control feed rates.

The fermenters may be operated in the batch, fed batch and repeated fed batch modes.

6.3.2 Fermenters and Associated Fittings

(i) The fermenters receive air from a single manifold system which has a prefilter and single sterilising filter in line. The sterilising filter is not routinely tested for integrity and is resterilised with formaldehyde vapour at 1-2 month intervals. Whilst adequate for Biogal's current type of work, the system is totally inappropriate for a modern biotechnology pilot plant in which each fermenter has its own individual air supply via a series of pre and absolute sterilising filters in line and which are resterilised at the beginning of each fermentation cycle. It is strongly recommended that air sterilising filter systems are fitted to each individual fermenter. (SE)

(ii) It is noted that the feed pipework arrangement on the fermenters requires that a number of the lines are used for more than one operation, e.g. the air supply/sparge line is used both as a sample and transfer line. This is not a good arrangement and can lead to problems of cross contamination (if different fermentations are being carried out in different fermenters) and incomplete sterilisation of pipework sections (if not all pipework sections are sterilised at one and the same time). (SE)

(iii) The air line to the sparge bell housing at the base of the fermenter is flanged. This is not a good arrangement as a flange located inside a fermenter can provide a location for difficult to remove

contamination . If a flange is absolutely necessary in this line, virgin PTFE tape or a sealed PTFE gasket should be used. (SE)

(iv) The method of emptying the fermenter continues to be by air pressure. Pressure is applied and material is blown via the sparge housing. There is no bottom run-off valve and it is not possible to completely empty the fermenter of broth. This residual heel will make sterilisation and cleaning very difficult. It is also unlikely that this type of design would be acceptable for GMP which requires that there is not possible source of contamination between batches. Hence the cleaning/sterilisation protocols would have to be extremely rigorous to prove that no contamination can occur between batches. (GL/MP) (SE)

(v) It is noted that the jacket on the fermenter covers only the cylindrical section of the fermenter and does not enclose the bottom shell. This will mean that the heat transfer into the bottom shell will be considerably less than through the side walls. If the jacket alone is to be used for heating up material to sterilising temperatures, it may prove difficult to ensure that the correct temperature at all points on the inside of the vessel can be reached.

(vi) The top bearing housing is fitted with a lip seal rather than a mechanical seal. Lip seals are not entirely reliable in these fermentation applications and are a possible source of contamination. It is also noted that grease in the top bearing could possibly penetrate the fermenter and cause contamination.

Furthermore, examination of the detailed drawing of this top bearing assembly shows that there are two areas which may be suspected as being extremely difficult to sterilise. These are marked on the sketch given overleaf. It is acknowledged that the elimination of these potential contamination traps would involve a major redesign/refit but will have to be addressed for a modern biotechnology pilot plant. (SE)

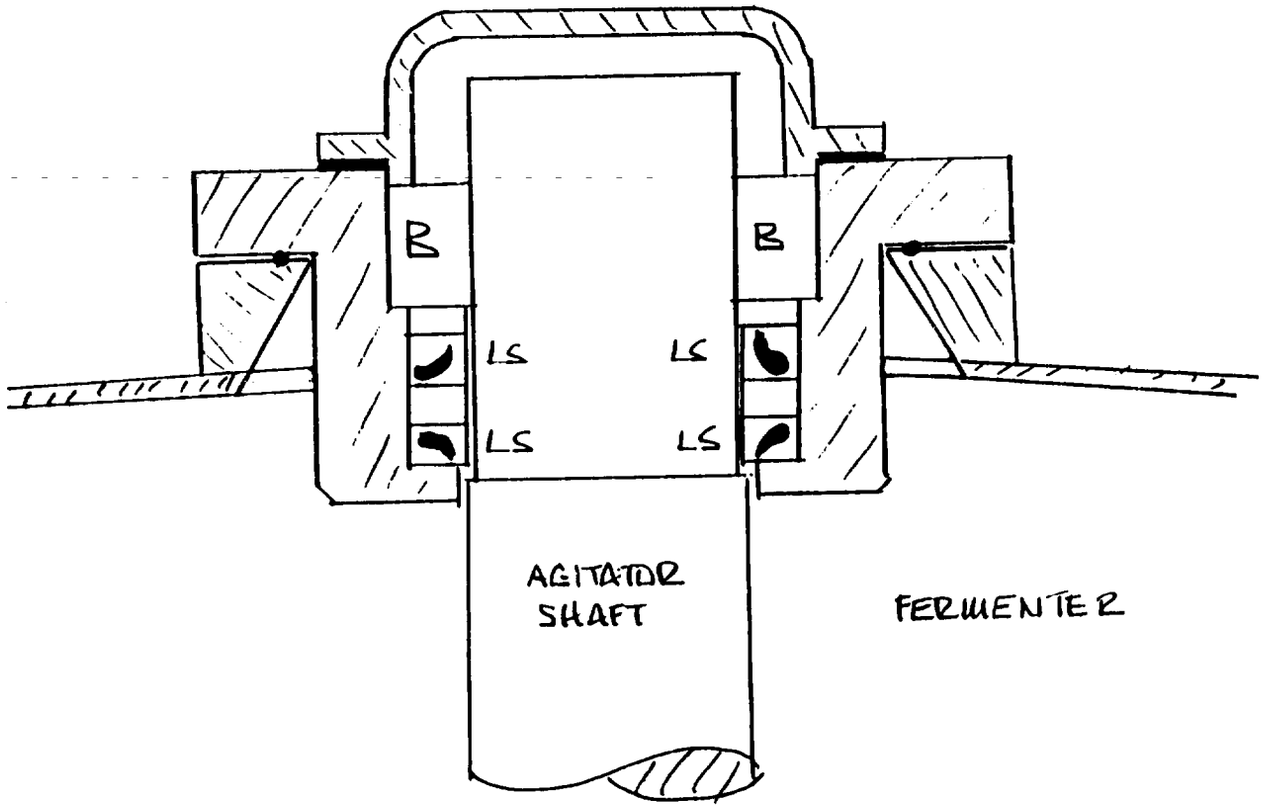
(vii) The bottom entry agitator is fitted with a 'CHETRA' double mechanical seal which is purged with steam condensate. A number of points may be made here regarding sterile engineering design:-

- The condensate is generated by condensing ordinary factory mains steam, which passes through a sintered metal filter before use. This quality steam may be adequate for Biogal's current fermentation programme but might be considered inappropriate in the future. There is always the possibility of the condensate from this 'factory' steam containing residual traces of additives which have been used in the factory boiler water treatment unit. Thus the condensate, whilst sterile, could contain harmful chemical agents which could pass into the fermenter via the seal. (SE)

- Whilst the condensate purge is maintained under a pressure greater than that in the fermenter, the flow of condensate through the purge space between the two seals depends entirely on a thermosyphon effect caused by warming of the condensate by friction in the seal housing. Some form of positive flow generation is preferable (once through flow to drain, etc).

AREAS FOR CONTAMINATION TRAP

B - BEARINGS
LS - LIP SEALS



FERMENTER

GRC CONSULTANTS WESTBROOKE HOUSE 70 HIGH STREET ALTON, HANTS GU34 1EN TEL: 0420 89847 FAX: 0420 89427	CLIENT UNIDO DATE: 1-5-93 SCALE: — DIMENSIONS IN: —	PROJECT BIDGAL COPYRIGHT RESERVED THIS DRAWING MAY NOT BE REPRODUCED IN ANY MANNER WITHOUT THE PRIOR WRITTEN CONSENT OF GRC CONSULTANTS	TITLE FERMENTER UPPER BEARING DRAWING NUMBER REV —

- Screwed fittings are used throughout the condensate pump system. The condensate system itself has to be viewed as a "sterile engineered" system and screwed fittings are not acceptable for contamination prevention (especially as one screwed fitting on the body of the condensate pot was clearly and obviously leaking). (SE)

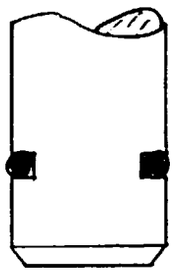
(viii) The 'Ingold' fittings ports were examined in detail and a number of points identified which could compromise good sterile engineering practice (see sketches overleaf):-

- The quality of finish on the Ingold type plugs is extremely variable. In several fittings, the base of the plug is either badly scratched or poorly finished.

- The inside surfaces of some capped ports are badly scratched or scored.

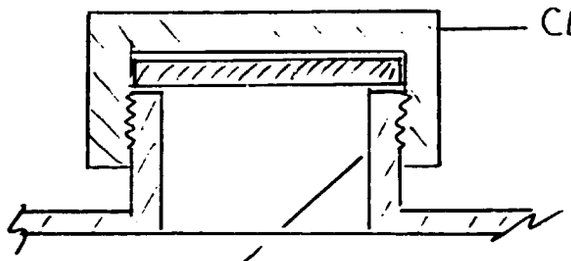
- Several instrument ports have very sharp edges at the open end. These sharp edges can easily damage the 'O' rings as the instrument sleeve, or closure plug, is inserted, thus potentially ruining the 'O' ring as a sterile seal. Evidence was actually seen of several 'O' rings damaged by this cutting effect.

Much greater attention has to be paid to the fabrication and handling of these Ingold type fittings since any damage to them can severely compromise the sterile integrity of the fermenters.



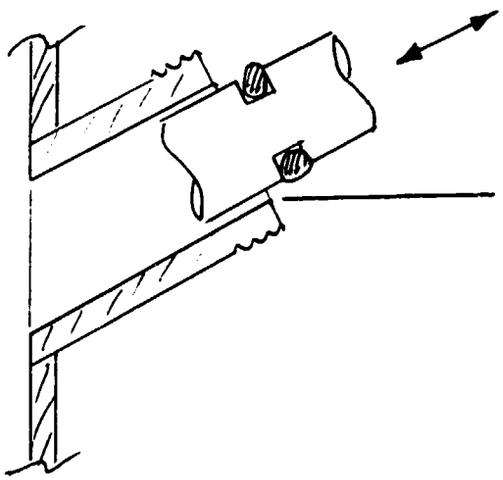
'INGOLD' PLUG

BADLY SCRATCHED SURFICE



CLOSURE CAP

HEAVY SCRATCHING / SCORING ON INSIDE



SHARP EDGE CUTS 'O' RING

(SHOULD BE CHAMFERED)

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6.3.3 Pipework Systems

(i) The fermenters (and feed vessels) are mounted on load cells and, therefore, have flexible connections in all the lines, both process and service, to and from the vessels. Unfortunately, the flexibles have screwed connections which are considered unacceptable in modern biotechnology facilities. They should be replaced, for process fluid use, by flexibles with an appropriate hygienic coupling of the IDF or equivalent type. (SE)

(ii) As in Section 6.2.4, diaphragm valves are installed in lines in the non free draining orientation. Advice must be sought from the valve supplier on the correct angle of inclination for each size of diaphragm valve. (SE)

(iii) The quality of the pipework welding remains to be improved considerably, but the remarks made in Section 6.2.4 equally apply here. (SE)

6.3.4 Miscellaneous Topics

(i) From a practical/operator point of view, access to bottom of the 600 litre fermenter is extremely restricted. Only major modifications to the pipework in this area can relieve this situation. (GL/MP)

(ii) The ground floor area, below the 1000l fermenters, continues to be very untidy and gives a very poor impression. It is acknowledged, however, that Biogal are in the process of renovating this area and the situation should improve in the future. However,

there is a great need to improve generally the housekeeping in this area and not to use it as a general storage area. (GL/MP)

(iii) There is evidence of continued infestation in the area beneath the fermenter floor. Attention must continue to be paid to this matter and a significant improvement in good housekeeping is required. (GL/MP)

(iv) The comments made in Section 6.2 about the segregation of fermenters applies equally here to the large fermenters. However, it is extremely difficult to see how effective segregation could be achieved in the large pilot plant area without a major rebuilding/layout exercise. The implications for GMP are quite serious and must be addressed and discussed further. (GL/MP)

6.4 DOWNSTREAM PROCESSING (DSP)

Since the first visits by GRC Consultants in 1990, Biogal have made some improvements to the layout and general organisation of the DSP areas. The following points are noted:-

- Some redundant vessels, autoclaves and a drier have been removed from the smaller DSP and this has noticeably improved the housekeeping and general appearance of this area.

- Light fittings have been replaced with new flameproof units.

- All the electrics have been overhauled as part of Biogal's safety review and maintenance procedure.

- Efforts have been made to put into practice many of the recommendations made previously for the reduction/elimination of electrostatic hazards in the solvent handling areas.

However, the overall layout of the DSP areas is still not good from a GMP point of view and significant modifications and upgradings are needed to bring the unit up to modern biotechnology facility standards.

The primary concern remains the problem of open plan operation with, possibly, a number of processes taking place at the same time (with maybe different products). Such a method of operation could lead to cross contamination and it is clear that a significant amount of physical segregation of operations (unit processes) is needed to satisfy GMP requirements. Improved and dedicated changing facilities would also be needed in the DSP areas to satisfy GMP, especially if any materials are produced for clinical trials.

A number of other concerns are noted as follows:-

- Some of the floors are not self draining and stagnant pools of water were noted. These are not only a safety hazard (slippage by operators) but are not acceptable from a GMP point of view.

- The floor drains do not have solvent traps or interceptors. In the event of an equipment breakage (extensive use of glassware) or accidental spillage, significant quantities of solvent would pass immediately and unchecked into the general building drain.

- As mentioned in the general safety section 3.3, some of the glassware appears to be inadequately supported or restrained and could be particularly vulnerable to being knocked by operators. One particular 'Liebig' condenser above a glass reactor appeared extremely poorly supported and vulnerable.

- Very many glassware connections, branches, sample points, taps, etc, are in 'exposed' positions and highly vulnerable to accidental damage by passing operators.

Overall it has to be said that the DSP area as a unit is not suitable for GMP processing in its present state and significant improvements are needed.

SECTION 7

UTILITIES AND SERVICES

7 UTILITIES AND SERVICES

A wide-ranging review was carried out of the main utilities and services supplied to and used in the pilot plants. It cannot be over-emphasized that in modern pharmaceutical and biotechnology development facilities, the quality and security of the utilities and services are vitally important and subject to stringent inspection by regulatory authorities.

Basically, the existing utilities and services are as follows:-

Air

- Oil-free compressed air (2 bar g) from a central supply.

- Pre treatment consists of humidity and temperature control.

- At the pilot plant, the air passes through 3 stages of filtration, rough, presterilization, sterilization.

- The air supply to the No. 1 pilot plant area (small fermenters) has a further single sterilizing filter and can be isolated from the supply to the No. 2 area (large fermenters) and from the main.

Steam

- Central generation at 3.5 bar g and is superheated for factory main distribution.

- The boiler feed water treatment consists of lime treatment followed by ion exchange softening. De-oxygenation is achieved by heating, after which the water is fed to the boilers.

- At the pilot plant, the steam is passed through a sintered metal filter (regenerated very infrequently with hydrochloric acid) to remove rust but is not positively desuperheated.

- The single quality steam is used both for jacket/process indirect heating and for 'live' use in sterilization and in the autoclaves.

- Condensate from jackets is discharged to drain; 'clean' condensate is returned to the boiler house.

- The pH of the steam is said to fluctuate frequently but is generally about 8. The pH is checked at the boiler house but not at the pilot plant.

Process Water

- From the Municipal supply and is of 'drinking' water quality.

- There is no on-site treatment of water.

- The microbiological quality of the water is checked occasionally by Biogal centrally; no checks are made of the water quality at the pilot plant.

Cooling Water

- Raw cooling water is obtained from two sources, Biogal's own deep wells and the public water network.

- A closed-loop ring main and cooling tower system is used to provide cooling water around the site.

- Supplied generally at 15-20°C and 2 bar g.

- The cooling water is treated with additives (biocides, antiseptic agents, descaling agents etc).

Chilled Water

- Generated from individual local chiller units as required, generally at 5-10°C and 2 bar g.

Drainage

Two independent systems are installed on the Debrecen site.

- Sewer network maintained under pressure (by pumps) and is regarded as a 'contained' unit.

- Open drainage system which takes floor washings etc and occasionally 'live' samples from fermenters are passed to this drain.

There is very little interconnection at the pilot plants between these two drainage systems and what little connection there is, is downstream of the fermenter pilot plants with little chance of back contamination.

As noted above, the whole subject of utilities and services is extremely important for the modern biotechnology development facility and it is believed by GRC Consultants that in certain key areas, particularly process water and steam, significant improvements and upgrades will have to be made for both GMP compliance and high quality biotechnology process development. These matters are dealt with further in the FED Study.

ADDENDUM

Following the first visit in February 1992 to carry out the audit of the fermentation and DSP pilot plants, 2 further visits to Biogal were made in May and July. On the occasion of the July visit, it happened that one of the 60 litre fermenters in the small pilot plant area was shut down and partly dismantled. This was, in fact, the first opportunity GRC Consultants had to examine the internals of a 60 litre fermenter. (On all other occasions all the 60 litre fermenters had been in operation).

A number of detail design features were noted, all of which relate to sterile engineering SE and the following notes are made as additions to those given in Section 6.2.3 of this report.

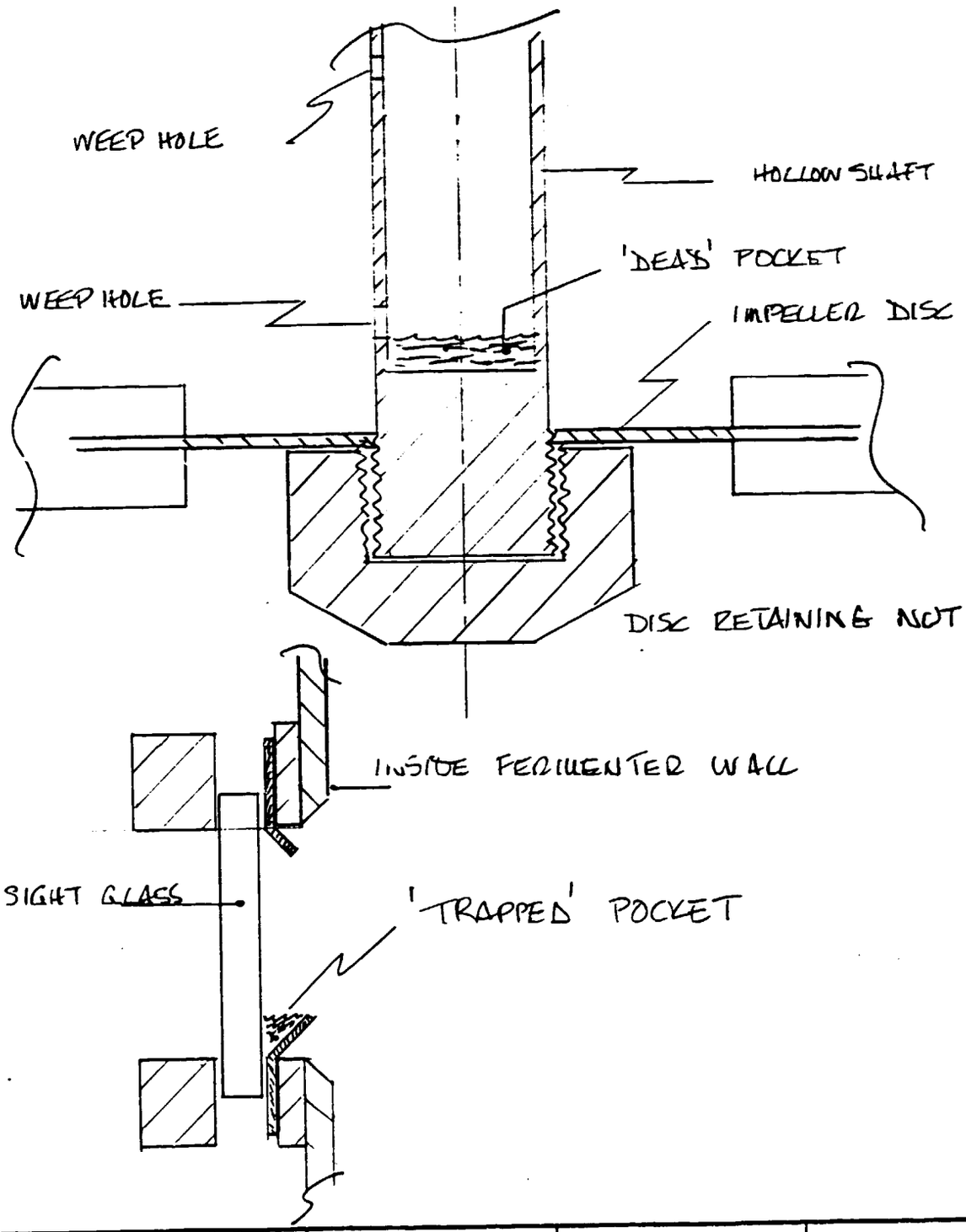
1. There appears to be a 'dead' pocket in the agitator shaft which is partly hollow section. See sketch overleaf.

2. The gasket on the sightglass is oversized and has 'flexed' so as to create a totally undrainable pocket between the gasket and the glass. See sketch overleaf.

3. There is a significant 'dead space' crevice where an inlet pipe passes through the fermenter wall (no internal welding). See sketch overleaf.

4. The attachment brackets for the internal baffles have significant crevices (at the fermenter wall) but at least they are in the vertical plane and should be self draining. See sketch overleaf.

5. The main top plate closure gasket appears to be of the 'asbestos rope' type and hardened/embrittled with age. This type of gasket is totally inappropriate in a modern biotechnology facility.



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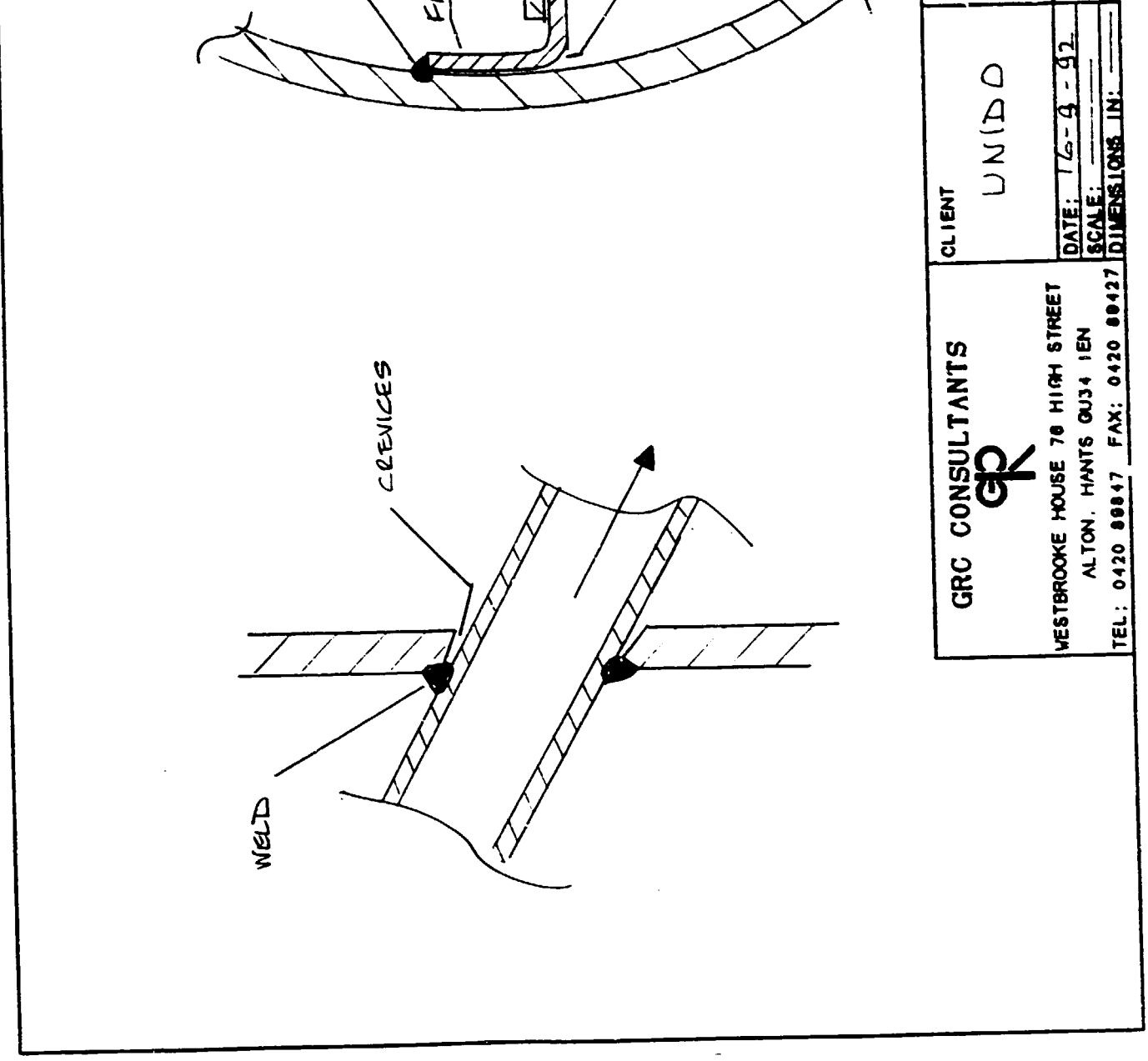

Sketches and drawings show not only plans, at various levels, but also elevations and views on various cross sections.

It is emphasized that for the purposes of this study, and within the Terms of Reference, no specific site is identified, hence the layout is developed from first principles on the basis of a 'Greenfield Site', hence the layout has to be accepted to some extent as 'ideal conceptual' rather than definitive, or based on a real site or in ready built accommodation.

- Section 12: Safety and Environment. The modern biotechnology pilot plant is designed with a number of safety features in mind. In particular, the organisms require some level of containment to limit their chance of escape, thus reducing the risk to workers or to the environment. This section includes the measures which have been taken in the biotechnology facility and reference is made to various other sections where the principles are applied in practice.

- Section 13: GMP/Validation. It is acknowledged that in the short term (next 2-3 years) Biogal have stated that they do not intend to use genetically manipulated organisms (GMOs) in the pilot plant. However, if the Biogal pilot plant is

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(2 of 3)

FRONT END DESIGN STUDY

FOR

BIOTECHNOLOGY DEVELOPMENT FACILITY

FOR

BIOGAL, DEBRECEN

(VOLUME 1)

UNIDO CONTRACT 92/030

G E GUIDOBONI
JUNE 1992

This report has been prepared for the United Nations Industrial Development Organisation (UNIDO) for the project TF/HUN/90/906 "Technical Assistance for the Fermentation and Downstream Processing Pilot Plants of Biogal"

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ACKNOWLEDGEMENT

GRC Consultants wishes to acknowledge the co-operation and support of many of the Biogal staff at Debrecen on the many visits made to the site during the preparation of this Front End Design Study. Particular acknowledgement is made to members of the fermentation and downstream processing pilot plants, without whose understanding and help, this FED would not be as comprehensive as it is.

CONTENTS

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 Biogal project and requested financial support from the UK/KHF through UNIDO.

In February 1992, GRC Consultants was awarded a contract to carry out this project and work began at the end of February 1992. (2)

The Terms of Reference for this project included a Front End Design (FED) study for the upgrading of the fermentation and downstream processing (DSP) pilot plants of the Biogal Company at Debrecen.

However, at the project kick-off meeting, it was agreed that the FED study would, in fact, be concerned not with the existing pilot plants at Debrecen, but with a new biotechnology development facility at a location yet to be decided, and with the maximum use being made of existing Biogal equipment (if judged suitable).

The results of the FED study are presented in this report in a number of self evident sections as shown in the Contents list.

It is appropriate to record that GRC Consultants and Biogal 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. Where such information is used in the development of the FED study, it is presented in a Technical Annex to this main FED study report. This Annex is supplied only and directly to Biogal in such a way that no other party has access to the information. It is noted, as appropriate, in the text of this FED study report when such information is included in the Technical Annex.

SECTION 2

SCOPE OF STUDY

2.1 GENERAL PURPOSE

2.2 SPECIFIC TO BIOGAL

2.3 STUDY CONTENTS

2 SCOPE OF STUDY

This study is concerned with the preparation of a Front End Design (FED) for fermentation and downstream processing (DSP) pilot plant facility which Biogal are considering building to replace their existing pilot plants at Debrecen in NE Hungary.

One of the most important features of the FED study is that GRC Consultants, as required by the project Terms of Reference, has developed the design, in its widest sense, from the basis that the unit should be designed, constructed and installed in full compliance with current best practices for a modern biotechnology pilot plant which is capable of handling genetically modified organisms (GMO's) in 'contained' facilities. It is appreciated by GRC Consultants that Biogal do not plan to use GMO's in the pilot plant in the short term (within 2-3 years). However, the facility is specified in this FED to accommodate GMO's with appropriate containment, on the basis that it would be extremely short-sighted and totally inappropriate for Biogal to plan to build a 'modern' biotechnology facility which, in 3-4 years time, could not handle GMO's except with extensive, costly and highly disruptive modifications. Hence the whole concept of the design in this FED study is based on the eventual use of GMO's (some in contained facilities) but with the complete freedom initially for Biogal to operate the whole facility with non genetically manipulated microorganisms.

2.1 GENERAL PURPOSE

The FED study is essentially a document which brings together, and presents in textual and graphic form, information about the process, the equipment and the layout, etc, in sufficient detail to enable suitably qualified contractors to tender for the detailed design, engineering, construction, installation and mechanical commissioning of the proposed facilities. The

FED study is not (and is never intended to be) a document from which the facility can be engineered and constructed directly. Such detailed information is prepared at the 'detailed engineering' phase of a project and normally is the first design activity of an engineering and construction project.

The FED study may be used in toto or in parts by the client at the "invitation to tender" stage in order to state clearly to the bidding contractors, the style, nature, size, quality, output, location, etc, of the intended facility. It is also used to advise bidding clients of the engineering standards required of equipment fabrication and building construction. etc. The FED study is also a vehicle for informing the contractors of the needs for VALIDATION and Good Manufacturing Practice (GMP) compliance if appropriate for the product(s).

The FED also is a document which brings together and co-ordinates the requirements of different departments (or sections) within the client's overall organisation. For instance control, instrumentation and electrical requirements are included (in outline) together with aspects of operation and safety.

2.2 SPECIFIC TO BIOGAL

The above comments are applicable to any FED study and the following items are specific to this project for Biogal.

- Nature of Facility: The basic function of the facility which is the subject of this FED study, is the carrying out of development work on a range of fermentation and DSP processes, mainly for antibiotics but also for a range of enzymes and other proteins. GRC Consultants understands that Biogal do not intend to produce material for clinical

trials, but the facility is specified so that it could be used, in the future, for the preparation of intermediates which could go on for further processing elsewhere.

- Nature of Products: GRC Consultants understands that the products from the development unit are generally antibiotics in the dry powder/crystal form in kilogram quantities.

- Status of Project: The project for the new biotechnology development facility is only at the planning stage. No firm decision has been taken to proceed with the detailed design and construction of the new facility. Such a decision is not expected before the wider plans for the Biogal company privatisation and possible takeover by a third party are complete.

2.3 STUDY CONTENTS

The contents of the study, as shown in the contents list, are self-evident but the following notes on key sections of the report are appropriate.

- Section 3: The Pilot Plant in General. GRC Consultants believes it is vital that the client is very clear about the intent of the pilot plants, otherwise the FED might reflect a project which is either totally over ambitious or unrealistic or technically unachievable within a given timescale or within given financial limits. The notes in this section are intended to enable a general consensus to be achieved on the nature and style of the proposed pilot plants together with some brief ideas on key development topics which might be the subject of work programmes for process development, yield improvement, scale-up, etc.

- Section 4: Basis of Design. This section includes specific technical/factual information on topics such as:

  - Fermentation batch sizes
  - Fermentation cycle times
  - Raw materials used/products made

  Only non confidential data are included in the FED study; other confidential information is included in the Technical Annex. Where GRC Consultants has made ASSUMPTIONS, they are identified and, as appropriate, explained and/or justified.

- Section 5: Process Description, is based on Biogal information on the processes which are expected to be the most frequently operated in the first few years of the new development facility. Sensitive data are included in the Technical Annex.

- Section 6: Facilities Description, contains a brief description of the function and purpose of each uniquely identified room in the new facility, including corridors.

- Section 7: Equipment. It is a basic feature of the project that Biogal wish to use as much of their existing equipment as possible in the new pilot plant facility. Hence details of all items of equipment currently available are collected, the condition and residual 'life' of all items assessed, and recommendations made for additional/new equipment to be purchased, especially if the capacity of the pilot plant is to be increased.

  The equipment list includes outline information such as overall dimensions, weight, motor power, material of construction, etc. The list includes every item shown in the preliminary equipment flow diagrams.

- Section 8: Utilities and Services. The quality of all the services required is noted together with any special features.

- Section 9: Instrumentation and Control, deals with the overall approach to instrumentation and control and concentrates on the needs for local control of equipment packages, e.g. fermentation, the extent of remote control, from a central control room, and the requirements for data acquisition, logging and manipulation.

  Advice is given on types of instruments considered most up-to-date for a Western European style biotechnology development unit.

- Section 10: Building Design. This section includes a listing of all 'rooms' in the facility together with information sheets for each room. These data sheets include information on ceiling, wall and floor finishes, the number and type of electrical fittings, the HVAC requirements, etc.

  This section also includes information on the HVAC design for the whole facility.

- Section 11: Layout, concerns three aspects of layout:-

  (i) Layout of equipment within rooms
  (ii) Layout of rooms within the building
  (iii) Layout of the whole site, including car parks, internal roads, security gatehouse, etc

  The whole topic of layout is subject to a certain amount of 'subjective opinion' but the requirements of a modern biotechnology facility dictate many aspects of layout which are relatively fixed with little room for 'subjective' development. These are taken into account in the layout.

case in the short term, but if it becomes a feature in the future, then retrospective validation could be a major problem.

- Section 14: Engineering Standards, contains examples of engineering standards appropriate for the modern biotechnology facility. Of special importance are the standards concerned with 'sterile engineering' such as fermenter design and pipework systems design/layout.

- Section 15: Site Selection, includes guidelines and strategies for identifying and evaluating potential sites and premises.

SECTION 3

THE PILOT PLANT IN GENERAL

3 THE PILOT PLANT IN GENERAL

3.1 TYPES OF PILOT PLANT

The phrase "a pilot plant" can mean different things depending on the situation and industry. In the specific context of biotechnology basically three types of pilot plant can be identified as follows:-

(i) A unit built primarily to produce technical information (process engineering design data) and to examine, for example, pressure drops, heat transfer coefficients, reaction rates, chemical and physical properties, etc.

Probably the most important information that the biotechnology pilot plant has to produce is concerned with demonstrating the genetic stability of the organism and its ability to perform satisfactorily on scale-up from shake flasks and small fermenters (typically 1 litre) to meaningfully sized fermenters of typically 10 to 100 litres.

The chief features of this type of pilot plant are:-

- accurate instrumentation
- accurate calibration
- accurate measurement
- accurate sampling and analysis

and attention is focused on quantitative measurement.

(ii) An assembly of equipment of the temporary production of trial quantities of materials for product evaluation and approval. In this type of pilot plant the chemistry of the process is the dominant factor with emphasis on production.

(iii) A completely integrated model plant or process. The emphasis is on proving the process on as large a scale as possible, so as to lessen the inaccuracies in predicting commercial scale operation.

A pilot plant also could be any combination of the above three.

3.2 PURPOSES OF A PILOT PLANT

Having defined and agreed on the general type of pilot plant required, a number of more specific purposes can be identified for the particular pilot unit.

These purposes include:

- Generation of process engineering data which are more reliable than those generated at the laboratory scale.
- Confirmation and generation of physical and chemical property data.
- Production of samples for testing, evaluation, market research, and, where required, governmental approvals and permissions.
- Testing facility for proprietary equipment.
- Development and optimisation of the process chemistry and processing steps.
- Development of equipment (as opposed to merely testing equipment).
- Testing of materials of construction and corrosion/erosion data generation.

- Operator familiarisation with techniques and processes.

- Product development, marketing and sales support.

- Control system development including evaluation and testing of sensors and instruments.

- Development of theoretical and mathematical models.

- Examination of by-product formation, particularly during recycle operations.

3.3 GENERAL FEATURES OF THE BIOTECHNOLOGY PILOT PLANT

Some general features common to any type of biotechnology pilot plant can be identified.

- There is a range of sizes of equipment necessary for establishing scale-up data.

- Equipment and piping systems have to be flexible and adaptable.

- All parts of the plant must be available for sampling unless special "hazards" exist.

- There will be an abundance of instrumentation and data logging (far in excess of that required on a commercial scale but absolutely essential at the pilot plant development scale).

3.4 GENERAL FACILITIES

A number of general facilities are identified:

- Analytical laboratory for routine chemical analysis and property measurement.

- Microbiology laboratory for routine examination of cultures and organisms by microscopy and plating, etc. Depending on the processes being investigated, these examinations may have to be undertaken under strictly controlled conditions of containment, etc.

- Secure, segregated and safe storage areas for:-
  - raw materials
  - intermediate products or batches
  - final products samples or batches

- Safe, secure storage area for gases.

- Space is available for the inclusion of a dedicated tank farm area in the future if required.

- Provision of collection and containment systems for all waste materials. There must be no general purpose conventional drains into which accidental spillages, or even routine washings, can pass. All wastes and washings must be totally contained for analysis and treatment, if necessary, prior to disposal.

- Small mechanical/electrical/instrument workshop dedicated to the servicing, repair and maintenance of the biotechnology pilot plant equipment.

- Small, secure plant and equipment store to prevent biotechnology equipment being used outside the biotechnology pilot plant area.

3.5 DEVELOPMENT TOPICS

This section of the report deals with the identification of prime targets for continuing laboratory work and pilot plant operation. It is not appropriate to define fully a detailed programme, but the key areas are identified and the type of data needed to be generated are outlined.

3.5.1 Targets for Research and Development

Temperature

The two main temperature considerations in any fermentation process are the absolute fermentation temperature, and an acceptable temperature range for efficient fermentation. The absolute temperature should be as high as possible to enable a lower grade of cooling media to be used, e.g. 'towns water'.

The temperature range defines the thermo tolerance of the process which in turn allows the control system to be specified. For example: wide tolerance - on/off control - economic solution; narrow tolerance - close control (analogue) - higher cost control system.

Conversion/Yield

It is clear that any development work must maximise the yield of active component. This conversion is affected by genetic engineering and fermentation environmental conditions. Development must try to produce a species that will maximise conversion for a particular compound.

Aseptic Operation

The precise level of aseptic operation should be determined. This quantification is important for the engineering, design and specification. For example, if the fermenter can simply be 'cleaned in place' using chemical cleaning and sanitising agents, and not require steam sterilization, this would affect the fermenter specification and capital and operating costs of the commercial scale plant.

The feasibility of controlling/eliminating any contamination in the fermentations must be demonstrated without having any significant effect on either the yield or rate of fermentation.

pH

The same remarks as for temperature apply but pH may have a marked effect on the fungal properties and will need special consideration.

Cycling

Cycling of organisms through temperature, pH, salts concentration within the fermenter, or in external heat exchangers, must be examined to determine if such cycling causes stress to the organism resulting in loss of performance.

Fermenter Broth Rheology

The extent to which the fermenter broth departs from standard Newtonian hydraulics must be determined. Of particular importance is the broth viscosity and any change of this

property either with changing fermentation conditions or with changes of agitation, etc. The viscosity of the broth is important in both hydraulic and heat/mass transfer calculations.

Operating Pressure

The fermenter operating pressure, due either to hydrostatic head or deliberately imposed back pressure, must be examined for its effect on oxygen transfer and carbon dioxide back pressure.

3.5.2 Process Engineering Development Topics

A number of topics are identified for process engineering development.

Mass Transfer Studies

These are concerned with oxygen mass transfer as they affect the growth and performance of the fungal fermentation. The fermentations will be carried out in agitated fermenters to generate oxygen transfer data and to examine the effect on oxygen transfer rate of parameters such as:

- agitator power
- agitator speed
- aeration (air rate)
- pressure
- agitator size/type
- cellular density
- pH

In parallel with the oxygen transfer correlation experiments, work is carried out to develop correlations for power dissipation in aerated fermentations, i.e. specific power input as used in the correlations, for oxygen transfer above. Such correlations involve:

- ungassed power
- stirrer speed
- impeller diameter
- fermenter diameter
- impeller - sparge separation
- air flow

The chief aim of all this work is to ensure that the agitation/oxygen transfer design correlations are as accurate as possible since at the commercial scale there will be little or no latitude to alter the agitation conditions (except at great expense and inconvenience). If the fermenter system does not dissipate the proper amount of power needed for satisfactory oxygen transfer (or possibly even substrate mass transfer, which may be shown to be critical or limiting), then the fermenter performance probably will fail to meet the design criteria.

Fermenter Type

Many developments study the suitability of various high aeration fermenters. However, this report assumes that the stirred tank fermenter is the preferred fermenter for the Biogal processes.

Cell Separation

In parallel with the laboratory work, process development is carried out in downstream processing. The first step is to develop the system to separate the cells from the growth medium. The separation technique generally used by Biogal is vacuum filtration but centrifugal sedimentation and crossflow microfiltration are technologies which are finding wider applications.

Cell Rupture

Homogenisation is a method to disrupt the cell structure and may be needed for some enzyme fermentations. It is a system which subjects the cells to a high pressure drop by pumping through a valve, causing cavitation, turbulence and high shear forces. Cell breakage conditions, particularly temperature, pressure, number of passes needed and pH are usually investigated. This will include cell breakage efficiency versus homogenisation pressures as this will determine downstream process parameters, e.g. volume of solvent.

Solvent Extraction

It is understood that development work is continuous on the solvent extraction stages of the Biogal processes. The main topic for development is the selection of solvent(s) based on the following criteria:

- Efficiency of metabolite removal
- Effect of processing stages for metabolite removal and solvent recovery
- Environmental and Health and Safety considerations
- Containment requirements for the solvent

3.5.3 Microbiology Development Topics

Some of these topics have been mentioned earlier but are summarised here for reference.

- Identification of and resistance to fermenter contamination by bacteria.

- Identification of and resistance to fermenter contamination by other organisms.

- Techniques for control or elimination of contamination by chemical cleaning agents.

- Effect of any contamination on efficiency or conversion.

- Strain development of organism with increased contamination resistance or improved efficiency.

- Effect of storage/preservation conditions on the organism strain.

- Effect of resuscitation conditions on organism from storage to inoculation.

- Preparation of inoculum and effects of inoculum size on subsequent fermentation. This topic is important with respect to the design of the whole inoculation system and the problems of apparent non-viability of very dilute inocula resulting in a failure to start.

3.5.4 Other Development Topics

There are often items which have to be specifically developed for a particular process. These include:-

- On-line analysis in the fermenter broth and the exit offgas. This will primarily consist of oxygen and carbon dioxide gas analysis. However, fungal growth (density) and nutrient levels may require measurement.

- Trace metal analysis in the feed streams and the fermenter broth. Ion ratios are as important (sometimes more so) as absolute individual ion concentrations.

- Raw material schedules and specifications have to be developed with special care since commercial grade chemicals may contain harmful elements which are not present in laboratory reagent grade chemicals. Some trace ions may need to be analysed with unusual accuracy.

- Spent biomass treatment and usage is a project in its own right. This product, although at present considered a waste material, could become a viable byproduct following product and process development work. Environmental legislation may be the driving force for this project especially as solvents are used in some of the Biogal processes.

3.6 FERMENTATION/DSP INTEGRATION

Throughout this report frequent reference is made to the fermentation pilot plant and the downstream processing (DSP) areas of the new development facility. GRC Consultants understands, from discussions with and visits made to Biogal over the last two years, that the fermentation and DSP research and development activities have been organised almost as separate functions within the one building. For historical

and other reasons, this arrangement has been understandable but it is GRC Consultants experience that biotechnology processing research and development has a number of key stages which are inextricably linked, two of these being fermentation and DSP, especially the primary separation stages immediately following fermentation.

The design of the new development facility, as presented in this report, is based on the complete integration of fermentation and primary DSP operation and it is GRC Consultants recommendation that Biogal should give serious consideration to this integration from both a practical and operational point of view. It may be anticipated that in the future, as Biogal undertake research and development of products and processes outside their traditional fields, the close integration of fermentation and primary product recovery (harvesting) will be very important since the "condition" of live fermenter broth can have a significant effect on the primary separation stage, particularly in terms of efficiency and stability and ease of processing. Recovery process parameters can depend markedly on fermentation broth parameters.

Furthermore, the primary separation parameters can also significantly affect subsequent recovery and purification steps. The need, therefore, for fermentation/DSP integration is clear and important, especially in biotechnological facilities which deal with 'living' and changing entities.

SECTION 4

BASIS OF DESIGN

4 BASIS OF DESIGN

In this section, all the data used for calculation purposes are noted together with reference to their source if appropriate. The key sources of process data are reports received from Biogal, the key points of which are included in the confidential Technical Annex. Also, all key ASSUMPTIONS made are identified and, where appropriate, they are explained/justified.

4.1 PROCESS DESIGN

4.1.1 General Parameters

- Operations cycle: 24 hours per day, 7 days per week
- Annual operating year: 330 days (approximately)
- Site Location: not specific
- Staff number, for amenities sizing purposes: approximately 30-35, see proposed staff structure, Fig. 4.1.1

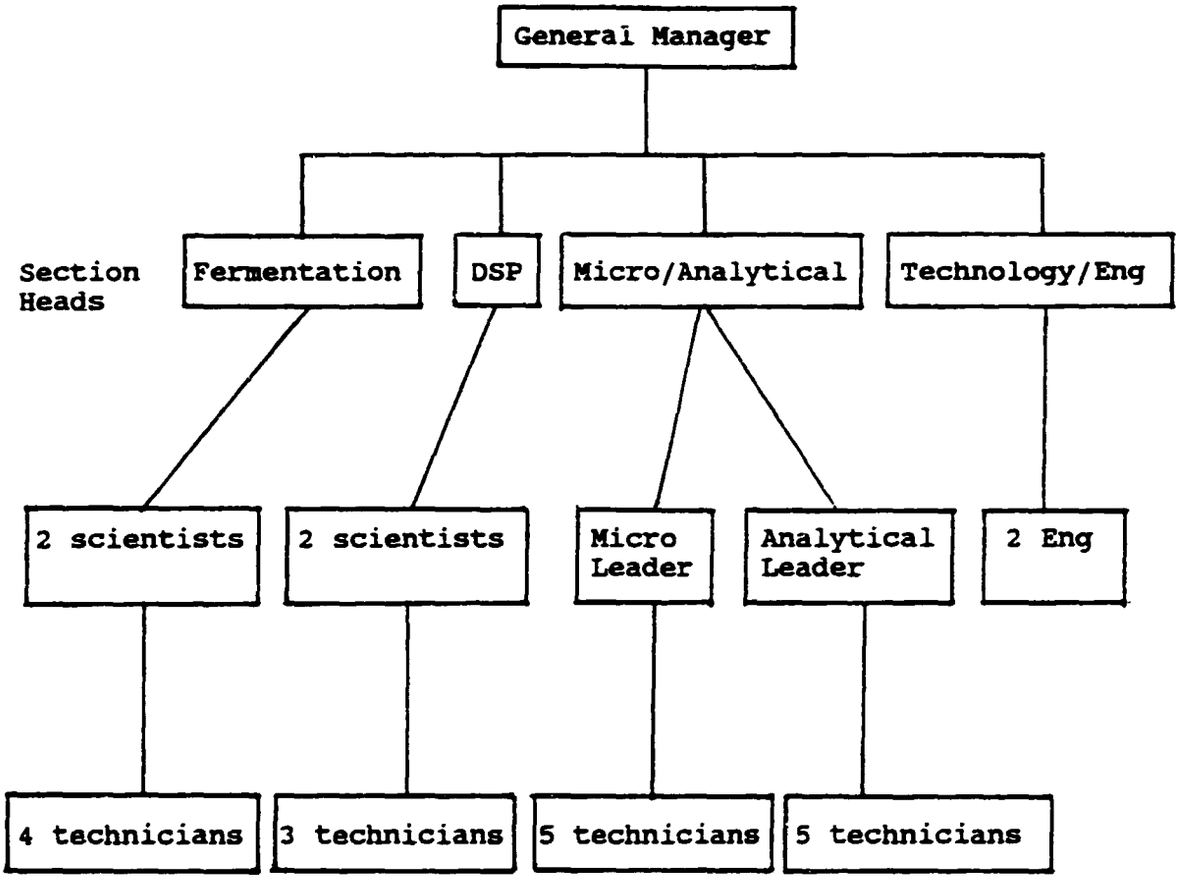
4.1.2 Materials Identification

The following lists identify materials received, or used, in the pilot plant and all the emissions, discharges, wastes and products which leave the unit.

Raw Materials and Feedstocks

- Fermentable carbon source: including powdered glucose, granulated sugar, dextrose, corn starch, potato starch, cornflour, soya flour, starch syrup, palm oil, sunflower oil
- Corn steep liquor
- Inorganic nitrogen, as ammonium sulphate and ammonium hydroxide

Fig. 4.1.1 Proposed Staff Structure



\+ 1 day man/plant technician
1 stores man
2 secretaries

Total staff = 30 (excluding security staff)

- Inorganic phosphorus, as potassium dihydrogen phosphate
- Magnesium sulphate, heptahydrate, zinc sulphate, manganese sulphate
- Yeast extract (dry powder form)
- Antifoam (polyalkylene glycol or equivalent)
- Caustic soda and sulphuric acid for process use, i.e. pH control and caustic potash
- Caustic soda, for CIP use
- Water, from mains for process use
- Water, from mains for general plant use
- Water, for cooling purposes, either mains for low volume, or from cooling tower for large volume uses
- Air (atmospheric) for fermentation, instrument air and general plant air
- Nitrogen for inert blanketing
- Solvents including chloroform (for solvent extraction), ethanol, propanol, butyl acetate, MIBK, amylacetate, methanol
- Miscellaneous analytical reagents for use in the chemistry and microbiology control laboratories
- Miscellaneous laboratory gases, in cylinders
- Miscellaneous chemicals: sodium chloride, sodium carbonate, phenoxyacetic acid, acetic acid, triethylamine, acetic acid anhydride, pyridine, emulsifiers, activated carbon, pearlite (filter aid), formalin, oxalic acid

Utilities and Services Components

- Electric power from mains via local substation/transformer
- Fuel oil, for boiler heating
- Gas, if appropriate, as standby or alternative to fuel oil
- Glycol (or equivalent) for refrigeration uses
- Water treatment chemicals, if needed for boiler feed water conditioning (e.g. sodium chloride, caustic soda and various proprietary chemicals)
- Liquid nitrogen, for cold storage purposes

Products and Emissions

- Antibiotic intermediates, enzymes and other active proteins.

- Biomass, as wet cake, semi dry cake or dry material, if recovered from aqueous streams.

- Fermenter off-gas, basically air but with reduced oxygen and increased carbon dioxide content, saturated with water vapour.

- Spent CIP liquor (waste caustic soda 2% solution with dissolved protein) probably sent to general purpose waste tank for "conditioning" before discharge to local authority sewer.

- Process aqueous waste - This is derived from biomass separation and from solvent extraction. The general aqueous waste is relatively innocuous (possibly high BOD) and may pass to the general purpose waste tank, but the aqueous waste from the solvent extraction stage will contain traces of solvent (whether or not the biomass has been recovered) and may need special treatment (possibly air blowing to strip out solvent) before discharge (see note below).

- General plant aqueous wastes, from washdown of floors, spillages, etc. These pass to the site general liquid waste collection system (see note below).

- Storage area drains/wastes, e.g. from bunded areas, may need separate collection and conditioning before discharge to general plant drainage system. Special attention must be paid to the handling of spillages in the solvent handling and storage areas.

- General surface water (rainwater) passes to conventional storm water drains.

- Domestic effluents from toilets and other amenity areas pass to a conventional foul sewer.

- Waste/blow-down solvent from the solvent recovery plant, if used, together with solvent 'sludge' from in-line filters in the solvent/oil phase from the extraction stage, stored in drums and sent for disposal.

- Boiler feed water treatment blowdown liquids pass to the site general drainage system, together with cooling tower (if used) blowdown water.

Note: If and when Biogal carry out work with GMO's, the collection and treatment of certain drains, especially process drains, will need modifying to achieve containment.

4.1.3 Materials Parameters

For the purposes of this FED study, and based on information collected at Biogal, raw materials and miscellaneous chemicals used in the pilot plant are generally received in a variety of containers/packages as follows:

- Most solvents and liquids: 25 and 200 litre drums (metal and plastic, various)
- Bulk used solids (sugar, starches, etc): 50 kg sacks (paper and plastic)
- Minor components: 25-50 kg fibre bags (poly lined)
- Miscellaneous chemicals: various smaller packages, generally plastic or glass jars, up to 1 kg weight.

The "products" from the pilot plant are generally contained in either polylined fibre kegs or glass/plastic specimen/sample jars, of up to 1 kg capacity.

4.1.4 Key Process Parameters

Feed and Equipment Preparation

- Antifoam sterilisation: Heat, 121°C for 15 mins max

- Carbohydrate and all other salts/media sterilisation by filtration, ambient temperature, 40 micron prefilter, 0.2 micron sterilising filter. Alternatively, heat stable liquids may be sterilized by heat, as above, in situ in feed vessels or fermenters.

- Fermenter vessel and associated equipment and pipework in 'sterile' service, sterilisation by heat (saturated steam) 125°C for 1/2 hour, preceded by cleaning-in-place (CIP) with 2% caustic soda solution at 30-40°C.

- Gases sterilized by filtration, 40 micron prefilter, 0.2 micron sterilizing.

Fermentation

- Temperature : 25°C ± 1°C to 40° ± 1°C
- pH : various, from 3.5 to 7.5
- Pressure : 1/2 bar g overpressure in fermenter headspace
- Aeration : 0.25 v/v/m generally, but range 0.25-1.0 v/v/m
- Agitation : up to 10 kW/m^3 (liquid volume) dissipated at impellers but variable

- Medium composition (based on information from Biogal) confidential (in Technical Annex)

Biomass Separation

- Primary separation by filtration, 1.2-1.3% solids to approx 20% solids filter cake

- Provision to be made for cooling mother liquors to 4°C

Solvent Extraction

- Solvent : Various, but including chloroform

- Temperature : Ambient, but provision to be made to cool to 4°C

- Number of solvent extractions : 3

- Solvent/aqueous contact time : 15 minutes approx

Evaporation/Product Recovery

- Solvent evaporation temperature : approx 40°C (under vacuum)

Chromatography

- by ion exchange, at ambient temperature

Drying

- in vacuum tray driers, or electrically heated agitated bed drier, or electrically heated spray drier (inlet drying air temperature up to 200°C) or freeze drier.

4.2 FACILITIES DESIGN

4.2.1 Basis of Concept Design

Following preliminary discussions with Biogal staff the key elements of the design concept for the new development facility are identified below:-

INTENT: To realise a facility which contains both laboratories and pilot scale units for the development of new and improved processes, and possibly, in the future, for the production of clinical trial quantities of materials.

LOCATION: To be decided, possibly within 20 miles of Debrecen, but not necessarily so.

STANDARDS: The plant will be designed and constructed so that, if required in the future, it could be validated and operated to comply with GMP so that it could receive appropriate approval for clinical trials materials.

CONTAINMENT: Those areas where fermentations involving more than 10 litres of GMO's are planned for the future are designated Containment Category 2. (Ref 3)

ADAPTABILITY: The facility must be adaptable so that a range of process options are available. The facility must be capable of handling both fungal and bacteria species and both intra- and extra-cellular products from these organisms. However, it is understood that Biogal intend, initially, to carry out work on a campaign basis on only one product at a time.

MANNING: Normal working hours will be 9 a.m. - 5 p.m., Monday to Friday, but cover will be provided 24 hours a day, 7 days a week for operations which must continue out of normal hours.

4.2.2 Key Facilities

Basically five main areas are identified as:-

- Pilot Plants
- Laboratories
- Support Areas/Services
- Administration/Amenities
- Utilities and Services

The pilot plants are intended for process development of new and existing processes at a meaningfully large scale. Such pilot plants have the necessary facilities and equipment to accommodate all the various typical anticipated processing steps such as seed preparation, inoculation and primary growth, product recovery and purification.

The laboratories cover a range of activities including:-

- analytical and development of processes before transfer to the GMP Suites
- purification and other process techniques development
- specialist activities possibly involving solvents and possibly cytotoxic materials
- cell culture and general microbiology for both analytical and process development

The Support Services cover a range of activities and facilities such as:-

- wash-up for decontamination, cleaning and preparation of glassware and other items
- make-up area for the preparation of media and buffers, etc, for use throughout the facility
- storage areas which may be combined to provide receipt and storage of raw materials, components, equipment (including quarantine zones)

- an engineering workshop and stores for minor engineering works (instrument testing and servicing, etc)

The Administration and Amenities areas include:-

- reception area and secretarial space
- manager's office
- general open plan office for scientists
- a general purpose meeting/conference room
- library (possibly combined with the meeting room)
- a staff room with drinks and simple food preparation
- computer room to accommodate a network
- the toilets, showers, changing rooms, etc, for both male and female staff

The Utilities and Services comprise essentially the following:-

- plant room for the generation of key utilities such as steam (heating and clean), pure waters, compressed air, etc
- gas cylinder storage compound and distribution manifold
- solvent store
- general delivery/marshalling yard and goods handling area

4.2.3 Key Features

Preliminary discussions with Biogal staff identified a number of features which the development facility must demonstrate. The following features are highlighted but their order does not imply significance or priority at this stage.

Adaptability

The very nature of a development facility implies the need for adaptability (sometimes synonymous with flexibility) of equipment and services. Hence the design and layout of the whole facility must be such as to enable equipment arrangements to be reconfigured to suit changing process needs, with absolutely minimal disruption to other work in the vicinity.

Containment

Certain areas may in the future handle pathogens and/or genetically engineered microorganisms and such areas are designed to satisfy the requirements for the appropriate containment category.

Security

Security of access to the building as a whole, and within the building, is to be strictly controlled at all times, even in the absence of supervisory staff. Extensive use of 'key card' or equivalent systems is anticipated together with a high degree of external surveillance of the premises. The degree/extent of security is partly dependent on the location of the development facility.

Computer Network

GRC Consultants understands that Biogal may wish to integrate a number of currently disparate computer based systems into a Group Central Computing Facility in the new development

building. Such a network would integrate research and development results with databases of research planning, statistical analysis, etc.

(Note: the nature, size and scope of such a computer system is outside the terms of reference of this concept design study, which nevertheless accommodates an appropriate computer room).

Segregated Services

It is anticipated that in the future different programmes of development work on different microorganisms may take place simultaneously but in different areas. Hence the air handling systems for each area are totally segregated and fully independent to prevent any chance of cross-contamination. Furthermore, the separation/segregation of rooms/areas/laboratories permits the independent fumigation of these areas.

Image

It is a recognised fact that modern pharmaceutical companies have a certain 'image' of quality, spaciousness, cleanliness, ambience and 'high tech'. For Biogal to establish and maintain a credibility in the pharmaceutical industry, attention must be paid to this image and the new development facility must reflect the perceived attitudes noted above. Hence, attention to layout is important, together with compliance with all the accepted norms for amenities and associated staff support services. All these must also be set against an acceptable local environment which could restrict the number of geographical areas in which the new development facility might be located.

Furthermore, the whole concept of "image" has a bearing on the ability to attract and recruit the right quality staff to the new facility.

Equipment

GRC Consultants understands that Biogal wish to maximise the use of existing laboratory and pilot scale equipment at Debrecen in order to contain the capital cost of the new facility.

Staff

For the purposes of this FED study, the number of staff is anticipated to be in the region of 30. Clearly the number of staff is linked closely to the number of key projects being progressed through the development facility at any one time. The number is also dependent on Biogal's philosophy regarding a phased build-up of the development capability but in any event, the staff amenities are designed to accommodate, from the outset, up to 30 staff (assumed to be 15 female, 15 male) as Fig. 4.1.1 earlier in this section.

Equipment Mobility

Preliminary discussions on the features of the new development facility included reference to the physical movement of equipment items to and from store and to and from pilot plants. The concept has certain attractions in theory but practical problems of such movements of relatively large assemblies of equipment are identified.

Such problems include:-

- connection/disconnection of services (steam, power, coolant, air)
- the requirements for total decontamination of possibly extremely bulky items
- the necessity (and cost) of large pass through hatches used infrequently for the transfer of heavy bulky items
- the extra storage space needed for bulky items (on the basis that if it is not in use, then it is put into store)

Clearly the concept of mobile media and product tanks is totally practical (and accepted practice) together with laboratory scale equipment items such as chromatography columns, etc. In the same way, mobile pump sets are featured prominently in development and pilot facilities.

It is concluded, therefore, that whilst provision is made for the physical movement/relocation of relatively small items, the large bulky, heavy, complicated assemblies are dedicated essentially to their key/main location. Provision is made, however, for their infrequent relocation (perhaps for overhaul or major repair) by means of totally sealed but demountable panels in strategic locations in the walls.

SECTION 5

PROCESS DESCRIPTION

5 PROCESS DESCRIPTION

The typical processes which are described in this section consist basically of a combination of seed, inoculation and fermentation protocols developed by Biogal and conceptual design by GRC Consultants based on their experience and understanding of biotechnology pilot scale practice for fermentation, biomass recovery and downstream processing of materials similar to those involved in this process. The description should be read in conjunction with the series of sketches and drawings included at the end of this section.

PROCESS BLOCK FLOW DIAGRAMS
These show the key unit operations carried out in a typical process but individual units may or may not involve process equipment items.

PROCESS FLOW SCHEMATIC
This single drawing shows all the key process equipment items and their relationship one to another.

EQUIPMENT FLOW DIAGRAMS
These are drawings which are developed from the overall schematic and show each and every equipment item which is included in the Equipment List, Section 7.

The description which follows is presented on an area by area basis and involves a typical process, which for the purposes of this study, is based generally on a typical 'Neomycin' process (confidential data in Technical Appendix).

5.1 AREA 100: MATERIALS RECEIPT/STORAGE AND FEEDSTOCK PREPARATION

The main carbohydrate sources, see Section 4.1.2, are received in bulk quantities on a lorry and unloaded into the main storage room.

Water from the local authority is metered onto site into the main water break tank. From here it is pumped to the various users for process use and to a demineralisation unit for use in the boilers.

The main salts such as magnesium sulphate, inorganic nitrogen, etc, are received from lorries, unloaded probably onto forklift trucks and delivered to the secure salts store. On receipt the salts are held in a designated quarantine area whilst samples are taken for QC and QA checks.

The salts and carbohydrates are taken on hand pallet trucks to the dispensary area where they are weighed out and then charged to the make-up tank.

This tank is fitted with an agitator and a transfer pump which also acts as an in-line recirculation device.

When the required salt solution has been made, it is transferred via a filter to the main salts holding tank. From here it is pumped, when required, to the fermenters (or feed tanks) for in situ sterilization. As an alternative, the solutions may be sterilized by pre/absolute filtration.

The antifoam is received and stored in drums which are transferred to the antifoam sterilizer vessel where the antifoam is sterilized by heat. It is then pumped direct to the various antifoam head tanks at the fermenters.

It may be noted here that, apart from the antifoam, all the other liquid streams can be cold filter sterilized rather than heat sterilized. This is very much in line with current industrial practice whereby the use of filters avoids problems of heat sterilization equipment start-up and shutdown with consequent problems of leakage through expanding and

contracting joints. Also the use of appropriate prefilters extends the life of the sterilizing filters significantly and these are no longer the traditional costly replacement items.

5.2 AREA 200: FERMENTATION PREPARATION

The basis for seed preparation and inoculation development is that developed by Biogal. Seed is prepared in the microbiology laboratory in shake flasks which are then used to inoculate the train of 3 fermenters. The first seed fermenter package is based on a 60l fermenter which is equipped with its own local controller and has a feed tank for caustic soda (for pH adjustment) and antifoam for foam control. Fermentation air is taken from the plant air main via pre and sterilizing filters. The fermenter offgas passes to the main offgas header via an outlet sterilizing filter, probably heated to avoid moisture condensation.

On completion of the seed fermentation the broth is transferred by sterile air overpressure to the second inoculation fermenter of 300l capacity. The set-up for this unit is virtually the same as for the first fermenter and is a stand-alone packaged unit.

When the inoculum is ready it is transferred, again by sterile air overpressure, to the third and main fermenter of 1000l capacity. This whole set-up is virtually the same as the previous two rigs and is again a stand-alone unit.

All the offgases from all the seed and inoculation fermenters are collected in the main offgas header for deodourising and scrubbing in the offgas scrubber associated with the main fermenters.

All the seed and inoculum fermenters are equipped for CIP and are sterilized in place. It is perceived that these fermenter rigs would be installed as totally equipped packaged units.

All the seed and inoculum fermenter rigs may be located in the main fermentation production hall close to the main fermenters, probably at an elevated level (on the same level as the microbiology laboratory and control room) so that transfer lines to the main fermenters, and between inoculation fermenters, are minimised in length.

5.3 AREA 300: MAIN FERMENTATION

The four identical main fermenters are conventional 2.5:1 aspect ratio vessels fitted with Rushton type impeller agitators. For the purposes of this study, three impeller discs per agitator shaft are anticipated and air sparging is via conventional perforated ring sparger beneath the lower impeller.

The fermenter is fitted with the conventional instrumentation for temperature control, pH adjustment, dissolved oxygen measurement (may be used to control the air flow and/or agitator speed). Two sets of instrument probes may be used at different positions in the fermenter to ensure homogeneity of the contents. A foam probe may be used automatically to add antifoam on demand. (In addition, the fermenter offgas may pass through a Turbosep device to collect and return any foam to the fermenter should a foamover occur.) The offgas itself is first of all cooled to condense out water vapour and is then heated to above condensation point before passage to the sterilizing outlet air filter, which itself may be steam jacketed to prevent condensation on the membrane. The offgas finally passes to the main offgas header to the scrubber.

For the purposes of this study, fermenter cooling is achieved with cooling or chilled water in the external jacket.

The fermenters are equipped with CIP facilities which are designed to irrigate all surfaces which come into contact with fermenter broth including the exit air offgas lines.

On completion of the batch fermentation, the broth is pumped to the appropriate harvest train depending on the process being carried out.

The final piece of equipment in this section is the offgas scrubbing and deodourising package which is actually designated as part of Area 900: Utilities and Services. All the offgases from the seed, inoculum and main fermenters are led to the scrubbing unit which consists essentially of a packed tower irrigated with dilute caustic or hypochlorite solution. The gases are ventilated through the packed tower and discharged to atmosphere at high level. It is not anticipated that any form of terminal filtration or sterilization or incineration of the offgases will be needed.

5.4 AREA 400: PRIMARY HARVESTING

The fermented broth is passed to the pH adjustment tank where pH is adjusted by means of acid addition. On completion of pH adjustment the broth is transferred either by pump or by mobile container to the rotary vacuum filtration unit. Here the broth is filtered and the mycellium cake removed and the liquor collected.

The biomass may be sent for disposal or sent to another part of the development unit for further developmental processing. The filtered liquor is then transferred to the next stage.

5.5 AREA 500: CHROMATOGRAPHY

Prior to the actual chromatography step, the liquor is once again pH adjusted, this time with alkali, and is then transferred to the feeder tank for the chromatography columns. The most commonly used chromatography step is an ion exchange column over which the feed is pumped at a controlled steady rate. The feed liquor, after passage through the columns, may be collected for disposal or for re-work. The chromatography proceeds by means of a water wash over the column followed successively by a dilute aqueous ammonia wash and finally elution with a strong solution of ammonia.

All the wash and eluate liquors are fed from overhead tanks at controlled and steady rates. The various eluate fractions are collected in closed wheeled liquid containers.

5.6 AREA 600: DECOLOURISING AND EVAPORATION

The liquor from the chromatography section (the eluate) is decolourised by contacting with activated charcoal in a pressure Nutsche filter unit. The decolourised liquor is collected in a mobile container and the spent charcoal is discharged from the filter for disposal either by incineration or landfill, or it may be reactivated and recycled.

The decolourised liquor is then evaporated in a standard rotary evaporator operated under vacuum. The concentrated liquor is collected in sealed containers and transferred to the next stage. The overhead vapour water is condensed and sent either to drain or recycled for developmental use.

5.7 AREA 700: SALTS FORMATION

Prior to the precipitation of the metabolite salt, the liquor is clarified yet again with activated charcoal in a general purpose glass reactor, at which time the pH is also adjusted by the addition of acid.

The liquor is filtered through a ceramic Nutsche filter and the liquor collected in a closed container. The waste charcoal is manually unloaded and sent to disposal (or possible reuse). The clarified liquor is charged to a further general purpose reactor to which the solvent is added which causes the precipitation of the metabolite salt. The slurry is then filtered through the ceramic Nutsche filter, but this time the waste liquors are sent to the solvent recovery unit for recycle. The collected precipitated metabolite is unloaded from the ceramic Nutsche into a sealed product container from which it is sent to the drying area.

5.8 AREA 800: DRYING

The solvent wet product is unloaded from the containers into vacuum tray drying ovens in which the solvent vapour is removed and condensed for disposal or recycle. When dry, the product is unloaded from the trays into closed containers and taken to the product store for quarantine whilst QC and QA checks are carried out. As an alternative to the vacuum tray drier, the solvent wet product may be dried either in a freeze drier or in the pilot scale spray drier. The use of a particular drying step will be determined by the particular process in use at the time.

5.9 AREA 900: UTILITIES AND SERVICES

The utilities and services area consists essentially of a number of packaged units as follows:-

There are basically four off gas and exhaust gas treatment systems which are shown essentially as manifolds on the various equipment flow diagrams.

The first system is the general purpose ventilation system which collects general fumes and offgases from the non hazardous areas of the facility and passes them to a general purpose scrubbing column.

The second system is essentially the offgas scrubbing and deodourising system for the fermenter offgases. This unit is probably sited in the fermenter hall or just outside of it.

A third system consists essentially of a solvent vapour absorption system in which the various solvent vapours are absorbed and possibly collected for incineration or reuse.

The fourth general exhaust system is concerned with dry dust handling and recovery from the few dust extraction areas of the process.

The other traditional typical utilities and services packages consist of the following:-

- The main cooling water system is based on the use of an atmospheric cooling tower with fan assisted air flow.

- A chiller package is used to generate chilled water (or alternatively brine) for use particularly in the fermentation and solvent extraction areas where the liquors may need to be maintained at a relatively cool temperature at about 4°C.

- The demineralised water package takes mains water and softens it for use either in the process or in the steam raising boilers.

- The steam boiler package consists of two independent steam boilers together with their hotwells and economisers. The generated steam passes either to process use or to the clean steam generator.

- A self-contained clean steam generator package is installed to provide clean steam for live sterilization purposes throughout the facility.

- There are basically two air compressor systems, one is the main air compressor for fermentation use and the second compressor provides general purpose plant air and instrument air.

- A cleaning-in-place (CIP) package is used to generate dilute caustic CIP liquor for use on a general basis throughout the facility. The package contains essentially the caustic dilution and feed tank and the feed circulating pump. Local return pumps throughout the plant return the CIP liquor back to the package which has its own local PC controller.

- Various vacuum generating devices such as water ring or oil ring pumps are installed in the utilities and services section for general vacuum use throughout the facility. There are also local vacuum sets as appropriate, e.g. in the solvent extraction and solvent distillation areas.

5.10 ALTERNATIVE PROCESSING

There are a number of minor process alternatives for penicillin type processes as follows.

Area 400P (Extraction and Separation)

In this process, fermented broth is transferred directly to a general purpose glass reactor in which pH adjustment and solvent extraction is carried out straight away. The two-phase liquor is then processed through a centrifuge in which the biomass (in the aqueous phase) is recovered and sent to solvent processing and the solvent phase, which contains the metabolite, is collected in a sealed container and sent to the next stage.

Area 600P (Extract Treatment and Precipitation)

The solvent extract liquor is then decolourised by charcoal treatment in the general purpose reactor and the liquor is filtered in the pressure Nutsche filter to remove the spent charcoal which is sent for disposal. Clarified solvent liquor is recharged to the general purpose reactor. At this point the metabolite is precipitated by the addition of acid and other solutions. The liquor is then filtered in the pressure Nutsche and in this case the liquor, which is essentially solvent, is sent to the solvent recovery unit whilst the precipitated filtered cake is sent to the next stage for washing.

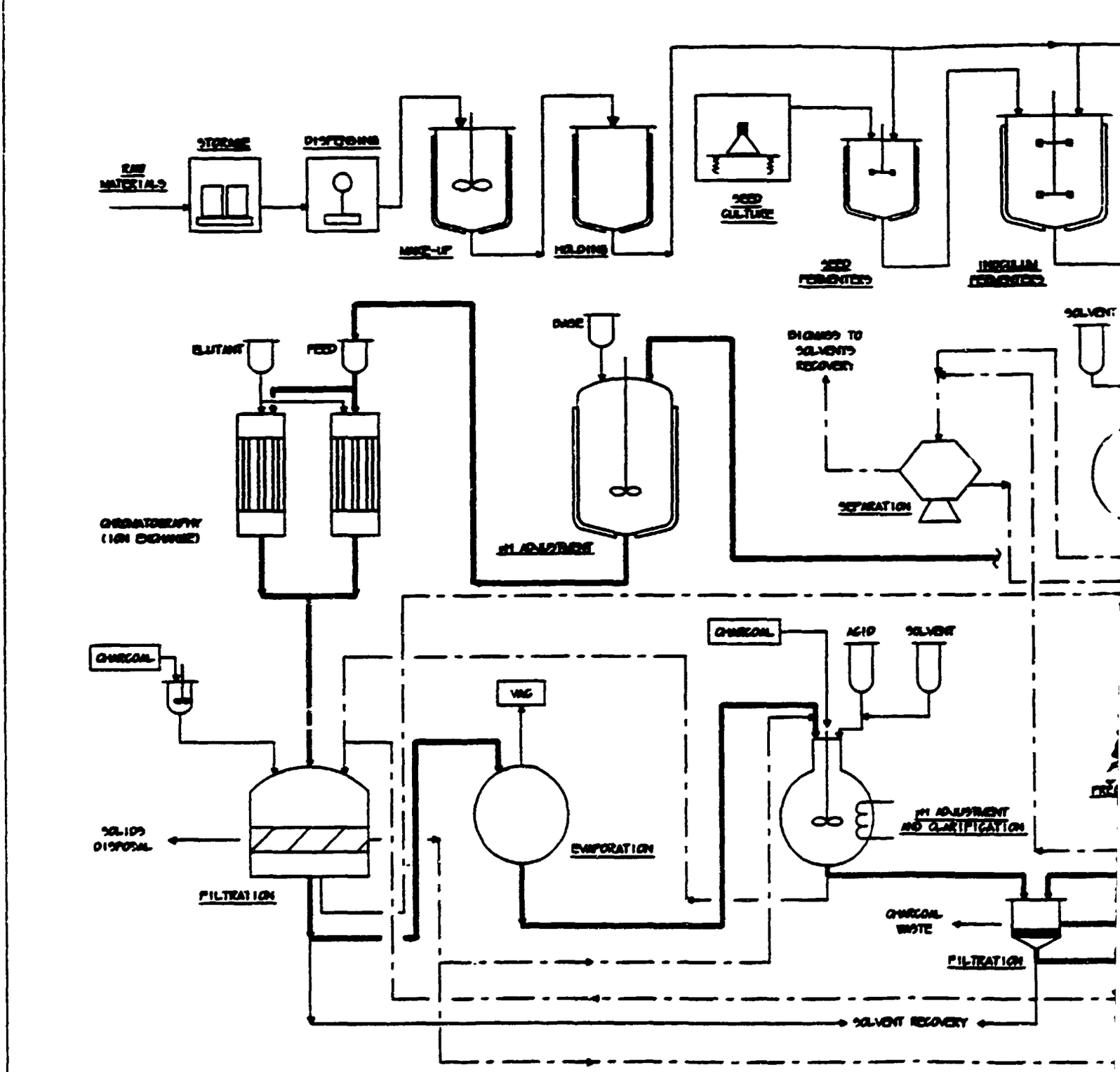
Area 700P (Precipitate Washing)

The precipitate from the pressure Nutsche filter is charged to a general purpose reactor and it is slurried and washed with solvent. The suspended liquor is then returned to the pressure Nutsche filter for recovery of the washed precipitate. This precipitate is then rewashed as before for a further two times in exactly the same way. After the final washing the solvent wet solids are sent to the drying stage. At each stage the solvent liquor is recovered for distillation and reuse.

Area 800P (Drying)

The solvent wet cake is then manually charged into the agitated bed drier in which the precipitate is dried free of the solvent, discharged into product containers and sent to the product store.

A general point may be made here regarding the overall nature of the processes described above. The processes just described are typical of those which GRC Consultants understands Biogal will operate in the early days of the new development facility. Clearly because of the very nature of the unit, many other similar types of processes are anticipated to be operated in the new facility. It is inappropriate to attempt to describe all the various permutations and combinations of processes which may be carried out, but the key to the whole operation is the adaptability, flexibility and reconfigurability of the various individual equipment items and process routes. The processes and equipment schemes described in this section are example processes only and are not meant to imply that these are the ones which will be exclusively operated.



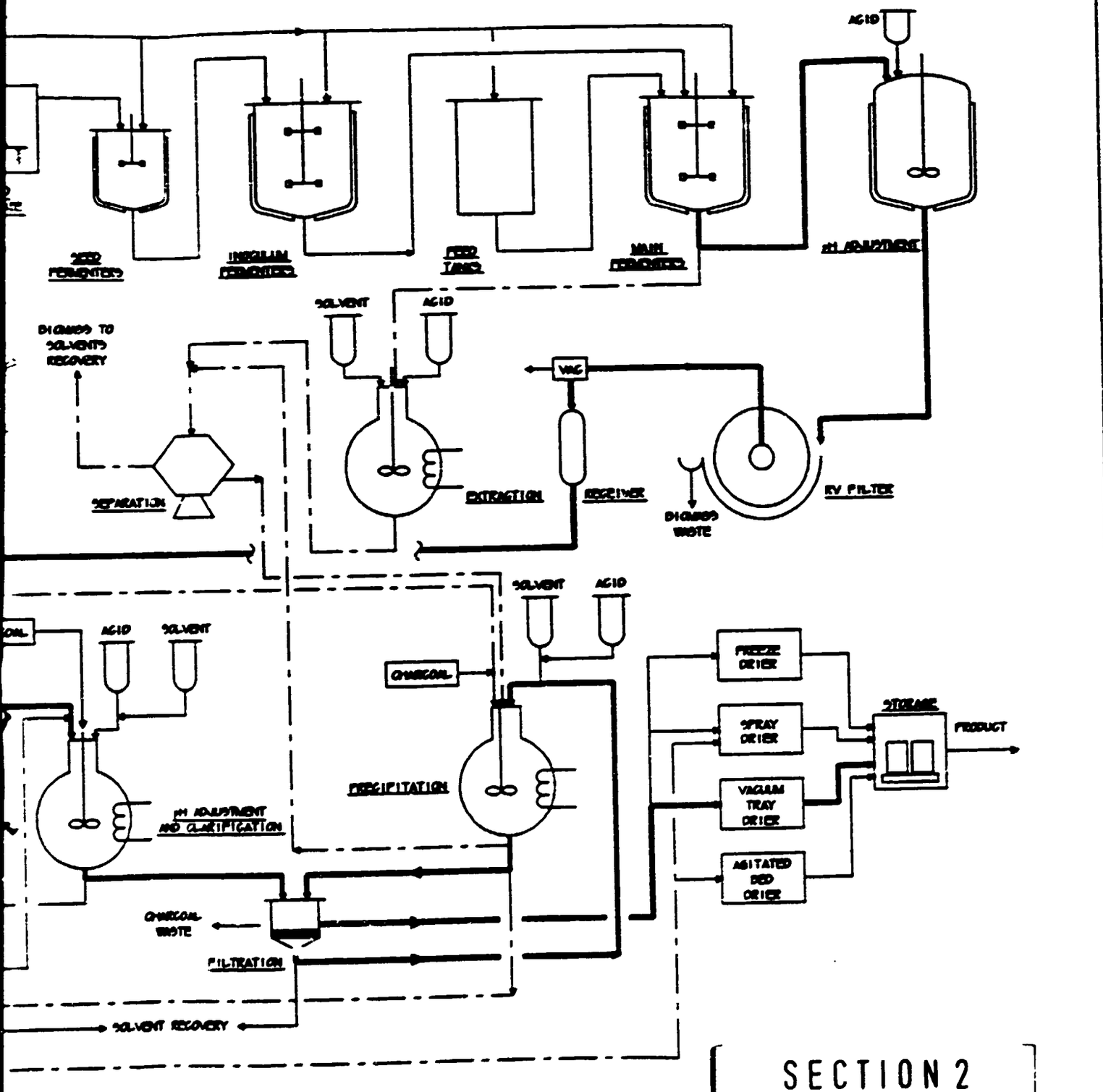
'NEOMYCIN' PROCESSING

'PENICILLIN' PROCESSING

SECTION 1

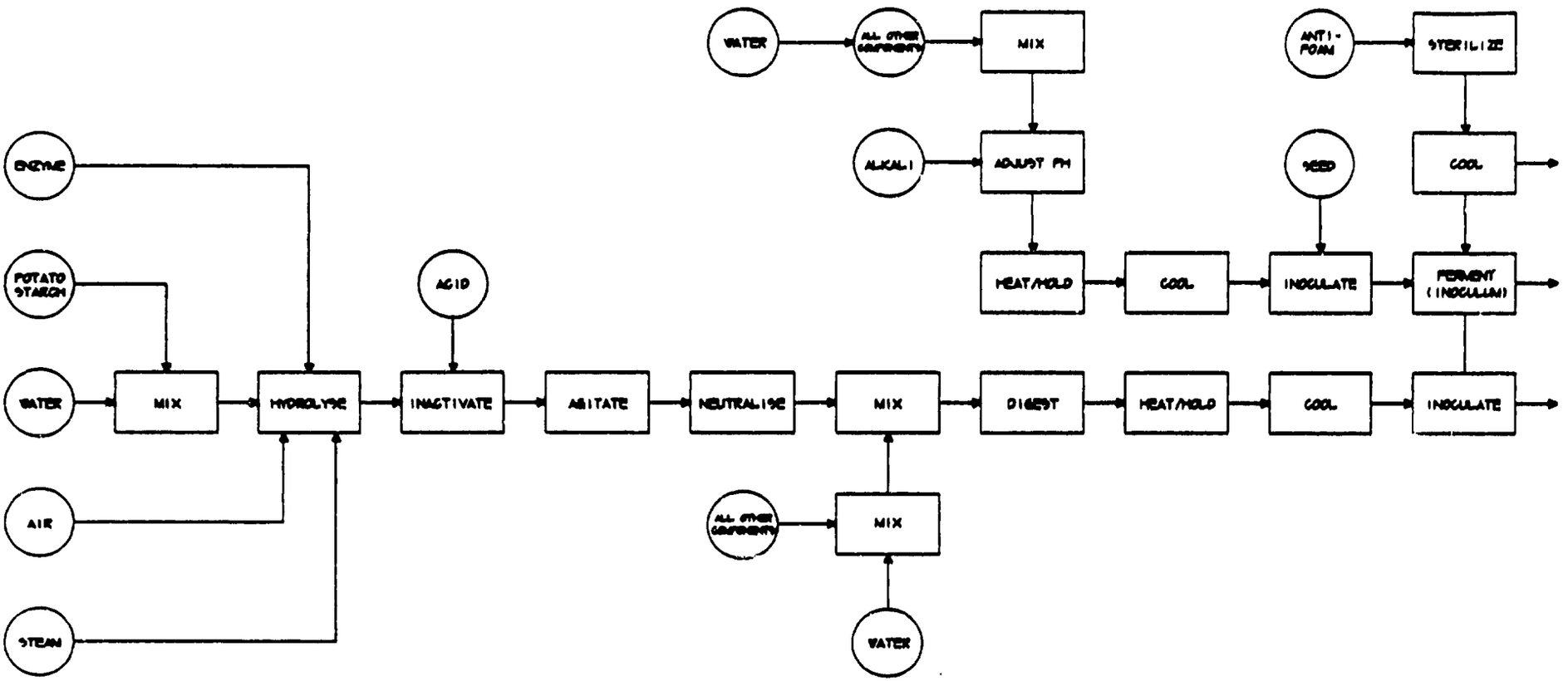
GRC CONSULTANTS

WESTBROOKE HOUSE 78 HIGH STREET
ALTON, HANTS GU34 1EN
TEL: 0420 88547 FAX: 0420 8842



SECTION 2

GRC CONSULTANTS WESTBROOKE HOUSE 78 HIGH STREET ALTON. HANTS GU34 1EN TEL: 0420 88847 FAX: 0420 88427	CLIENT UNIDO PO BOX 300 A-1 400 VIENNA AUSTRIA. FAX 232 96	PROJECT DIOGAL TF/HUN/90/906	DRAWING TITLE PROCESS FLOW SCHEMATIC DRAWING NUMBER 92/004/20 — REV A



GRC CONSULTANTS WESTBROOKE HOUSE 78 HIGH STREET ALTON, HANTS GU34 1EN TEL: 0420 88847 FAX: 0420 88427	CLIENT UNIDO P.O. BOX 300 A-1 400 VIENNA AUSTRIA, FAX 2321 36	PROJECT BIOGAL TF/HUN/90/406	DRAWING TITLE PROCESS BLOCK DIAGRAM (TYPICAL PROCESS) SHEET 1 OF 1
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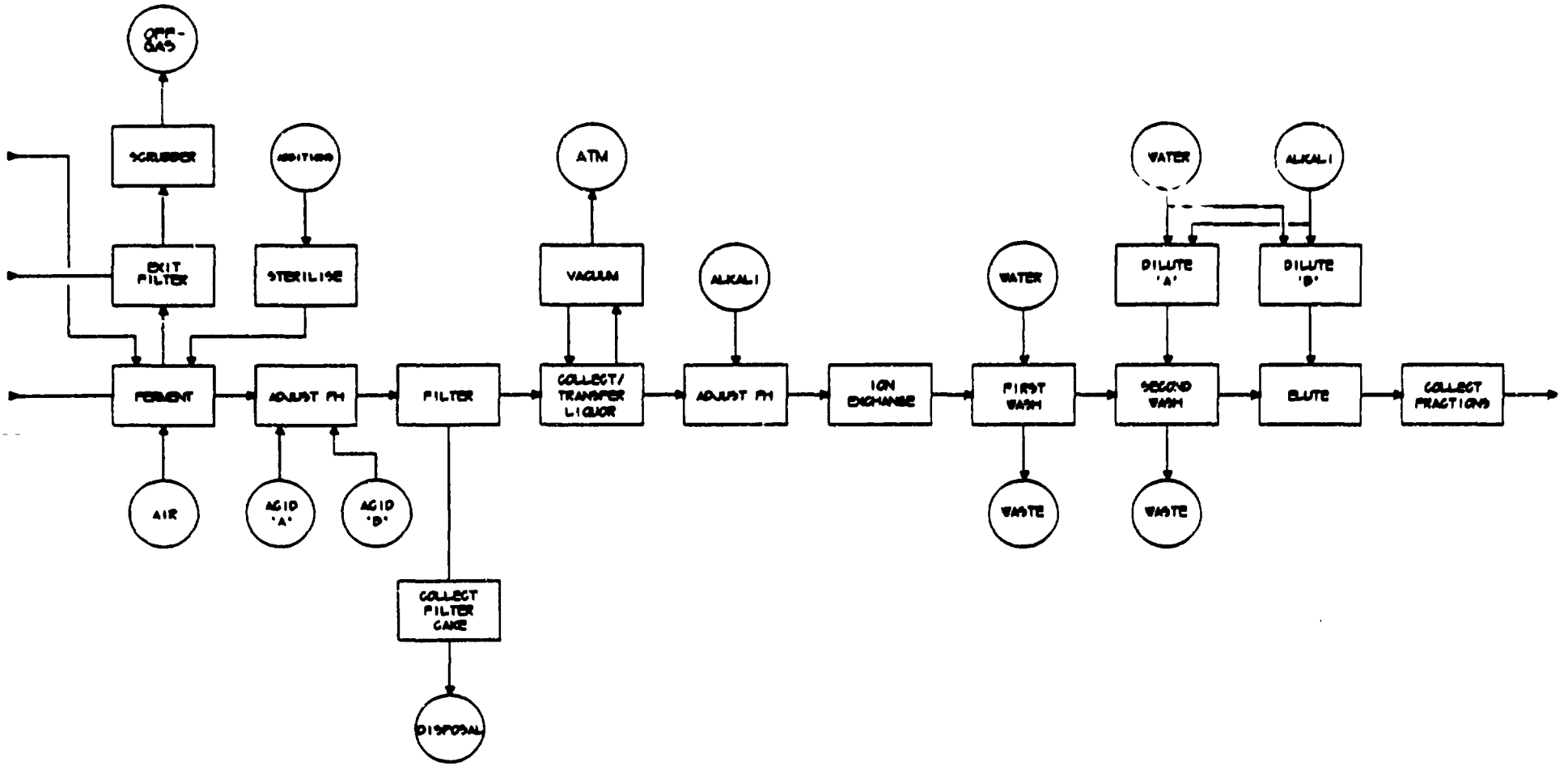
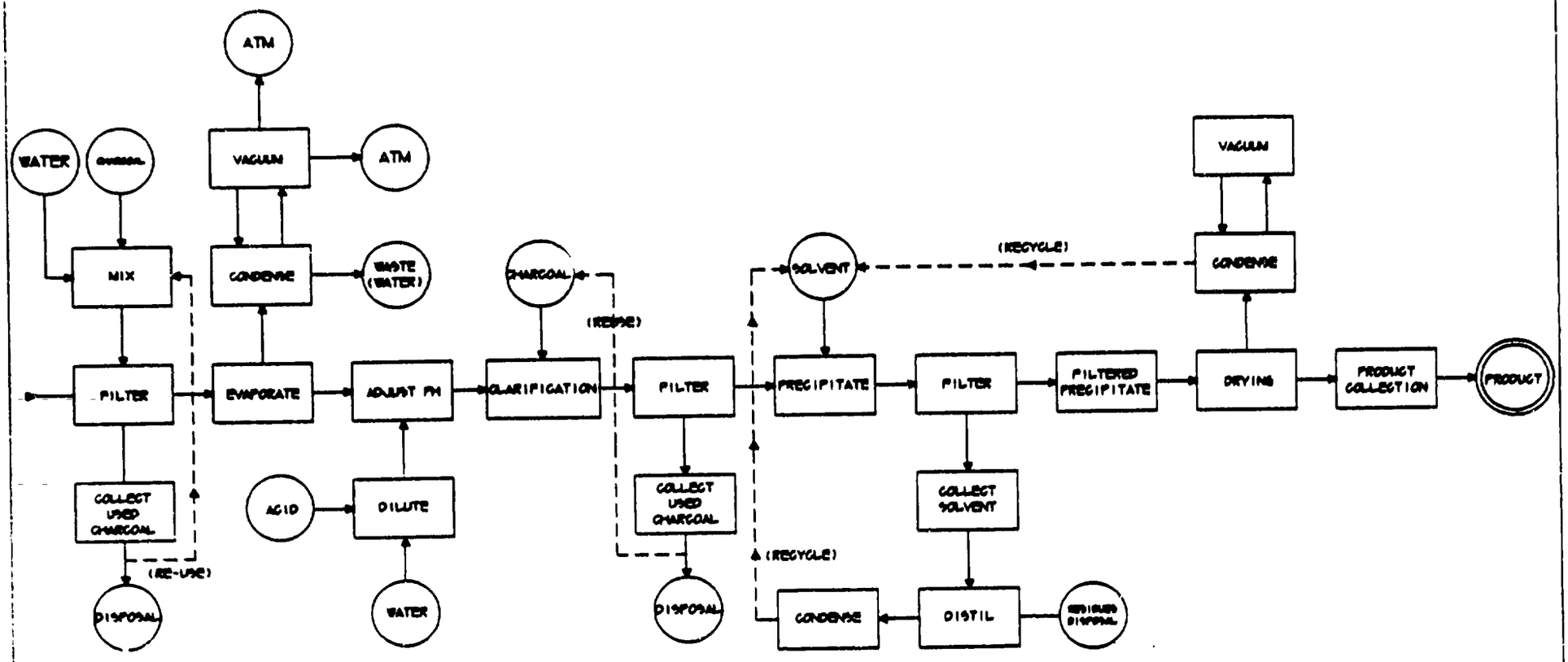
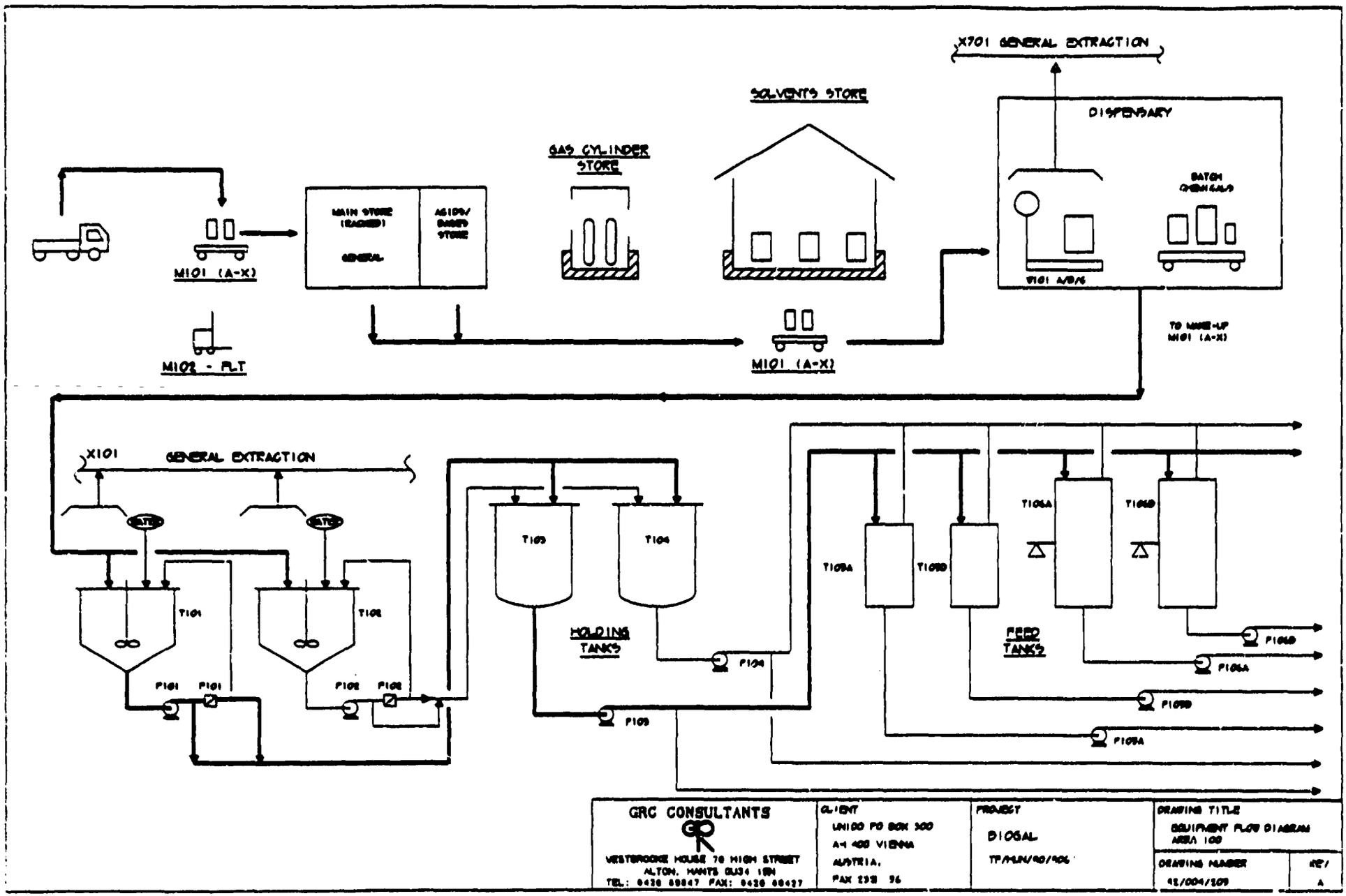
			REV A

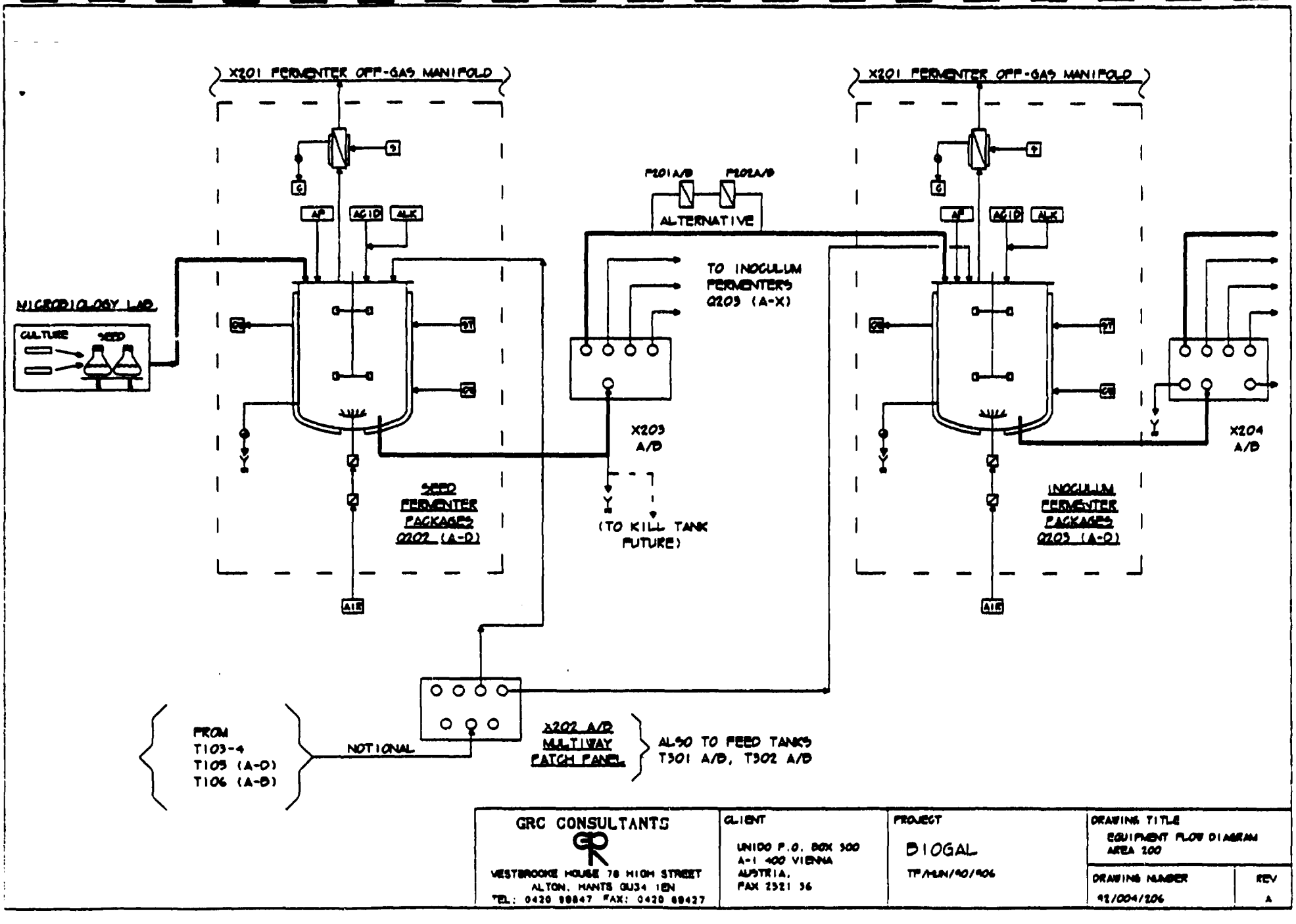


GRC CONSULTANTS WESTBROOKE HOUSE 78 HIGH STREET ALTON, HANTS GU34 1EN TEL: 0420 88847 FAX: 0420 88437	CLIENT UNIDO P.O. BOX 300 A-1 400 VIENNA AUSTRIA. FAX 2321 36	PROJECT BIOGAL TF/MLN/90/906	DRAWING TITLE PROCESS BLOCK DIAGRAM (TYPICAL PROCESS) SHT 1 OF 1 DRAWING NUMBER 42/004/103 REV A

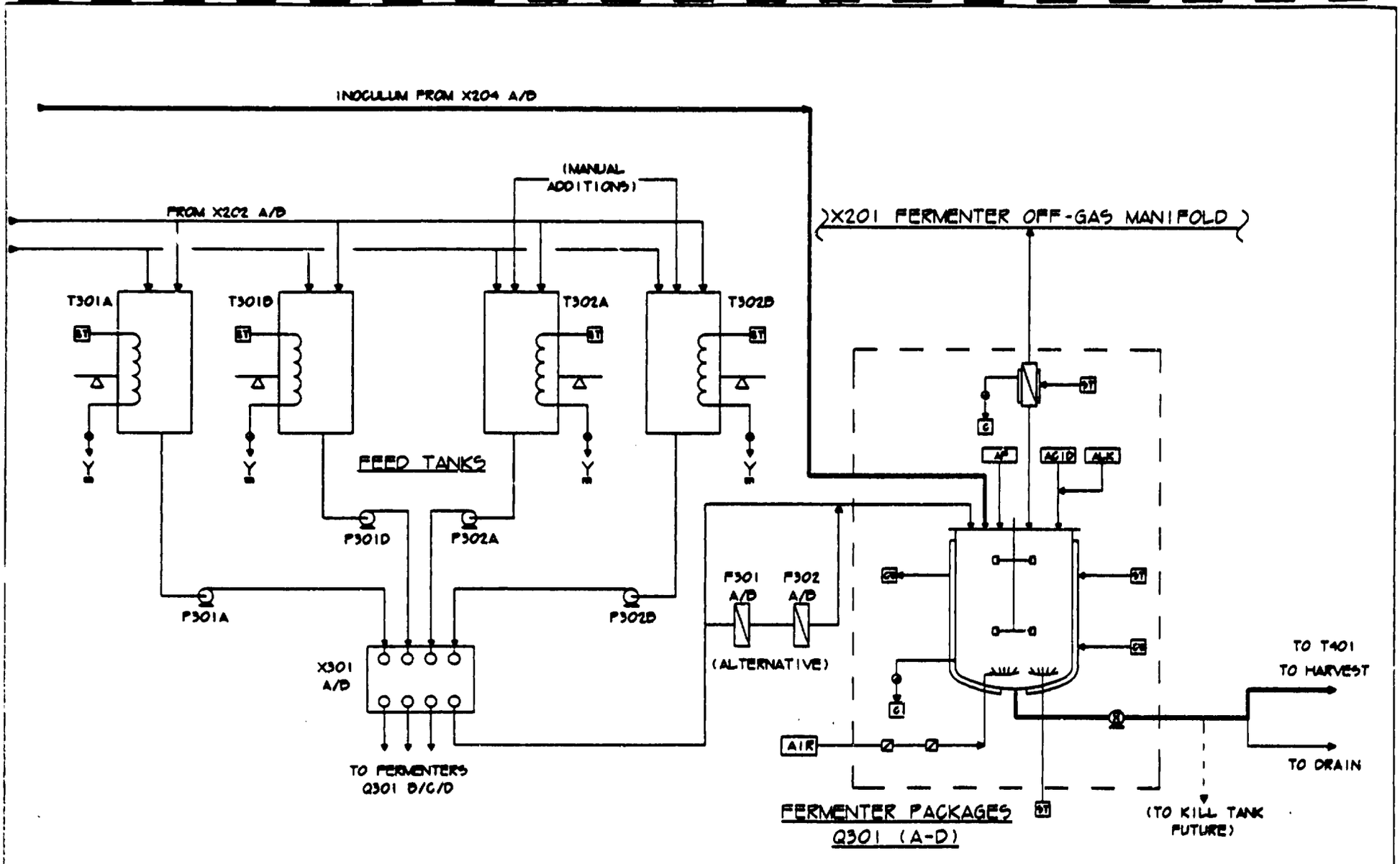


GRC CONSULTANTS WESTBROOKE HOUSE 78 HIGH STREET ALTON, HANTS GU34 1EN TEL: 0420 88847 FAX: 0420 88427	CLIENT UNIDO P.O. BOX 300 A-1 400 VIENNA AUSTRIA, FAX 2321 36	PROJECT BIOGAL TF/MUN/90/906	DRAWING TITLE PROCESS BLOCK DIAGRAM (TYPICAL PROCESS) DRAWING NUMBER 92/004/204 REV A

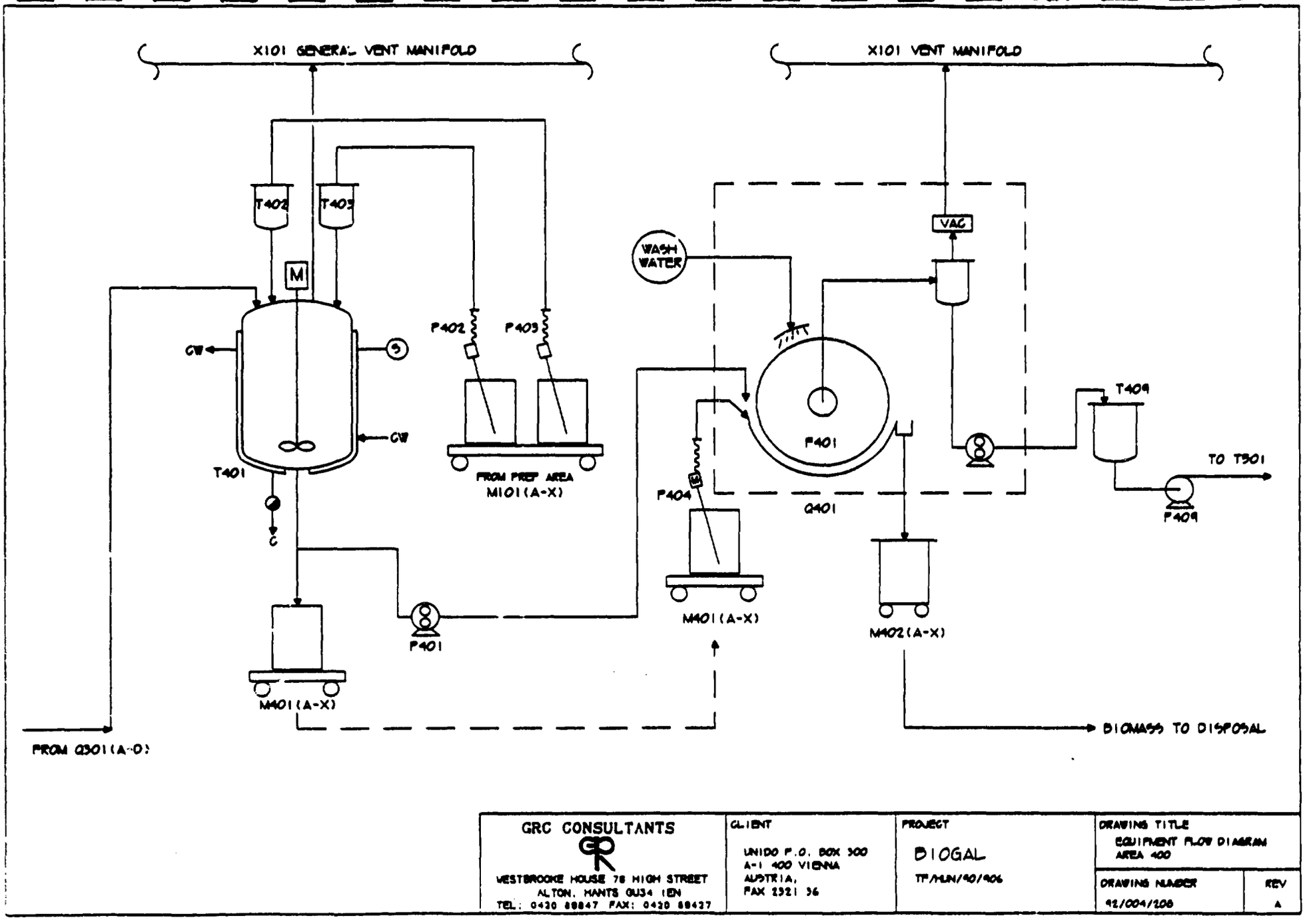

X701 GENERAL EXTRACTION
SOLVENTS STORE
DISPENSARY
GAS CYLINDER STORE
MAIN STORE (RACKED)
GENERAL
ASSOC/ BASED STORE
M101 (A-X)
M102 - FLT
M101 (A-X)
TO MAKE-UP M101 (A-X)
X101 GENERAL EXTRACTION
ATC
ATC
T101
T102
T103
T104
HOLDING TANKS
T105A
T105B
T106A
T106B
FEED TANKS
P101
P101
P102
P102
P104
P103
P106B
P106A
P105B
P105A
GRC CONSULTANTS
VESTERGORE HOUSE 76 HIGH STREET
ALTON, HANTS GU34 1BN
TEL: 0420 88847 FAX: 0420 88437
CLIENT
UNIDO PO BOX 300
A-1400 VIENNA
AUSTRIA.
FAX 232 96
PROJECT
BIOGAL
TP/PLN/90/906
DRAWING TITLE
EQUIPMENT FLOW DIAGRAM
AREA 100
DRAWING NUMBER
92/004/109
REV
A



GRC CONSULTANTS WESTBROOKE HOUSE 78 HIGH STREET ALTON, HANTS GU34 1EN TEL: 0420 88847 FAX: 0420 88427	CLIENT UNIDO P.O. BOX 300 A-1 400 VIENNA AUSTRIA. FAX 2521 36	PROJECT BIOGAL TP/HUN/90/906	DRAWING TITLE EQUIPMENT FLOW DIAGRAM AREA 200 DRAWING NUMBER 92/004/206 REV A



GRC CONSULTANTS WESTBROOKE HOUSE 78 HIGH STREET ALTON. HANTS GU34 1EN TEL: 0420 88847 FAX: 0420 89427	CLIENT UNIDO P.O. BOX 300 A-1 400 VIENNA AUSTRIA. FAX 2321 36	PROJECT BIOGAL TP/MLN/90/906	DRAWING TITLE EQUIPMENT FLOW DIAGRAM AREA 300 DRAWING NUMBER 92/004/107 REV A



GRC CONSULTANTS WESTBROOKE HOUSE 78 HIGH STREET ALTON, HANTS GU34 1EN TEL: 0420 88847 FAX: 0420 88427	CLIENT UNIDO P.O. BOX 300 A-1 400 VIENNA AUSTRIA, FAX 2321 36	PROJECT BIOGAL TF/HUN/90/906	DRAWING TITLE EQUIPMENT FLOW DIAGRAM AREA 400
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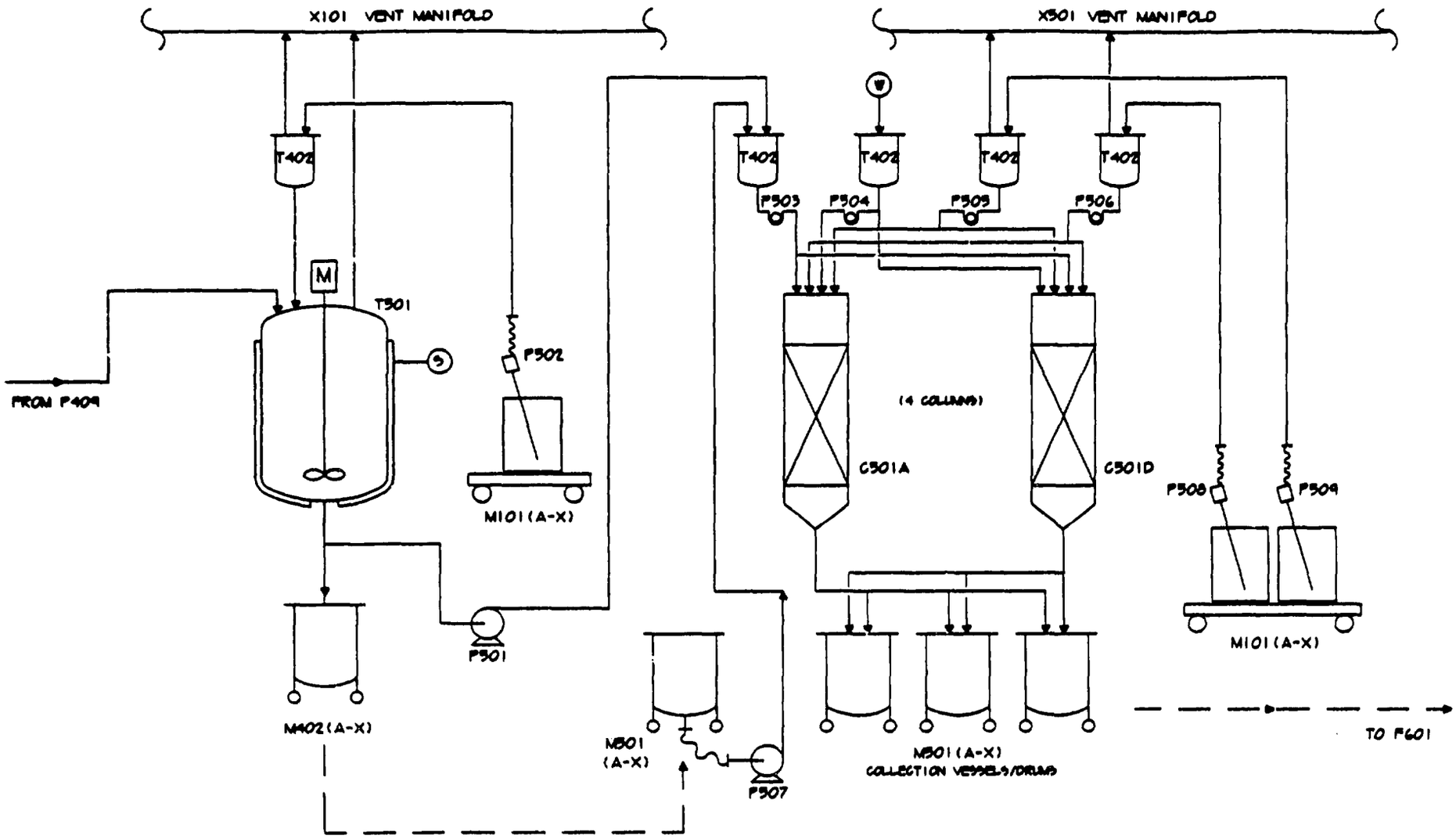
			REV A



GRC CONSULTANTS WESTBROOKE HOUSE 78 HIGH STREET ALTON, HANTS GU34 1EN TEL: 0420 88847 FAX: 0420 88427	CLIENT UNIDO P.O. BOX 300 A-1 400 VIENNA AUSTRIA, FAX 2321 36	PROJECT BIOGAL TF/HUN/90/906	DRAWING TITLE EQUIPMENT FLOW DIAGRAM AREA 500
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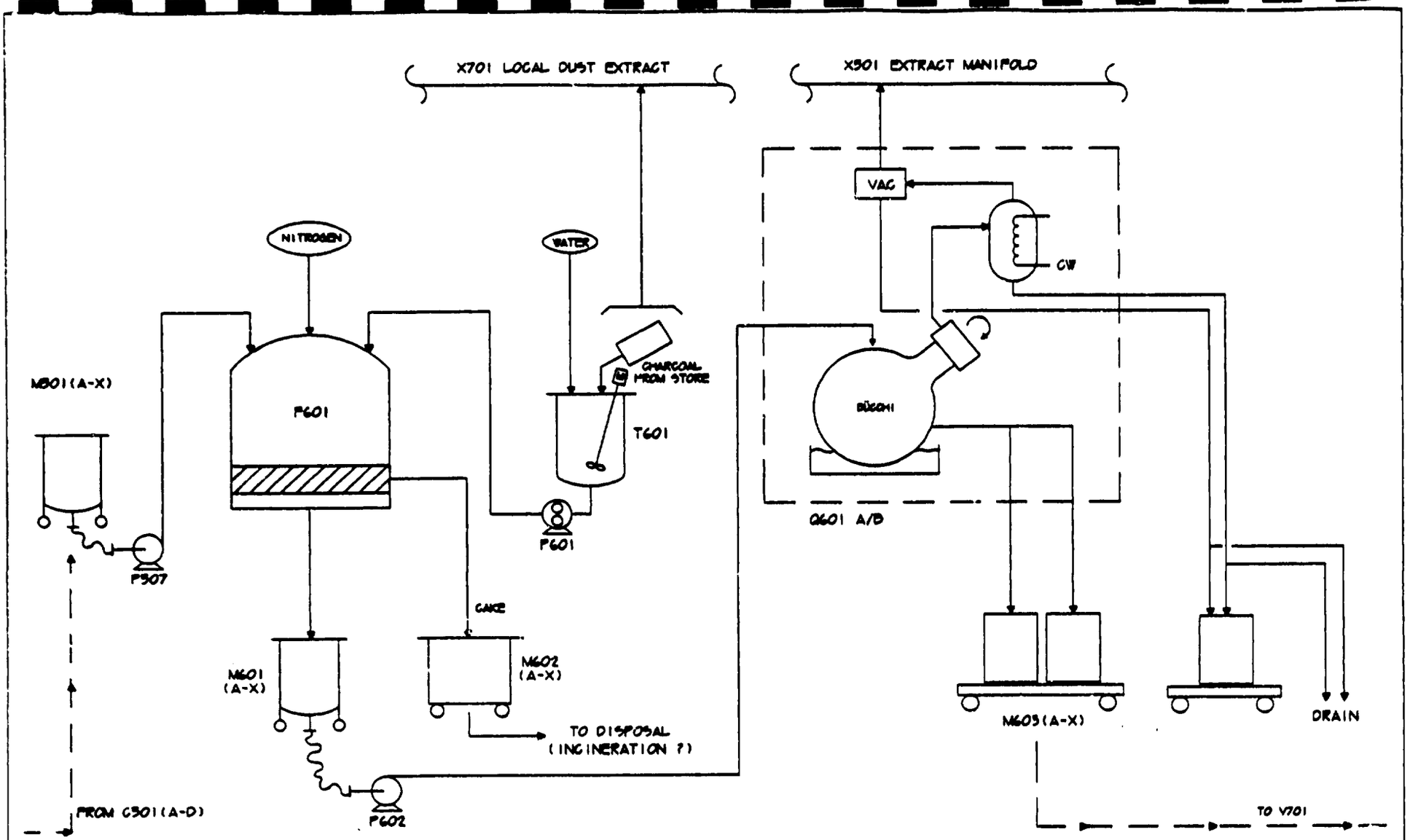

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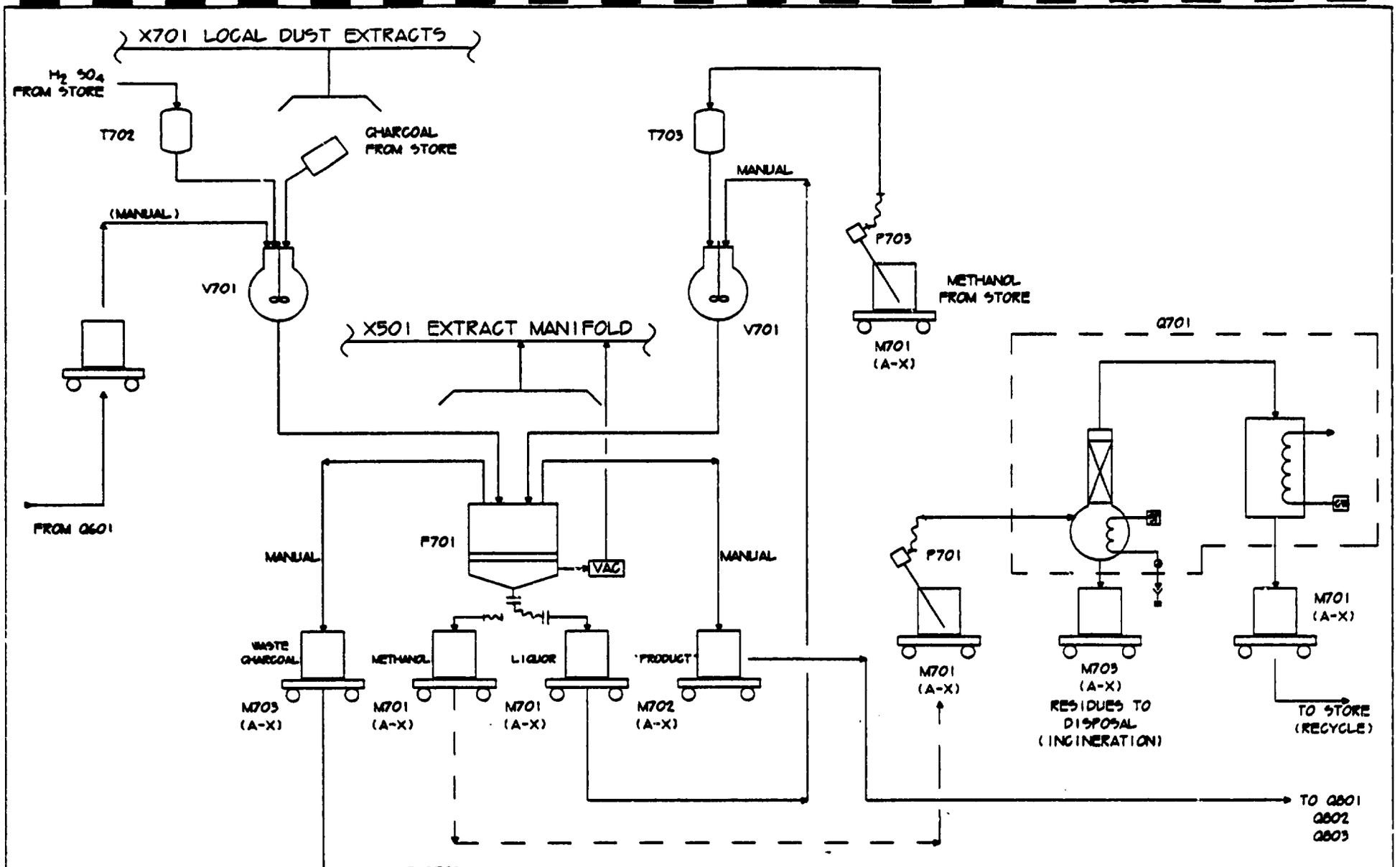
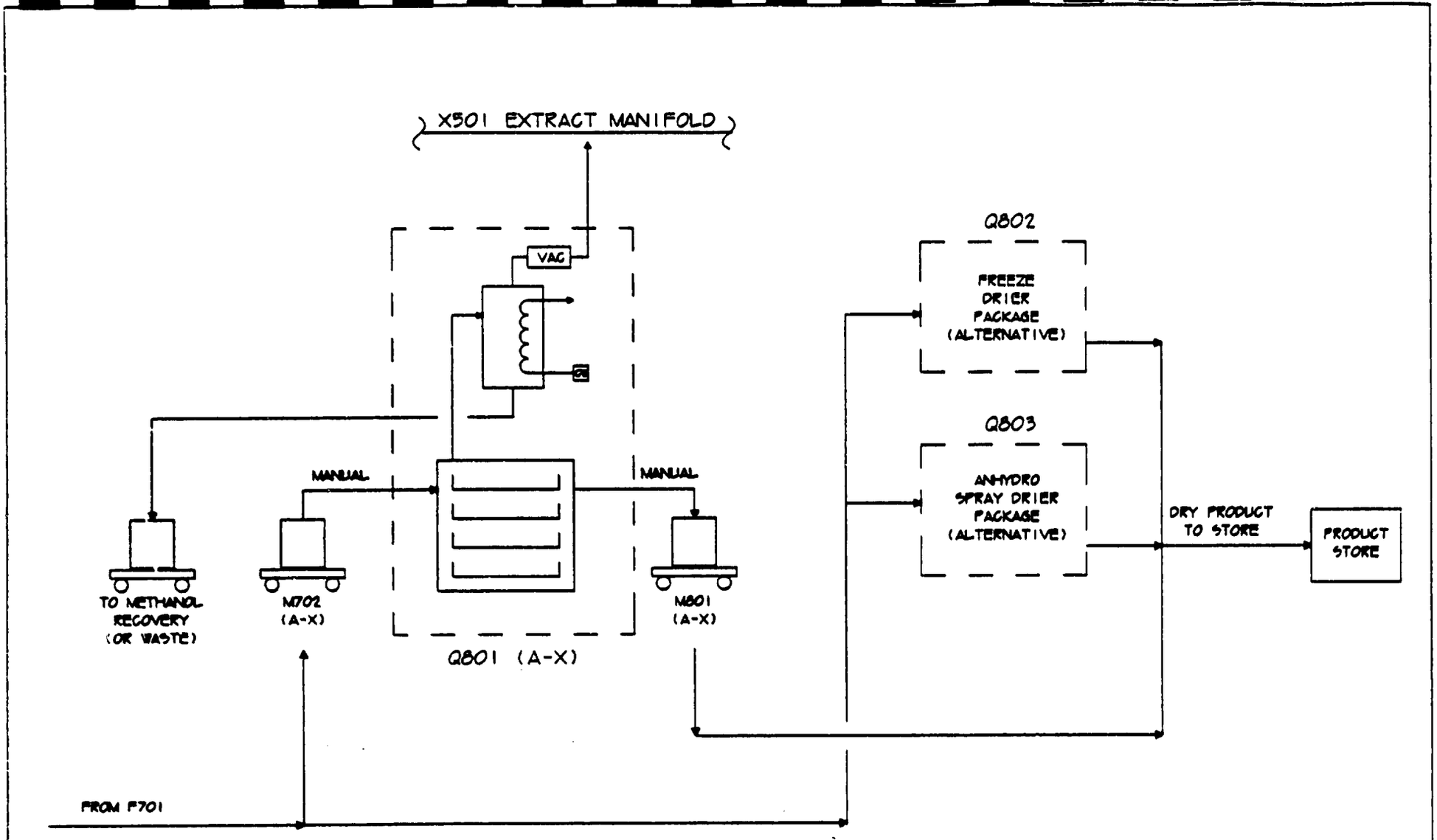
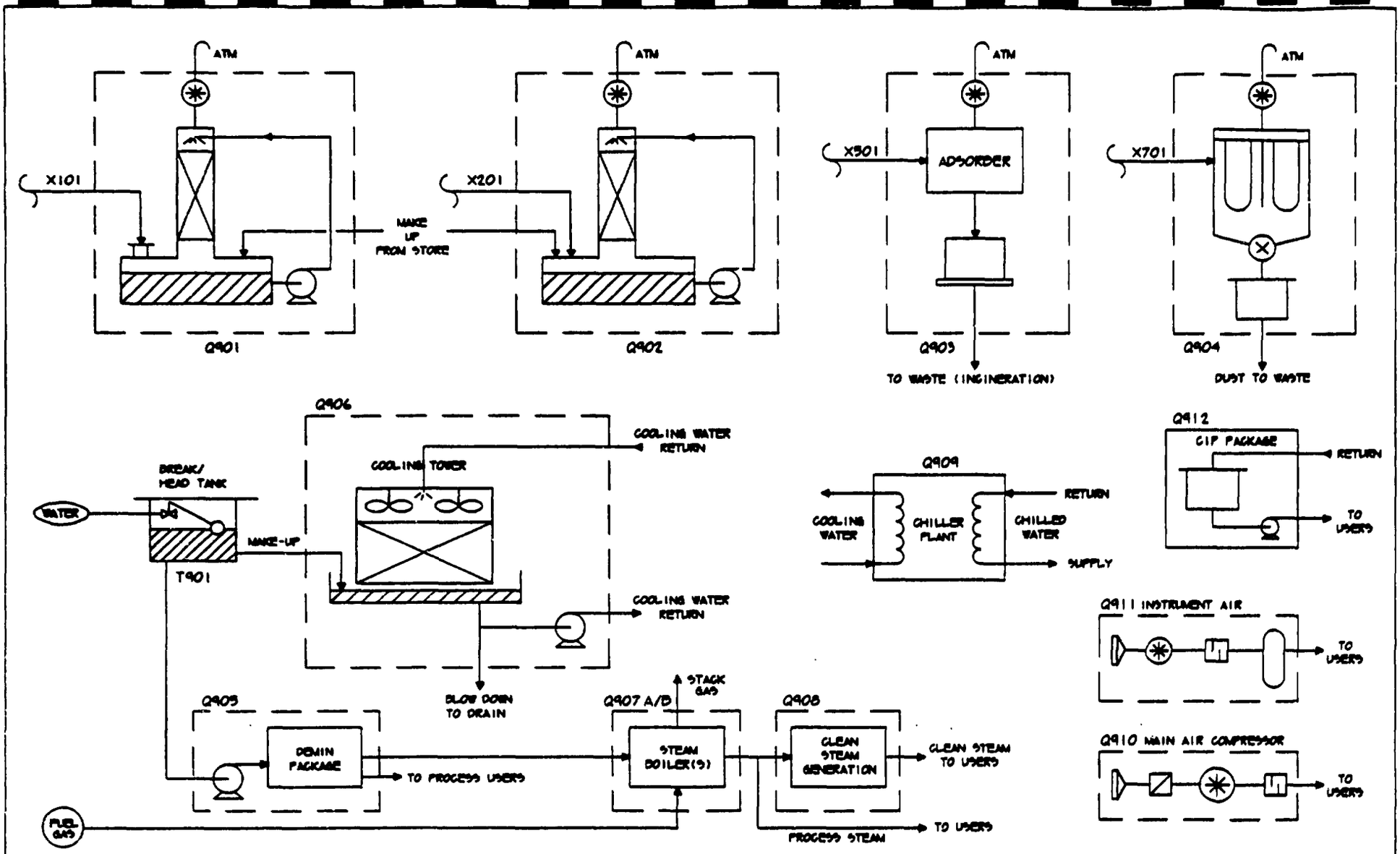


GRC CONSULTANTS WESTBROOKE HOUSE 78 HIGH STREET ALTON, HANTS GU34 1EN TEL: 0420 88847 FAX: 0420 88427	CLIENT UNIDO P.O. BOX 300 A-1 400 VIENNA AUSTRIA. FAX 2921 56	PROJECT BIOGAL TF/HUN/90/906	DRAWING TITLE EQUIPMENT FLOW DIAGRAM AREA 700 DRAWING NUMBER 92/004/211 REV A



GRC CONSULTANTS VESTBROOKE HOUSE 78 HIGH STREET ALTON, HANTS GU34 1EN TEL: 0420 88847 FAX: 0420 88427	CLIENT UNIDO P.O. BOX 300 A-1 400 VIENNA AUSTRIA, FAX 2321 56	PROJECT BIOGAL TF/MLN/90/906	DRAWING TITLE EQUIPMENT FLOW DIAGRAM AREA 800 DRAWING NUMBER: 92/004/212 REV: A



GRC CONSULTANTS WESTBROOKE HOUSE 78 HIGH STREET ALTON. HANTS GU34 1EN TEL: 0420 88847 FAX: 0420 88427	CLIENT UNIDO P.O. BOX 300 A-1 400 VIENNA AUSTRIA. FAX :1321 56	PROJECT BIOGAL TP/MUN/90/906	DRAWING TITLE EQUIPMENT FLOW DIAGRAM AREA 900
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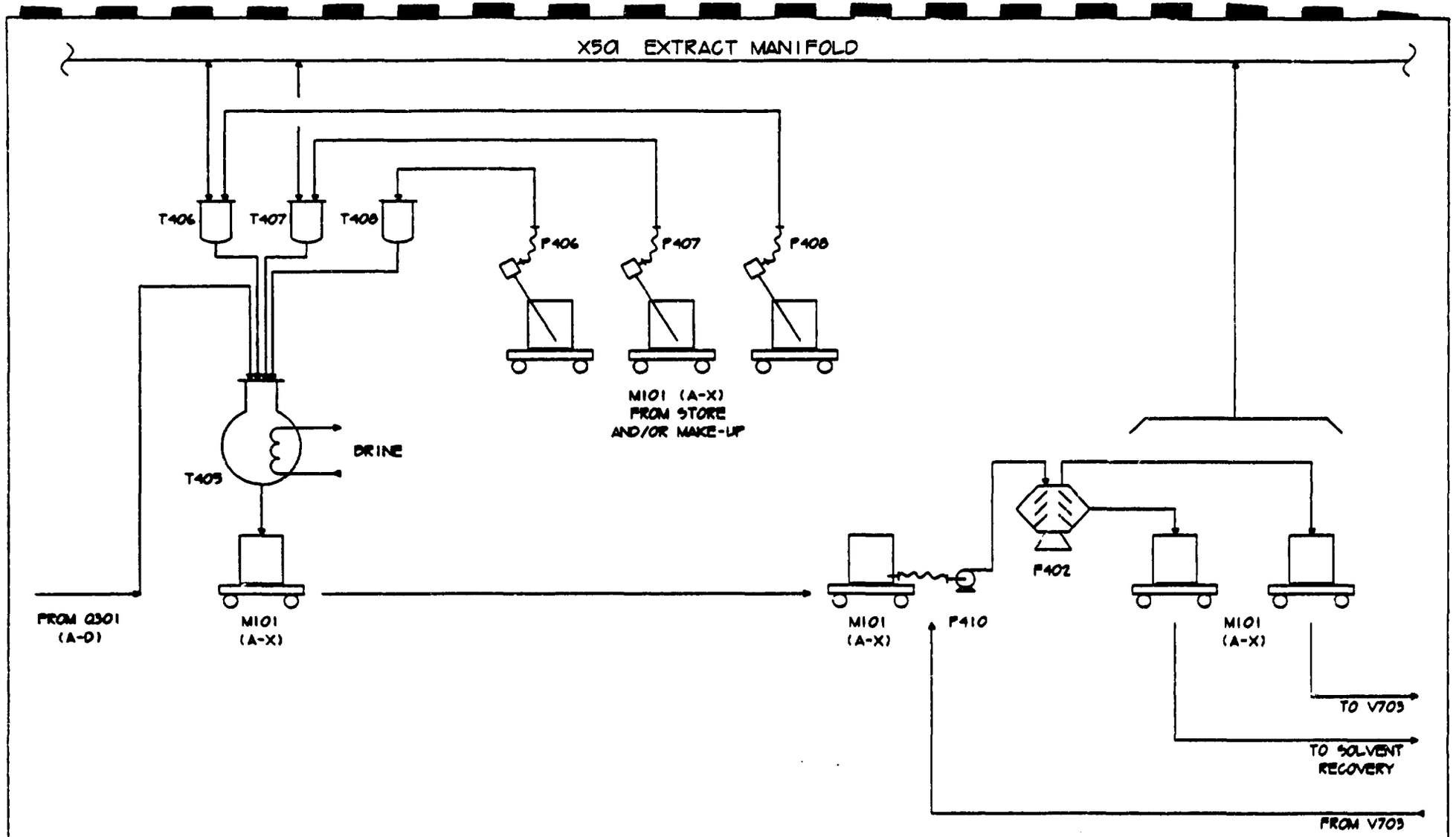
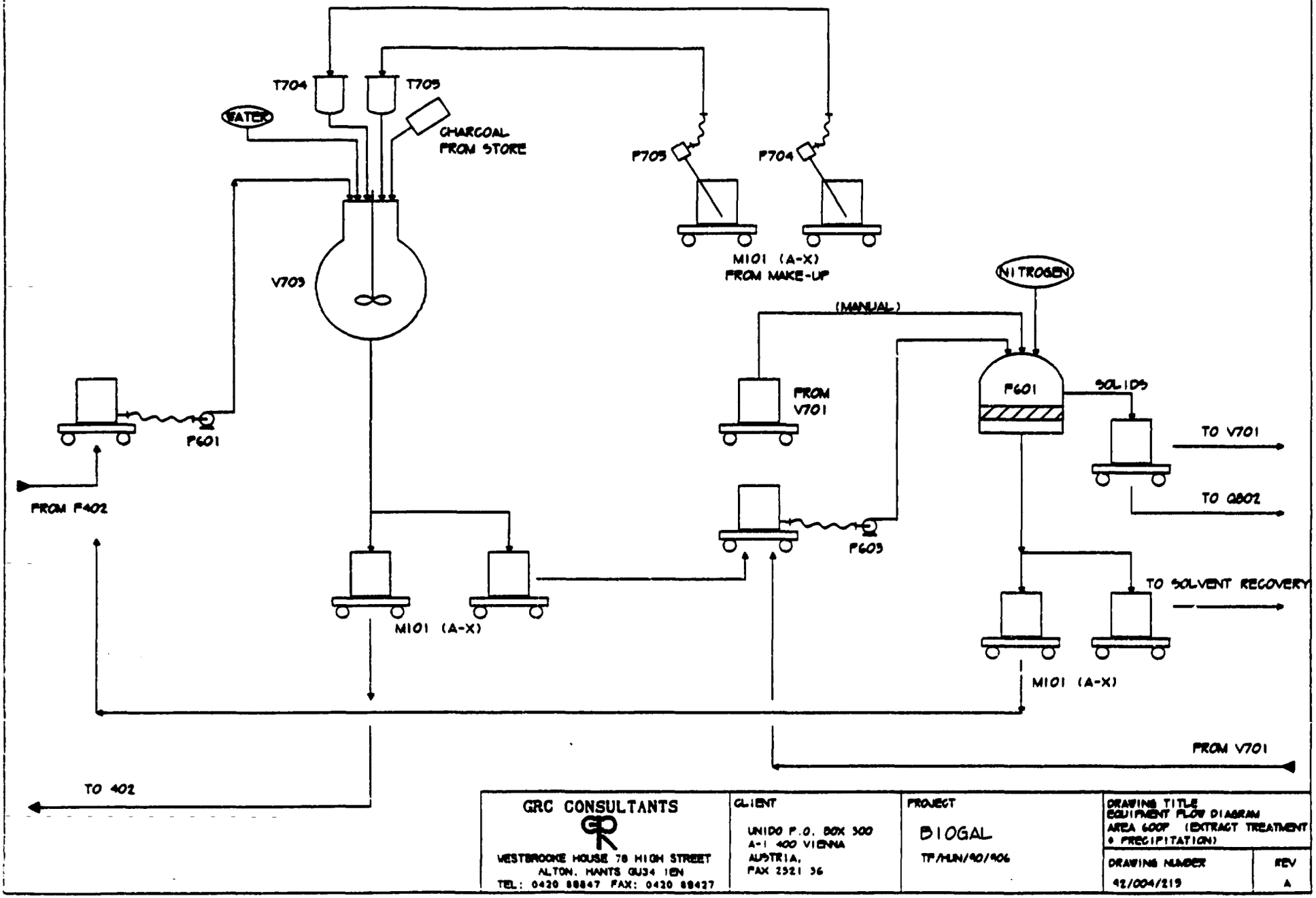
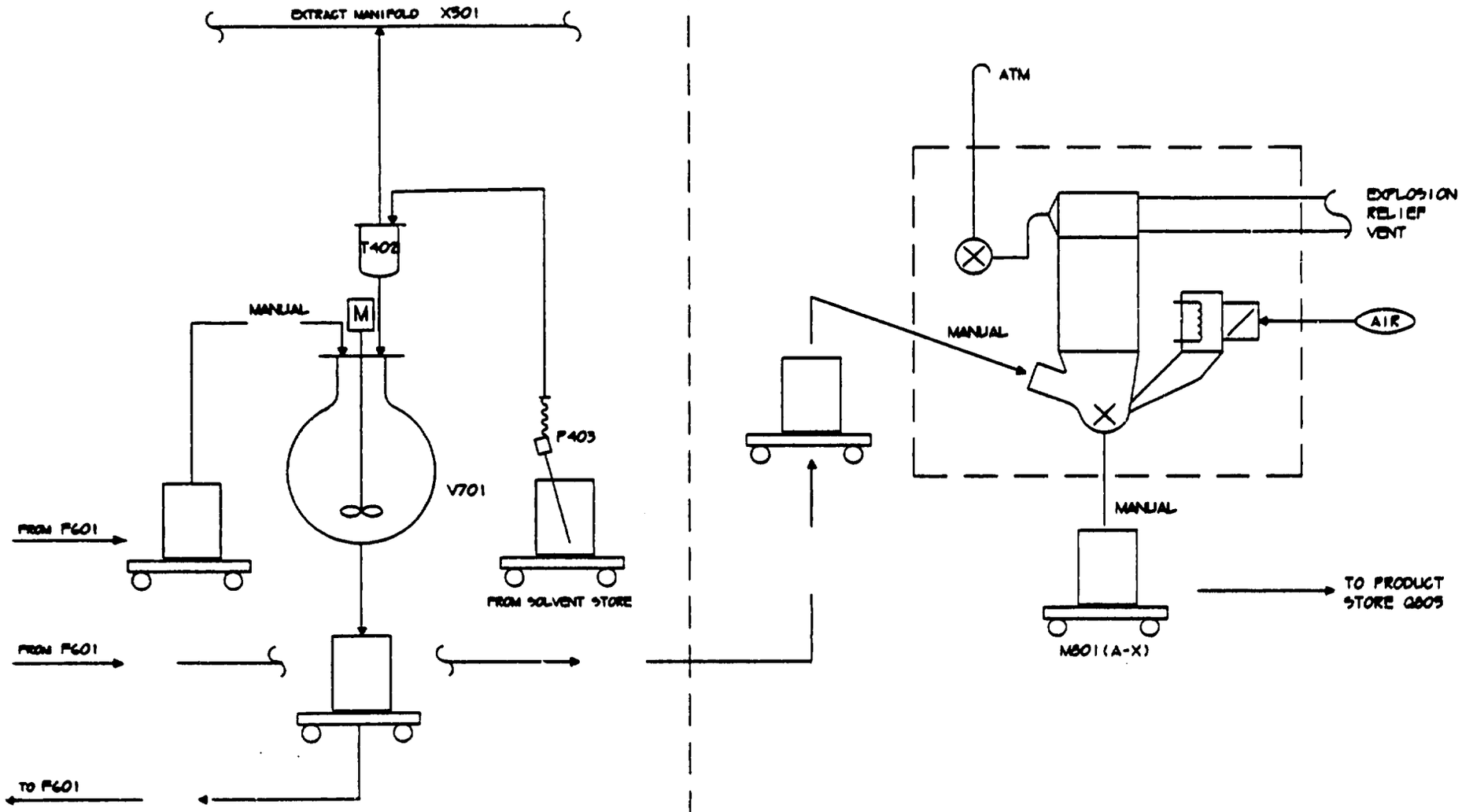


GRC CONSULTANTS WESTBROOKE HOUSE 78 HIGH STREET ALTON, HANTS GU34 1EN TEL: 0420 88847 FAX: 0420 88427	CLIENT UNIDO P.O. BOX 300 A-1 400 VIENNA AUSTRIA. FAX 2321 36	PROJECT BIOGAL TF/HUN/90/906	DRAWING TITLE EQUIPMENT FLOW DIAGRAM AREA 400P DRAWING NUMBER: 92/004/214 REV: A



GRC CONSULTANTS WESTBROOKE HOUSE 78 HIGH STREET ALTON, HANTS GU34 1EN TEL: 0420 88847 FAX: 0420 89427	CLIENT UNIDO P.O. BOX 300 A-1 400 VIENNA AUSTRIA, FAX 2321 36	PROJECT BIOGAL TF/HUN/90/906	DRAWING TITLE EQUIPMENT FLOW DIAGRAM AREA 600F (EXTRACT TREATMENT & PRECIPITATION) DRAWING NUMBER: 92/004/219 REV: A



AREA 700P (PRECIPITATE WASHING)

AREA 1100P (DOZYING)

GRC CONSULTANTS WESTBROOKE HOUSE 78 HIGH STREET ALTON, HANTS GU34 1EN TEL: 0420 88847 FAX: 0420 88427	CLIENT UNIDO P.O. BOX 300 A-1 400 VIENNA AUSTRIA. FAX 2321 36	PROJECT BIOGAL TF/MLN/90/906	DRAWING TITLE EQUIPMENT FLOW DIAGRAM AREAS 700P & 800P DRAWING NUMBER 92/004/216 REV A

SECTION 6

FACILITIES DESCRIPTION

6 FACILITIES DESCRIPTION

6.1 OVERVIEW OF FACILITY

The facility is located on a greenfield site with space for expansion. The main offices and plant areas are located inside a central main building which is built on two levels. Ancillary buildings including service generation and storage facilities are located close by.

There is a secure site entrance and exit guarded by a manned gatehouse as shown in the site layout 92/004/106. All personnel and delivery vehicles entering the site must be checked by gatehouse personnel.

Cars are parked outside the secure plant area in a 980m^2 car park overlooked by the gatehouse which is suitable for parking 37 staff and visitors cars.

An expansion zone for the main building is identified on the site layout and access to any future connecting expanded part of the facility can be achieved via the main process corridor (room 526) for new process areas, or by conversion of the photocopy room (room 117) for new office areas, see Ground Floor Room Layout drg. 92/004/101. The first floor room layout is detailed in drg. 92/004/103.

All corridors are 2m wide which gives good access for process trolleys.

Office areas, as shown in building section drg. 92/004/102, have an internal room height of 2.5m, fermentation and process areas have a room height of 3.5m. HVAC and other services are located in the service void provided above these rooms.

All undeveloped parts of the site are attractively landscaped with particular attention paid to the landscaped area in front of the main building which is clearly visible from the public road.

The site is designed to be self contained with offices provided to hold administrative staff. A full range of process services are generated in the service building on site and a range of goods and waste storage facilities are available.

The facility is designed to comply with the appropriate EC and USA GMP regulations for medicinal chemical production. However in order to operate to these standards installed equipment must be of a suitable high standard.

It is understood that in the future the facility may need to handle Group II Classification 2 (ref 3) genetically modified organisms. The facility is designed so that a specified contained area may be modified to handle this level of containment without substantial structural modifications. The contained area part of this section of the report describes the contained area as it will operate if installed in the future.

The facility is designed to operate in compliance with GMP or containment regulations.

The contained area will incorporate facilities for storage, fermentation and primary separation of contained organisms. Process materials leaving the contained area will be deactivated before entering any other part of site.

An analytical laboratory is located on the first floor which is used for process material analysis work and small scale process development work utilising solvent handling extracted cabinets.

A suite of microbiology rooms contains facilities for the storage and growth of production organisms to the shake flask stage.

The facility is split for the purposes of this section of the report into five areas: office, downstream processing, contained, service and stores and general laboratory areas. Note that these areas and the numbering system below are not intended to tie in with the numbering system used in Section 5, Process Description.

The positions of these areas are given in the area classification drgs 92/004/104 and 92/004/105.

The rooms are numbered on the basis of these areas as below:

Prefix	Area	Floor Level
100	Office	Ground
200	Office	First
300	Contained	Ground
400	Contained	First
500	Downstream Processing	Ground
600	General Laboratory	First
700	Services and Stores	Ground

Note that if the room number begins with an odd digit it is located on the ground floor and if it begins with an even digit it is located on the first floor.

The room numbers and room locations are given in drgs. 92/004/101 and 92/004/103.

The pilot plant has a variety of types of equipment covering many aspects of biochemical production and often uses fermentation to produce process material.

The two fermentation halls contain identical equipment to ensure consistency of development data. Each hall contains two fermentation trains containing fermenters of 60l, 300l and 1600l total capacity. The fermenters are arranged to ensure flexibility of operation with particular emphasis on flexibility of in-process feeding configurations.

The downstream processing section contains a range of pilot scale equipment allowing several options for a particular unit operation. For instance a solid liquid separation step may be achieved by using one of a number of filters and centrifuges.

A significant part of the downstream processing section is designed to handle solvent and explosive dusts.

Equipment location in general has been identified in terms of unit operations, for example, a pressure filter is located in the filter room. The general flow of materials through the processing area begins with raw materials entering the plant via the goods in store, on the left of the main building, and products emerging via the goods out, on the right of the main building. Hence an overall materials flow of left to right is achieved.

A description of each area and each room in the facility is given below and is referenced to a layout sketch where appropriate.

6.2 OFFICE AREA

The office area located on the ground and first floors accommodates the administrative staff for the facility to the level of general manager. Communal write-up facilities are provided for junior staff and a process analysis room is provided for computational analysis of process data.

Visitors enter the facility via the reception (room 102). Staff may bypass the reception via a lockable door leading directly into the stairs lobby (room 106).

A mess room is provided which is shared by all the staff at break and mealtimes.

A first aid room, including a sick bed, is provided for the use of all staff. This room is also used as an examination room by the visiting consulting doctor while performing regular personnel health checks.

101 Entrance Lobby

This lobby forms a weather break between the outside and reception and incorporates doormats for wiping heavily soiled shoes.

The door from the lobby leads directly past the reception desk.

102 Reception

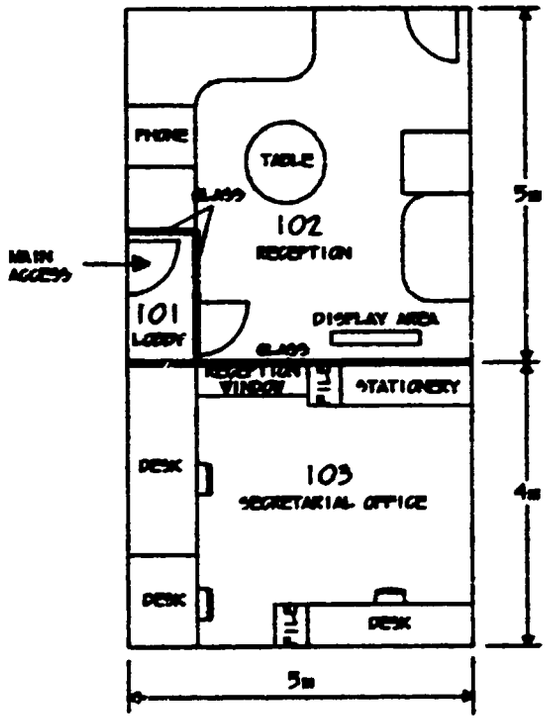
This is the main reception area for the whole facility and is overseen by the secretarial staff located in the adjacent area and linked by a reception window.

The reception area includes a public area which has a moderate amount of occasional seating, a magazine table and a telephone.

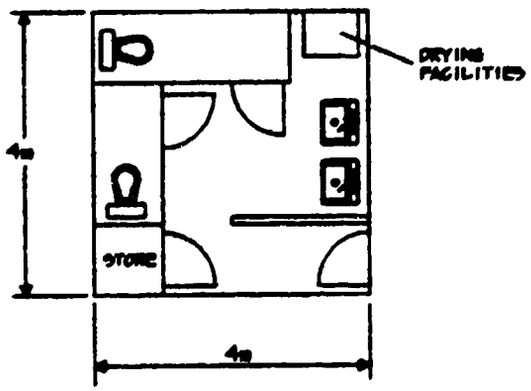
Since this is the main public access to the facility it is finished to a relatively high specification commensurate with the image of the overall facility as a pharmaceutical development unit.

SKETCH No 92/004/140D

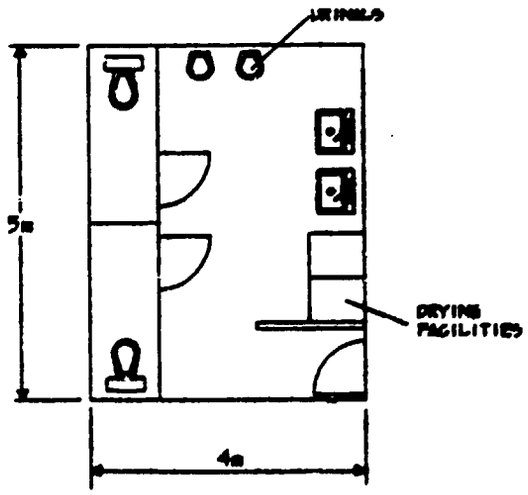
ROOM 101 LOBBY
ROOM 102 RECEPTION
ROOM 103 SECRETARIAL OFFICE



104 FEMALE OFFICE AND LABORATORY TOILET



105 MALE OFFICE AND LABORATORY TOILET



Note: As shown on the room layout, drg. 92/004/101, the main staff access to the facility is via a corridor adjacent to the reception area but with its own secure door operated on a key card or similar system. This corridor has a large window area in it to enable staff movements to be viewed from the secretarial/reception area for security purposes.

103 Secretarial Office

Two secretaries share this office and the secretarial duties for the facility. One of these secretaries is also responsible for reception duties.

The secretarial office is substantially glass fronted from desk level to give a full security view over the entrance lobby, the reception area and the staff entrance lobby. The only exit from the reception area is via a secure door remotely operated from the secretarial office or during out of hours by a key card system.

This office accommodates the fax machine, stationery store and control of the public address system if used.

104 Female Office and Laboratory Toilet

This toilet facility is located on the first floor and will be accessed by female office and laboratory staff. Laboratory staff as seen in drg. 92/004/101 must change out of their laboratory wear in the first floor change rooms before entering the office area corridor leading to the toilets.

Based on the staffing levels detailed in Section 4 and assuming a 50/50 female/male distribution this toilet facility has been sized nominally to handle 13 staff.

This female toilet facility is equipped with two WCs and washhand basin and appropriate drying facilities. It also contains a WC store for toilet supplies and WC cleaning materials for both the female and male toilet facilities.

This facility is equipped to a standard modern level complete with appropriate ventilation, etc.

105 Male Office and Laboratory Toilet

This facility is adjacent to the female office and laboratory toilet (room 104). It is finished to the same standard and accessed by the office and laboratory staff in the same way. It has been generously sized to handle a nominal 13 staff.

The facility is equipped with two WCs, two urinals, and two washhand basins with appropriate drying facilities.

Cleaning materials and disposable goods for this facility are stored in the female facility adjacent (room 104).

106 Stairs and Lobby

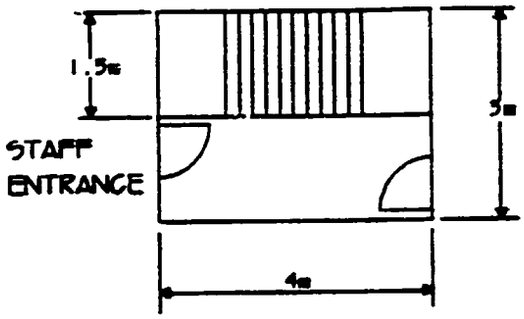
This lobby is accessed by staff directly from the outside via a key card system on the external door. The receptionist overlooks activities via glass panelling between this lobby and the reception area.

107 Technology and Engineering Office

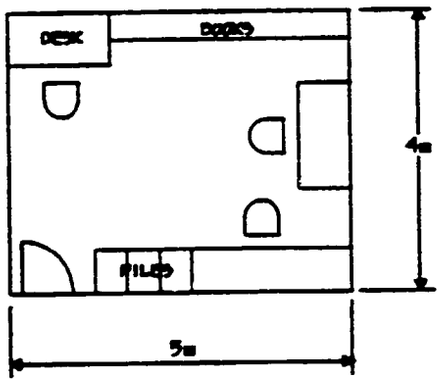
This office is shared by the technology section head and two engineers. One of the engineers also has responsibility for the engineering workshop and is based in the service building for part of the time.

SKETCH No 92/004/141A

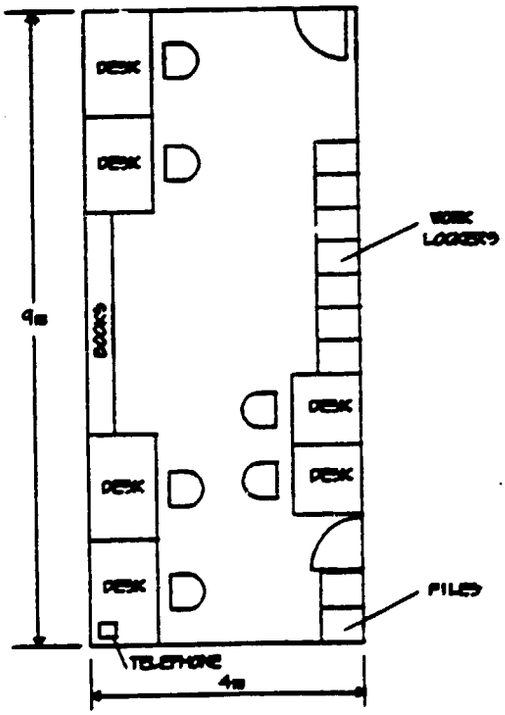
106 STAIRS AND LOBBY



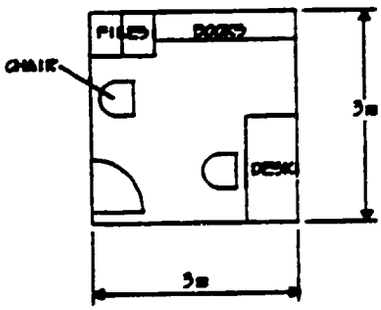
107 TECHNOLOGY AND ENGINEERING OFFICE



109 FERMENTATION AND DSP GENERAL OFFICE



110 DSP SECTION HEAD



There is space for three desks and a significant amount of book and file storage.

109 Microbiological and Analytical General Office

This area is used as a writing up area by team leaders and technicians in the Microbiological and Analytical departments.

6 desks are provided for general use and work lockers are provided for storage of work between write-ups. The desks are partitioned into booths to aid concentration and prevent the use of this room as a social area. File space, book storage space and a telephone are provided for staff use.

110 DSP Section Head

This office contains a table and space for files and bookshelves.

111 Fermentation Section Head

This office contains a table, space for files and bookshelves and an additional table for a PC. The PC is used for fermentation trend analysis and data manipulation.

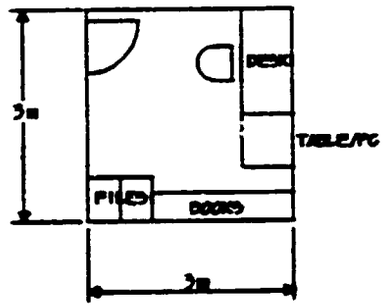
112 General Managers Office

Provision is made for a desk, side desk, file and book storage as well as a small conference table.

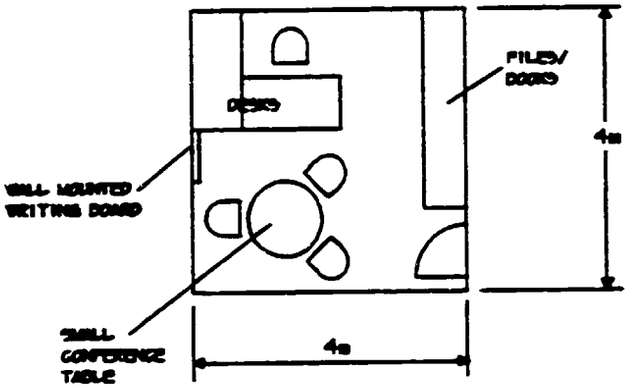
Space is included for the inclusion of a wall mounted erasable writing board for use in group discussions.

SKETCH No 92/004/142A

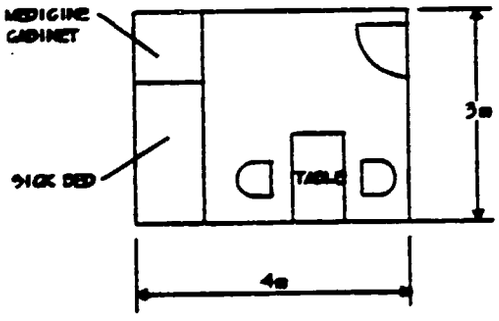
111 FERMENTATION SECTION HEAD



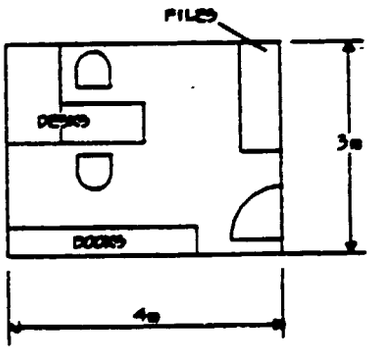
112 GENERAL MANAGERS OFFICE



113 FIRST AID ROOM OFFICE



114 MICROBIOLOGICAL AND ANALYTICAL HEADS OFFICE



113 First Aid Room

The first aid room is located in a convenient place for stretcher removal of injured parties.

Provision is made for a sick bed and wall mounted medicine cabinets. First aid materials as specified by the appropriate local legislation should be freely available in this room.

This room doubles as an examination room for the visiting consultant doctor performing routine staff medical checks. A small table is provided for this purpose.

114 Microbiological and Analytical Heads Office

This office contains ample desk space and provision for files and bookshelves.

115 Fermentation and DSP General Office

This room has a function similar to the Microbiological and Analytical General Office (room 109) and has a similar layout.

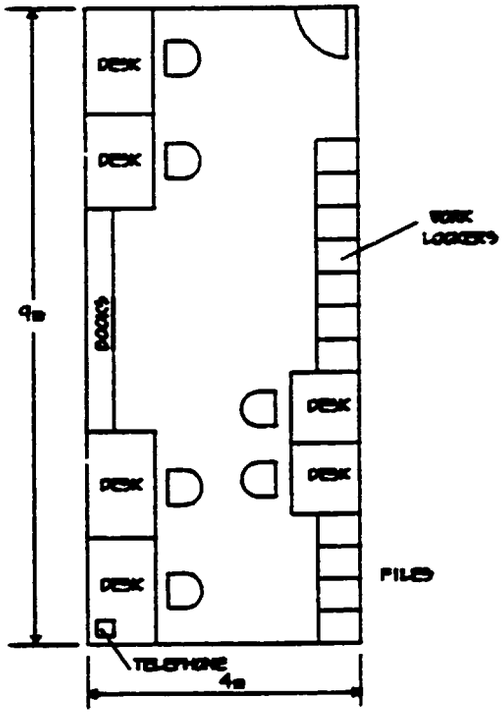
It is used for writing up reports and process results by fermentation and DSP scientists and technicians.

6 desks are provided for general use and work lockers are provided for storage of work between write-ups. The desks are partitioned into booths to aid concentration and minimise noise. File space, book storage space and a telephone are provided for staff use.

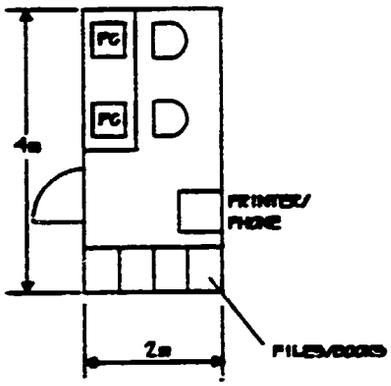
The fermentation process analysis room (room 116) is accessed through this room.

SKETCH No 92/004/143A

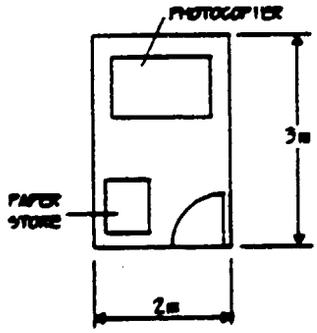
115 MICROBIOLOGICAL AND ANALYTICAL GENERAL OFFICE



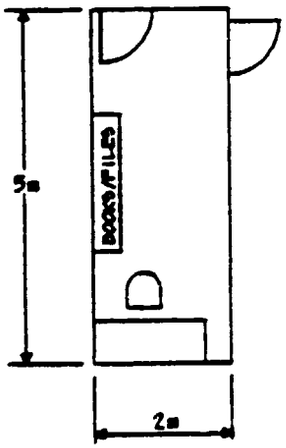
116 PROCESS ANALYSIS ROOM



117 PHOTOCOPYING ROOM



118 STOREMANS OFFICE



116 Process Analysis Room

This room contains PCs and printers and is used for the analysis of fermentation and other process data.

The fermentation process analysis computer has access to current fermentation data and has read access via a network to the fermentation data hard disk. This computer, however, cannot change any process parameters or write to the fermentation hard disk. Data for validation purposes is stored in the computer in the fermentation process control room.

The data is stored in a form and programs are available that allow easy recall of data and facilitates on screen displays of parameters from more than one batch.

A telephone is provided for communicating with the plant.

117 Photocopying Room

A small room containing a photocopier for office use. The room also holds stores of photocopy paper.

118 Storemans Office

An office is provided for the storemans use with good views over the goods in store (room 701).

Space for filing goods movement, delivery and despatch receipts is allocated.

201 Meeting Room

This room is used for project meetings, seminars, group lectures, training sessions, etc. It is designed essentially as an open plan area capable of seating all the anticipated facility staff. Seating for 16 people is kept permanently in this room arranged around a large subdividable central table. For larger meetings, seating is available from the mess room.

The room is capable of being divided into two separate soundproof subrooms by appropriate partitions so that two concurrent sessions may be held. It also has projection facilities for slides, overheads, video display facilities and other devices.

A significant portion of the room is fitted with library shelves, floor to ceiling, so that this meeting room in effect doubles as the library. Up to date books and current journals are on display. These materials help in the ongoing training of staff and give visitors a favourable impression.

The use of video training on an ongoing basis is available and coupled with appropriate written tests forms a useful and cost effective training aid.

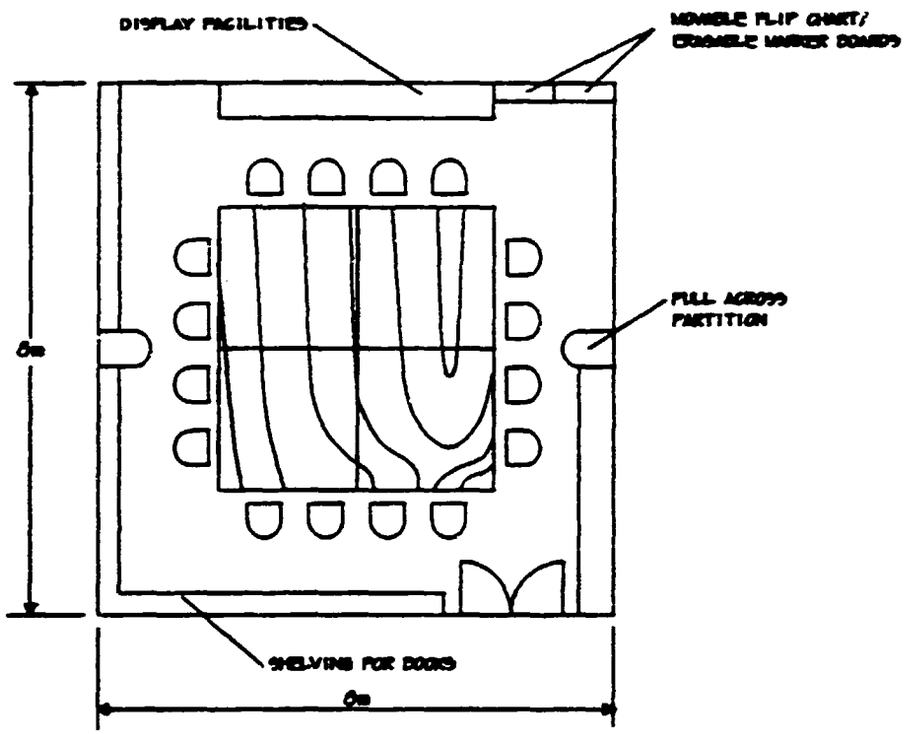
The windows in this room are fitted with appropriate blinds for use when the projection facilities are in operation.

202 Spare Office

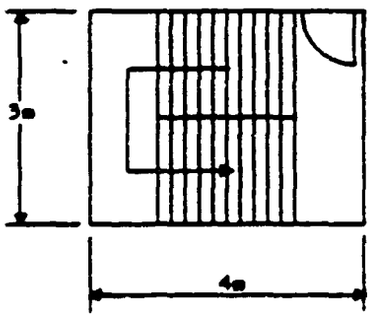
This small office is provided for a management role created by a possible future facility staff expansion. No layout is given for this office.

SKETCH No 92/004/144A

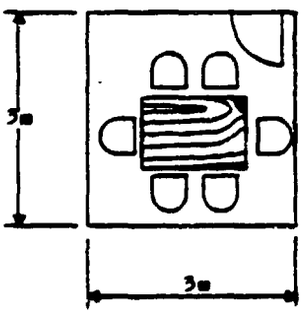
201 MEETING ROOM



203 STAIRS AND LOBBY



206 SMALL MEETING ROOM



203 Stairs and Lobby

These stairs are provided to access the office area, laboratory area and selected access to the contained area.

Access for process workers to the fermentation halls and downstream processing is via the change areas on the ground floor.

204 Mess Room

This facility is provided for staff to spend breaks and lunchtimes. Tea, coffee and food preparing facilities are available.

The area is generously spaced to seat 25 people.

206 Small Meeting Room

A small meeting room is provided for small group discussions and interviews. This room shares display equipment with the main meeting room (room 201).

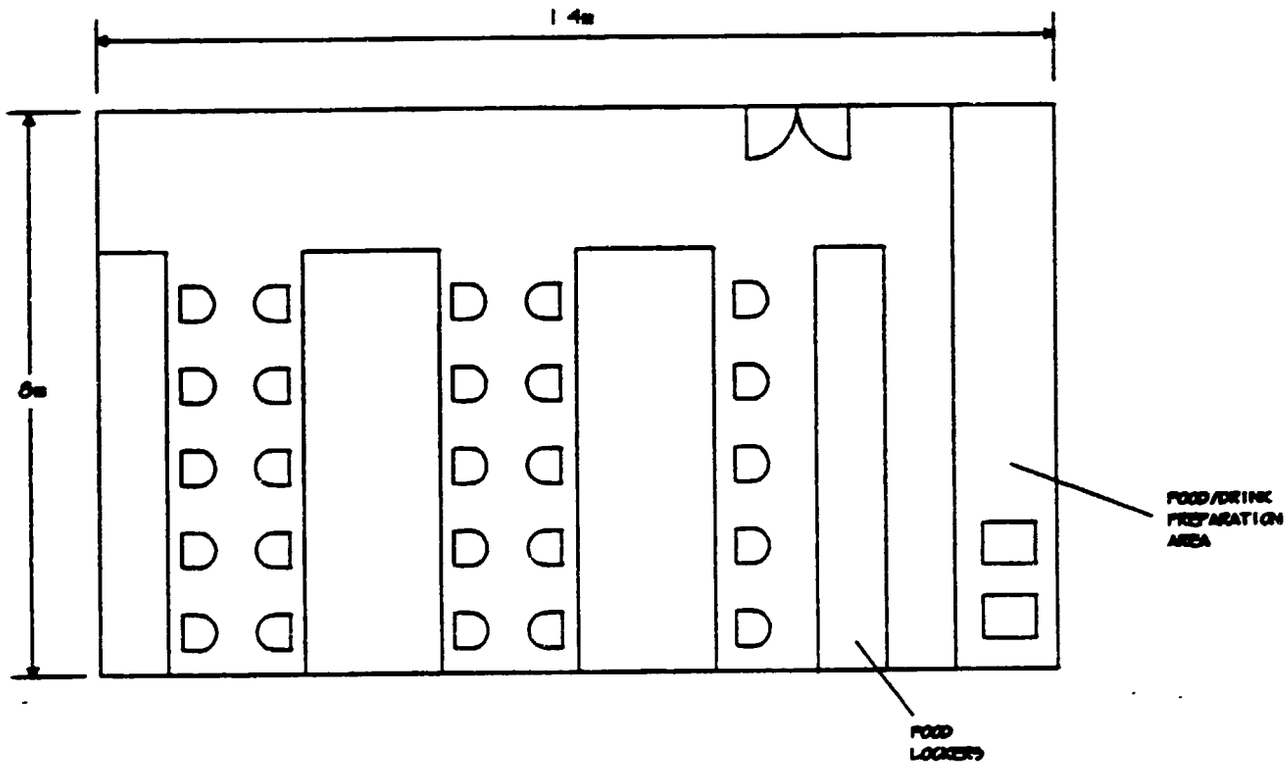
207 Clean Materials Store

This small store contains the cleaning equipment and materials for the office areas.

No layout is given for this room.

SKETCH No 92/004/145A

204 MESS ROOM



6.3 CONTAINED AREA

This area is designed for the handling of Group 2 Class 2 genetically modified organisms (ref 3). No material will leave this area unless it has been validatedly killed or securely wrapped and all rooms in the contained area will have full fumigation facilities. The area includes the fermentation halls and the microbiology suite.

There is space on the ground floor of the fermenter halls for the possible future inclusion of a contained centrifuge for use as a primary separation device.

Materials after separation by the contained centrifuge are transferred to the deactivation room (room 308) where the material is deactivated and pumped to a non-contained area, the deactivated receipt room (room 308). The material is then transferred to the downstream processing area and requires no further special handling for containment considerations.

The means of primary containment of the controlled organism is the process equipment itself which must be capable of containing the organism, releasing samples in a contained manner, and being subsequently sterilized after use.

Secondary containment is achieved by means of the facility itself. Material will not leave the contained area without being validatedly sterilized.

All drains are piped to the waste treatment room (room 301) for sterilization. Through autoclaves are provided in Fermentation Hall 1 (room 304) and the microbiological laboratory (room 405) for the sterilization and subsequent movement of contaminated solids and other materials to the non contained area main laboratory corridor (room 604). Air inlet

and outlet points contain HEPA filters. Process liquors are transferred to the downstream processing area via the deactivation room (room 307) as described above.

A contained area protects the areas external to the plant from the contained organism and hence any air movement must flow from the external area into the plant to retain any airborne contained organisms. Conversely, a GMP clean area protects the organism/product from contamination by the area external to the plant and hence any air movement must flow from the plant to the external area to exclude any airborne contamination.

Clearly there is a conflict between the conditions required for containment and those required for GMP. The plant layout is suitable for operating in a contained or GMP manner. Further design work is required if the plant must operate to contained and GMP regulation, at the same time, and the new design may incorporate novel isolation techniques.

Process and laboratory workers enter the contained area via the ground floor and first floor changing rooms respectively.

It is understood that the new facility will not operate at this level of containment initially and hence ancillary equipment, such as the drain waste treatment sterilization package, may be purchased and installed at a later date. The designed design should, however, contain detailed specification and installation details of all equipment which may be added later.

301 Waste Treatment Room

All liquid wastes including sink drains in the contained area are routed into a $3m^3$ sump which is located under the waste treatment room and accessed via this room.

This room also contains the equipment required for liquid waste treatment. Liquid waste leaving the contained area must contain no viable organisms and the required sterilization must be achieved in a validatable manner. The room contains an in-line sterilizer, a post sterilization cooler, tanks and the necessary control and instrumentation. The layout of this room and the details of sterilization are performed as part of the detailed desig..

302 Change Area

Process workers entering the contained area must change into a new set of outer clothing. This outer clothing is removed and retained in the contained area when the process worker leaves this part of the plant.

This change area contains access to the contained area ground floor wash room (room 303).

303 Wash Room

Wash facilities for process staff leaving the contained area.

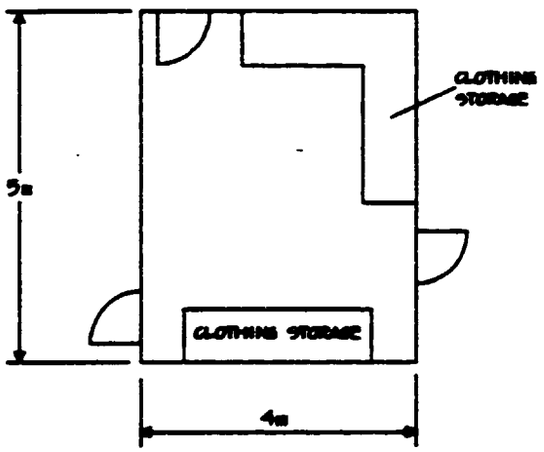
304 Fermentation Hall 1

This room is the lower level of Fermentation Hall 1 and contains the lower half of two 1000l fermenters.

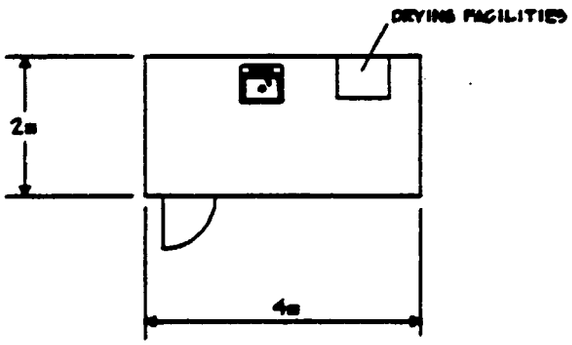
There is space available for the installation of temporary equipment for trials.

SKETCH No 92/004/146A

302 CHANGE AREA

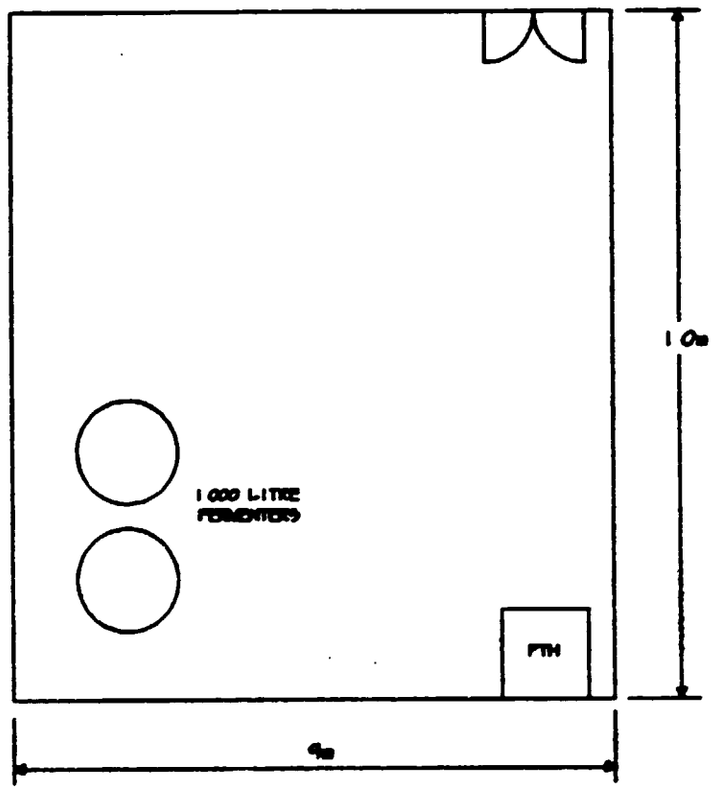


303 WASH ROOM



SKETCH No 92/004/147D

304 FERMENTATION HALL 1



305 Fermentation Hall 2

This room is similar to the lower floor of Fermentation Hall 1 and also contains the lower half of two 10001 fermenters.

A CIP system and a fermenter gas scrubbing package are located in this room.

There is also space available for the installation of temporary equipment for trials.

306 In Process Laboratory

This laboratory is shared between the two fermentation halls and contains basic process testing equipment such as a spectrophotometer. The area also contains enough desk space to allow a batch sheet on a clipboard to be filled in.

307 Process Deactivation Room

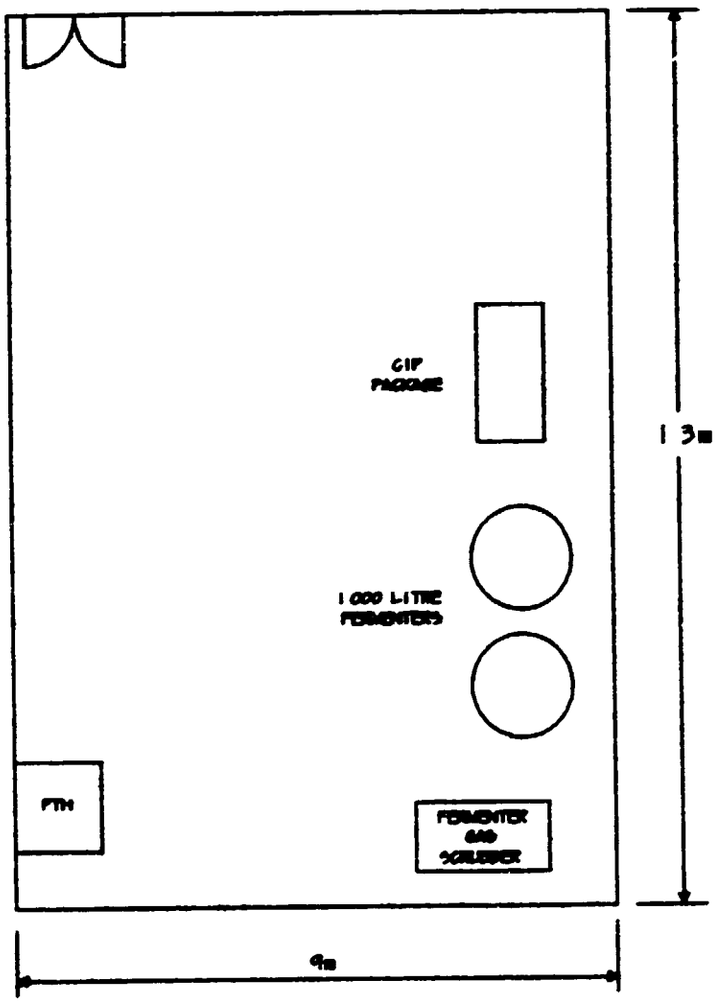
Process material generated by the fermentation and separation of contained organisms must be validatably deactivated before leaving the contained area for further processing.

Process material is deactivated in this room which forms part of the contained area and then pumped through to the deactivated receipt room (room 528) which is not in the contained area. The material in 528 may then be transferred to the downstream processing section.

No layout is given for this room.

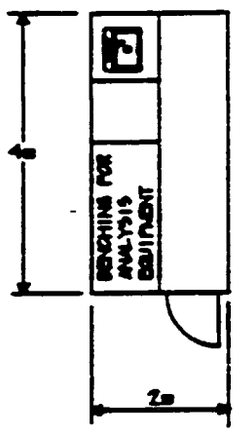
SKETCH No 92/004/1400

305 FERMENTATION HALL 2

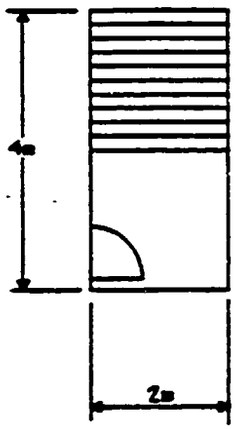


SKETCH No 92/004/149A

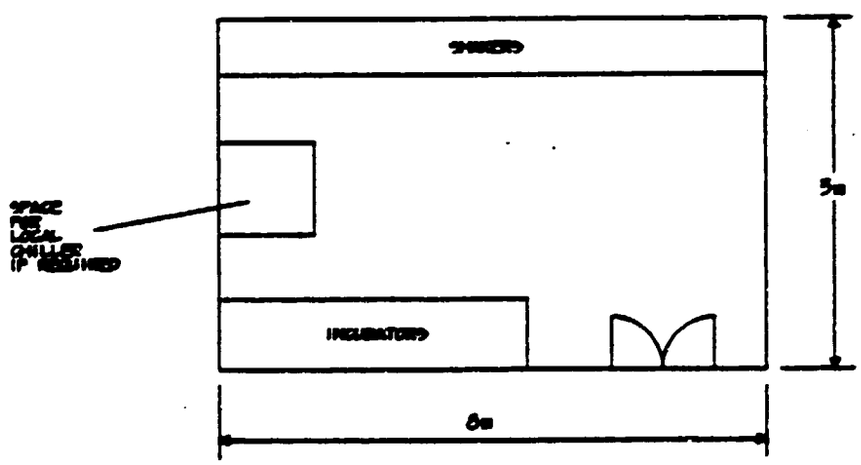
306 IN PROCESS LABORATORY



308 STAIRS AND LOBBY



401 SHAKER AND INCUBATOR



308 Stairs and Lobby

Access to the upper part of the contained area is achieved using these stairs.

401 Shaker and Incubator Room

The shaker and incubator room is used for the growth of production organisms and in process microbiological tests.

402 Seed Store

The seed store contains production and development organisms stored in freezers and possibly liquid nitrogen. A table is provided for the maintenance of a seed movement log.

403 Clean Room

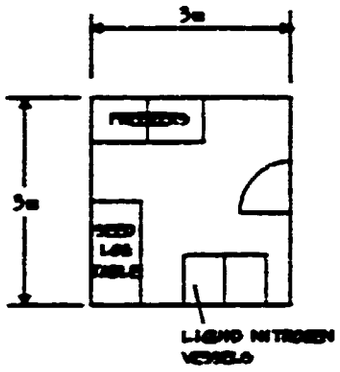
All critical production sterile transfers are performed in this room under laminar flow. This includes production organism plate transfers and production organism to flask transfers.

Non critical transfers, which include pre-inoculation media sterility spread plates should be performed in the microbiological suite main area under laminar flow. This keeps traffic in this very clean area to a minimum.

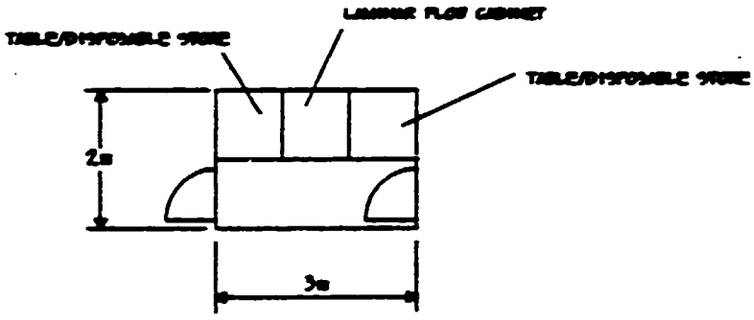
The clean room contains a laminar flow cabinet, work surface and disposables storage space.

SKETCH No 92/004/150A

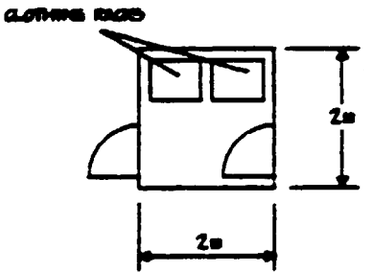
402 SEED STORE



403 CLEAN ROOM



404 CLEAN CHANGE



404 Clean Change

This is a pass through clean change area which leads to the clean room and the seed store.

405 Microbiological Suite Main Area

This area is provided with microbiological instruments and generously equipped with benching. In the future if required small development fermenters, of the order of several litres, could be installed in the central benching area.

Wall mounted storage cupboards could be installed to provide extra storage space.

Note that there is no segregated area for actual genetic manipulation work, which will be undertaken at a separate facility.

406 Microbiology Change Area

This pass through change area leads to areas which potentially contain Group 2 genetically modified organisms. (Ref 3)

This change area is used by microbiological lab workers who also have limited access to the fermentation halls.

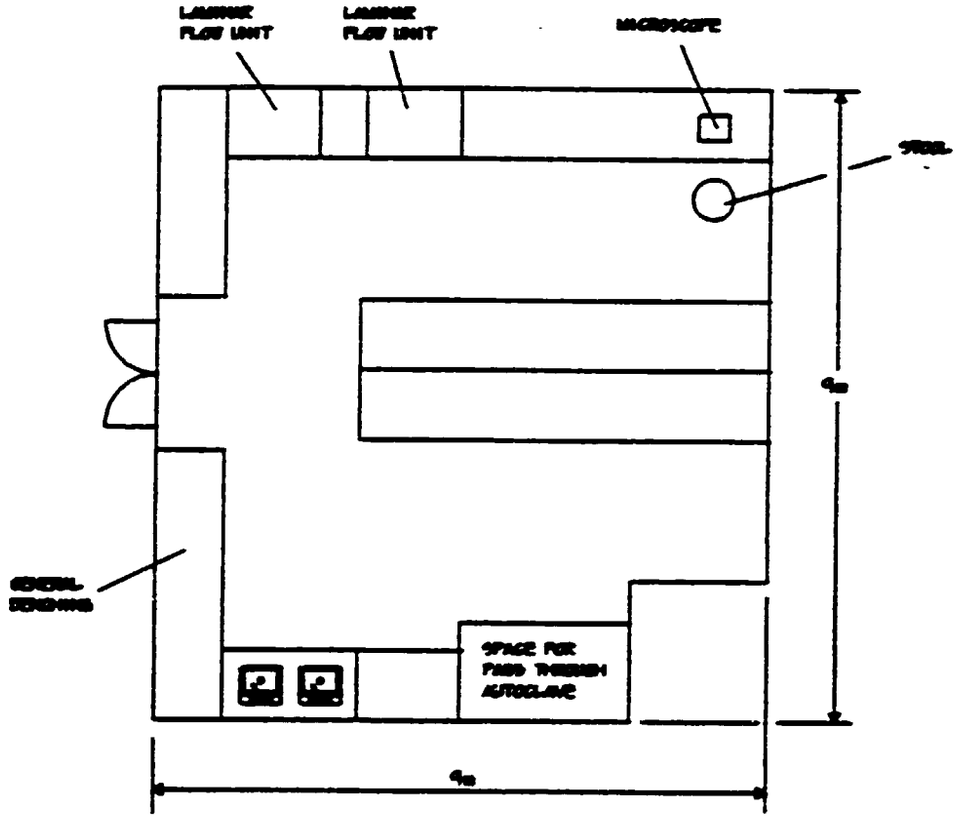
Washing facilities are provided for outgoing staff in the adjacent wash room (room 411).

When operating in a non-contained manner this area serves as a connecting corridor.

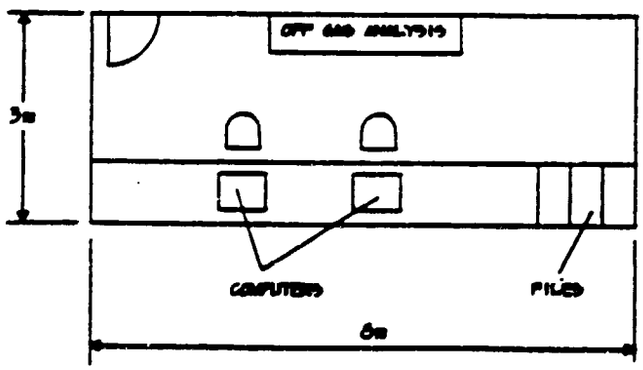
No layout is given for this room.

SKETCH No 92/004/151A

405 MICROBIOLOGICAL LABORATORY



408 PROCESS CONTROL ROOM



408 Process Control Room

The process control room contains the fermentation supervisory computers and holds the master hard and soft copies of all batches for validation purposes. Data analysis and batch comparisons take place at a remote workstation connected to the supervisory computer via some form of network. This remote computer is located in the process analysis rcom (room 116) on the ground floor. Scientists examine historical data as an aid to process development.

The process control room also contains the gas analysis instruments.

409 Fermentation Hall 1

This room is the top floor of the fermentation hall. The 1000l fermenters in this room are mounted between the two floors of the fermentation hall.

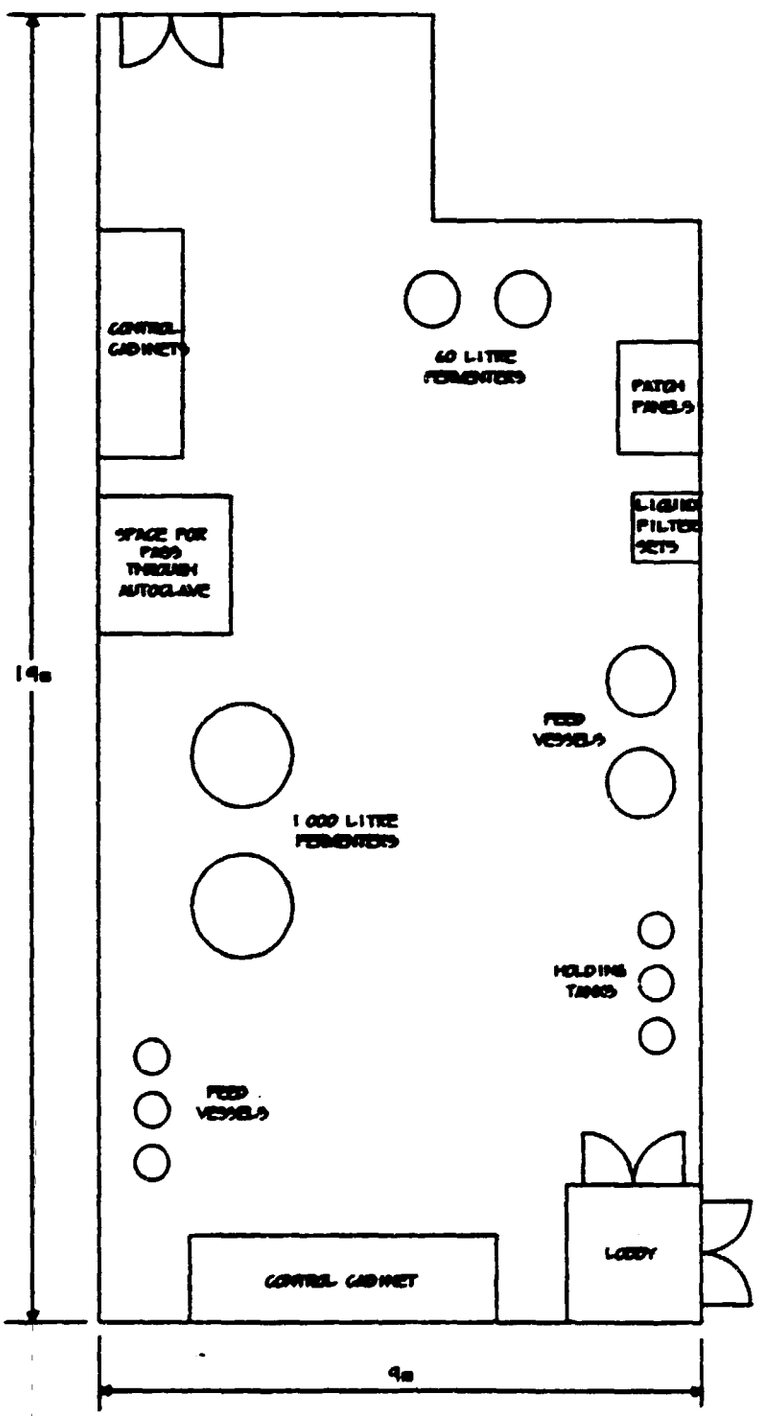
Two fermenter trains are located in this area. Each train contains 3 fermenters, 60l, 300l and 1000l. It is expected that these will be connected in a variety of ways and so all the fermenters are connected to a patch panel system. This is located in an area to minimise the length of pipe runs from the smaller fermenters. A patch panel access way to Fermentation Hall 2 is provided.

The 300l and 1000l fermenters both have 3 associated feed vessels mounted on load cells.

Liquid filter sets are provided for sterilizing heat sensitive media.

SKETCH No 92/004/152D

409 FERMENTATION HALL 1



The operating parameters of all the fermenters are logged automatically by a computer based system located in the adjacent process control room.

Fermenter media may be pumped directly from the media make-up room or transported in a container to the fermenter area via the material lift, transferred through the lift lobby (room 529).

410 Fermentation Hall 2

This area is very similar to the top floor of Fermentation Hall 1 and contains identical equipment.

The layout is a mirror image of Fermentation Hall 1.

It can be seen that the two fermentation halls share many facilities including the process control room, stairs and lift. The two halls are therefore essentially part of the same area and personnel from each hall will mix in the common areas.

411 Wash Area

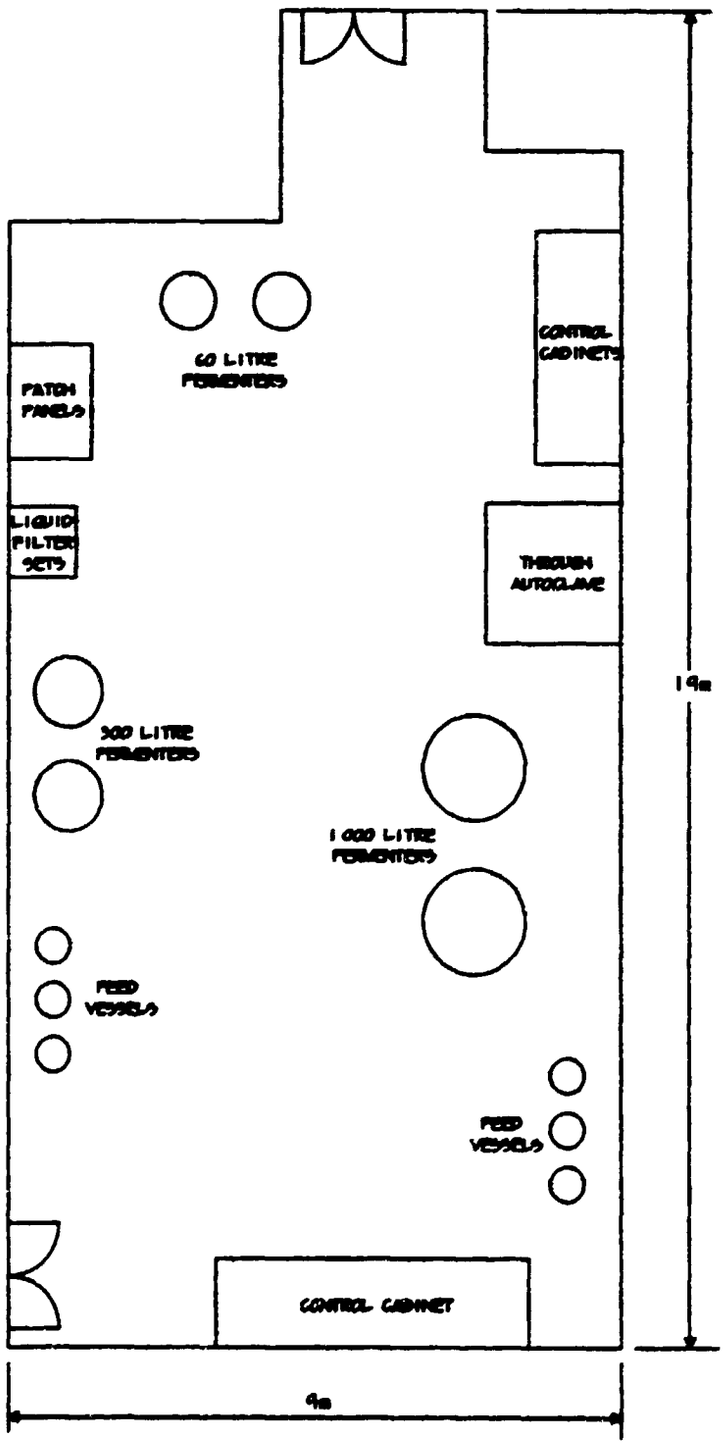
This room is adjacent to the contained change area (room 406) and provides washing facilities for personnel leaving the contained area.

412 Stairs and Lobby

Access to the lower part of the contained area is achieved using these stairs.

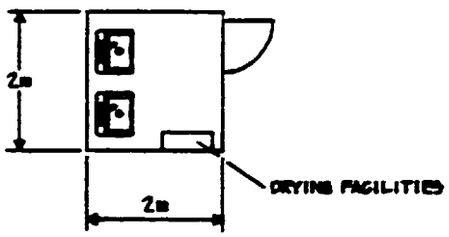
SKETCH No 92/004/153D

410 FERMENTATION HALL 2

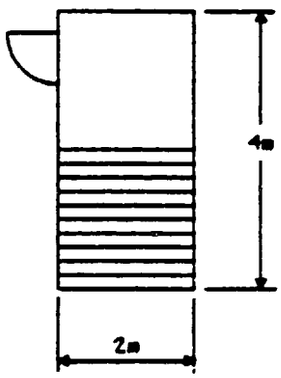


SKETCH No 92/004/154A

411 WASH ROOM



412 LOBBY AND STAIRS



6.4 DOWNSTREAM PROCESSING

Process material from the fermentation area (as and when required) enters the downstream area and may leave in the form of a blended dry powder.

A large number of the rooms in the downstream processing area handle solvents or potentially explosive powders and hence much of the downstream equipment is certified flameproof. The hazardous zone classification is detailed in Section 12.

The downstream processing area includes facilities for chemical synthesis, separation by centrifugation and filtration, solvent extraction, chromatography, ultrafiltration, drying, milling, sieving and blending.

Wheeled bins are in general used for materials transfer between process rooms.

A materials dispensary (room 507) holds a stock of currently used chemicals and is equipped with weighing facilities. Weighed materials from this area are transferred and used in the appropriate media make-up area.

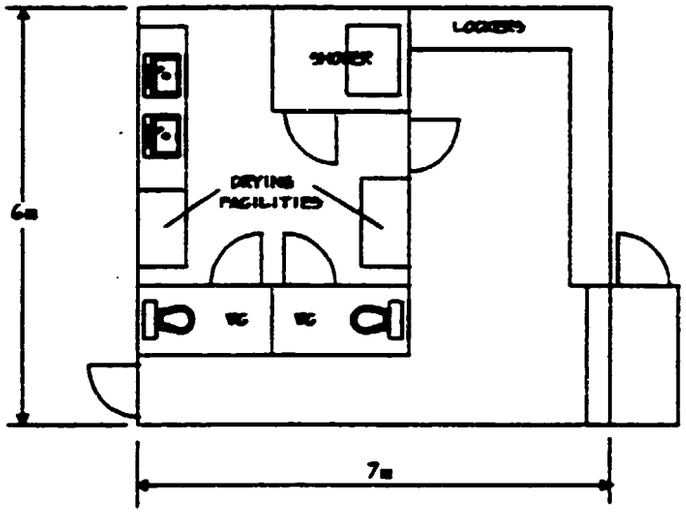
501 Male Primary Change Area

Process workers change out of their street clothes into work clothes in this area.

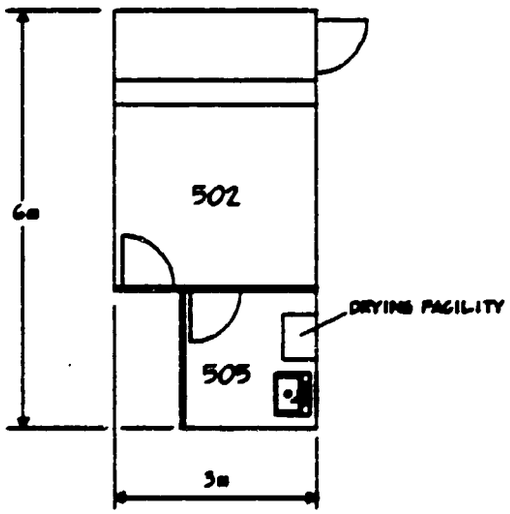
The male primary change area contains lockers, two WCs and a shower. Personnel use a stepover bench to exit the area. This area has been generously sized for a male staff of around 7. This assumes a female/male ratio of 1:1 and staff numbers as in Section 4.

SKETCH No 92/004/1 55A

501 MALE PRIMARY CHANGE AREA



502 MALE SECONDARY CHANGE AREA AND 503 MALE SECONDARY CHANGE HANDWASH



All the rooms in these change areas are used by incoming and outgoing staff. Company changing protocols should aim to minimise congestion of these facilities.

502 Male Secondary Change Area

Process workers clothe themselves in a clean coverall and other clean wear in this area. The area is left via a stepover bench and through a door to the process area.

503 Female Primary Change Area

Identical to Room 501 Male Primary Change Area.

504 Female Secondary Change Area

Identical to Room 502 Male Secondary Change Area.

505 Male Primary Change Handwash

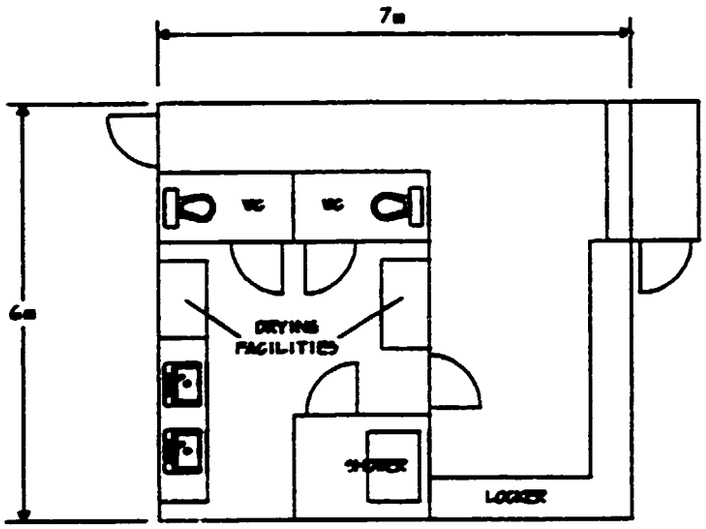
A room which contains clean handwash facilities and is accessed via male secondary change area (room 502).

506 Female Primary Change Handwash

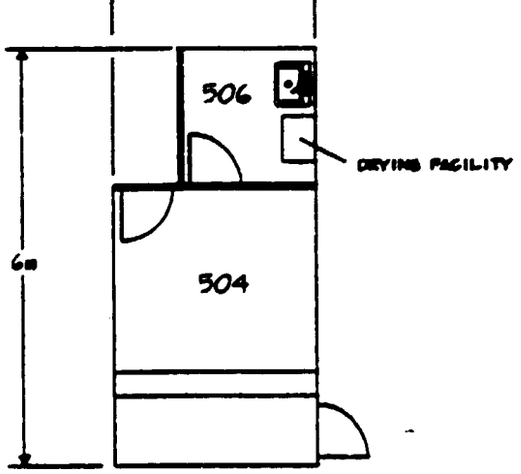
Identical to Room 505 Male Primary Change Handwash.

SKETCH No 92/004A 56A

503 FEMALE PRIMARY CHANGE AREA



504 FEMALE SECONDARY CHANGE AREA AND 506 FEMALE SECONDARY CHANGE HANDWASH



507 Dispensary

The dispensary is used for weighing out all chemicals in the process area. A shelved area contains current chemicals.

Note that the stock of chemicals includes the current chemicals in the dispensary which are considered to be in use and the stock contained in the goods in store.

Goods are transferred from the goods in store through a pass through hatch to the dispensary in a manner which may involve the cleaning of the containers. The exact method of transfer will be confirmed in the detailed design.

The dispensary contains 3 weigh booths, one of which will contain a balance for weighing less than 1 kg. All weigh booths have local extraction.

508 Fermentation Make-up Room

The fermentation make-up room contains several stirred tanks which are capable of being heated or chilled. Pumps are provided for transfer to the fermentation halls.

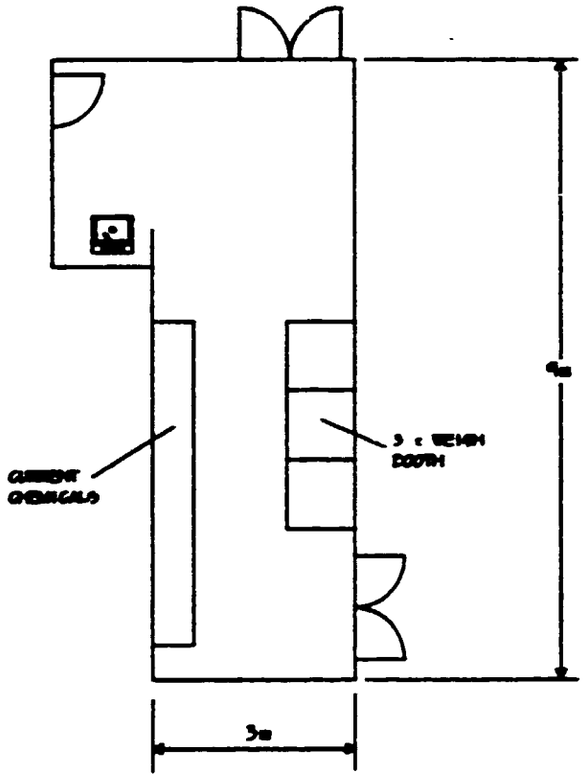
A lift is provided for transfer to the upper floor of quantities of solids, and liquids which are too small in quantity to be effectively pumped.

510 Centrifuge Room

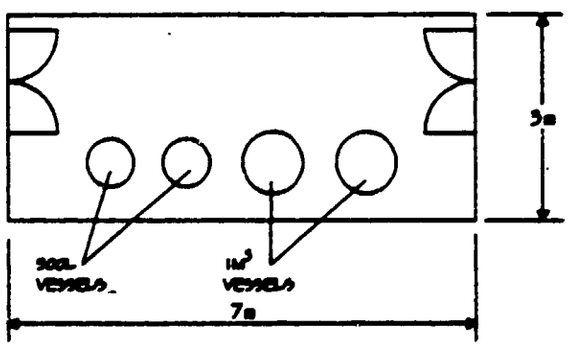
The centrifuge room contains two centrifuges, a Westfalia disk stack type and a vertical Sharples type. If required the vertical Sharples type centrifuge bowl may be dismantled on a table (not shown in the drawing) on the top right hand corner of the room.

SKETCH No 92/004/157A

507 DISPENSARY

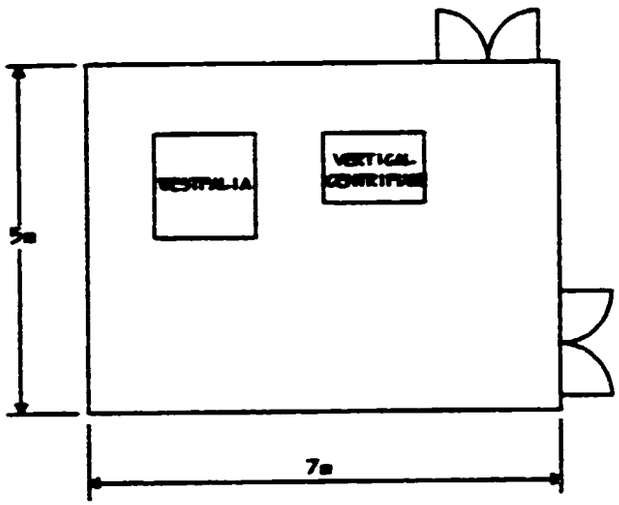


508 FERMENTATION MAKE-UP ROOM

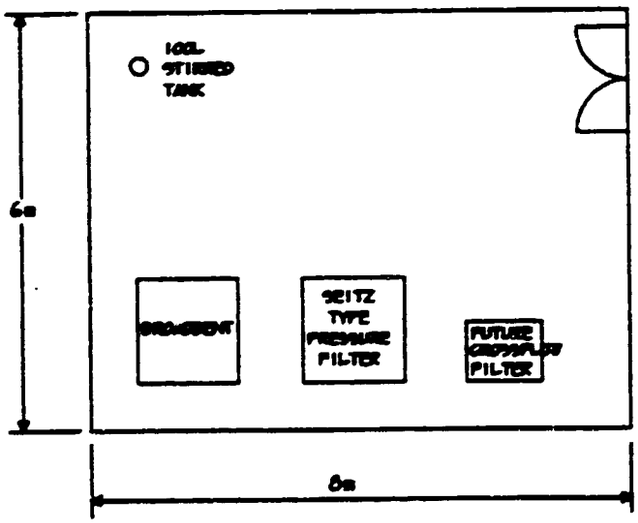


SKETCH No 92/004A 58A

510 CENTRIFUGE ROOM



511 FILTER ROOM



Space is left in this room for the later possible inclusion of a homogeniser which may be used for protein purification work.

511 Filter Room

This room holds the presently owned Broadbent centrifuge and a Seitz pressure filter. There is space in this room for the possible future inclusion of a cross flow filter.

512 Solvent Extraction/Synthesis Room

This room contains equipment for chemical synthesis and extraction. Space is left for the possible future inclusion of a continuous extractor.

The solvent extraction room is located adjacent to the centrifuge room to enable a centrifugation step to be easily performed if required following an extraction step.

513 Chromatography Room

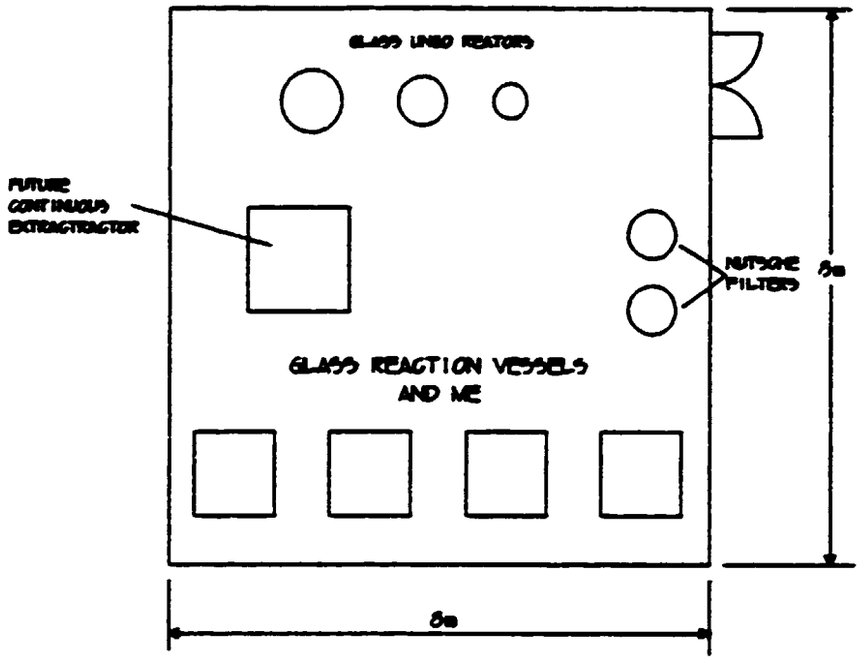
This room contains chromatography columns and associated vessels. Space is allotted for the possible future inclusion of a final filter primarily for use in protein purification.

514 Wash Room

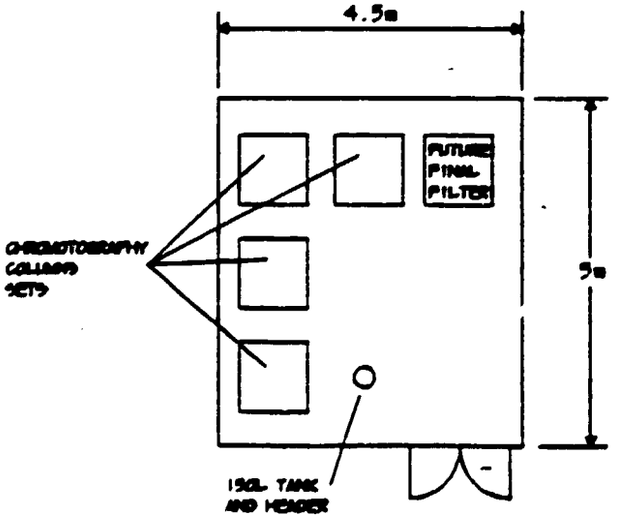
The wash room is used for cleaning process equipment. Equipment will typically be washed in hot or cold towns water and may have a final demineralised water rinse. The equipment is dried in a separate section of this room, and the dry equipment is carried through to the adjacent equipment room for reuse.

SKETCH No 92/0041 59A

512 SOLVENT EXTRACTION AND SYNTHESIS ROOM

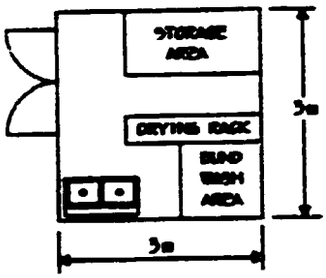


513 CHROMOTOGRAPHY ROOM

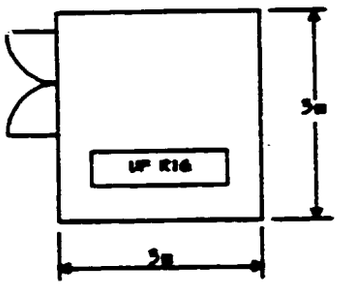


SKETCH No 92/004/160A

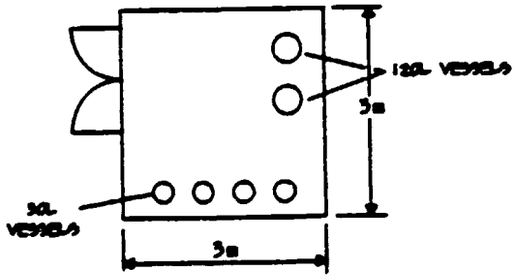
514 WASH ROOM



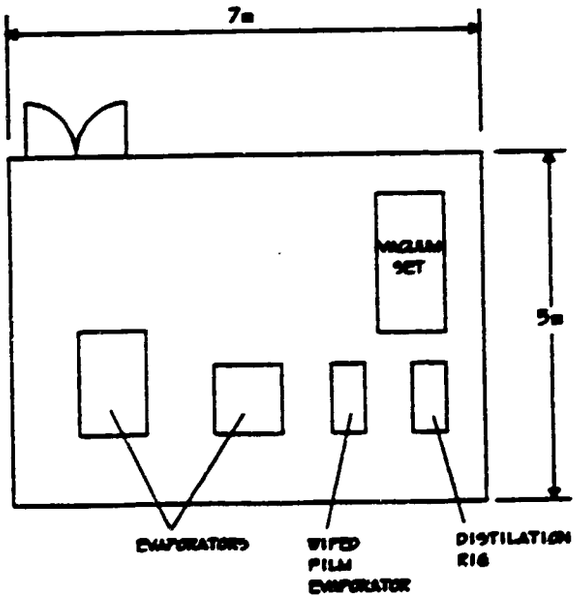
515 ULTRAFILTRATION ROOM



516 CLEAN MAKE UP ROOM



517 EVAPORATION ROOM



Attention to detail in the HVAC system design will ensure that no contaminating aerosols from the wash area enter the drying area.

515 Ultrafiltration Room

This room is to contain a small ultrafiltration rig and associated vessels is provided.

516 Clean Make-up Room

This room is primarily used for making up solutions and buffers for use in the chromatography and ultrafiltration room.

Weighed materials are transported from the dispensary to this area and solutions are then typically transported in wheeled vessels to the area they are required.

Tanks of various sizes are provided for make-up duties.

Portable pH and conductivity meters and other portable instruments used in this room are kept in the in process lab.

517 Evaporation Room

This room contains evaporation equipment and could be used for process and small solvent recovery applications.

518 In Process Laboratory

This laboratory is used for simple analytical tests in the downstream processing area. It is equipped with benching, a sink and underbench and wall mounted storage cupboards. Appropriate analytical equipment is installed.

More complex analytical tests are performed in the analytical laboratory.

519 Equipment Room

This room contains racking and space for the storage of clean equipment which is dry and ready for reuse on the plant.

520 Cleaning Equipment

The cleaning equipment for the downstream processing area is stored in this room. Equipment includes a vacuum cleaner and mop and buckets.

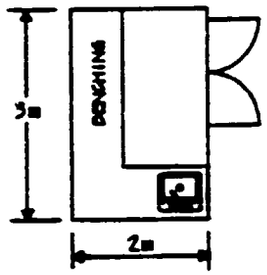
No sketch is given for this store.

521 Drying Room

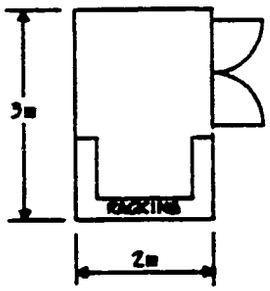
This room contains drying equipment, a spray drier, a horizontal vacuum paddle drier, an agitated bed drier and several drying ovens.

SKETCH No 92/004/161A

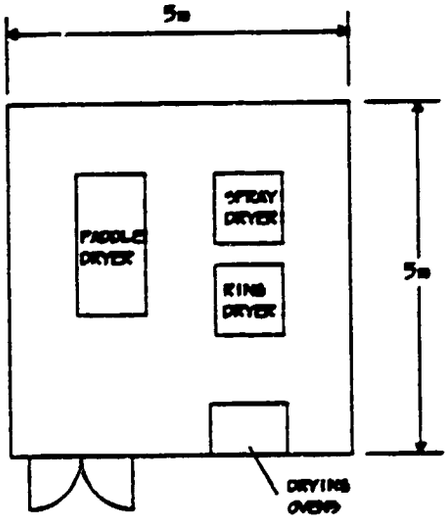
518 IN PROCESS LABORATORY



519 EQUIPMENT ROOM



521 DRYING ROOM



522 Drier Services

In order to minimise equipment in the clean process drying room the drier service equipment is brought together in a room which is accessed from the outside via external doors.

No layout is given for this room.

523 Freeze Drying Room

A freeze drier is mounted flush to the wall in this room and the drying chamber is accessed via this room. The back of the freeze drier is located in the drier services room and serviced via this room.

The room is 2 x 3m and contains no permanent additional equipment hence a layout is not given.

524 Milling and Sieving Room

A small mill and sieve are located in this room for use in product finishing.

525 Blending and Packing

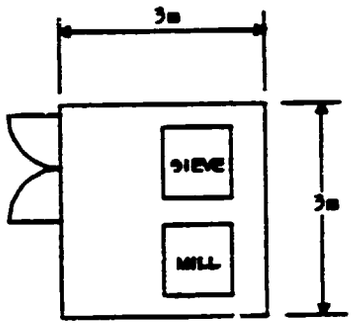
This room contains a blending apparatus which may be caged for safety reasons and a weighing scale.

527 Deactivated Receipt Room

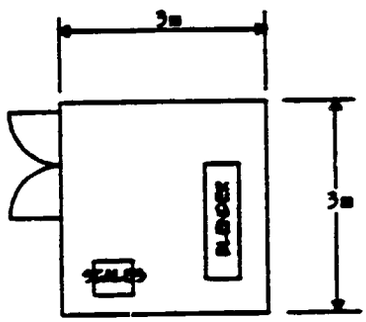
Deactivated material from the deactivation room is received here, ready for transfer to the downstream processing section.

SKETCH No 92/004/162A

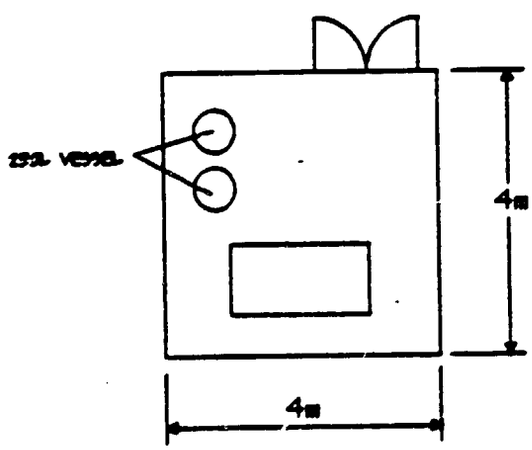
524 MILLING AND SIEVING ROOM



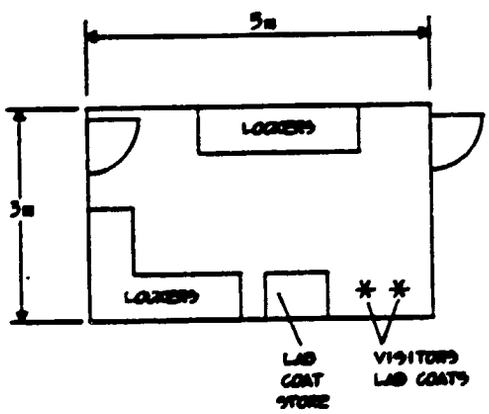
525 MILLING AND BLENDING



528 ROTARY VACUUM FILTER ROOM



601 FEMALE LABORATORY CHANGE



528 RVF Room

This room contains chilled tanks and a rotary vacuum filter with a local vacuum set. The filter is used as the primary separation stage of contained processes.

6.5 LABORATORY AREA

This area contains the primary laboratory change areas and the analytical laboratory. Microbiological laboratory personnel will undergo a secondary change in room 406 if the contained area is operating in contained mode.

601 Female Laboratory Change

Female laboratory personnel remove their overcoats and put on a laboratory coat in this room before entering the laboratory area.

The area contains enough space for full length lockers, a fresh laboratory coat store and an area for visitors lab coats store.

602 Analytical and Development Laboratories

This space is 13 x 10m and is set aside for analytical and development work. The area contains analytical equipment such as HPLC, GC, etc, for use in process testing. An area will also used for small scale development work, this area will probably be a room containing extraction booths for solvent handling.

A layout will be established at the detailed design stage when the split between analytical/development work is more clearly identified.

603 Male Laboratory Change

Identical to room 601, Female Laboratory Change.

6.6 SERVICE AND STORES AREAS

The service area accommodates all the equipment and facilities used for generating and redistributing the utilities and services which include the following.

Steam Generation - two independent boilers to provide domestic heating steam and industrial grade steam to heating jackets on tanks and vessels as appropriate.

Clean Steam - a clean steam generator, fed from the steam boilers, is installed to provide clean sterilizing steam used on the internals of fermenters, etc, and in various autoclaves.

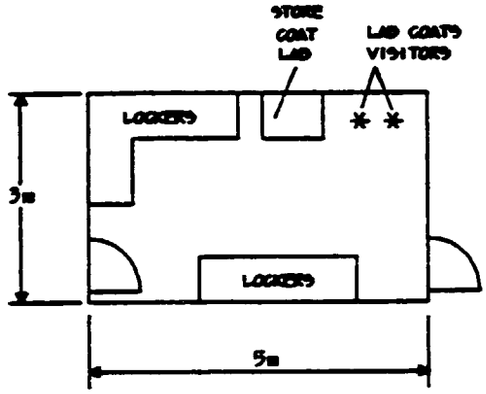
Demineralised Water Unit - this is used to provide boiler feed water and also water for the washing up area and is distributed around the facility as required.

Air Compressors - two compressors are installed to provide air to the fermenters, general plant air, instrument air and possibly breathable air.

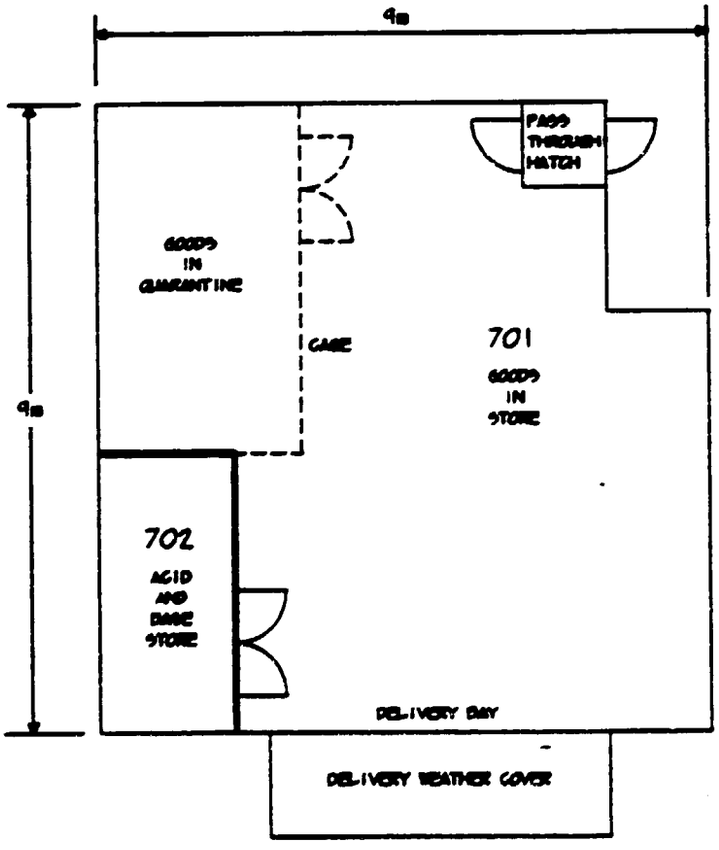
Vacuum - two general purpose vacuum sets are supplied to provide vacuum for the downstream plant areas. Vacuum in the contained areas will be supplied locally.

SKETCH No 92/004/163A

603 MALE LABORATORY CHANGE



701 GOODS IN STORE
702 ACID AND BASE STORE



Chilled Water - a small fridge unit is installed to generate chilled water for use primarily in the downstream plant area. It may also be utilised in the HVAC system to be defined at a later stage.

Attached to the service rooms is a plant engineers office and workroom where a limited amount of mechanical fitting work, overhaul and repair, may be carried out.

A gas cylinder cage and a cooling tower are located outside the services building.

A goods in and goods out store are provided. The solvent store and solvent waste store are located away from the main building for safety reasons. A secure area containing two skips is provided for the disposal of general waste.

701 Goods-In Store

All materials entering the facility are received in this store.

There is a caged area inside the store for goods awaiting quality control approval before release.

The delivery bay has a weather overhang to minimise environmental contamination of goods being unloaded.

A forklift operates in this area and space has been left to allow it to manoeuvre.

702 Acid and Base Store

This bunded storage area forms part of the Goods-In Store. It contains various acids and alkalis for use in the demineralised water generating equipment and throughout the plant.

703 Service Area

It is assumed that no services are available from elsewhere on site, therefore all generated services for the plant are produced in the service area.

The service equipment to be located here is; boilers (2 off), compressors (2 off), vacuum pump sets (2 off), demineralised water unit, chiller and clean steam generation unit. A cooling tower will be located outside the service area on the blind side of the building as viewed from the site entrance. A fuel oil tank if required and a gas cylinder storage cage will also be located in this region.

704 Engineering Stores

A small shelved store 3m x 2m for storage of engineering parts and materials.

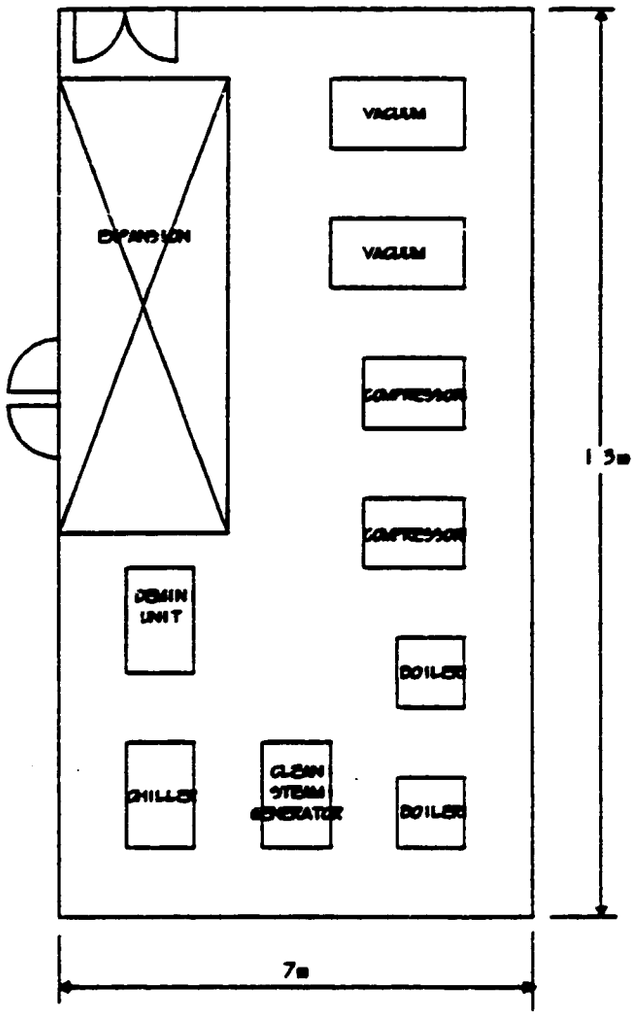
The administration of the log of these stores is done in the engineering workshop office and the store is accessed through the office.

705 Engineering Workshop Office

This office keeps records of equipment details, service schedules and spares lists.

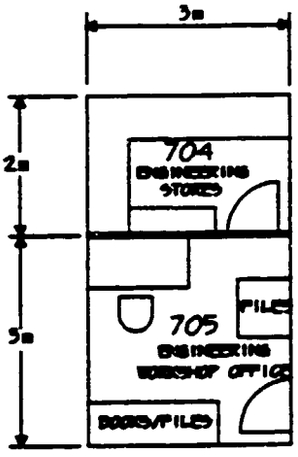
SKETCH No 92/004/1 64A

703 SERVICE AREA

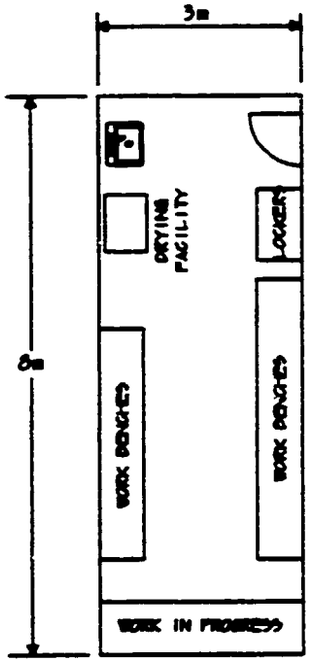


SKETCH No 92/004/1 65A

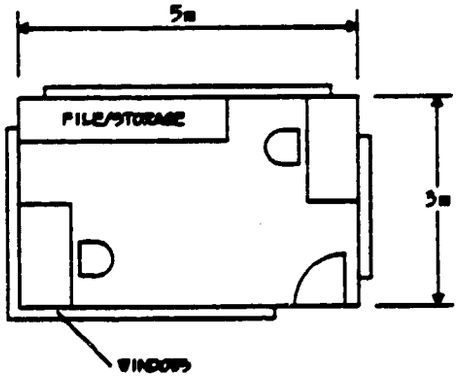
704 ENGINEERING STORES
705 ENGINEERING WORKSHOP OFFICE



706 ENGINEERING WORKSHOP



711 GATE HOUSE



It is staffed on a day to day basis by an engineer who co-ordinates the activities of engineering workshop personnel.

706 Engineering Workshop

In this workshop minor repairs and servicing of plant items, such as pumps, are carried out.

707 Solvent Store

The solvent store is constructed with partial wire mesh sides and bunded. All large quantities of solvent required on the plant are stored here. The area includes facilities for measuring volumes of solvent and common solvents may be tapped and mounted horizontally for easy discharge.

A solvent pump section is located close by for the transfer of large volumes of solvent to the plant.

708 Solvent Waste Area

A suitable outdoor sheltered lockable compound (4 x 3m) is provided for the storage of solvent wastes.

It is anticipated that solvent waste will be removed in the form of labelled drums complying with the appropriate local regulations.

709 General Waste Area

A secure and lockable outdoor compound (5 x 3m) is provided for the storage of general wastes for municipal disposal or incineration.

It is anticipated that these wastes will be contained in covered skips and sufficient space is allowed for 2 skips and skip loading.

710 Gas Cylinder Store

A traditional outdoor but sheltered storage compound for compressed gases and nitrogen is provided. The compound is secure and lockable, and designed and fitted to the appropriate regulations. It is anticipated that the commonly used gases will be manifolded in this area for distribution to individual laboratories and other points of use.

Empty cylinders awaiting recycle are also stored in this area but in a separate compound.

711 Gatehouse

All personnel and vehicles entering the facility must pass and be authorised by security personnel at the gatehouse.

The gatehouse is the base for security on site and will contain a telephone link to the main building and an outside line.

It is substantially glazed and commands a good view over the site and car park. It is expected that security will be provided on a 24 hour basis.

Two desks and discrete tea and coffee making facilities are provided for security personnel. Filing and storage space contains appropriate security documentation.

712 Goods Out Store

Goods awaiting despatch are stored in this area.

If GMP regulations are in force, a cage will be installed for secure storage of completed product awaiting quality control approval. A despatch weather cover is provided around the despatch door to protect outgoing goods from rain, etc, while being loaded.

6.7 PROCESS ROOMS CONTENTS LIST

Table 6.7.1 lists the process equipment contained in each room and has been used as the basis of the room layout sketches.

Each piece of equipment is prefixed by a meaningful code.

If the prefix is a letter, followed by three numbers then the equipment has been specified as being required for one of the two processes analysed in Section 7.

A prefix of PFE (Possible Future Equipment) indicates that a space has been allocated in the room for this item of equipment, which may be purchased and installed after the facility installation is complete.

A prefix of TBA (To be Advised) indicates that this piece of equipment is currently held by Biogal and not required for the specific process analysed but which may be usefully utilised in this room depending on the future development plans of Biogal and the condition of the equipment itself. Advice would therefore be sought before installation of this equipment.

In summary:

Q104 - Equipment required for specific process (Q104 in this example)

PFE - Possible Future Equipment

TBA - To Be Advised

TABLE 6.7.1 - ROOM CONTENTS LIST

PROCESS AND SERVICE EQUIPMENT LOCATION

304 Lower Fermentation Hall 1

301 (A&B) - 1000l Fermenters

305 Lower Fermentation Hall 2

Q301 (C&D) - 1000l Fermenters
Q912 - CIP Package
Q901 - Fermenter Gas Scrubber

409 Upper Fermentation Hall 1

F201A, F202A - Liquid sterilizing set suitable for 300l volumes
F301A, F302A - Liquid sterilizing set suitable for 1000l volumes
T301 (A&B) - 120l feed vessels
P301 (A&B) - Pumps for T301 (A&B)
T302A - 200l feed vessel
P302A - Pump for T302A
Q202 (A&B) - 60l fermenter packages
Q203 (A&B) - 300l fermenter packages
Q301 (A&B) - 1000l fermenter packages
X202A - Patch panel (fermenter make-up, fermenters)
X203A - Patch panel (60l, 300l fermenters)
X204A - Patch panel (300l, 1000l fermenters)
X301A - Patch panel (fermenter feeds)
TBA - 30l feed vessel and pumps
TBA - 120l feed vessel and pumps

410 Upper Fermentation Hall 2

F201B, F202B - Liquid sterilizing set suitable for 300l volumes
F301B, F302B - Liquid sterilizing set suitable for 1000l volumes
T301 (C&D) - 120l feed vessels
P301 (C&D) - Pumps for T301 (C&D)
T302B - 200l feed vessel

P302B	-	Pump for T302B
Q202 (C&D)	-	60l fermenter packages
Q203 (C&D)	-	300l fermenter packages
Q301 (C&D)	-	1000l fermenter packages
X202B	-	Patch panel (fermenter make-up, fermenters)
X203B	-	Patch panel (60l, 300l fermenters)
X204B	-	Patch panel (300l, 1000l fermenters)
X301A	-	Patch panel (fermenter feeds)
TBA	-	2 x 30l feed vessel and pumps
TBA	-	120l feed vessel and pumps

507 Dispensary

W101 (A,B&C)	-	Scales

508 Fermentation Make-up

T101	-	1 m^3 stirred tank
T102	-	500l stirred tank
T103	-	1 m^3 non-stirred tank
T104	-	500l non-stirred tank
P101	-	Pump for T101
P102	-	Pump for T102
P103	-	Pump for T103
P104	-	Pump for T104
F101	-	Clarifying filter for T101
F102	-	Clarifying filter for T102

510 Centrifuge Room

F402	-	Westfalia centrifuge
TBA	-	Vertical centrifuge

511 Filter Room

F600	-	Seitz pressure filter
T601	-	Stirred tank 100l
P601	-	Pump for T601
TBA	-	Broadbent
PFE	-	Crossflow filter

512 Extraction

V701	-	10l stirred glass reaction vessel
T702	-	10l header vessel for V701
V703	-	50l stirred glass reaction vessel
T703	-	25l header vessel for V703
T704	-	25l header vessel for V703
T705	-	25l header vessel for V703
T405	-	150l glass reaction vessel
T406	-	50l header vessel for T405
T407	-	50l header vessel for T405
T408	-	50l header vessel for T405
F701	-	Ceramic Nutsche filter
F702	-	Stainless steel Nustche filter
TBA	-	500l Lampart
TBA	-	250l Lampart
TBA	-	150l Lampart
TBA	-	50l Lampart
TBA	-	30l Lampart
TBA	-	Glass reaction vessel

513 Chromatography Room

T501	-	150l glass lined tank
T502	-	50l glass header vessel for T501
P501	-	Pummp for T501
C501 (A-D)	-	25 cm D glass chromatography columns
C503	-	Header tank for C501A
C504	-	Header tank for C501B
C505	-	Header tank for C501C
C506	-	Header tank for C501D
P503	-	Pump for C501A
P504	-	Pump for C501B
P505	-	Pump for C501C
P506	-	Pump for C501D
P507	-	Pump for wheeled vessel
PFE	-	Final product filter

515 Ultrafiltration Room

PFE	-	Ultrafiltration rig

516 Clean Make-up Room

T105 (A-D)	-	301 non-stirred vessel
T106 (A&B)	-	1201 non-stirred vessel
P105 (A-D)	-	Pumps for T105 (A-D)
P106 (A&B)	-	Pumps for T106 (A&B)

517 Evaporation Room

Q601 (A&B)	-	Buchi evaporation packages
Q701	-	Distillation package
E201	-	Vacuum set
E205	-	Wiped film evaporator

521 Drying Room

Q801 (A-X)	-	Drying ovens
Q803	-	Spray drier
Q804	-	Agitated bed drier
TBA	-	Paddle drier

522 Drier Services

Q802	-	Freeze drier

523 Freeze Drying Room

Q802	-	Freeze drier

524 Milling and Sieving Room

PFE	-	Mill and sieve

525 Blending and Packing Room

PFE	-	Blending equipment and scales

528 Rotary Vacuum Filter Room

Q401	-	Rotary vacuum filter package
T401	-	250l stirred jacketted vessel
T402	-	50l unstirred header tank for T401

T403	-	501 unstirred header tank for T401
P401	-	Pump for T401
T409	-	250l unstirred tank
P409	-	Pump for T409

701 Goods In Store

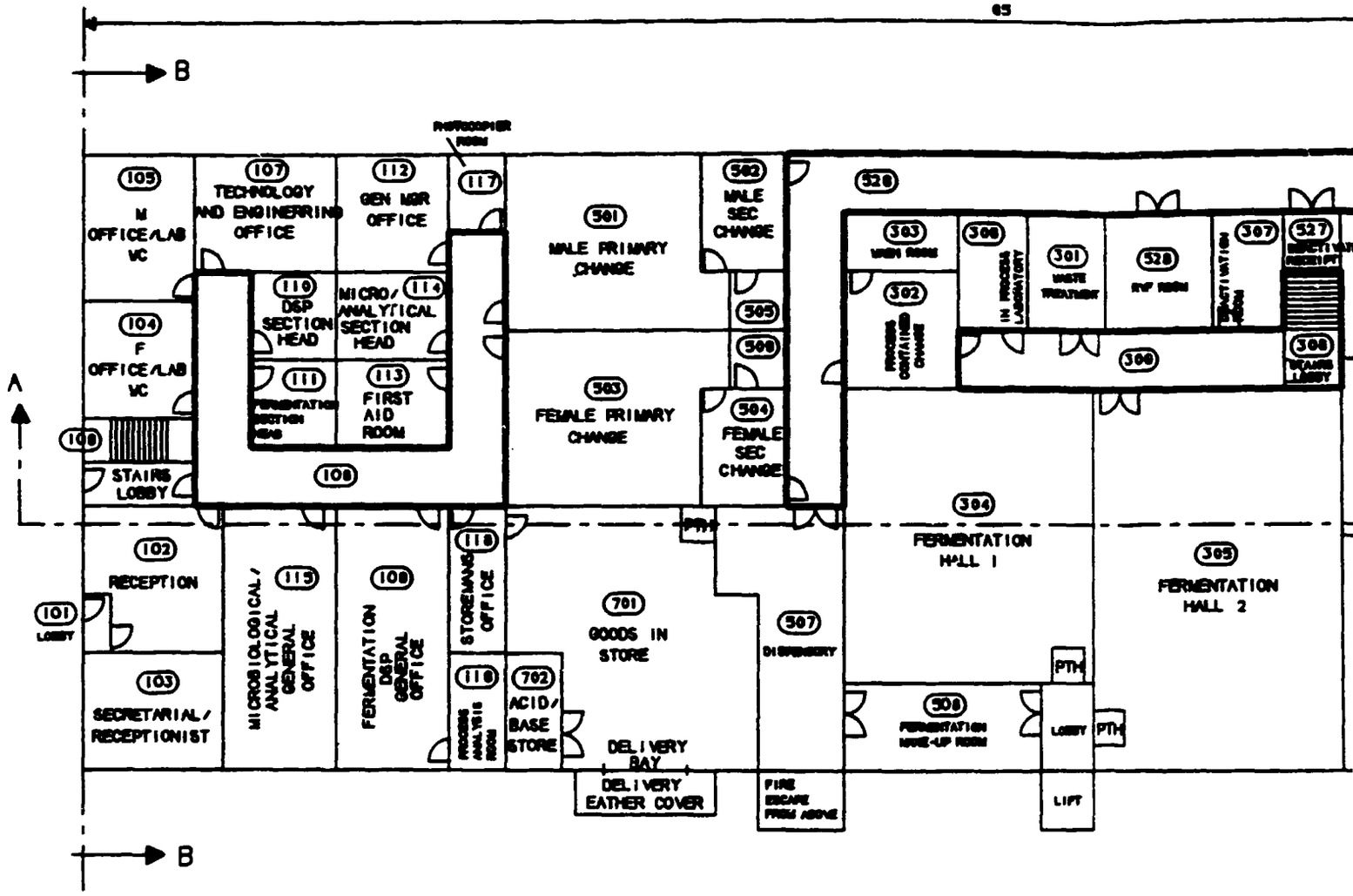
M102	-	Fork lift truck

703 Service Area

Q905	-	Demineralised water package
Q907 (A&B)	-	Steam boiler packages
Q908	-	Clean steam generator packages
Q909	-	Chiller package
Q910	-	Main air compressor
Q911	-	Secondary air compressor
Q913A	-	Water ring vacuum pump
Q913B	-	Oil ring vacuum pump
PFE	-	Expansion space left for unknown additional equipment

MISC

T901	-	Water break tank
Q(902-904)	-	Gas scrubber packages
Q906	-	Cooling tower package

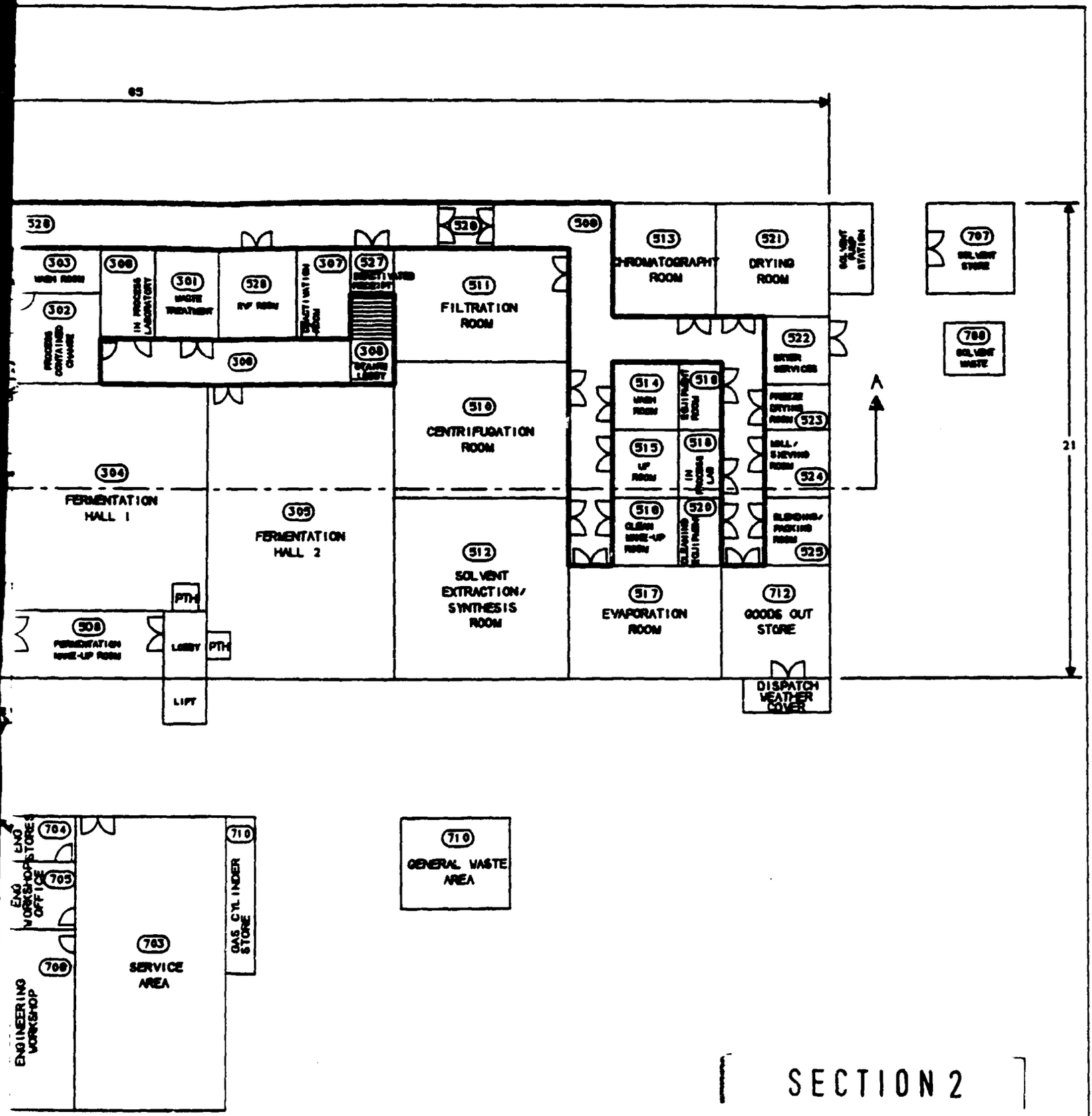


SECTION 1

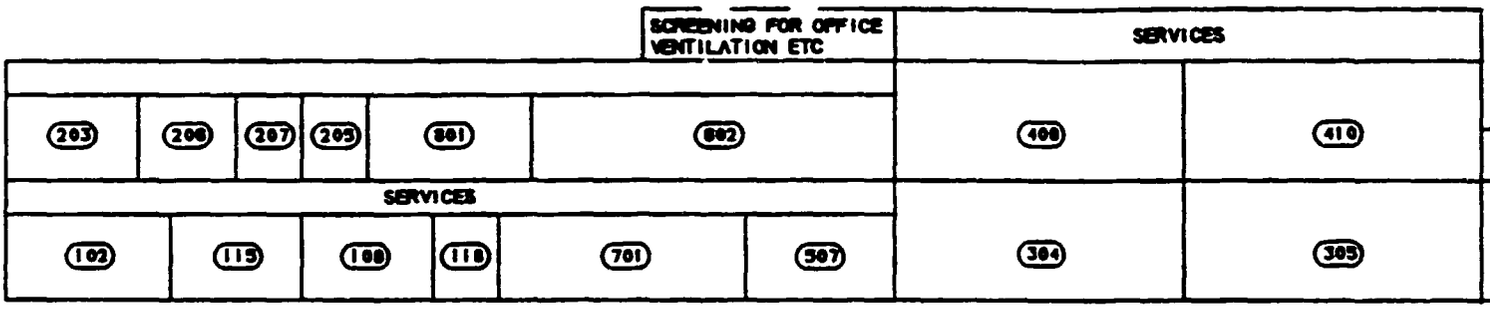
GRC CONSULTANTS
WESTBROOKE HOUSE 78 HIGH STREET
ALTON HANTS GU34 1EN
TEL: 0420 88847 FAX: 0420 88427

CLIENT

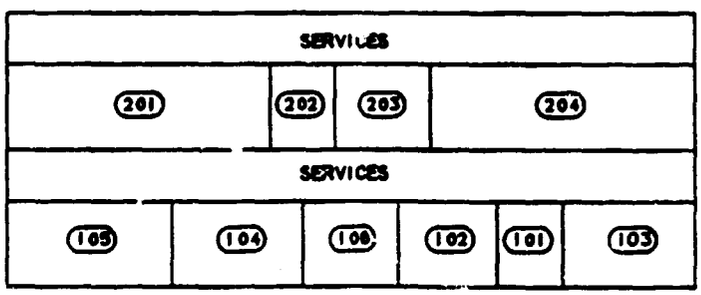
UNIDO P.O. BOX
A-1 400 VIENNA
AUSTRIA.
FAX 232138



GRC CONSULTANTS WESTBROOKE HOUSE 78 HIGH STREET ALTON HANTS GU34 1EN TEL: 0420 88847 FAX: 0420 88477	CLIENT UNIDO P.O. BOX 300 A-1 400 VIENNA AUSTRIA. FAX 232156	PROJECT BIOGAL TF/MLN/80/808	TITLE GROUND FLOOR ROOM LAYOUT DRAWING NUMBER 92/004/101	REVISION C



SECTION AA



SECTION BB

SECTION 1

GRC CONSULTANTS
WESTBROOKE HOUSE 70 HIGH STREET
ALTON HANTS GU34 1EN
TEL: 0420 88647 FAX: 0420 88427

CLIENT

UNIDO P.O. BOX 300
A-1 400 VIENNA
AUSTRIA.
FAX 232138

PROJECT

BI
TF

CE	SERVICES	
	(400)	(410)
	(304)	(305)

SERVICES					
(510)	(508)	(515)	(518)	(508)	(524)

SECTION AA

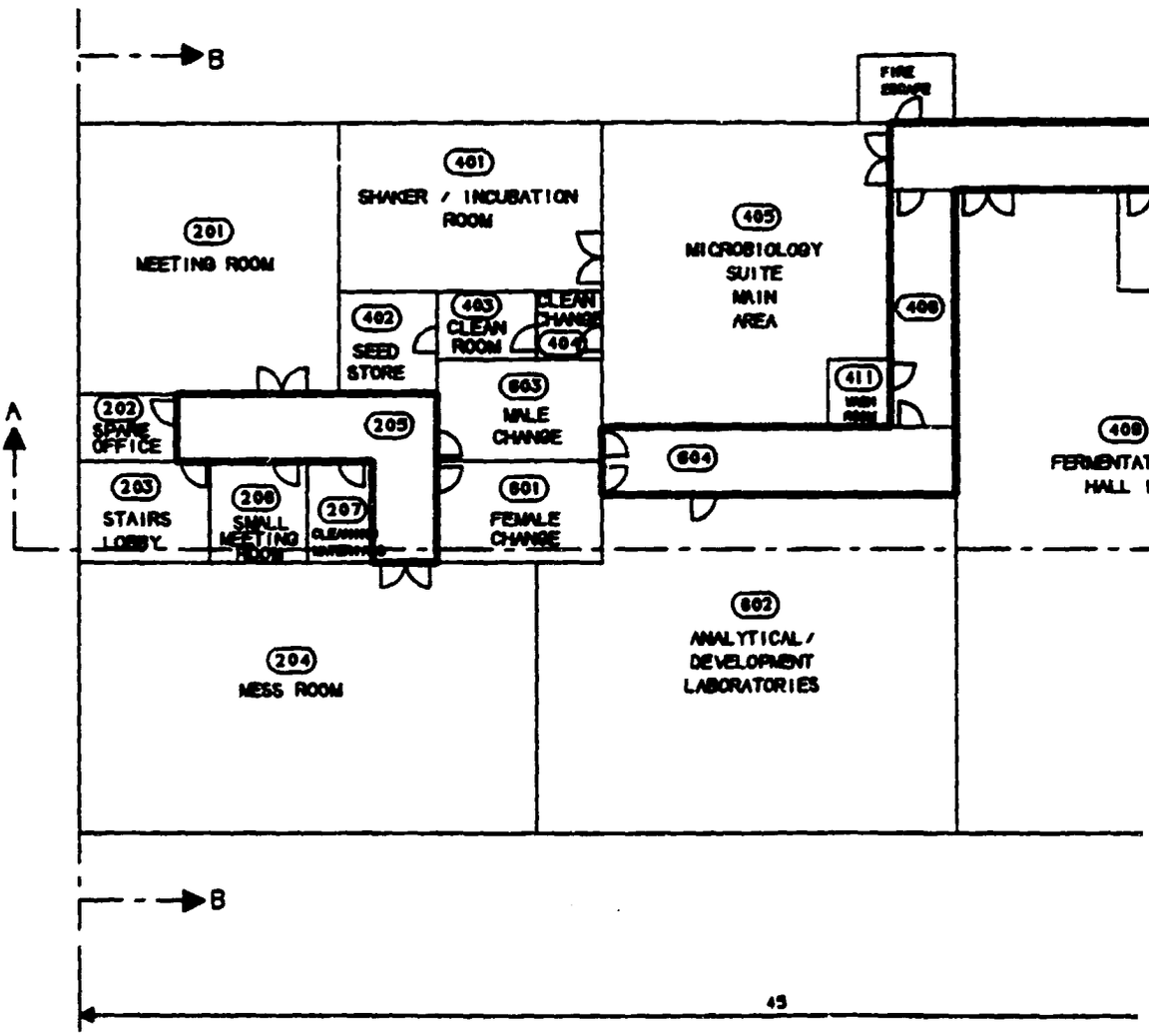
SERVICES			
(201)	(202)	(203)	(204)

SERVICES				
(104)	(106)	(102)	(101)	(103)

SECTION BB

SECTION 2

GRC CONSULTANTS	CLIENT	PROJECT	TITLE	
TERRACINE HOUSE 78 HIGH STREET ALTON HANTS GU34 1EN TEL: 0420 88847 FAX: 0420 88427	UNIDO P.O. BOX 300 A-1 400 VIENNA AUSTRIA. FAX 232136	BIOGAL TF/MLN/80/006	PROPOSED PILOT PLANT SECTIONS	
			DRAWING NUMBER 92/004/102	REVISION B



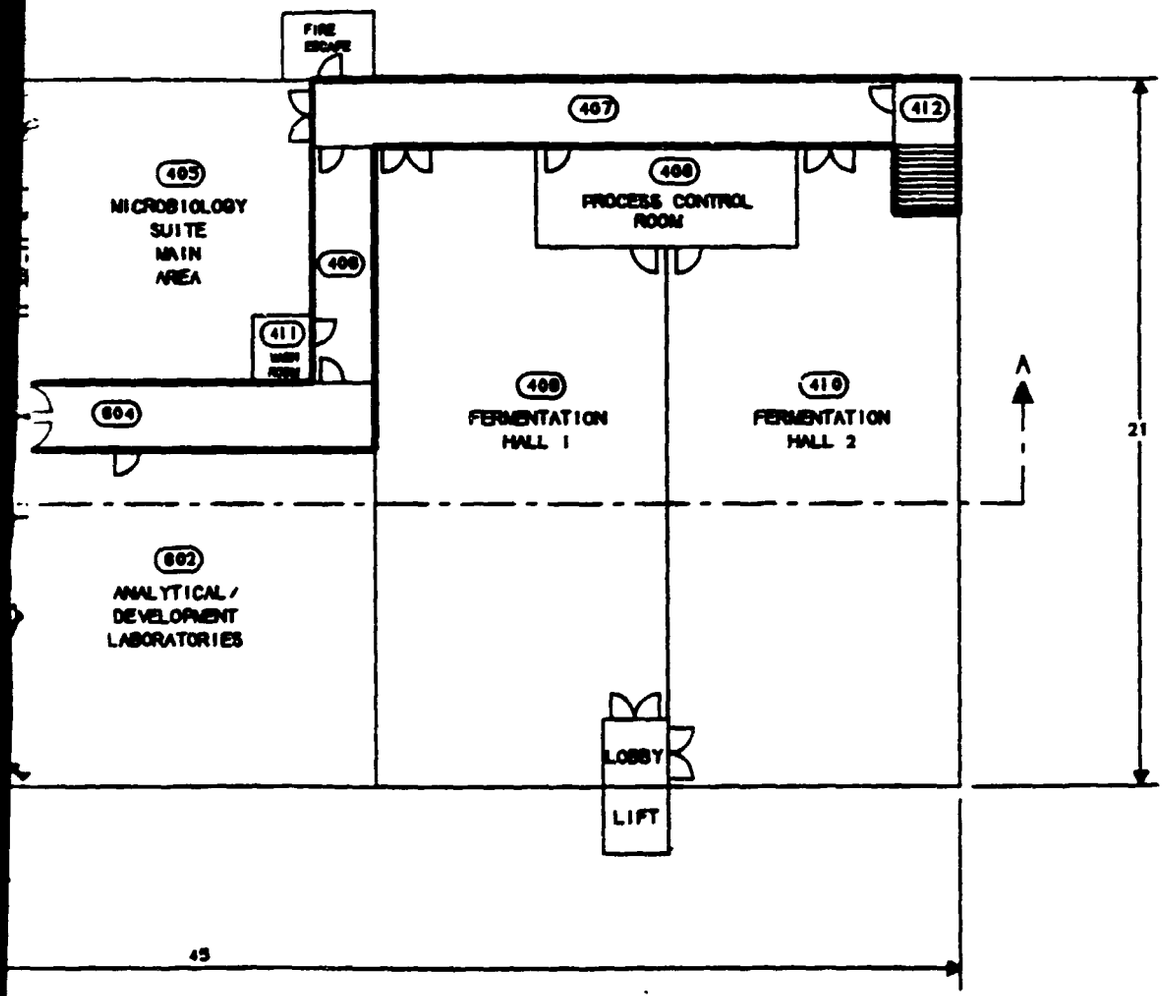
SECTION 1

GRC CONSULTANTS

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

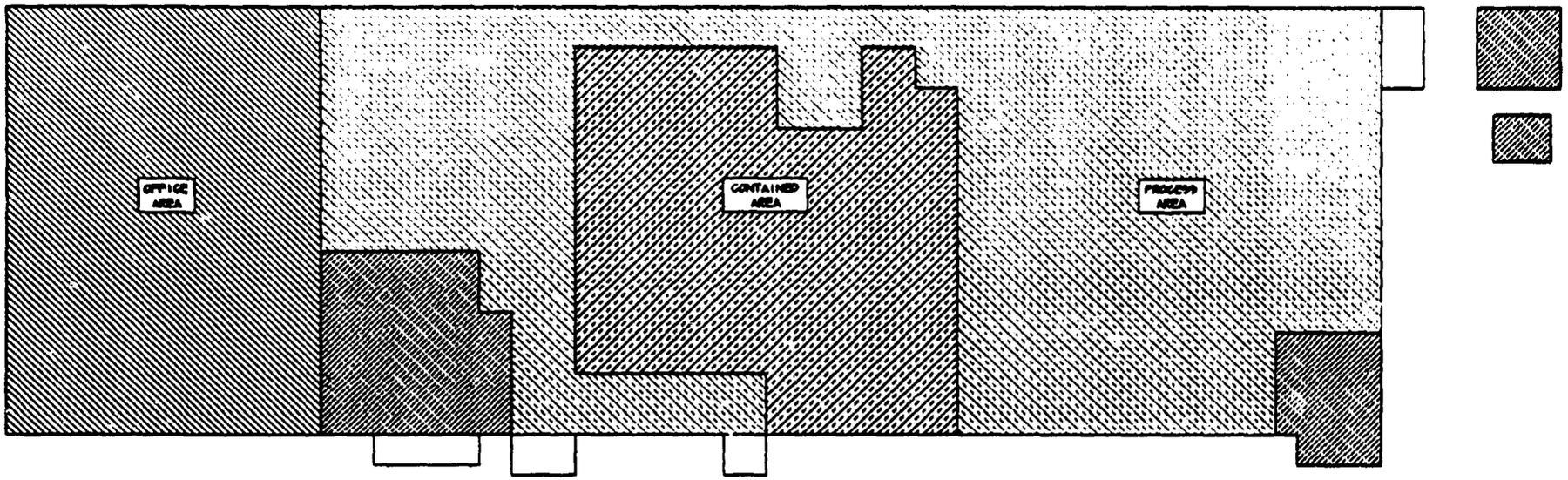
CLIENT

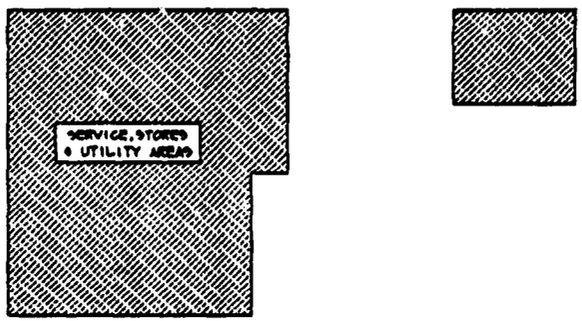
UNIDO P.O. BOX 3(
A-1 400 VIENNA
AUSTRIA.
FAX 232136



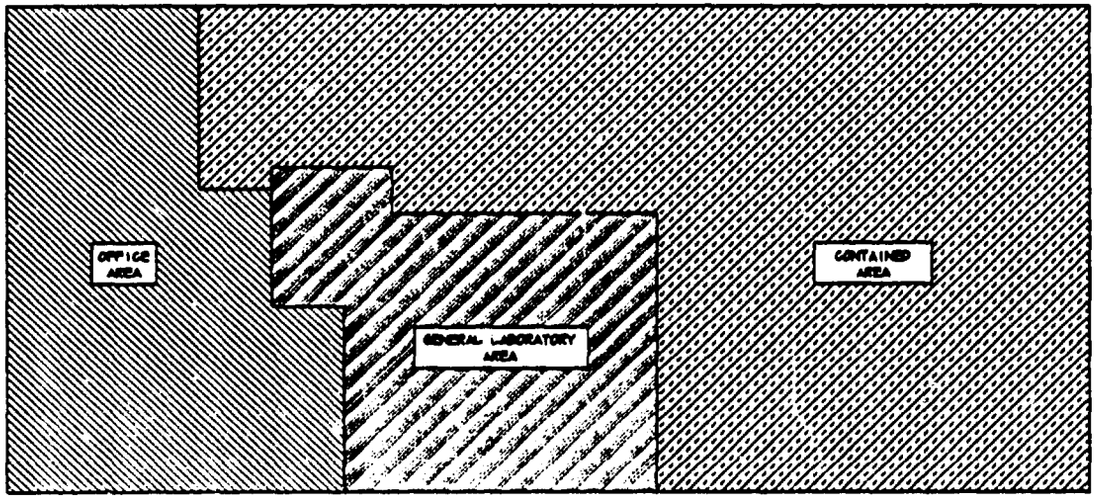
SECTION 2

GRC CONSULTANTS WESTBROOKE HOUSE 78 HIGH STREET ALTON HANTS GU34 1EN TEL: 0420 88849 FAX: 0420 88429	CLIENT UNIDO P.O. BOX 300 A-1 400 VIENNA AUSTRIA. FAX 232156	PROJECT BIOGAL TF/HUN/88/808	TITLE PROPOSED PILOT PLANT TOP FLOOR	
			DRAWING NUMBER 92/004/103	REVISION D

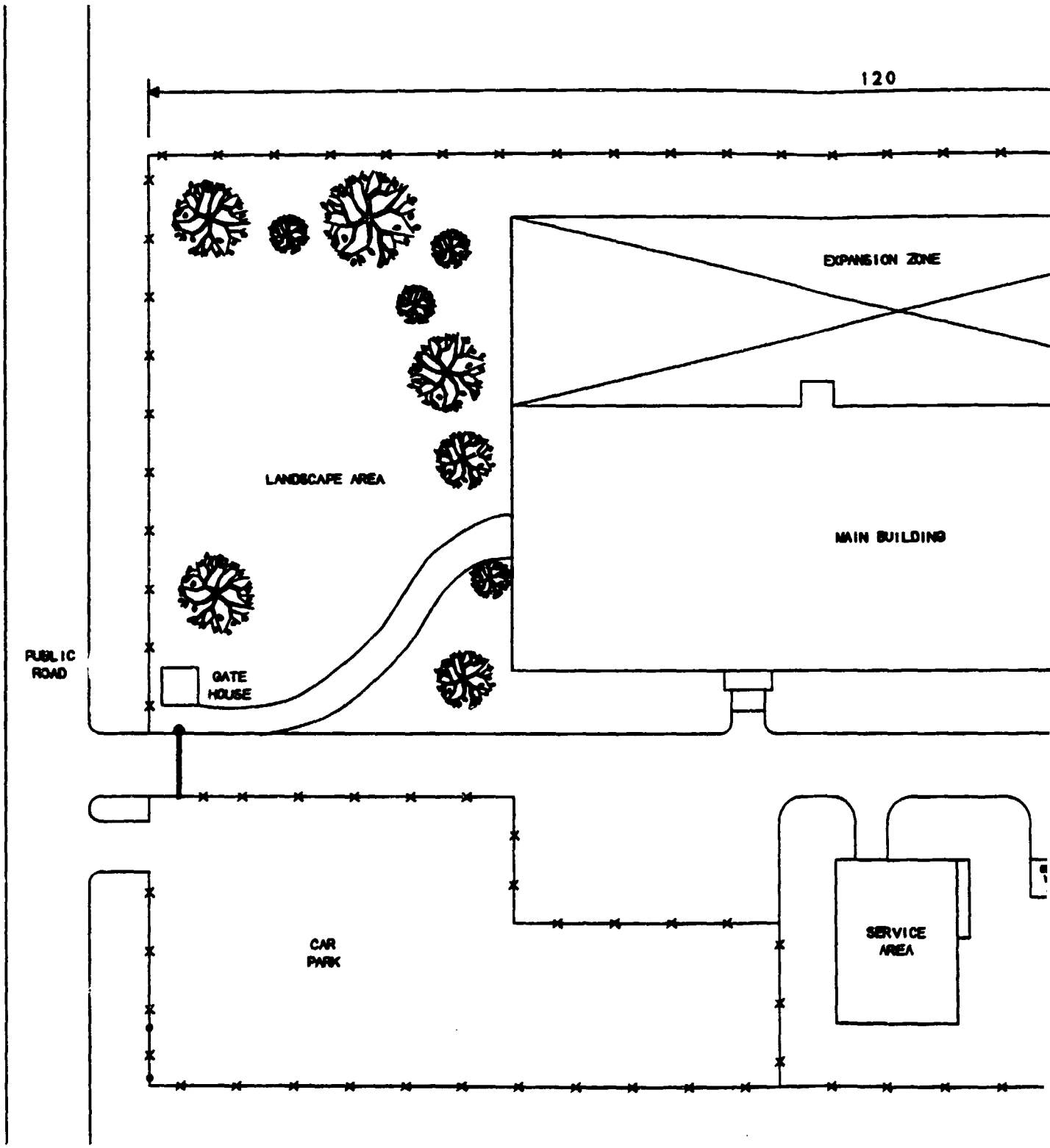




GNC CONSULTANTS WESTBROOKE HOUSE 70 HIGH STREET ALTON HANTS GU34 1EN TEL: 0420 88847 FAX: 0420 88427	CLIENT UNIDO P.O. BOX 300 A-1 400 VIENNA AUSTRIA. FAX 232138	PROJECT BIOGAL TF/GLN/88/888	TITLE GROUND FLOOR AREA LAYOUT DRAWING NUMBER 82/004/104 REVISION D



GRC CONSULTANTS WESTBROOKE HOUSE 78 HIGH STREET ALTON HANTS GU34 1EN TEL: 0420 88847 FAX: 0420 86427	CLIENT UNIDO P.O. BOX 300 A-1 400 VIENNA AUSTRIA. FAX 233130	PROJECT BIOGAL TF/KLN/88/808	TITLE FIRST FLOOR AREA LAYOUT	
			DRAWING NUMBER 92/004/105	REVISION A



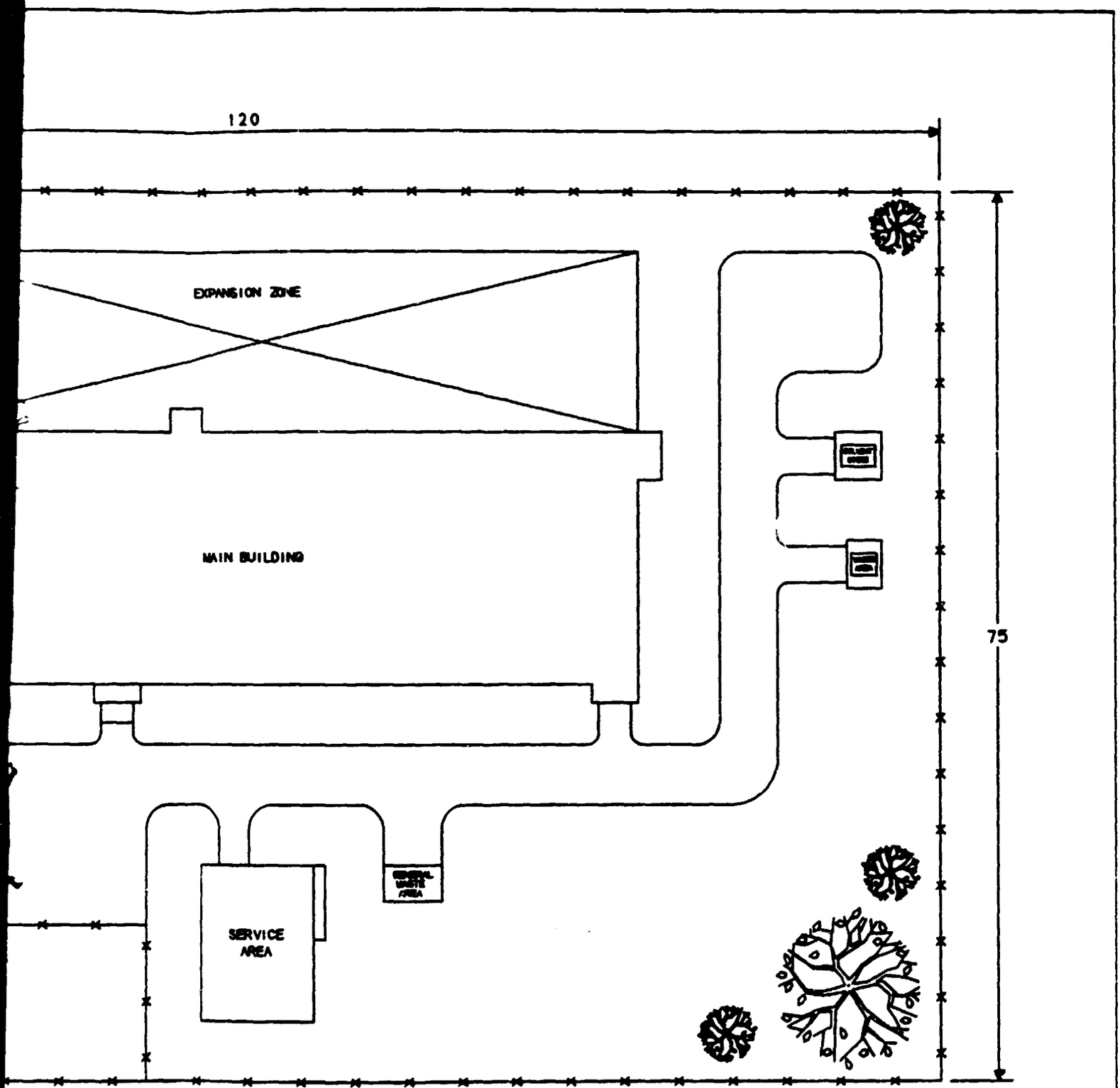
SECTION 1

GRC CONSULTANTS

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

CLIENT

UNIDO P.O. BOX 30
A-1 400 VIENNA
AUSTRIA.
FAX 232136



SECTION 2

GRC CONSULTANTS STRODE HOUSE 78 HIGH STREET ALTON HANTS GU34 1BN [illegible] FAX: [illegible]	CLIENT UNIDO P.O. BOX 300 A-1 400 VIENNA AUSTRIA. FAX 232136	PROJECT BIOGAL TF/HUN/90/008	TITLE PROPOSED SITE LAYOUT	
			DRAWING NUMBER 92/004/108	REVISION A

SECTION 7

EQUIPMENT

7.1 EQUIPMENT LIST

7.2 EXISTING BIOGAL EQUIPMENT

7 EQUIPMENT

7.1 EQUIPMENT LIST

The following equipment lists contain sufficient basic information to allow a reasonable order of magnitude capital cost estimate to be made (not part of this FED study). There is an entry for each identified key item of equipment, as per the Equipment Flow Diagrams, although some units are shown as complete packaged items with little detailing of individual components within a package.

The following abbreviations and notes apply to the Equipment List:-

Amb = Ambient Temperature
Atmos = Atmospheric Pressure
SS = Stainless steel, generally 316 grade
STD = Manufacturers Standard

A note is made in the 'Remarks' column if the item is a piece of equipment which exists in the present pilot plant at Debrecen and which could be used in the new facility, always providing its condition is satisfactory and its design suitable. Reference should be made to Section 7.2 which lists the existing equipment together with comments on conditions and suitability.

GRC Consultants
EQUIPMENT LIST

PLANT DESCRIPTION: BIOGAC PILOT PLANT
PROJECT NO.: TF/HUN/90/906
AREA NO.: 100
AREA:
LOCATION:
CLIENT: UNIDO
SHEET NO.: 1 OF 19

ITEM NO.	DESCRIPTION	NO. OFF	MATERIALS	CAPACITY OR RATE EACH	TEMPERATURE		PRESSURE		MOTOR POWER (EACH)		REMARKS	PROVISIONAL DIMENSIONS
					WORKING	DESIGN	WORKING	DESIGN	ABSORBED	INSTALLED		
M101	HAND POWERED TROLLEY	X	VARIOUS	—	—	-	—	—	—	—	MULTIPLE USE	NOMINAL 1000×500
M102	FORK LIFT TRUCK	1	VARIOUS	500kg	AMB.		ATMOS		—	-	MULTIPLE USE	
T101	SALTS DISSOLVING TANK	1	SS	1 m³	25	50	ATMOS		FRACTIONAL AGITATOR			
T102	SALTS DISSOLVING TANK	1	SS	500L	25	50	ATMOS		FRACTIONAL AGITATOR			
T103	SALTS SOLUTION HOLDING TANK	1	SS or GRP	1 m³	25	50	ATMOS		-	—	MAY BE COMBINED WITH T105-106	
T104	SALTS SOLUTION HOLDING TANK	1	SS or GRP	500L	25	50	ATMOS		-	—		
T105 A-D	HOLDING/FEED TANK	4	SS	30L	30	125	ATM.	2kg	—	—	E 106 (A→D)	
T106 A/B	HOLDING/FEED TANK	2	SS	120L	30	125	ATM.	2kg	—	—	E 107 (A/B)	
P101	SOLUTION TRANSFER PUMP	1	VARIOUS		25	50			0.5 kW NOMINAL		CENTRIFUGAL	
P102	SOLUTION TRANSFER PUMP	1	VARIOUS		25	50			0.5 kW NOMINAL		CENTRIFUGAL	

ISSUE LETTER	A	B	C	D	E	F	G
	7/7/92						

NUMBER OF ITEMS TO BE AGREED

GRC Consultants EQUIPMENT LIST	PLANT DESCRIPTION BIOGAC PILOT PLANT	PROJECT NO. TF/IHUN/10/906 LOCATION —	AREA NO. 100	AREA CLIENT UNIDO	SHEET NO. 2 OF 19

ITEM NO.	DESCRIPTION	NO. OFF	MATERIALS	CAPACITY OR RATE EACH	TEMPERATURE		PRESSURE		MOTOR POWER (EACH)		REMARKS	PROVISIONAL DIMENSIONS
					WORKING	DESIGN	WORKING	DESIGN	ABSORBED	INSTALLED		
P101	SOLUTION TRANSFER PUMP	1	VARIOUS		25	50			0.5 kW NOMINAL		CENTRIFUGAL	
P104	SOLUTION TRANSFER PUMP	1	VARIOUS		25	50			0.5 kW NOMINAL		CENTRIFUGAL	
P105 A-D	SOLUTION TRANSFER PUMP	4	VARIOUS		25	50			0.5 kW NOMINAL		CENTRIFUGAL	
P106 A/B	SOLUTION TRANSFER PUMP	2	VARIOUS		25	50			0.5 kW NOMINAL		CENTRIFUGAL	
F101	IN-LINE FILTER/STRAINER	1	SS	4m³/h	25	50			—		DUPLEX TYPE	
F102	IN-LINE FILTER/STRAINER	1	SS	4m³/h	25	50			—		DUPLEX TYPE	

ISSUE LETTER	A	B	C	D	E	F	G
	7/7/92						

GRC Consultants

EQUIPMENT LIST

PLANT DESCRIPTION	PROJECT NO.	AREA NO.	AREA
BIOGAL PILOT PLANT	TF/HUN/90/906	200	
	LOCATION —	CLIENT UNIDO	SHEET NO. 3 OF 19

ITEM NO.	DESCRIPTION	NO. OFF	MATERIALS	CAPACITY OR RATE EACH	TEMPERATURE		PRESSURE		MOTOR POWER (EACH)		REMARKS	PROVISIONAL DIMENSIONS
					WORKING	DESIGN	WORKING	DESIGN	ABSORBED	INSTALLED		
	MICROBIOLOGY CULTURE SUITE	—	—	CONTAINS AND VARIOUS	CULTURE STORAGE, SHAKERS, INCUBATORS LABORATORY ITEMS — ALL FROM BIOGAS							
X202 A-D	SEED FERMENTER PACKAGES	4	MAINLY SS	60 L	30	125	ATM	2bg			E102 (A-D)	
	COMPLETE WITH CONTROLLER, ACID, BASE, ANTIFOAM FEED TANKS AND PUMPS. REQUIRES INLET AIR STERILISING FILTERS AND OFF-GAS FILTERS (HEATED)											
X303 A-D	INOCULUM FERMENTER PACKAGES	4	MAINLY SS	300L	30	125	ATM	2bg			E103 (A-D)	
	COMPLETE WITH CONTROLLER, ACID/BASE/ANTIFOAM FEED TANKS AND PUMPS. REQUIRES INLET AIR STERILISING FILTERS AND OFF-GAS FILTERS (HEATED)											
X201	OFF-GAS MANIFOLD	1	VARIOUS	NOMINAL	— THIS MANIFOLD FEEDS TO X902 —							
X[illegible] A/B	PATCH PANEL	2	SS	THIS PANEL TO HOLDING TANKS OR FERMENTERS	COLLECTS FROM SALTS SOLUTION AND							FEEDS
X[illegible] A/B	PATCH PANEL	2	SS	THIS PANEL THE	COLLECTS INOCULUM		SEED		BROTH AND FERMENTERS		DISTRIBUTES	TO

ISSUE LETTER	A	B	C	D	E	F	G
	7/7/92						

GRC Consultants

EQUIPMENT LIST

PLANT DESCRIPTION	PROJECT NO.	AREA NO.	AREA
BIOGAL PILOT PLANT	TF/HUN/90/906	200	
	LOCATION ——	CLIENT UNIDO	SHEET NO. 4 OF 19

ITEM NO.	DESCRIPTION	NO. OFF	MATERIALS	CAPACITY OR RATE EACH	TEMPERATURE		PRESSURE		MOTOR POWER (EACH)		REMARKS	PROVISIONAL DIMENSIONS
					WORKING	DESIGN	WORKING	DESIGN	ABSORBED	INSTALLED		
X201 A/B	PATCH PANEL	2	SS	THIS PANEL COLLECTS INOCULUM BROTH AND DISTRIBUTES TO MAIN FERMENTERS							(OR TO HARVEST TRAIN)	
F201 A/B	LIQUID PREFILTER	2	SS		25	125	THESE ARE AS ALTERNATIVES TO HEAT		STERILISATION			
F202 A/B	LIQUID STERILISING FILTER	2	SS		25	125	—— AS ALTERNATIVES TO HEAT STERILISATION					

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EQUIPMENT LIST

PLANT DESCRIPTION	PROJECT NO.	AREA NO.	AREA
BIOGAC PILOT PLANT	TF/IHUN/90/906	300	
	LOCATION ——	CLIENT UNIDO	SHEET NO. 5 OF 19

ITEM NO.	DESCRIPTION	NO. OFF	MATERIALS	CAPACITY OR RATE EACH	TEMPERATURE		PRESSURE		MOTOR POWER (EACH)		REMARKS	PROVISIONAL DIMENSIONS
					WORKING	DESIGN	WORKING	DESIGN	ABSORBED	INSTALLED		
T301 A-D	FEED/STERILISING TANKS	4	SS	120L	30	125	ATMOS	2bg	——	——	E 108 (A-D) E 109 (A/B)	
T302 A/B	FEED/STERILISING TANKS	2	SS	200L	30	125	ATMOS	2bg	——	——	E 108 (A-D) E 109 (A/B)	
P301 A-D	FEED PUMP	4	SS	5 m³/h	30	125			NOMINAL 0·5	1 kW	CENTRIFUGAL OR METERING	
P302 A/B	FEED PUMP	2	SS	5 m³/h	30	125			NOMINAL 0·5	1 kW	CENTRIFUGAL OR METERING	
F301 A-D	FERMENTER	4	MAINLY SS	1000L	30	125	ATMOS	2bg			E 105 (A-D)	
	COMPLETE WITH EQUIPS NOT	CONTROLLER, ACID/BASE/ANTI FOAM FEED TANKS AND PUMPS. AIR STERILISING FILTER AND OFF-GAS FILTERS (HEATED)										
X301 A/B	PATCH PANEL	2	SS	THIS PANEL COLLECT FEED SOLUTIONS/MEDIA AND DISTRIBUTES TO THE FOUR FERMENTERS								

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EQUIPMENT LIST

PLANT DESCRIPTION	PROJECT NO.	AREA NO.	AREA
BIOGAC PILOT PLANT	TF/HUN/90/906	400	
	LOCATION ——	CLIENT UNIDO	SHEET NO. 6 OF 19

ITEM NO.	DESCRIPTION	NO. OFF	MATERIALS	CAPACITY OR RATE EACH	TEMPERATURE		PRESSURE		MOTOR POWER (EACH)		REMARKS	PROVISIONAL DIMENSIONS
					WORKING	DESIGN	WORKING	DESIGN	ABSORBED	INSTALLED		
T501	PH ADJUSTMENT VESSEL	1	GLASSLINED MILDSTEEL	250L	4/30	0/50	ATMOS	0·5bg			E 209 (POSSIBLE)	
T502	ACID HEAD TANK	1	SS OR GLASS	50/100 L	AMB	50	ATMOS	—			POSSIBLE FROM E213 (A-6)	
T503	ACID HEADTANK	1	GLASS	50/100L	AMB	50	ATMOS	—			POSSIBLE FROM E 213 (A-6)	
T504	RVF LIQUOR COLLECTION TANK	1	SS	250L	AMB	50	ATMOS	—				
P401	TRANSFER PUMP	1	SS		AMB				NOMINAL 1kW		POSITIVE DISPLACEMENT TYPE	
P402	DRUM TRANSFER PUMP	1	VARIOUS		AMB				NOMINAL		* THE NUMBER / TYPE OF THESE PUMPS	
P403	DRUM TRANSFER PUMP	1	VARIOUS		AMB				NOMINAL		TO BE AGREED SINCE SEVERAL	
P404	DRUM TRANSFER PUMP	1	VARIOUS		AMB				NOMINAL		COULD BE USED IN COMBINATION	
P405	LIQUOR TRANSFER PUMP	1	SS		AMB				NOMINAL		CENTRIFUGAL	

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EQUIPMENT LIST

PLANT DESCRIPTION	PROJECT NO.	AREA NO.	AREA
BIOGAC PILOT PLANT	TF/HON/90/906	400	
	LOCATION —	CLIENT UNIDO	SHEET NO. 7 OF 19

ITEM NO.	DESCRIPTION	NO. OFF	MATERIALS	CAPACITY OR RATE EACH	TEMPERATURE		PRESSURE		MOTOR POWER (EACH)		REMARKS	PROVISIONAL DIMENSIONS
					WORKING	DESIGN	WORKING	DESIGN	ABSORBED	INSTALLED		
M401 (A-x)	CLOSED CONTAINER (LIQ.)	X	SS	100L	25	50	ATMOS		—	—	MOVED ON HAND TROLLEY M101	
M402 (A-x)	CLOSED CONTAINER (SOLIDS)	X	SS	100L	25	50	ATMOS		—	—	MOVED ON HAND TROLLEY M101	
P401	ROTARY VACUUM FILTER	1	VARIOUS SS	$1 m^2$	25	50	ATM — VAC				PACKAGED E223	UNIT
	CONTAINING		THE RVF, VACUUM SET, VAPOUR/LIQUID SEPARATOR AND POSSIBLY A LIQUOR DISCHARGE PUMP									

NUMBER OF THESE UNITS TO BE AGREED - THEY ARE MULTIPLE USE.

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EQUIPMENT LIST

PLANT DESCRIPTION: BIOGAC PILOT PLANT

PROJECT NO.: TF/HUN/90/906

AREA NO.: 400 (P)

AREA:

LOCATION: ——

CLIENT: UNIDO

SHEET NO.: 8 OF 17

ITEM NO.	DESCRIPTION	NO. OFF	MATERIALS	CAPACITY OR RATE EACH	TEMPERATURE		PRESSURE		MOTOR POWER (EACH)		REMARKS	PROVISIONAL DIMENSIONS
					WORKING	DESIGN	WORKING	DESIGN	ABSORBED	INSTALLED		
T105	GENERAL PURPOSE VESSEL	1	SS or GLASS	150L	4/20	0/50	ATMOS		NOMINAL AGITATOR		E210 OR E214	
T106	HEAD TANK	1	SS or GLASS	50L	AMB		ATMOS		——		CONTAINS SOLVENT	
T107	HEAD TANK	1	SS or GLASS	50L	AMB		ATMOS		——		CONTAINS SOLVENT	
T108	HEAD TANK	1	GLASS	50L	AMB		ATMOS		——		CONTAINS ACID	
* P106	DRUM TRANSFER PUMP	1	VARIOUS		AMB		—		NOMINAL		SEE P102 etc	
* P107	DRUM TRANSFER PUMP	1	VARIOUS		AMB		—		NOMINAL			
* P108	DRUM TRANSFER PUMP	1	VARIOUS		AMB		—		NOMINAL			
P110	CENTRIFUGE FEED PUMP	1	SS		AMB				1.2kW		CENTRIFUGAL	
P102	CENTRIFUGE	1	CHANKY SS		25	50	—				SELF DISCHARGING DISC-STACK TYPE E218	

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GRC Consultants

EQUIPMENT LIST

PLANT DESCRIPTION: BIOGAC PILOT PLANT

PROJECT NO.: TF/HUN/90/906

AREA NO.: 500

AREA:

LOCATION: ——

CLIENT: UNIDO

SHEET NO.: 9 OF 19

ITEM NO.	DESCRIPTION	NO. OFF	MATERIALS	CAPACITY OR RATE EACH	TEMPERATURE		PRESSURE		MOTOR POWER (EACH)		REMARKS	PROVISIONAL DIMENSIONS
					WORKING	DESIGN	WORKING	DESIGN	ABSORBED	INSTALLED		
T501	PH ADJUSTMENT TANK	1	GLASS LINED MILD STEEL	150L	A/25	D/50	ATMOS		NOMINAL AGITATOR		POSSIBLE E210	
T502	HEAD TANK	1	GLASS	50L	AMB		ATMOS		—		POSSIBLE FROM E213 (A-G)	
T503	HEAD TANK	1	GLASS	100L	AMB		ATMOS		—		E213 (A-G)	
T504	HEAD TANK	1	GLASS	100L	AMB		ATMOS		—		E213 (A-G)	
T505	HEAD TANK	1	GLASS	100L	AMB		ATMOS		—		E213 (A-G)	
T506	HEAD TANK	1	GLASS	100L	AMB		ATMOS		—		E213 (A-G)	
C501 A-D	ION EXCHANGE COLUMN	4	GLASS		AMB		ATMOS		—		E217 A-D	
M501 (1-x)	CLOSED WHEELED CONTAINERS (LIQ.)	x	SS	250L	AMB		ATMOS		—		MULTIPLE USE	
X501	EXTRACT MANIFOLD	1	VARIOUS	—	AMB		ATMOS		—		COLLECTS SOLVENT VAPOURS - TO X903	

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PLANT DESCRIPTION	PROJECT NO.	AREA NO.	AREA
BIOGAC PILOT PLANT	TF/14UN /90/906	500	
	LOCATION _____	CLIENT UNIDO	SHEET NO. 10 OF 19

ITEM NO.	DESCRIPTION	NO. OFF	MATERIALS	CAPACITY OR RATE EACH	TEMPERATURE		PRESSURE		MOTOR POWER (EACH)		REMARKS	PROVISIONAL DIMENSIONS
					WORKING	DESIGN	WORKING	DESIGN	ABSORBED	INSTALLED		
P501	LIQUOR TRANSFER PUMP	1	SS		AMB				NOMINAL 0.5— 1.2kW		CENTRIFUGAL FLAME PROOF MOTOR	
* P502	DRUM TRANSFER PUMP	1	VARIOUS		AMB				NOMINAL		ANY MOTOR MUST BE FLAME PROOF - SEE P402 etc.	
P503	FEED PUMP	1	VARIOUS		AMB				NOMINAL		PERISTALTIC - FLAME PROOF MOTOR	
P504	FEED PUMP	1	VARIOUS		AMB				NOMINAL		PERISTALTIC FLAME PROOF MOTOR	
P505	FEED PUMP	1	VARIOUS		AMB				NOMINAL		PERISTALTIC FLAMEPROOF MOTOR	
P506	FEED PUMP	1	VARIOUS		AMB				NOMINAL		PERISTALTIC FLAME PROOF MOTOR	
P507	LIQUOR TRANSFER PUMP	1	SS		AMB				NOMINAL		CENTRIFUGAL - FLAMEPROOF MOTOR	
* P508	DRUM TRANSFER PUMP	1	VARIOUS		AMB				NOMINAL		MOTOR MUST BE FLAMEPROOF SEE P402 etc	

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EQUIPMENT LIST

PLANT DESCRIPTION: BIOGAS PILOT PLANT

PROJECT NO.: TF/HUN/90/906

AREA NO.: 600

AREA:

LOCATION: ——

CLIENT: UNIDO

SHEET NO.: 11 OF 19

ITEM NO.	DESCRIPTION	NO. OFF	MATERIALS	CAPACITY OR RATE EACH	TEMPERATURE		PRESSURE		MOTOR POWER (EACH)		REMARKS	PROVISIONAL DIMENSIONS
					WORKING	DESIGN	WORKING	DESIGN	ABSORBED	INSTALLED		
F601	PRESSURE NUTSCH FILTER	1	MAINLY SS		4/25	0/50			—		E215 (SEITZ)	400ϕ
M601 (A-X)	CLOSED WHEELED CONTAINER (LIQ.)	x	SS	100L	AMB		ATMOS		—		MULTIPLE USE	
M602 (A-X)	CLOSED WHEELED CONTAINER (SOLIDS)	x	SS	100L	AMB		ATMOS		—		MULTIPLE USE	
M603 (A-X)	CLOSED LIQUID CONTAINER	x	SS	100L	AMB		ATMOS		—		MULTIPLE USE, ON HAND TROLLEY/MIDI	
T601	SLURRY MAKE-UP TANK	1	CS	100L	AMB		ATMOS		NOMINAL AGITATOR		(HANDLES CHARCOAL)	
P602	TRANSFER PUMP	1	SS		AMB		—		NOMINAL		CENTRIFUGAL — FLAMEPROOF MOTOR	
P601	TRANSFER PUMP	1	CS		AMB		—		NOMINAL 0.5—1 kW		POSITIVE DISPLACEMENT — FLAMEPROOF MOTOR	
P603	TRANSFER PUMP	1	SS		AMB		—		NOMINAL		CENTRIFUGAL — FLAMEPROOF MOTOR	
A601	EVAPORATOR PACKAGE.	1	MAINLY GLASS	25/50L	20/50	50/100	ATMOS. TO FULL VAC		NOMINAL		E203 OR E204 (Büchi) FLAMEPROOF MOTOR	
	CONTAINS EVAPORATOR, HEATING BATH/MANTLE, CONDENSER, RECEIVERS (VACUUM SET?)											

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EQUIPMENT LIST

PLANT DESCRIPTION	PROJECT NO.	AREA NO.	AREA
BIOGAC PILOT PLANT	TF/HUN/90/906	600 P	
	LOCATION —	CLIENT UNIDO	SHEET NO. 12 OF 19

ITEM NO.	DESCRIPTION	NO. OFF	MATERIALS	CAPACITY OR RATE EACH	TEMPERATURE		PRESSURE		MOTOR POWER (EACH)		REMARKS	PROVISIONAL DIMENSIONS
					WORKING	DESIGN	WORKING	DESIGN	ABSORBED	INSTALLED		
V703	GENERAL PURPOSE VESSEL	1	SS or GLASS	50L	4/25	0/50	ATMOS		NOMINAL	STIRRER	POSSIBLE EX. IT	
T701	HEAD TANK	1	GLASS	25L	AMB		ATMOS		—		CONTAINS ACIDS	
T705	HEAD TANK	1	GLASS	25	AMB		ATMOS		—		CONTAINS VARIOUS SOLUTIONS	
P603	FILTER FEED PUMP	1	SS		AMB				NOMINAL		CENTRIFUGAL — FLAMEPROOF MOTOR	
P608	TRANSFER PUMP	1	SS		AMB				NOMINAL		CENTRIFUGAL — FLAMEPROOF MOTOR	
F601	PRESSURE NUTSCH FILTER	1	MAINLY SS		4/25	0/50			—		E(215) (SEITZ)	400 ϕ

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EQUIPMENT LIST

PLANT DESCRIPTION	PROJECT NO.	AREA NO.	AREA
BIOGAC PILOT PLANT	TF/HUN/90/906	700	
	LOCATION: —	CLIENT: UNIDO	SHEET NO. 13 OF 19

	ITEM NO.	DESCRIPTION	NO. OFF	MATERIALS	CAPACITY OR RATE EACH	TEMPERATURE WORKING	TEMPERATURE DESIGN	PRESSURE WORKING	PRESSURE DESIGN	MOTOR POWER (EACH) ABSORBED	MOTOR POWER (EACH) INSTALLED	REMARKS	PROVISIONAL DIMENSIONS
	V701	REACTION VESSEL	1	SS OR GLASS	10L	0/25	0/50	ATMOS		NOMINAL STIRRER		POSSIBLE E 214	
	V703	REACTION VESSEL	1	SS OR GLASS	50L	0/25	0/50	ATMOS		NOMINAL STIRRER		POSSIBLE E 214	
	T701	HEAD TANK	1	GLASS	10L	AMB		ATMOS		—		CONTAINS ACIDS	
	T703	HEAD TANK	1	GLASS	50L	AMB		ATMOS		—		CONTAINS SOLVENTS	
	F701	NUTSCH FILTER.	1	CERAMIC SS OR		AMB		ATMOS TO FULL VAC.				E 216 OR E232	
*	P701	DRUM TRANSFER PUMP	1	VARIOUS		AMB				NOMINAL		FLAMEPROOF MOTOR	SEE P402 etc
*	P703	DRUM TRANSFER PUMP	1	VARIOUS		AMB				NOMINAL		FLAMEPROOF MOTOR	SEE P402 etc
	X701	EXTRACT MANIFOLD	1	VARIOUS		AMB		ATMOS		—		COLLECTS DUSTS — TO Q904	

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EQUIPMENT LIST

PLANT DESCRIPTION	PROJECT NO.	AREA NO.	AREA
BIOGAZ PILOT PLANT	TF/HUN/90/906	700	
	LOCATION ——	CLIENT UNIDO	SHEET NO. 14 OF 19

ITEM NO.	DESCRIPTION	NO. OFF	MATERIALS	CAPACITY OR RATE EACH	TEMPERATURE		PRESSURE		MOTOR POWER (EACH)		REMARKS	PROVISIONAL DIMENSIONS
					WORKING	DESIGN	WORKING	DESIGN	ABSORBED	INSTALLED		
M701 (4 x)	CLOSED CONTAINER (CLIQ.)	x	SS	100L	AMB		ATMOS		—	—	MULTIPLE USE	
M702 (4 x)	CLOSED PRODUCT CONTAINER	x	SS	100L	AMB		ATMOS		—	—	MULTIPLE USE — ON HANDTRUCK / M101	
M703 (4 x)	CLOSED WASTE CONTAINER	x	ALUMINIUM	100L	AMB		ATMOS		—	—	MULTIPLE USE — ON HANDTRUCK / M101	
P701	DISTILLATION PACKAGE	1	MAINLY GLASS		90/100	0/150	ATMOS TO FULL VAC		—	—	POSSIBLE E202	
	CONTAINING —		REBOILER, PACKED COLUMN, CONDENSER,								RECEIVERS	
			(VACUUM SET LOCAL?)				ANY MOTORS MUST BE FLAMEPROOF.					

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EQUIPMENT LIST

PLANT DESCRIPTION	PROJECT NO.	AREA NO.	AREA
BIOGAC PILOT PLANT	TH/IHUN/90/906	800	
	LOCATION ——	CLIENT UNIDO	SHEET NO. 15 OF 19

ITEM NO.	DESCRIPTION	NO. OFF	MATERIALS	CAPACITY OR RATE EACH	TEMPERATURE		PRESSURE		MOTOR POWER (EACH)		REMARKS	PROVISIONAL DIMENSIONS
					WORKING	DESIGN	WORKING	DESIGN	ABSORBED	INSTALLED		
1801	DRYING OVENS	4	VARIOUS MAINLY SS		20/100	20/150	ATMOS TO FULL VAC.		——		E219 (A-D) CONNECTED TO INTEGRAL VACUUM SET	
1802	LYOPHILISER	1	VARIOUS				ATMOS TO FULL VAC				E 221	
1803	SPRAY DRIER	1	MAINLY SS		50/200	50/300	ATMOS		ELECTRICALLY HEATED		E220 · MOTORS etc MAY NEED TO BE FLAME PROOF	
MA801 (1-x)	CLOSED PRODUCT CONTAINER	x	SS	100L	AMB		ATMOS		——		MULTIPLE USE ON HAND TROLLEY	M101

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EQUIPMENT LIST

PLANT DESCRIPTION	PROJECT NO.	AREA NO.	AREA
FROGAL PILOT PLANT	TF/HUN/90/906	800 P	
	LOCATION ———	CLIENT UNIDO	SHEET NO. 16 OF 19

ITEM NO.	DESCRIPTION	NO. OFF	MATERIALS	CAPACITY OR RATE EACH	TEMPERATURE		PRESSURE		MOTOR POWER (EACH)		REMARKS	PROVISIONAL DIMENSIONS
					WORKING	DESIGN	WORKING	DESIGN	ABSORBED	INSTALLED		
V-801	GENERAL PURPOSE VESSEL	1	SS or GLASS	10L	4/25	D/50	ATMOS		NOMINAL STIRRER		POSSIBLE E214	
V-702	HEAD TONIC	1	GLASS	10L	AMB		ATMOS		——		CONTAINS SOLUBILITS	
* P-701	DRUM TRANSFER PUMP	1	VARIOUS		AMB				NOMINAL		FLAMEPROOF MOTOR SEE P402 etc.	
S-801	AGITATED BED DRYER	1	VARIOUS, MAINLY SS		50/100	150	ATMOS		NOMINAL 1— 2 kW		MOTORS MAY NEED TO BE FLAMEPROOF	
	THIS DRYER IS FITTED WITH DUST EXPLOSION RELIEF DUCTING (HENCE LOCATION OF THE UNIT IS IMPORTANT										E222	
M-801 (1-7)	CLOSED PRODUCT CONTAINERS	7	SS	100L	AMB		ATMOS		——		MULTIPLE USE, ON HAND TROLLEY M101	

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		LOCATION —	CLIENT UNIDO	SHEET NO. 17 OF 19

ITEM NO.	DESCRIPTION	NO. OFF	MATERIALS	CAPACITY OR RATE EACH	TEMPERATURE		PRESSURE		MOTOR POWER (EACH)		REMARKS	PROVISIONAL DIMENSIONS
					WORKING	DESIGN	WORKING	DESIGN	ABSORBED	INSTALLED		
P101	EXTRACT SCRUBBING PACKAGE	1	VARIOUS		AMB		ATMOS		NOMINAL FAN 2kW			
	PACKAGE INCLUDES		SCRUBBING LIQUOR		TANK,		PACKED COLUMN,		CIRCULATING PUMP		AND EXHAUST FAN	
P102	EXTRACT SCRUBBING PACKAGE	1	VARIOUS		AMB		ATMOS		NOMINAL FAN 2kW			
	PACKAGE INCLUDES		SCRUBBING LIQUOR (USES CAUSTIC SODA		TANK,		PACKED LIQUOR)		COLUMN,		CIRCULATING PUMP AND EXHAUST FAN	
V103	SOLVENT VAPOUR ADSORBER	1	MAINLY CS		AMB		ATMOS		NOMINAL			
	THIS PACKAGE CONTAINS SOLVENT ADSORPTION BEDS, RECOVERY AND ADSORBENT REGENERATION.								COMPLETE WITH MOTORS MUST BE FLAME-PROOF			
X-104	DUST EXTRACT SYSTEM	1	MAINLY CS		AMB		ATMOS		NOMINAL FAN 2kW			
	THIS PACKAGE		CONTAINS	DUST COLLECTION UNIT (BAG FILTERS) AND EXHAUST FAN.								
T105	WATER DEMINERALISING PACKAGE	1	VARIOUS		AMB/50				NOMINAL-			
	PACKAGE TO BE PROPRIETARY REGENERATION						ION EXCHANGE UNIT		COMPLETE WITH FEED TANKS			
	CONTROLS AND						SALTS/LIQUIDS AND					

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PLANT DESCRIPTION	PROJECT NO.	AREA NO.	AREA
BIOGAC PILOT PLANT	TF/HUN/90/906	900	
	LOCATION ——	CLIENT UNIDO	SHEET NO. 18 OF 19

ITEM NO.	DESCRIPTION	NO. OFF	MATERIALS	CAPACITY OR RATE EACH	TEMPERATURE		PRESSURE		MOTOR POWER (EACH)		REMARKS	PROVISIONAL DIMENSIONS
					WORKING	DESIGN	WORKING	DESIGN	ABSORBED	INSTALLED		
V-06	COOLING TOWER	1	VARIOUS		AMB		ATMOS		NOMINAL 5 kW FANS			
	PACKAGED UNIT COOLING	—	FAN ASSISTED AIR FLOW, COMPLETE WITH WATER BASIN, WATER SUPPLY/CIRCULATION PUMP AND BLOW-DOWN.									
(P-07)	STEAM BOILER	2	VARIOUS	(TO BE DECIDED)								
	PACKAGED UNITS, CONTAINING BOILERS, HOTWELLS, CONDENSATE RETURN, FLUE GAS STACKS — BOILER WATER FEED PUMPS — CONTROLS											
D-08	CLEAN STEAM GENERATOR	1	MAINLY SS	(TO BE AGREED —)					NOMINAL		PROPRIETARY PACKAGED UNIT	
V-09	CHILLER	1	VARIOUS	(TO BE DECIDED —)					COULD BE 10 kW		PROBABLY BRINE (COULD BE GLYCOL)	
	PROPRIETARY PACKAGE, CONTAINING COMPRESSOR, COOLER, BRINE TANK, BRINE CIRCULATION PUMP CONTROLS											
P-10	AIR COMPRESSOR (FERMENTATION)	1	MAINLY CS	(TO BE DECIDED —)					UP TO 10 kW		SUPPLIES AIR TO MAIN FERMENTERS	
	COMPLETE PACKAGE TO CONTAIN, INLET AIR FILTER/SILENCER, COMPRESSOR, COOLER, AND AIR CONTROLS											
V-11	AIR COMPRESSOR (INSTRUMENTS)	1	MAINLY CS	(TO BE DECIDED)	—		PACKAGE AS PER Q-10 - SUPPLIES PLANT AND INSTRUMENT AIR					

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PLANT DESCRIPTION	PROJECT NO.	AREA NO.	AREA
BIOGAC PILOT PLANT	TF/HUN/90/906	900	
	LOCATION ——	CLIENT UNIDO	SHEET NO. 19 OF 19

ITEM NO.	DESCRIPTION	NO. OFF	MATERIALS	CAPACITY OR RATE EACH	TEMPERATURE		PRESSURE		MOTOR POWER (EACH)		REMARKS	PROVISIONAL DIMENSIONS
					WORKING	DESIGN	WORKING	DESIGN	ABSORBED	INSTALLED		
X112	CIP PACKAGE	1	MAINLY SS	$1 m^3$	25/110	150	ATMOS		NOMINAL PUMP 1 kW		CONTAINS 20% CAUSTIC SODA	
	PROPRIETARY PACKAGE CONTAINING CONTROLS, CIRCULATION TANK, SUPPLY PUMP, IN-LINE FILTER (DUPLEX TYPE) REMOTE LOCATION RETURN PUMP(S).											
T113	VACUUM	X	VARIOUS	(TO BE DECIDED)							COULD BE E201	
	VARIOUS SETS		INCLUDING OIL RING, WATER RING PUMPS AND STEAM EJECTOR TYPE.								E 225 E 226	
T101	WATER BREAK/HEAD TANK	1	GALVANISED STEEL	$5 m^3$	AMB		ATMOS		—		LOCATED AT HIGHEST LEVEL.	

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7.2 EXISTING BIOGAL EQUIPMENT

The following tabulation gives outline details of existing Biogal equipment which may be usable in the new development facility. The following notes apply:

(x) = Age in years (as quoted by Biogal)
(?) = age unknown

(N) = New condition, or not more than 1 year old

(GC) = Good condition, reusable with little or no modification

(RC) = Reasonable condition but may need some refurbishment, e.g. new seals, gaskets, needed, components need overhaul or renewal

(PC) = Poor condition, not recommended for reuse

See also Notes (x) as appropriate. Reference may also be made to the GMP Audit of the existing pilot plants (4) for notes on the suitability of equipment in a new biotechnology development facility. Particular attention is drawn to the notes made in (4) concerning the various fermenters.

ITEM	DESCRIPTION	AGE	CONDITION	NOTES
E101	Lab Fermenter Rig 15L	14	RC	-
E102 (A-D)	Seed/Inoculum Fermenters 60L	15	GC	(1)
E103 (A-D)	Inoculum/Main Fermenters 300L	4	GC	(1)
E104 (A-D)	Main Fermenters 600L	Old	PC	(2)
E105 (A-D)	Main Fermenters 1000L	1	N	(1)
E106 (A-D)	Feed Vessels 30L	4	GC	
E107 (A/B)	Feed Vessels 120L	4	GC	(3)
E108 (A-D)	Feed Vessels 120L	1	N	(3)
E109 (A/B)	Feed Vessels 200L	1	N	(3)
E110	Air Filter	Old	PC	
E111	Various Glass Feed Vessels			(4)
E201	Steam Jet Vacuum Set	10	GC	
E202	Distillation Unit 50L	10	GC	
E203	Rotating Evaporator 50L	10	RC	
E204	Rotating Evaporator 25L	10	GC	
E205	Wiped Film Evaporator	10	GC	
E206	Basket Centrifuge 800 dia	30	PC	(5)
E207	Tubular Centrifuge 300 dia	10	RC	
E208	GLMS Reaction Vessel 500L	15	RC	(6)
E209	GLMS Reaction Vessel 250L	5	RC	(6)
E210	GLMS Reaction Vessel 150L	5	RC	(6)
E211	GLMS Reaction Vessel 50L	12	RC	(6)
E212	GLMS Reaction Vessel 30L	12	RC	(6)
E213 (A-G)	Glass Feed Vessel 3 x 50L, 4 x 100L	?	GC	(4)
E214 (A-E)	Glass Reaction Vessel Range of volumes, 10-50-100L	Old	RC	(7)
E215	Pressure Nutsche Filter 400 dia	7	RC	
E216	Ceramic Nutsche Filter 300 dia	5	RC	
E217 (A-D)	Ion Exchange Columns	?	RC	(8)
E218	Centrifugal Separator	8	RC	
E219 (A-D)	Drying oven - two off - two off	5 1	GC N	
E220	Spray Drier	1	N	
E221	Freeze Drier	20	GC	

E222	Agitated Bed Drier	15	GC	
E223	Rotary Vacuum Filter 1 m^2	5	GC	
E224	Centrifugal Pumps - various	?	various	(9)
E225	Vacuum Pump (Water Ring)	10	RC	
E226	Vacuum Pump (Oil Ring)	10	RC	
E227	Scales 0-5 kg	?	GC	
E228	Scales 0-50 kg	?	GC	
E229	Scales 0-200 kg	?	GC	
E230	Vacuum Tank 1 m^3	Old	PC	
E231	Water Tank 1 m^3	Old	PC	
E232	Pressure Nutsche Filter 300 dia (stainless steel)	?	RC	(10)
E233	Scales 0-100 kg	?	GC	
E234	Scales 0-1 kg	?	GC	
E235	Solvent Sensor	?	GC	
E301	Mass Spectrograph (FQ64) Liquid	2	GC	(11)
E302	Mass Spectrograph (FQ64) Liquid	2	GC	(11)
E303	Mass Spectrograph (FQ64) Liquid	2	GC	(11)
E304	Mass Spectrograph (FQ64) Liquid	2	GC	(11)
E305	Mass Spectrograph (FQ64) Gas phase	2	GC	(11)
E306	Mass Spectrograph QC300C	8	GC	
E307	HPLC (Gilson)	1	N	
E308	HPLC (LKB)	1	N	
E309	HPLC (H.Pack)	5	GC	
E310	Contiflow Photometric Analyser	3	GC	
E311	Contiflow Photometric Analyser	3	GC	
E312	Contiflow Photometric Analyser	3	GC	
E313	Spectrophotometer	5	GC	
E314	Lab Balances - various	?	GC	
E315	Lab Bench Centrifuges (2 off)	?	GC	
E316	Lab Size Fridges (4 off)	?	GC	
E317	Laminar Flow Bench	Old	GC	
E318	Small Bucchi Evaporator	?	GC	
E319	Domestic Washing Machine	?	GC	

Notes:

(1) See Ref (4) for fuller description of condition and possibilities for reuse.

(2) Agreed to be scrapped.

(3) All fitted with in situ weighing devices.

(4) May need plastic film overwrapping for extra protection.

(5) Not recommended for reuse.

(6) The condition of the glass lining on all these vessels needs thorough checking with spark and continuity detectors.

(7) Need careful checking and improved seals on stirrers.

(8) See Ref (4) for need for extra protection of nozzles, etc.

(9) Only the newer pumps should be considered for reuse.

(10) Made by Biogal, internal condition not known.

(11) All the laboratory, E301-E319, is in good condition and should be relocated to the new facility.

SECTION 8

UTILITIES AND SERVICES

8 UTILITIES AND SERVICES

For the purposes of this FED study, it is assumed that the new facility is located on a 'greenfield' site and utilities will have to be generated as needed.

The plant room contains all the equipment and facilities used for generating and distributing the more significant utilities and services which include the following:

- Steam generation: two independent 75% capacity boilers to provide general domestic heating steam and industrial grade steam to heating jackets on tanks and vessels as appropriate.

- Clean steam: a clean steam generator, fed from the steam boilers, is installed to provide clean sterilizing steam used on the internals of fermenters, etc, and in the various autoclaves if and when used.

- Demineralising water unit: this is used to provide boiler feed water and also water for the washing up area and is distributed generally around the facility as required.

- Pyrogen Free Water (PFW): In the future a PFW unit may be installed to provide this utility mainly to the large volume users in the pilot plant. It may be appropriate to install a PFW ring main to serve the other laboratories but, depending on the usage requirements in these individual laboratories, it may be more appropriate to provide them with their local individual PFW water generators.

- Water for Injection (WFI): it is unlikely that WFI will be generally required but if the need arises for this utility, it may be more appropriate to provide it from sterile containers as and where needed.

- Air compressors: two compressors are installed, one to provide air to the large users in the fermentation pilot plants and a second smaller compressor is installed to provide general plant air throughout the facility together with instrument air.

- Vacuum: general purpose vacuum sets are installed to provide a general vacuum utility. Vacuums in the laboratories may be provided if required by underbench mounted individual vacuum pump sets.

- Chilled water: a small fridge plant is installed to generate chilled water for use primarily in the fermenter halls. It may also be needed for the various HVAC urits but this will be determined at a later stage when the precise requirements for HVAC are known and the design of the units is agreed. Such units may well have their integral fridge plants, hence the need for the plant room chilled water unit may be limited to providing this utility for fermenter and other equipment cooling in the downstream processing areas.

Attached to the plant room is a plant engineers office and workroom where a limited amount of mechanical fitting work, overhaul and repairs to such things as pumps, etc, may be carried out. It is also anticipated that the Engineers Workshop is also located in this area.

SECTION 9

INSTRUMENTATION AND CONTROL

9 INSTRUMENTATION AND CONTROL

It is generally recognised and accepted that one of the key functions of a development facility is to generate, acquire and process data from experiments and test runs, etc. The Biogal new development facility is no exception and they already have a computer based data acquisition and fermenter process control computer installed at the existing Debrecen pilot plant. It is therefore intended that the new development facility should continue to use a computer-based automated approach to process control and data processing.

The notes given in this section are intended to give a general view of the approach intended; they are not meant to be a definitive statement of exactly what has to be installed. The details of the system will be developed and agreed with Biogal at the detailed design stage.

9.1 CONTROL PHILOSOPHY

9.1.1 System Structure

Broadly speaking two distinct control architectures exist for the 'automation' of the development facility. The first is a centralised process control structure in which all the process operations are controlled and monitored directly from a central computer. The second structure is termed distributed control. Under this arrangement, process areas or packages have their own control systems which are responsible for all local control and monitoring. Centralised control and monitoring is achieved by having a computer system which communicates with the individual control packages but this computer system is not responsible for the control of the individual process elements within each package.

A centralised process control system has the advantage that the control and monitored data are by the nature of the system available at one place. Control interlocks between the process stages are easy to implement. However, system design is complicated and difficult to co-ordinate. Installation is expensive and time consuming as there are many more cable runs required. If the central control system goes down then all processing and control ceases.

Distributed control, however, gets round many of the disadvantages of a single central control system by leaving the control of individual process packages to localised stand-alone controllers such as programmable logic controllers (PLC). These individual units are linked together, with a network, to a central computer which can provide supervisory control and data acquisition (SCADA) as required. The advantages offered by distributed control systems are:

- Greater intrinsic reliability. If one area of the plant goes down this will not affect unrelated areas of the process.

- Maintenance can be carried out on individual process packages without having to shut down the whole system.

- Control system faults can be isolated more easily.

- Installation and commission is simplified as individual packages can be debugged separately.

- Display of parameters and control can easily be provided local to the process.

- Easier expansion of the process.

There are, however, some disadvantages with the distributed control approach. Many process packages are controlled by vendor specified controllers. This can sometimes make network interfacing to these packages complex. Maintenance is also more of a problem as knowledge of more control systems is required. This problem is offset by the reduced complexity of the individual systems when compared with the huge complexity of a centralised controller.

9.1.2 Overview of Proposed System

The control philosophy proposed for the new development facility is based on a distributed control structure. This control structure mirrors the following discrete processing areas:

- Salts make-up and feedstock preparation
- Seed fermenters, main fermenters, harvest tanks and CIP plant
- Biomass filtration and handling system
- Solvent extraction and evaporation package
- Solvent storage and recovery plant
- Plant utilities

Each area has various plant items and process parameters to control and monitor. Areas which are duplicated such as the fermenters and centrifuges have their own control system. This is imperative if the system is to be truly distributed and offer system reliability.

It is envisaged that local operator control of each process area is required, hence process parameters and data are available locally to the operator, together with alarm notification and overrides. Although the control systems for each process area are autonomous there is some communication between each system to provide necessary control interlocks.

These interlocks prevent incorrect, untimely and dangerous operation of processes. It is preferable for these interlocks to be implemented by direct connection between the individual control systems rather than indirectly through a supervisory control system. This removes the risk of the supervisory system going down and stopping all operations within the facility.

The supervisory control and data acquisition system is responsible for monitoring and logging all aspects of the plant and is control room based PC which communicates directly with the individual control systems via a low volume data network.

The operator is alerted to alarm conditions detected by the individual control packages. Additional alarm conditions are able to be programmed into the systems in the control room.

9.1.3 Individual Area Philosophy

Salts Make-up and Feedstock Preparation

The salts and feedstock preparation area contains packages which only require local control by an operator. There is direct communication with the fermentation area to allow medium transfer along with interlocking of the filter steam sterilization system.

Seed Fermenters, Main Fermenters, Harvest Tanks and CIP Plant

Each item in this area has its own local controller which is connected to the main SCADA system. Process information is provided locally for the operator but logging is handled by the SCADA system.

The seed and main fermenters will require close process control and be able to monitor and control the following key parameters:

Dissolved oxygen and rate of addition
Temperature
pH and caustic addition
Agitation control
Antifoam addition
Pressure control

Alarm conditions are detected locally and operators alerted. Alarm detection locally, as well as by the SCADA system, should enable the problem to be isolated quickly and at the same time provides a trackable record of events.

The CIP plant is a self-contained control package with communications to all areas that require cleaning. These services are locally controlled with connections to the SCADA network.

The CIP system is expected to provide cleaning solutions to any area of the plant that requests CIP if it is available to do so. If the CIP unit is busy then the requesting unit waits until the CIP system becomes available to service the request. Although the CIP unit is required to provide different cleaning regimes for different areas of the plant, it is not responsible for setting up the process system to be cleaned. This is the responsibility of the system requesting CIP. Logging parameters for CIP basically consists of time, temperature, duration and concentration.

Biomass Recovery

This is a 'stand alone' area with a requirement only for local operator control. There are no benefits in having direct links with the SCADA system.

Solvent Extraction and Evaporation Packages

The control system in this area may consist of two separate parts. The first controls and monitors the solvent addition, agitation and separation tank along with transfer and storage. The second control system is an integral part of the solvent evaporation plant. Both systems are interlocked and communicate with the upstream and downstream processes. Limited information on the state of the extraction unit and the amount of solvent extracted is made available to the SCADA system for logging and alarm monitoring. Since this area operates with solvent, both internal and external emergency shutdown facilities are available.

Solvent Recovery and Storage

The solvent storage and distillation recovery system has a centralised control system which communicates with the solvent extraction area. Limited information for logging is required, but local and remote alarm and shutdown facilities are required.

Plant Utilities

Plant utilities are supplied with their own local control packages, e.g. steam boiler control panel. The SCADA system simply monitors the running operation of all utilities and alarm should the utility fail during normal working time.

9.2 INSTRUMENTATION

The notes given in this section are for sterile and non-sterile service and are based on equipment which is generally readily available in Western Europe.

Where model and/or serial numbers are quoted, these refer to items in the standard catalogues of the various instrument suppliers.

9.2.1 Sterile Service

pH - The most important consideration is that the probe must withstand repeated steam sterilization. The most widely used probe is made by Ingold which is obtained in the UK through Life Science Laboratories Ltd (LSL). The most probable type is the InFit 764-50. Alternatives are the InTrac 796 and the InTrac 797.

An alternative supplier to Ingold is B Braun and probes are obtained either from Braun in UK or B Braun Melsungen in West Germany.

pO_2 - Again, the most widely used probe is made by Ingold and should be of the polarographic type (not galvanic). This sensor must be used with the Ingold amplifier, probably type 170.

Foam Probe - One of the few reliable foam probes currently in service is that supplied by B Braun. It is known as a "single shaft anti foam electrode" and has a ceramic coated sleeve which can be fragile and needs careful handling.

Pressure - For simple local display of pressure, the Budenberg hygienic diaphragm type is extensively used and attached with standard IDF, ISS or RJT fittings.

For remote indication of pressure (and indirectly for level by pressure difference) the Endress & Hauser Ltd piezo resistive diaphragm sensor is extensively used.

Two alternative types are also possible, the VEGA sensor and the piezo resistance (Keller) type which is used in B Braun fermenters.

Level Switch - Two approaches are possible.

(i) Use a pressure sensor, above, to trigger a level switch, or

(ii) Use an Endress & Hauser 11370 probe in connection with the FTW 420 Nivotester switch. This probe needs a special weld-in boss.

Temperature - If a retractable temperature probe is used, the standard Ingold type is completely satisfactory. For permanently installed temperature probes, GRC Consultants would use a welded-in thermowell (best possible solution for sterile engineering) and any reliable Platinium resistance or thermocouple device in the thermowell. There are literally hundreds of suppliers of these devices, all much the same. GRC Consultants makes no particular recommendation.

Liquid Flowrate - This parameter continues to be a difficult one to measure in "sterile" applications. GRC Consultants would also try to measure liquid flowrates, with conventional instruments, in the non-sterile side of the process but if this is not possible, the Endress & Hauser mass flowmeter "In-point" should be considered.

An alternative device, using the same principle, is made by Rosemount.

9.2.2 Non-Sterile Service

Off-Gas Analyser - For medium accurate measurement of oxygen and carbon dioxide in fermenter off-gas, there are many commercially available machines which use a paramagnetic device for O_2 and infra red for CO_2. The best known make is that of KENT but many other systems are available, including Hartmann and Braun.

If, however, better than average accuracy is required for O_2/CO_2 and Respiration Quotient (RQ) measurement for glucose feed rate control (or dissolved oxygen control via agitator speed) then the more expensive mass spectrometer type instruments have to be considered.

A current system with which GRC Consultants is familiar uses a quadrapole mass spectrometer made by VG Gas Analysis Ltd, with Pall gas conditioning (water droplet coalescence and removal) and GAP flow rotameters upstream of the mass spectrometer. An IBM PC is used for read-out/print out and the software is FERMENT-SOFT.

This particular mass spectrometer also analyses for ethanol in the off-gas stream.

Agitator Speed/Power - There are very many systems available for both agitator speed and power drain measurement and GRC Consultants does not have any particular recommendation to make. It is suggested that it would be best to ask the eventual supplier of the power drive system for their standard instrumentation.

Load Cells - Very many types/makes of electronic based load cells are available. One of the most widely used is that made by BOFORS but the following also supply extensively:-

Bran & Luebbe
Hunting Electric Controls
Philips Industrial Automation (Pye Unikam) Ltd

A widely used PNEUMATIC load cell device is marketed by DARENTH and is intrinsically safe electrically as the weighing uses pneumatics, not electronics.

Pressure Transmitters - There is such a wide range to choose from that it is inappropriate to recommend any single make. All the well-known instrument manufacturers can supply to meet Biogal's detailed needs.

Gas Flowrate - There are literally hundreds of suppliers/types and all of the well-known makers/suppliers can provide gas flowrate measurement devices. In the EC the "big" names include:

Kent
Flowquip
Platon
Yokogawa
KDG Instruments
Philips Ind Auto

GRC Consultants

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(3 of 3)

FRONT END DESIGN STUDY

FOR

BIOTECHNOLOGY DEVELOPMENT FACILITY

FOR

BIOGAL, DEBRECEN

(VOLUME 2)

UNIDO CONTRACT 92/030

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CONTENTS

SECTION 10

BUILDING DESIGN

10 BUILDING DESIGN

10.1 ROOM LIST AND SPECIFICATIONS

The rooms in each area of the facility are listed in table 10.1.1.

External buildings, stores and corridors are all classified as rooms in this and one table generated from this room list.

A total of 90 rooms are identified and listed with room specification parameters which will be covered in detail later in this section.

TABLE 10.1.1 ROOM LIST & SPECIFICATIONS

No.	ROOM	DIMENSIONS & AREA	GRC ROOM STANDARD	EC CLASS	HAZARD ZONE	PRESSURE Symbols	PRESSURE Pa
	OFFICE AREA GROUND FLOOR						
101	Lobby	1x2, 2m²	C5				NC
102	Reception	5x5, 23m²	C5				NC
103	Secretarial Office	5x4, 20m²	C5				NC
104	Female Office and Laboratory Staff Toilet	4x4, 16m²	C5				NC
105	Male Office and Laboratory Staff Toilet	4x5, 20m²	C5				NC
106	Stairs and Lobby	4x3, 12m²	C5				NC
107	Technology and Engineering Office	5x4, 20m²	C5				NC
108	Corridor	2m wide, 24m²	C5				NC
109	Fermentation and DSP General Office	4x9, 36m²	C5				NC
110	DSP Section Head Office	3x3, 9m²	C5				NC
111	Fermentation Section Head Office	3x3, 9m²	C5				NC
112	General Managers Office	4x4, 16m²	C5				NC
113	First Aid Room	4x3, 12m²	C5				NC
114	Microbiological and Analytical Heads Office	4x3, 12m²	C5				NC
115	Microbiological and Analytical General Office	4x9, 36m²	C5				NC
116	Process Analysis Room	2x4, 8m²	C5				NC
117	Photocopier Room	2x3, 6m²	C5				NC
118	Storemans Office	2x5, 10m$_2$	C5				NC
	OFFICE AREA FIRST FLOOR						
201	Meeting Room	8x8, 64m²	C5				NC
202	Spare Office	3x2, 6m²	C5				NC
203	Stairs and Lobby	4x3, 12m²	C5				NC
204	Mess Room	14x8, 112m²	C5				NC
205	Corridor	2m wide, 18m²	C5				NC
206	Small Meeting Room	3x3, 9m²	C5				NC
207	Cleaning Materials Room	2x3, 6m²	C5				NC
	CONTAINED AREA GROUND FLOOR						
301	Waste Treatment Room	3x4, 12m²	C3			+++	45
302	Change Area	4x4, 16m²	C3			+++	45
303	Wash Room	4x2, 8m²	C3			++	30
304	Fermentation Hall 1	9x10, 90m²	C3	D		+++++	75
305	Fermentation Hall 2	9x13, 117m²	C3	D		+++++	75
306	In Process Laboratory	2x4, 8m²	C3	D		+++	45
307	Deactivation Room	3x4, 12m²	C3			+++	45
308	Stairs and Lobby	2x4, 8m²	C3	D		+++	45
309	Corridor	12x2, 24m²	C3	D		+++	60

No.	ROOM	DIMENSIONS & AREA	GRC ROOM STANDARD	EC CLASS	HAZARD ZONE	PRESSURE Symbols	PRESSURE Pa
CONTAINED AREA FIRST FLOOR							
401	Shaker and Incubator Room	8x5, 40m²	C2	C		+++	45
402	Seed Store	3x3, 9m²	C2	C		+++++	75
403	Clean Room	3x2, 6m²	C2	C		++++	60
404	Clean Change	2x2, 4m²	C2			+++	45
405	Microbiology Laboratory	9x9, 77m²	C3			++	30
406	Corridor	2m wide, 128m²	C3	D		++	30
407	Corridor	2m wide, 36m²	C3	D		+++	45
408	Process Control Room	8x3, 24m²	C3			++++	60
409	Fermentation Hall 1	9x19, 155m²	C3	D		+++++	75
410	Fermentation Hall 2	9x19, 151m²	C3	D		+++++	75
411	Wash Room	2x2, 4m²	C3			+	15
412	Lobby and Stairs	2x4, 8m²	C3	D		++	30
DOWNSTREAM PROCESSING AREA							
501	Male Plant 1° Change	7x6, 42m²	C3			+	15
502	Male Plant 2° Change	3x6, 14m²	C3			++	30
503	Female Plant 1° Change	7x6, 42m²	C3			+	15
504	Female Plant 2° Change	3x6, 14m²	C3			++	30
505	Male Plant 2° Wash Area	2x2, 4m²	C3			+	15
506	Female Plant 2° Wash Area	2x2, 4m²	C3			+	15
507	Dispensary	3x9, 31.5m²	C3	D		++	30
508	Fermentation Make-up Room	7x3, 21m²	C3	D		+++	30
509	Corridor	2m wide, 84m²	C3	D	2	++++	60
510	Centrifuge Room	8x6, 48m²	C2	C	1	*	10
511	Filter Room	8x5, 40m²	C2	C	1	*	10
512	Solvent Extraction and Synthesis Room	8x8, 64m²	C2	C	1	*	10
513	Chromatography Room	5x5, 25m²	C2	C	1	*	10
514	Wash Room	3x3, 9m²	C2		1	*	10
515	UF Room	3x3, 9m²	C2	C	1	*	10
516	Clean Make-up Room	3x3, 9m²	C2	C	1	*	10
517	Evaporation Room	7x5, 35m²	C2	C	1	*	10
518	In Process Laboratory	2x3, 6m²	C2		2	*	10
519	Equipment Room	2x3, 6m²	C2		2	*	10
520	Cleaning Equipment	2x3, 6m²	C2		2	*	10
521	Drying Room	3x3, 9m²	C2	C	1	*	10
522	Drier Services	3x3, 9m²	C5		2		NC
523	Freeze Drying Room	3x2, 6m²	C2	C	1	*	10
524	Milling and Sieving Room	3x3, 9m²	C2	C	1	*	10
525	Blending and Packing Room	3x3, 9m²	C2	C	1	*	10

No.	ROOM	DIMENSIONS & AREA	GRC ROOM STANDARD	EC CLASS	HAZARD ZONE	PRESSURE Symbols	PRESSURE Pa
526	Corridor	2m wide, 32m²	C3	D		++++	60
527	Deactivated Receipt	2x2, 4m²	C2	C		+++++	75
528	RVF Room	4x4, 16m²	C3	D		+++++	75
529	Lobby	2x3, 6m²	C3	D		+++++	75
	GENERAL LABORATORY AREA FIRST FLOOR						
601	Female Laboratory Change	5x3, 15m²	C3			+	15
602	Analytical and Development Laboratory	13x10, 126m²	C5				NC
603	Male Laboratory Change	5x3, 15m²	C3			+	15
604	Corridor	2m wide, 22m²	C3			++	30
	SERVICE, STORES AND UTILITY AREAS GROUND FLOOR						
701	Goods-In Store	9x9, 76.5m²	C4			+	15
702	Acid and Base Store	2x4, 8m²	C4			++	30
703	Service Area	7x13, 91m²	C5				NC
704	Engineering Stores	3x2, 6m²	C5				NC
705	Engineering Workshop Office	3x3, 9m²	C5				NC
706	Engineering Workshop	3x8, 24m²	C5				NC
707	Solvent Store	4x4, 16m²	C4		1		NC
708	Solvent Waste Area	3x2, 6m²	C5		1		NC
709	General Waste Area	5x4, 20m²	C5				NC
710	Gas Cylinder Store	7x2, 14m²	C5				NC
711	Gatehouse	5x3, 15m²	C5				NC
712	Goods-Out Store	5x5, 25m²	C4			+++++	75

Key

\+ = 15 Pa

* = 10 Pa

NC = No Control

10.2 ROOM STANDARDS

10.2.1 General Classification

In this section, five room standards are defined as shown below.

Table 10.2.1

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 Cortrolled 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)
EEC Standard is GGMP (1992)
UK Standard is BS5295 (1989)

The table shows, where applicable, the approximate clean room standards which may be met by these standards of room.

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 Biogal 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 Biogal 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 Biogal 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 Biogal management

10.2.2 Room Standard Specification

The room standard specification is given in drawings 92/004/107 and 92/004/108 and in table 10.1.1. For a full specification this table should be read in conjunction with this section.

This table characterises all the rooms with reference to the GRC room standards defined in section 10.2.1. Where appropriate the room is further specified using the EC classificatory system (GGMP, 1992). In cases where a GRC room class and an EC class are given, the room must satisfy both sets of criteria.

Process rooms, where the product is exposed, and rooms containing equipment which come into contact with the product are specified as 'C2 Intermediate Controlled Class'. These rooms must also meet EC Class C (GGMP, 1992).

Rooms also forming part of the clean plant area but in which the product is normally not exposed, are specified as 'C3 Low Controlled Class'. The rooms are designed generally to meet EC Class C (GGMP, 1992). The changing areas are included in this specification.

Table 10.2.1 shows that a room specified as 'C3 Low Controlled Class' will meet EC Class D under suitable operating conditions. However, for example, the male plant primary change (room 501) is specified as 'C3 Low Controlled Class' but this does not mean that this particular room must meet the specification of EC Class D (GGMP, 1992). These regulations include dust load specifications which may be difficult to achieve, given, for example, the changing room will hold dust laden overcoats. This room is given the specification 'C3 Low Controlled Class' to ensure this room may be easily cleaned. Details of which rooms must be 'C3 Low Controlled Class' and meet EC Class D are given in table 10.1.1.

The plant handles solvents and powders capable of producing a flammable atmosphere. Each room is given a hazardous areas zone number to quantify the hazard as shown in table 10.1.1 which also details individual room areas. The definition of hazardous areas is covered in Section 9.2. All electrical equipment used in each room must be suitable for use in the appropriate hazardous zone.

10.3 ROOM PRESSURES

The pressure under non-contained operation in each room has been allocated using the following logical steps.

1. By Hungarian norms, the corridor must be 50 Pa greater than the rooms which may contain a flammable atmosphere.

2. The minimum pressure differential between two rooms is 15 Pa.

3. The pressure differential is set so that areas of higher cleanliness have higher pressures in order to ensure any contaminating material travels away from the cleanest areas.

4. The solvent and dust handling downstream processing area is segregated from the rest of the plant by use of high pressure in the downstream processing lobby (room 527).

5. Rooms where water is present are kept at a negative relative to the surroundings to prevent dispersal of aerosols.

The room pressures are detailed on drawings 92/004/109 and 92/004/110 and tabulated in table 10.1.1.

Note the high pressure of the main corridor (room 509) with respect to the downstream processing rooms. This pressure differential tends to keep the bulk of any solvent vapour produced in the process rooms inside the process rooms.

The detailed design of the HVAC system will incorporate the pressures defined here.

10.4 HVAC

10.4.1 General Considerations

The detailed design and installation of a pharmaceutical heating, ventilation, and air conditioning system is a highly 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.

10.4.2 Detailed Considerations

Individual room specifications are given in table 10.1.1 with reference to the GRC room specification defined in Section 10.2.

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.

Biogal have indicated that they do not require sophisticated humidity control for process reasons. A humidity of around 60-70% RH is expected to be suitable for the pilot plant.

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.

10.4.3 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.

10.5 BUILDING FINISHES

The building contains rooms with differing levels of cleanliness as given in the room standard specification, table 10.1.1.

A sealed suspended ceiling is installed in the process areas with flush light fittings of an appropriate flameproof type where necessary. Ventilation ducts and pipework run in the void above the suspended ceiling.

The basic principles of clean room design can be applied to all rooms in varying degrees, and guidelines are given below.

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.)

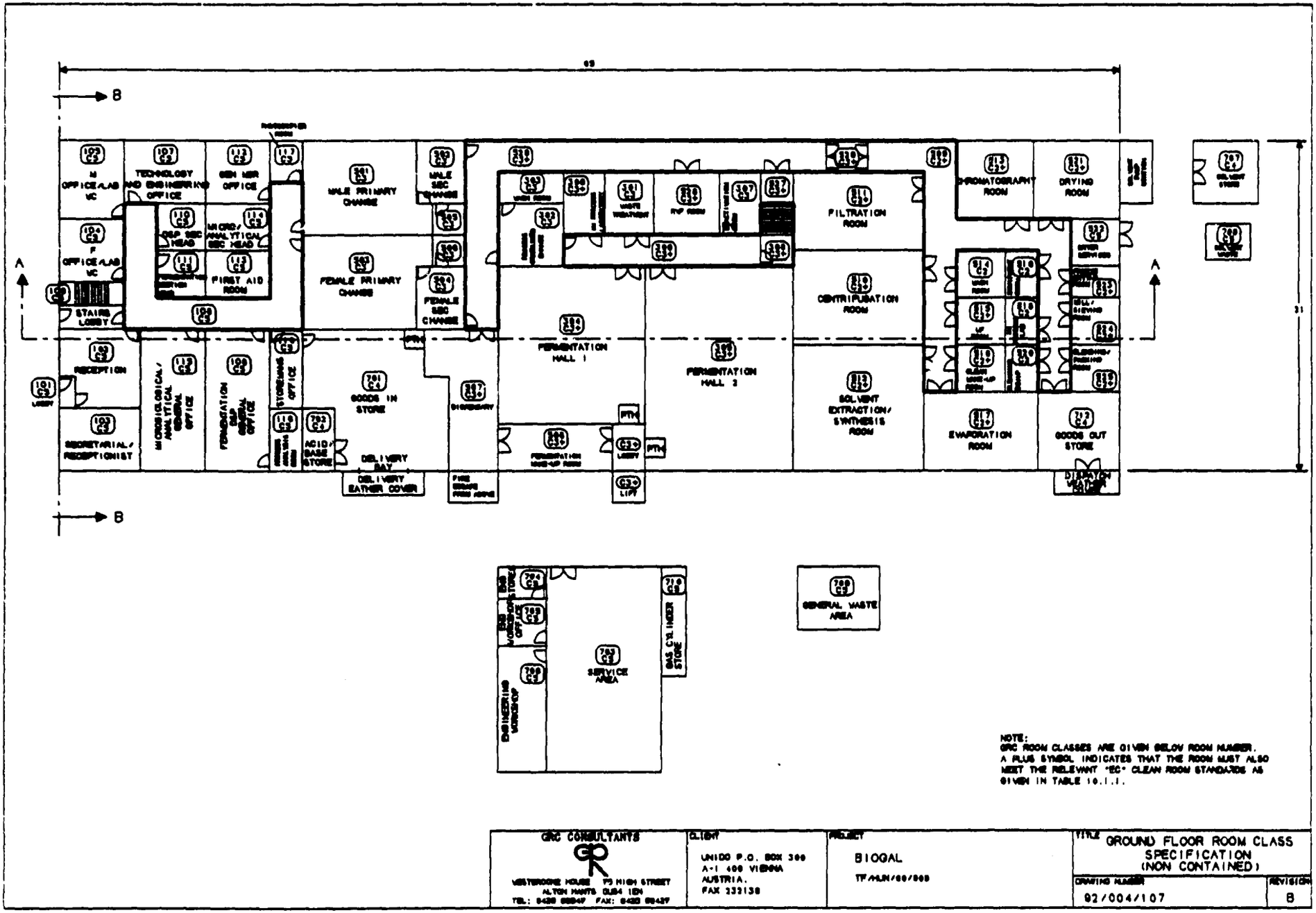
The room surface finishes must be sealed, non-shedding, non-reactive to a range of disinfectants and must be capable of continuing maintenance and repair should damage occur. The ideal finish is entirely joint free. Particular attention should be paid to the connection point of the surface finish to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

Interfacing of equipment also requires attention. For example, the tray drier requires a stainless fascia plate. Consideration must be given to the interfacing of this and other fascias with the clean room fabric. The junctions must be easy to clean and avoid any unnecessary recesses.

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

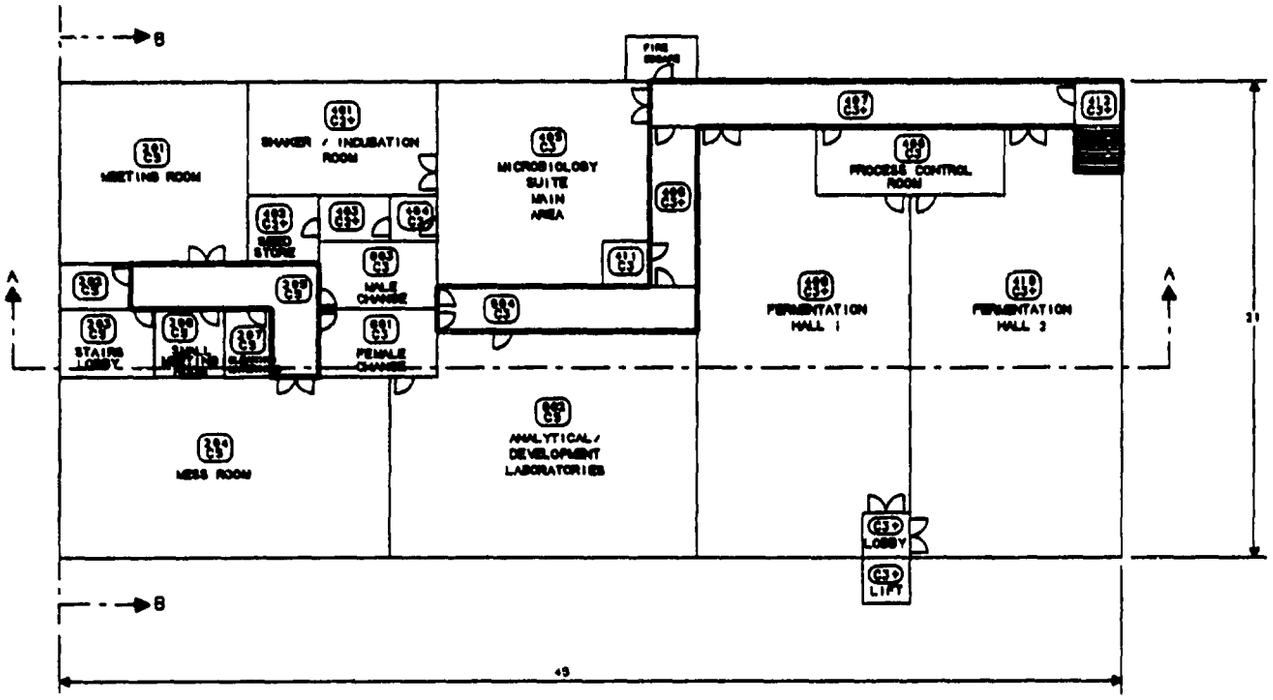
Where piped services penetrate the clean room finish, they must be carefully designed with closing plates and sealed using an elastomer such that allowance is made for expansion and contraction whilst maintaining an unbroken seal.

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.



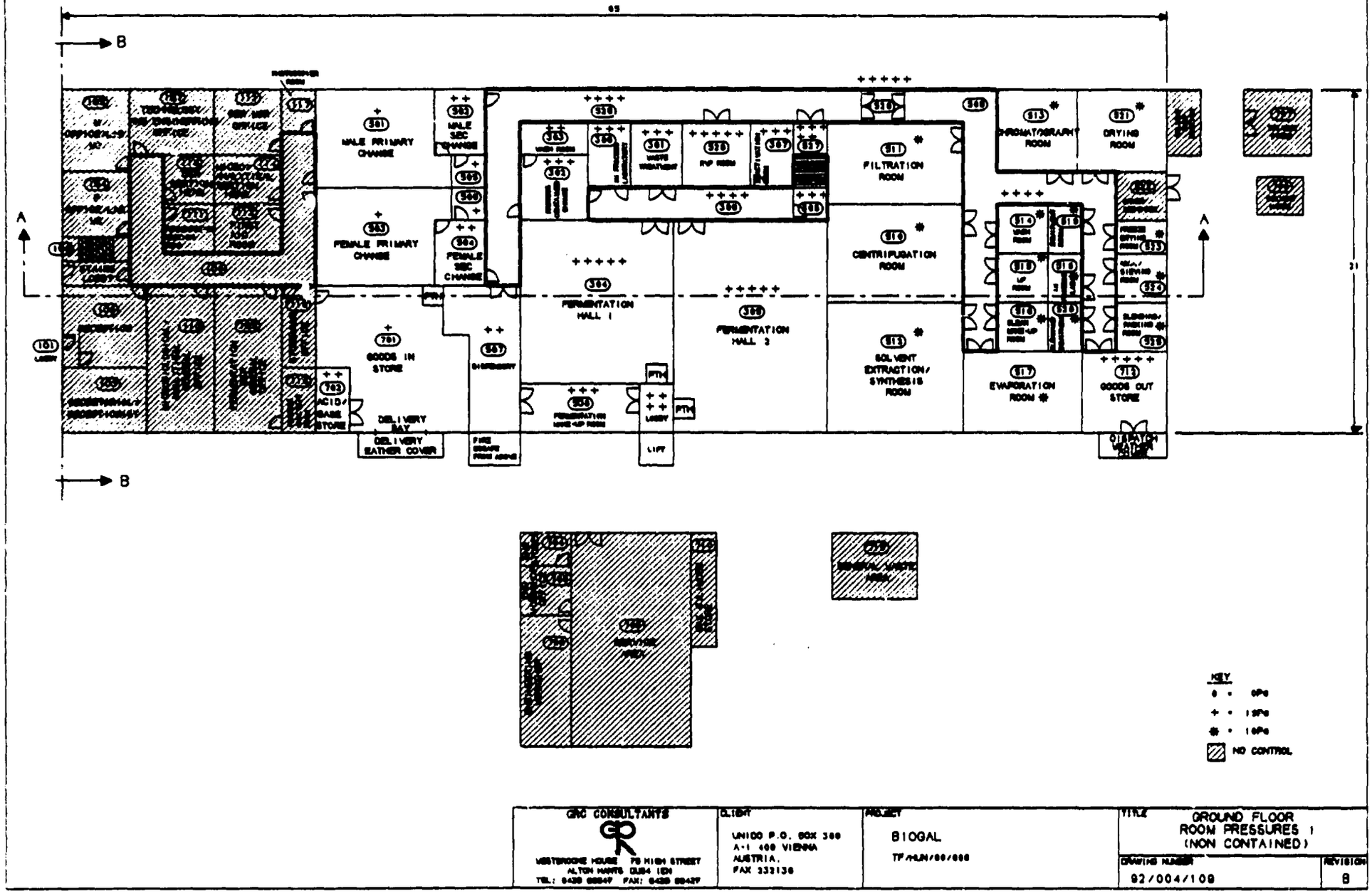
NOTE:
GRC ROOM CLASSES ARE GIVEN BELOW ROOM NUMBER.
A PLUS SYMBOL INDICATES THAT THE ROOM MUST ALSO MEET THE RELEVANT "EC" CLEAN ROOM STANDARDS AS GIVEN IN TABLE 10.1.1.

GRC CONSULTANTS WESTBROOKE HOUSE 93 HIGH STREET ALTON HANTS GU34 1EN TEL: 0420 88847 FAX: 0420 89427	CLIENT UNIDO P.O. BOX 300 A-1 400 VIENNA AUSTRIA. FAX 232156	PROJECT BIOGAL TF/HUN/88/008	TITLE GROUND FLOOR ROOM CLASS SPECIFICATION (NON CONTAINED)
			DRAWING NUMBER 92/004/107
			REVISION B

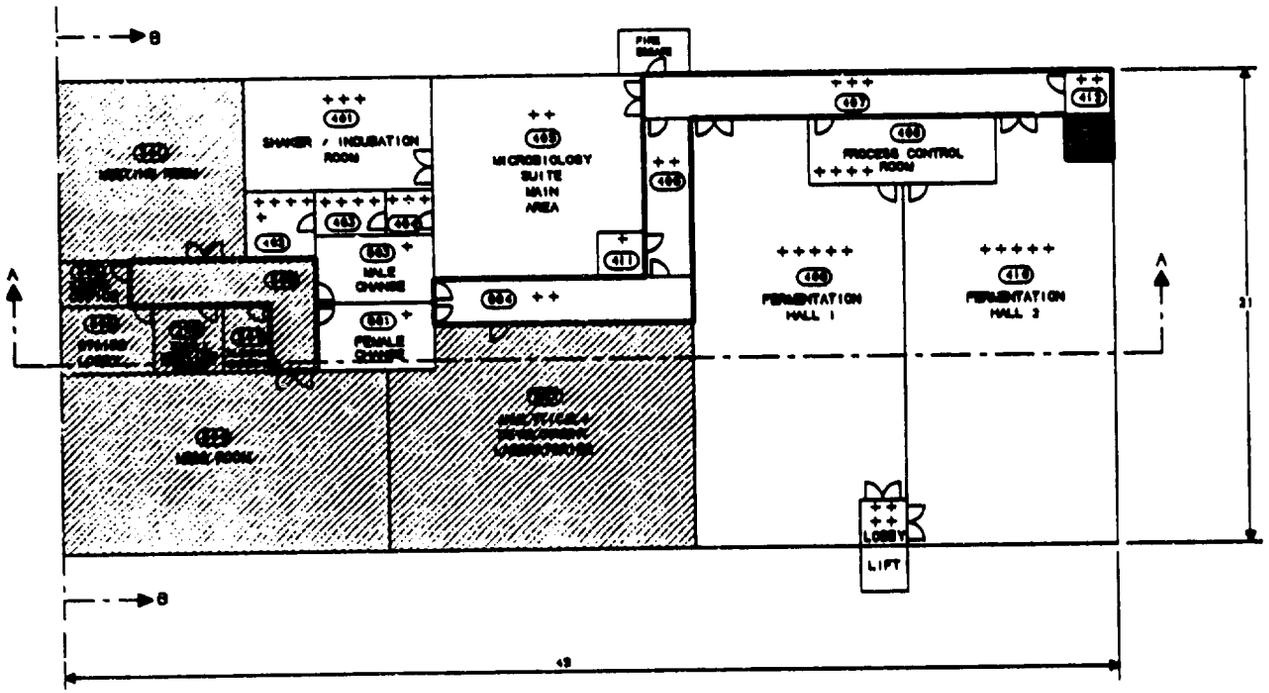


NOTE:
GMC ROOM CLASSES ARE GIVEN BELOW ROOM NUMBER.
A PLUS SYMBOL INDICATES THAT THE ROOM MUST ALSO MEET THE RELEVANT "BS" CLEAN ROOM STANDARDS AS GIVEN IN TABLE 10.1.1.

GMC CONSULTANTS WESTBROOKE HOUSE 70 HIGH STREET ALTON HANTS GU34 1EN TEL: 0420 88847 FAX: 0420 88427	CLIENT UNIDO P.O. BOX 300 A-1 400 VIENNA AUSTRIA. FAX 233136	PROJECT BIOGAL TP/MUN/89/008	TITLE FIRST FLOOR ROOM CLASS SPECIFICATION (NON CONTAINED)	
			DRAWING NUMBER 92/004/108	REVISION B



GNC CONSULTANTS WESTBROOKE HOUSE 78 HIGH STREET ALTON HANTS GU34 1EN TEL.: 0420 88847 FAX: 0420 88427	CLIENT UNIDO P.O. BOX 300 A-1 400 VIENNA AUSTRIA. FAX 232136	PROJECT BIOGAL TF/HUN/88/008	TITLE GROUND FLOOR ROOM PRESSURES 1 (NON CONTAINED)
			DRAWING NUMBER 92/004/109
			REVISION B



KEY

- 0 : 0Pa
- + : 15Pa
- * : 10Pa
- ▨ NO CONTROL

GNC CONSULTANTS WESTERGATE HOUSE 78 HIGH STREET ALTON HANTS GU34 1EN TEL: 0420 88847 FAX: 0420 88427	CLIENT UNIDO P.O. BOX 300 A-1 400 VIENNA AUSTRIA. FAX 232138	PROJECT BIOGAL TF/HUN/88/006	TITLE TOP FLOOR ROOM PRESSURES 1 (NON CONTAINED) DRAWING NUMBER 92/004/110 REVISION B

SECTION 11

LAYOUT

11.1 GENERAL

11.2 PERSONNEL/MATERIALS FLOW

11.2.1 Personnel

11.2.2 Materials

11.3 BUILDING LAYOUT

11.4 OVERALL PLOT LAYOUT

11 LAYOUT

11.1 GENERAL

At this stage of the overall project for the realisation of the new development facility, layout is concerned essentially with the estimation and arrangement of the total area needed to accommodate the various requirements described in Section 6. Within the context of this study, a layout has been developed based on the following assumptions.

- Neither a site nor suitable premises have been selected/purchased/leased, hence the layout is not constrained by any imposed dimensions or shape.

- The downstream processing and purification areas, laboratories and storage areas are laid out at ground level.

- Offices, some of the amenities and the microbiology and analytical laboratories are envisaged at this stage as being on the upper floor.

- Space for future expansion is allowed for by extension at grade and not by building upwards.

The layout accommodates the rooms and areas given in table 10.1.1 in Section 10.1. It must be appreciated that the dimensions and areas are preliminary at this stage but are unlikely to change significantly, except possibly in a few minor areas, when the detailed design phase takes place.

Architectural views of the facility have been prepared and are given in Figs. 11.1, 11.2 and 11.3. These drawings are included as an aid to the visualisation of the new facility.

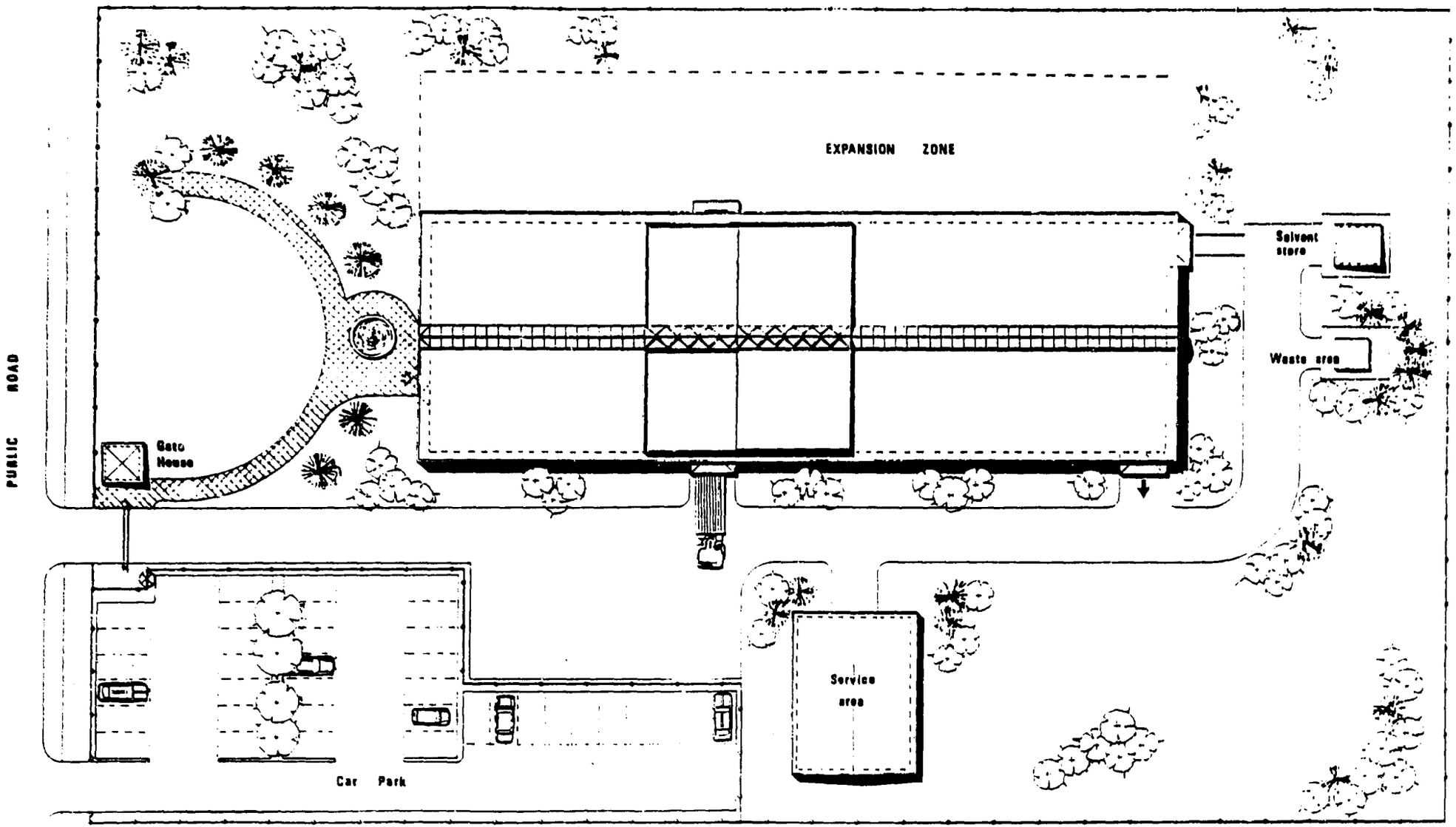

PUBLIC ROAD
EXPANSION ZONE
Solvent store
Waste area
Gate House
Service area
Car Park

Fig. 11.1 Plan

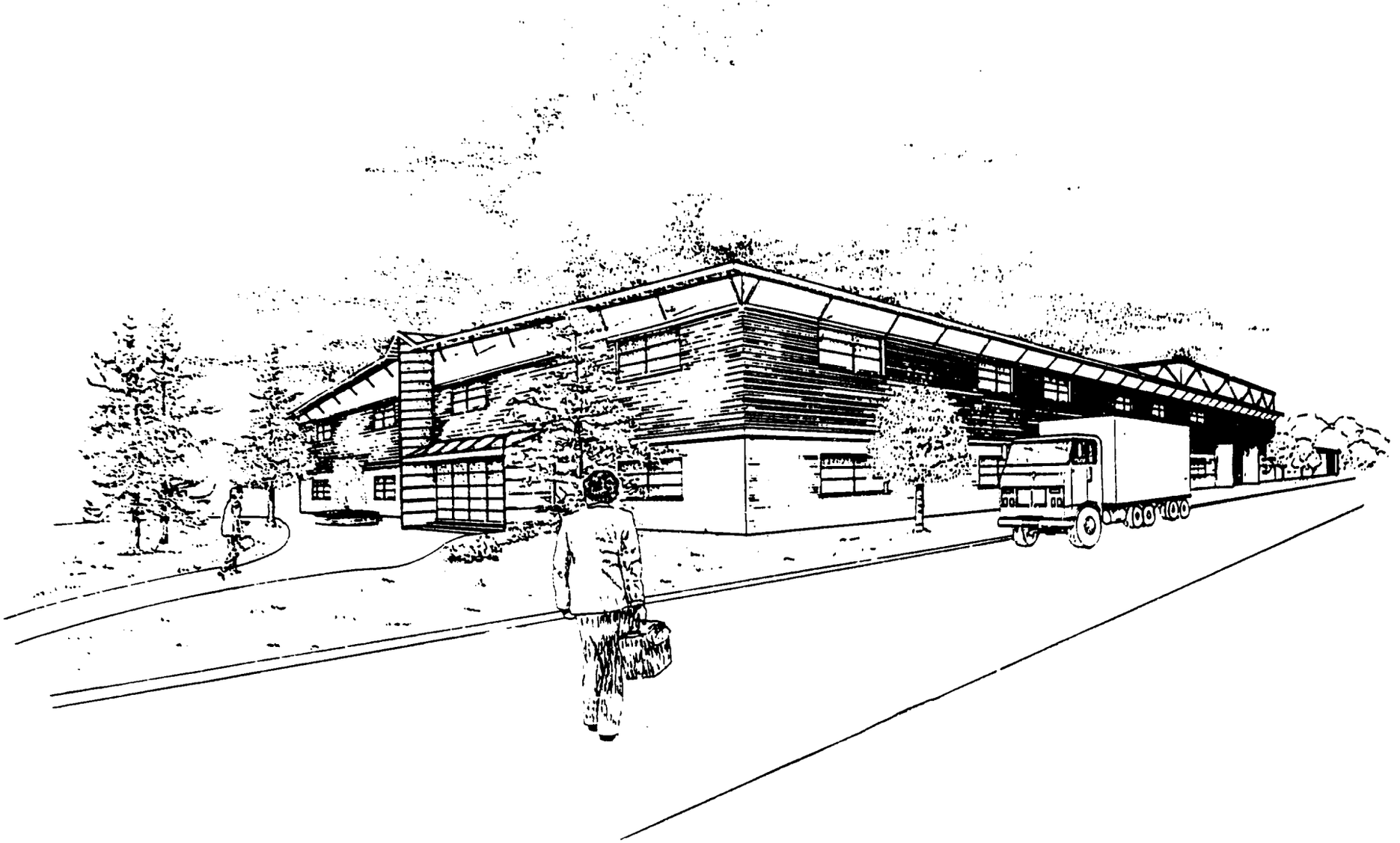


Fig. 11.2 Front/Side Elevation

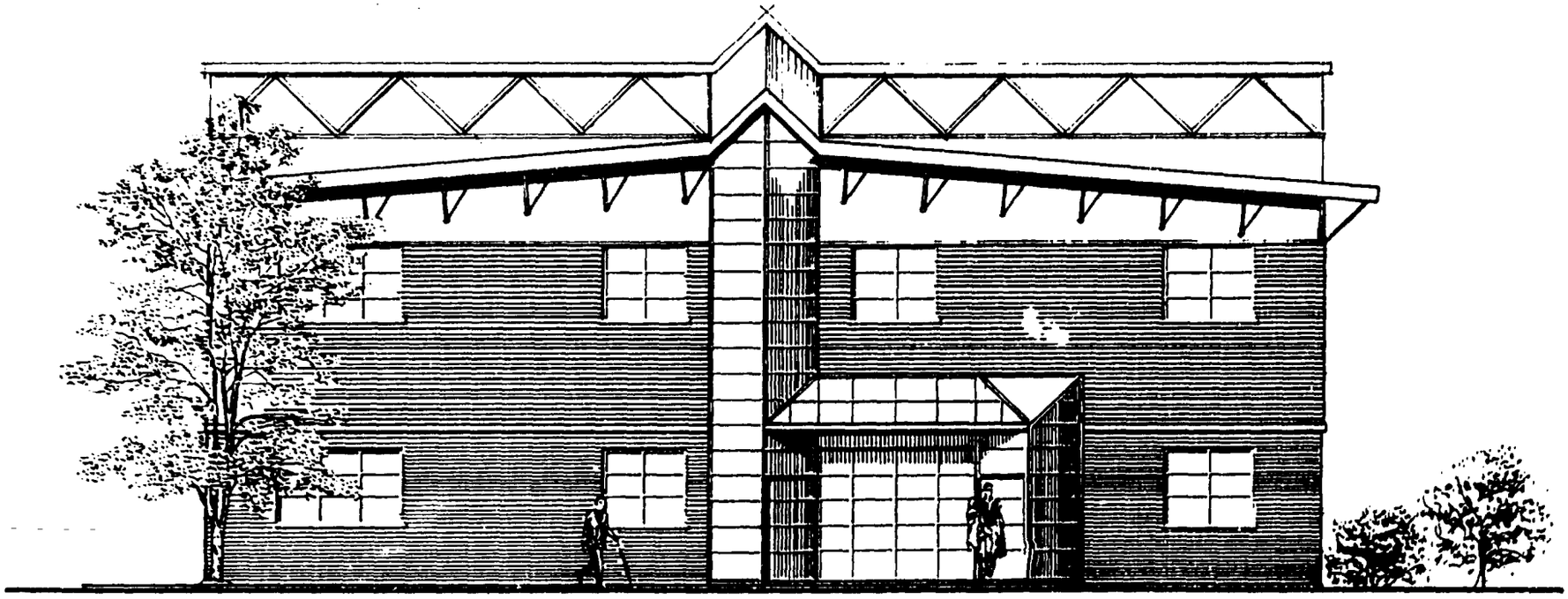


Fig. 11.3 Front Elevation

11.2 PERSONNEL/MATERIALS FLOW

Personnel and materials flow patterns have an effect on overall layout and a brief description of the key features of both now follows. These notes should be read in conjunction with the overall room layout drawings 92/004/101 and 92/004/103 and the site layout drawing 92/004/106.

11.2.1 Personnel

All visitors and members of the public enter the reception area. They can only progress from here when accompanied by a responsible member of staff and the exit from the reception area is via a controlled/locked door.

Members of staff enter via a key-card or similar controlled door which is also visible from the reception area.

Beyond the reception area on the ground floor is an office area consisting of mainly individual offices. A first aid room (room 113) is located off the main ground floor office corridor (room 108).

Staff may use the stairs (room 106) located near reception to access the first floor office area consisting of mainly communal facilities such as meeting rooms. A mess room is provided in this area for all staff.

The laboratories are located together on the first floor and these are accessed by passing through the first floor office corridor (room 305) into the laboratory changing rooms (rooms 601 and 603). Certain microbiological personnel are allowed limited access to the fermentation halls, and they will enter the halls via corridor 407.

Beyond the office areas on the ground floor are the process rooms which are accessed by downstream process workers via the plant changing rooms. Fermentation process workers will also access the fermentation halls via these changing rooms.

MATERIALS

There is a single point of entry into the building for all materials. Materials are received and checked by the storekeeper in the goods-in store. Materials are then placed in appropriate racking in the stores or transferred to the dispensary, office area or specific laboratory. If GMP regulations apply a quarantine cage will be installed in the goods-in area for the segregation of goods awaiting approval by quality control.

Process materials movement is generally from left to right as viewed on the ground floor room layout drawing 92/004/101.

Other materials are distributed about the facility as follows:-

Gas Cylinders

The primary storage of gas is in a compound area (room 710) which is part of the service building. Large gas bottles will be off loaded in the yard area and moved directly to the gas store.

Small gas bottles for hydrogen or carbon dioxide, etc, are stored in the cylinder storage area and then moved by pallet truck for use in a laboratory. Empty cylinders are returned to the store for collection by the supply company.

Where possible, all gases are piped from the gas store in a distribution system to each laboratory. This is considered by to be a more appropriate method of handling hazardous gases rather than individual cylinders being located in laboratories.

Non Hazardous Chemicals

Chemicals enter the facility via the stores goods entrance and are held in the main store prior to distribution to the laboratories or dispensary. Specialist reagents are transferred directly to the specific laboratory which has ordered them, to prevent the main stores becoming overstocked.

Solvents

Solvents enter the facility via the main goods entrance and as soon as they are logged in, they are transferred immediately to the solvent storage area (room 707) at the rear of the facility for subsequent distribution as needed.

Radioactive Materials & Isotopes (if used)

Radioactive materials enter the facility via the stores goods entrance and once logged in are immediately transferred to the Radioactive Store in the laboratory of use.

Outward Goods

Material which is transferred from the facility will be held in the Goods Out Store (room 712) to await transport.

If GMP regulations apply a cage will installed in the goods out store (room 712) for goods awaiting quality control approval.

11.3 BUILDING LAYOUT

The overall layout concept for the building is shown in the site layout drawing 92/004/106 which clearly is based on a purpose designed facility, on a new site, without any imposed dimension or boundary constraints. If the new facility is built into any existing shell, or any other suitable premises, there will, of necessity, be some constraints of shape and dimension. In this case the overall layout proposed in this section may change, but the extent of such a change cannot be anticipated until a definite building shell or premises have been identified.

The overall concept shows the office facilities at one end of the main building, with laboratory facilities above, followed by the Fermentation Hall with the downstream processing area at the other end of the building.

Future expansion is accommodated by new buildings or extension to the present building in the clear ground at the top of the present main building as laid out in the site layout drawing 92/004/106.

More detailed proposals for a possible building layout are given in the facilities description in Section 6, which also includes individual room sketches.

11.4 OVERALL PLOT LAYOUT

The overall plot layout is shown in drg. 92/004/106 which clearly relates to a new facility on a new site. The building layout from Section 11.3 is shown in context of the overall site which includes the 'outdoor' areas such as the gas cylinders compound and the solvent storage area.

Some of the key features of the overall plot include the following:-

- Access to the whole new development is from the public road via a security/gatehouse area which controls entrance to the service road which leads to the marshalling/general yard at the back of the building.

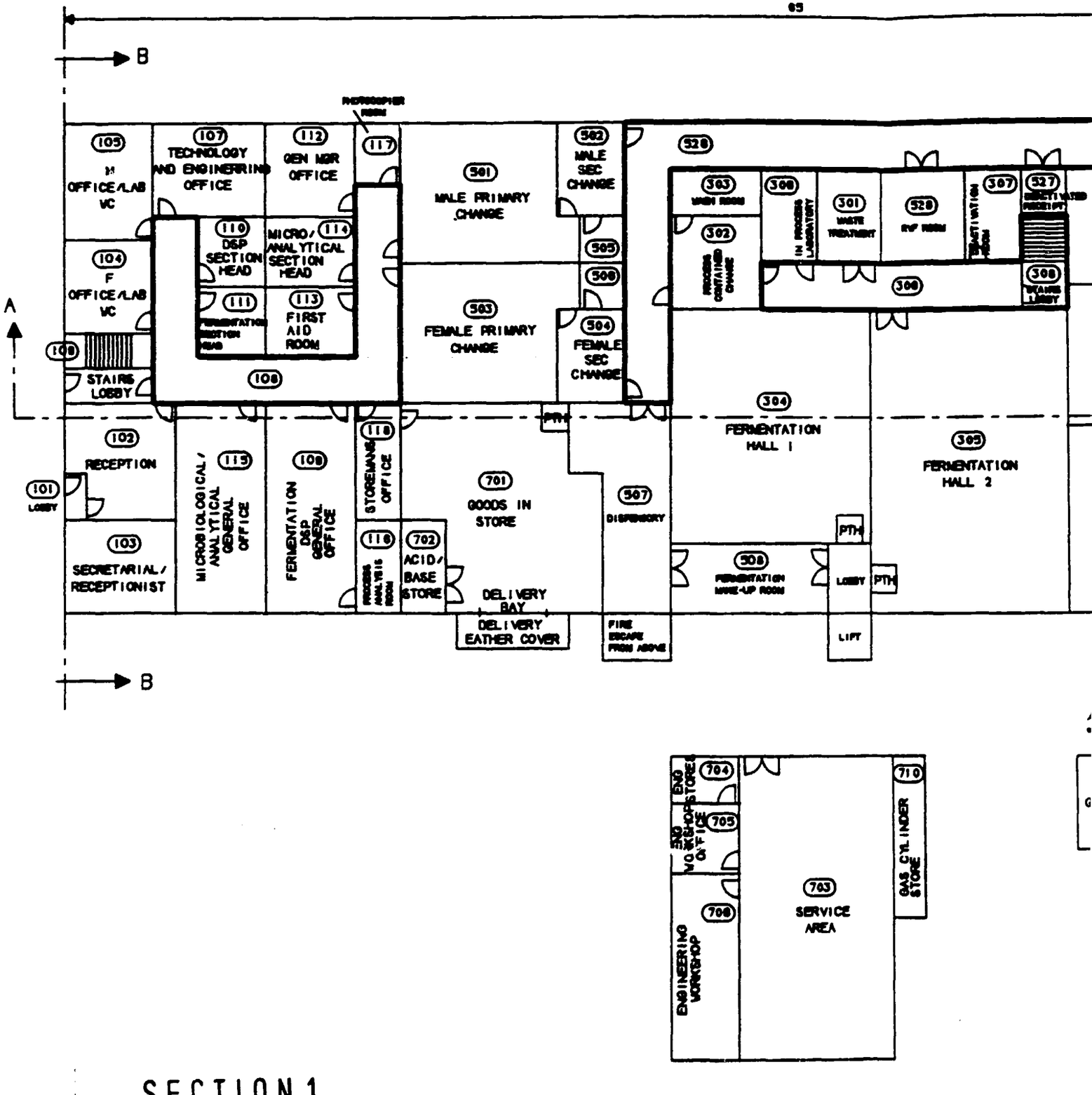
- The only pedestrian access (staff and visitors) to the building is at the front. People park in the car park and walk across to the gatehouse for authorised entry to the site.

- The service road has an unloading/delivery bay alongside the main store.

- The access road is two-way via the gatehouse.

- The area designated for expansion is either landscaped or grassed over and the marshalling yard area is screened by fencing and/or trees or some other visually attractive device.

- The entire facility is surrounded by a secure perimeter fence which, until the expansion zone is developed, may follow the line of the top of the main building to the turning zone (located in the top right corner) so as not to enclose the upper landscaped grassed area initially.



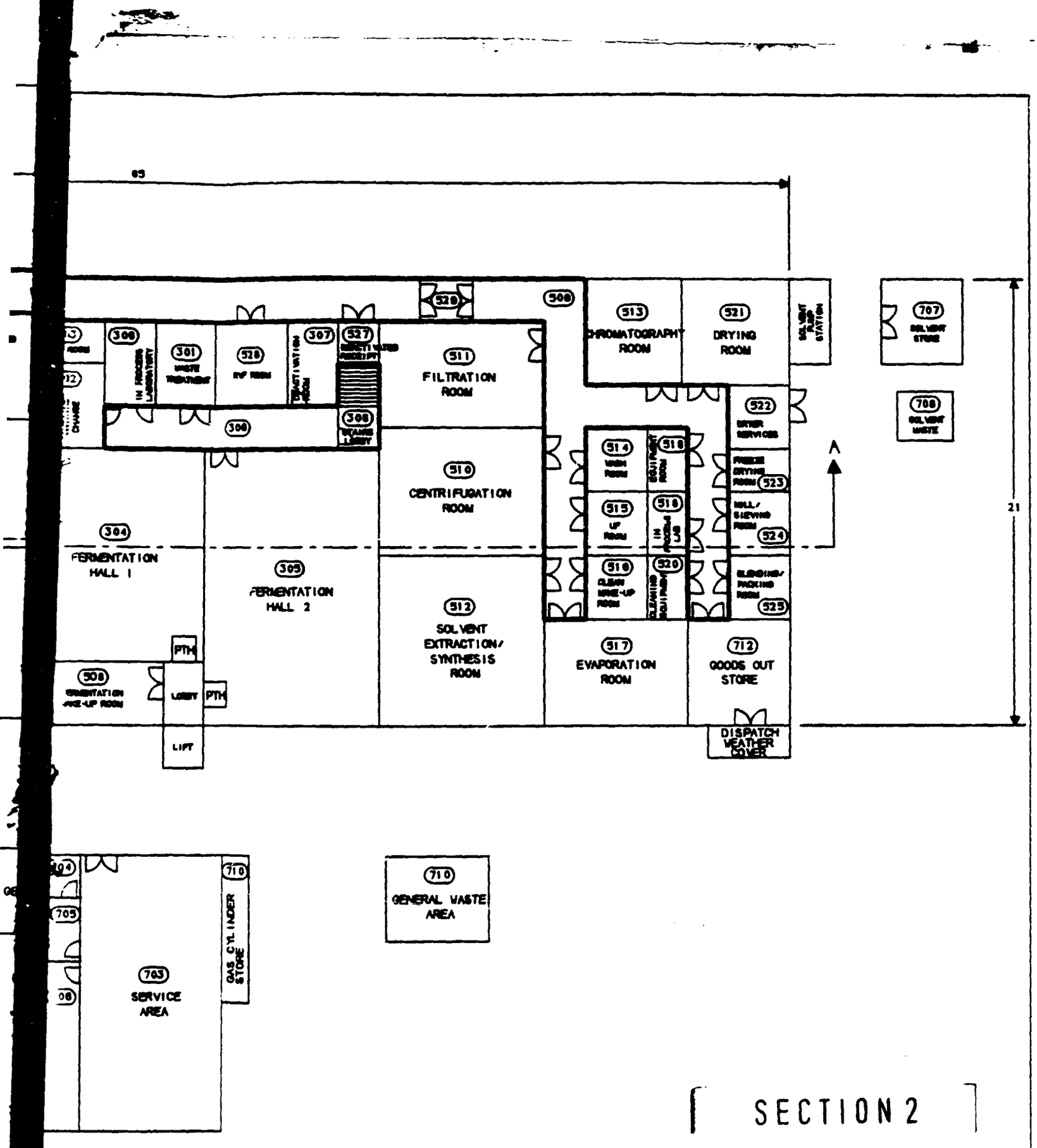
SECTION 1

GRC CONSULTANTS

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

CLIENT

UNIDO P.O. BOX 30
A-1 400 VIENNA
AUSTRIA.
FAX 232138



SECTION 2

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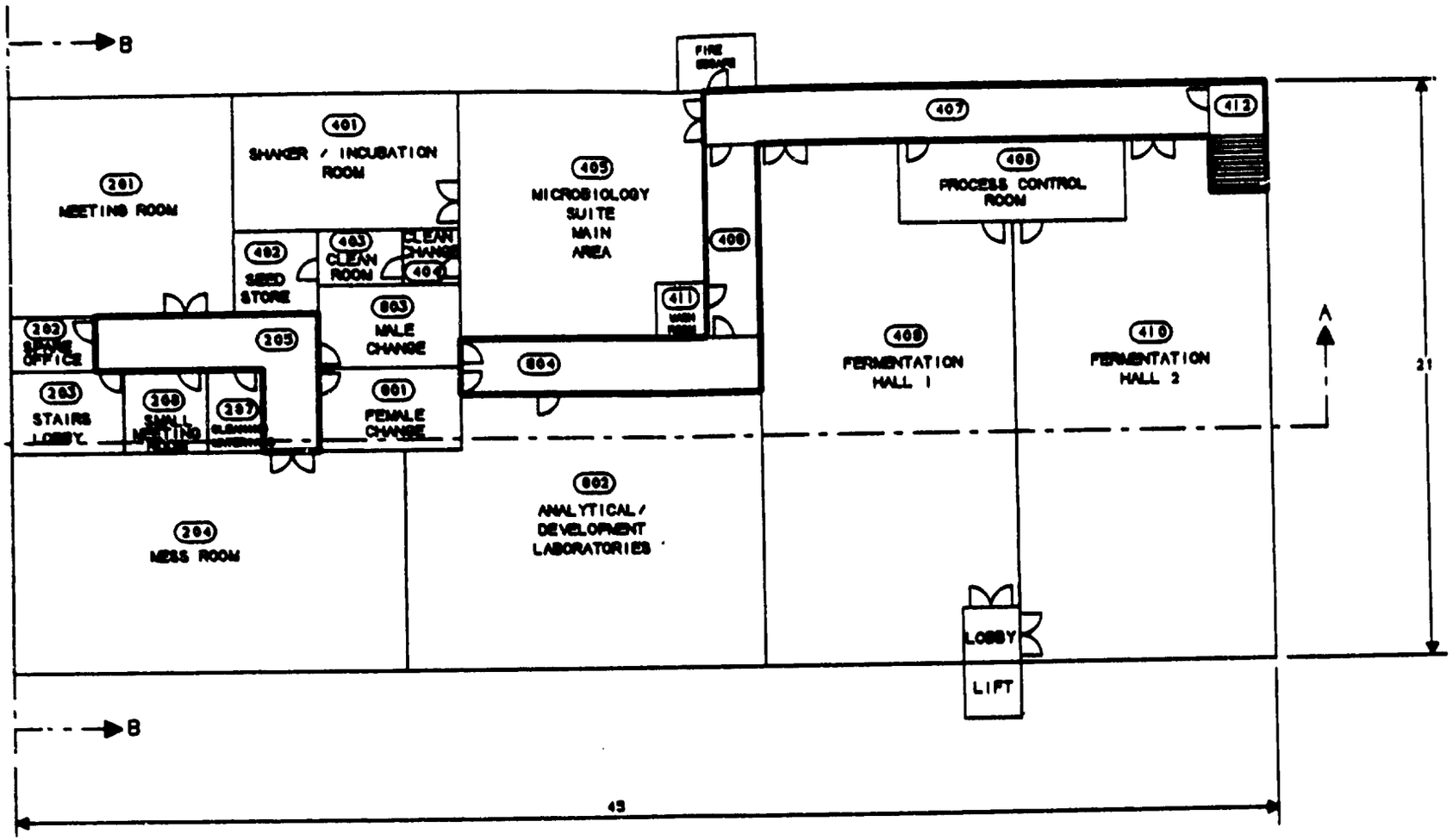

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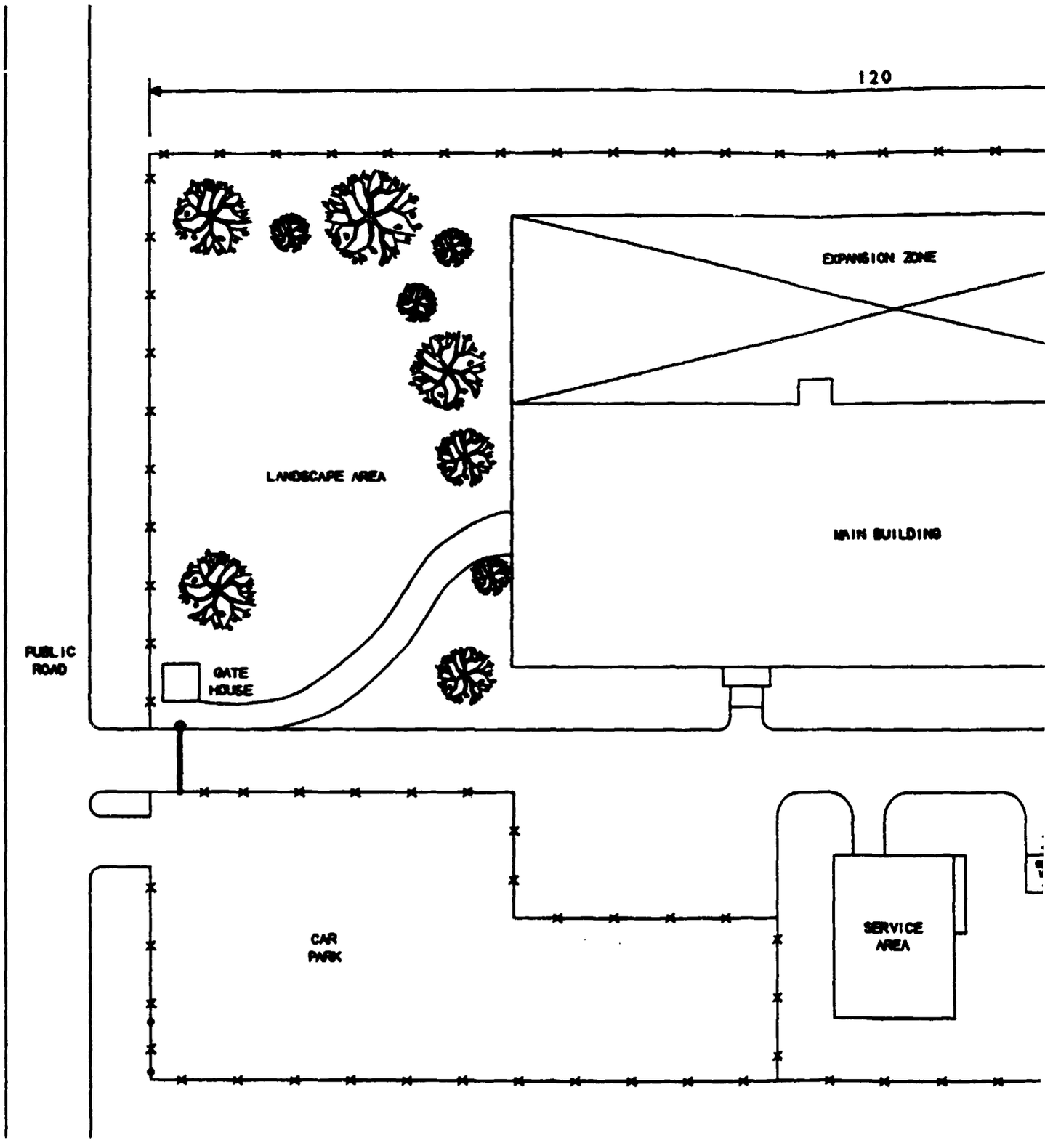
			DRAWING NUMBER 92/004/103	REVISION D



SECTION 1

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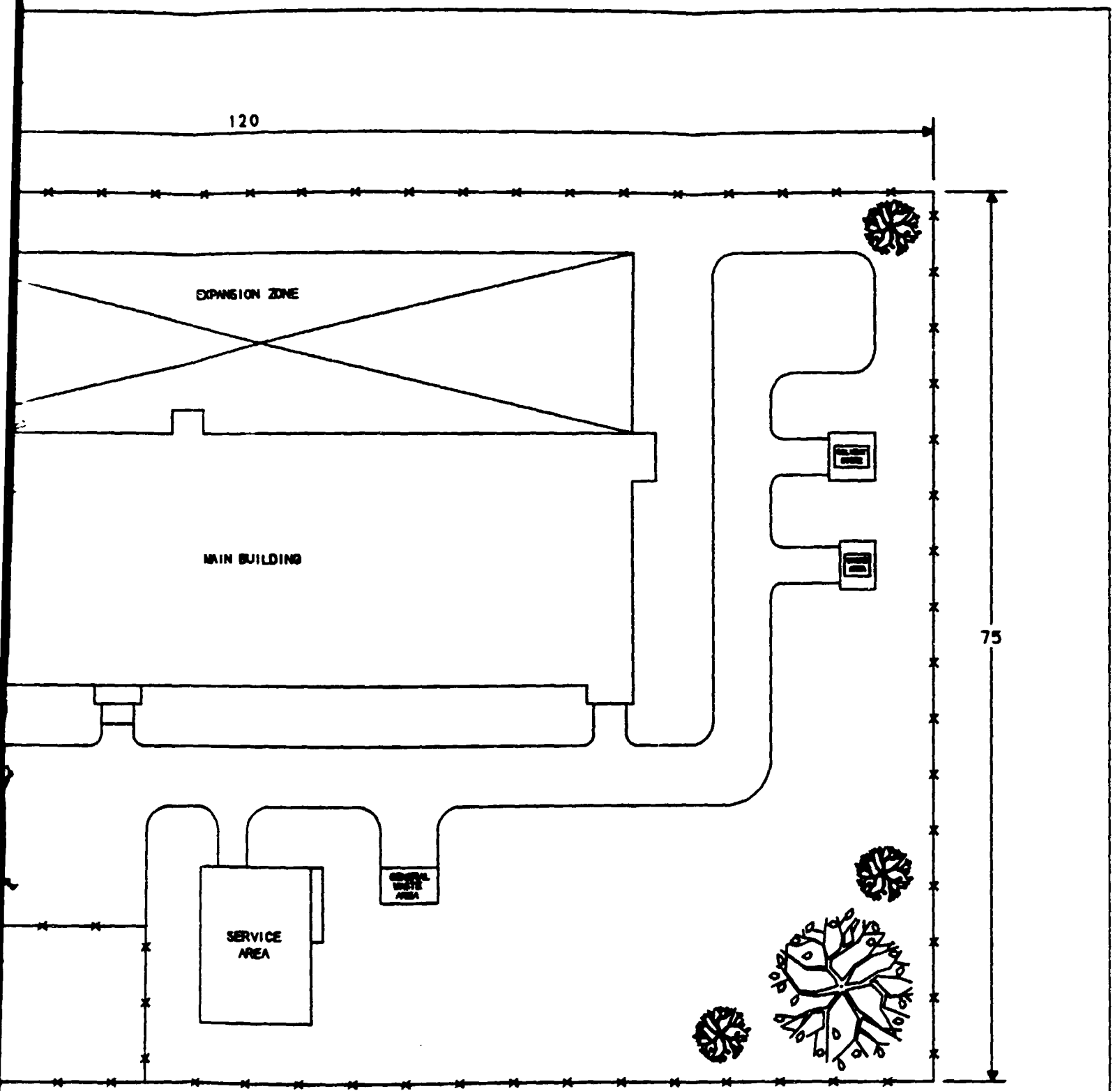


SECTION 2

GRC CONSULTANTS	CLIENT	PROJECT	TITLE	
STERBRIDGE HOUSE 78 HIGH STREET ALTON HANTS GU34 1BN TEL: 0420 88849 FAX: 0420 89427	UNIDO P.O. BOX 300 A-1 400 VIENNA AUSTRIA. FAX 232138	BIOGAL TF/MLW/90/008	PROPOSED SITE LAYOUT	
			DRAWING NUMBER 92/004/106	REVISION A

SECTION 12

SAFETY AND THE ENVIRONMENT

12 SAFETY AND THE ENVIRONMENT

The material presented in this section is intended to give a broad overview (with some specific details) fo several important environmental and safety matters as they concern the Biogal new biotechnology development facility.

12.1 ENVIRONMENTAL MATTERS IN GENERAL

Public and political interest in environmental issues has grown significantly in recent years. Environmental management is aimed at reducing the impact of human activity to such a level that environmental harm and hence legal liability is minimised. All business activities are managed with the minimisation of environmental impact in mind, such as selection of operating site, selection of process, disposal of waste, etc.

In some EC member states the principle of anticipation (or precautionary principle) is being developed. The main principle is that man should emit the least possible amount of pollutant since it is not possible to predict the effect of any pollutant on the environment until it may be too late. Stringent controls should be placed at the source of the pollution since controls at the environmental level, e.g. on river quality, can only serve as post pollution confirmation.

Politicians of the European Parliament have been spurred into action by the growing 'Green Vote' and it is now only the rate at which tighter legislation on environmental control comes into force that is open to question.

The EC is moving towards ever tighter controls and better implementation of EC environmental legislation. There are moves to set up a European environmental agency and to establish a common EC environmental labelling scheme.

Companies throughout the EC could be obliged to carry out environmental audits under a directive currently being prepared by the European Commission.

A significant EC proposal awaiting adoption is COM(89) 282 Civil Liability for Damage Caused by Waste. There are three aims behind the proposal:

(i) To establish a system whereby waste producers, or other persons directly responsible for waste, bear the costs of any environmental damage caused by their waste. This would demonstrate the true cost of waste management, a cost which would eventually be incorporated into the prices of the goods and services giving rise to the waste.

(ii) To make the system of liability uniform throughout the EC so that waste does not migrate to those countries where standards and/or regulations are the most lax.

(iii) To enforce EC environmental law through the use of the civil law courts.

Note that environmental damage includes any significant physical, chemical or biological deterioration and will probably include damage to flora and fauna.

The directives once finalised will be expected to be adopted in 1992 and liability will not be retrospective.

The environmental policies of the European Commission are based on three major principles:

- that prevention is better than cure
- that the polluter pays, and
- that other EC and therefore national policies should take the environmental dimension into account

Forward thinking companies who plan ahead for forthcoming regulations may well obtain commercial benefits in the process.

The UK Industrial Society suggests that apart from any ethical, moral or legal obligations there are at least three reasons why a company should be seen to be environmentally conscious:

(a) The problem of recruiting high calibre staff is likely to increase; young people and graduates in particular will be less willing to work for companies with poor environmental records. (Similarly the ethical investment business is growing.)

(b) Staff can be potential whistleblowers if a company fails to meet the claims of its marketing department.

(c) A good record of involvement in and support for the local community can provide a company with a core of goodwill when a sensitive environmental issue arises.

In the pharmaceutical industry the high cost of product relicensing after a major process change means that any environmental considerations should begin during the initial research and development phases of a new product. Consideration should in particular be given to the impact of any new and forthcoming legislation on the cost and feasibility of disposing of the process waste.

12.2 SPECIFIC SAFETY MATTERS

12.2.1 Hazardous Area Classification

Area classification is based on probability, frequency and duration with which a potentially flammable concentration of gas, vapour or mist may occur in the normal operation of plants. Although the area classification procedure does consider some abnormal operating conditions it does not take into account 'catastrophic abnormalities' such as the rupture of a process vessel or large pipeline.

Area classification is used as a means to allow the selection of the appropriate types of electrical apparatus (and their correct use and maintenance) in areas where flammable materials are encountered.

The international definitions for the zones used in hazardous area classification are as follows:

Zone 0 - A zone in which a flammable atmosphere is continuously present for long periods.

Zone 1 - A zone in which a flammable atmosphere is likely to occur in normal operation.

Zone 2 - A zone in which a flammable atmosphere is not likely to occur in normal operation and if it occurs will only exist for a short time.

A non-hazardous area is an area not classified as Zone 0, 1 or 2.

All the hazardous zones in the plant are contained in the downstream processing area or the solvent stores.

The hazardous zones are restricted to ground floor level and are specified in drg. 92/004/113 and listed in table 10.1.1 (see Section 10).

The process rooms which may contain solvents and/or explosive powder are classified Zone 1.

The corridors in the downstream processing area are classified as Zone 2 and not Zone 1 since process materials transferred between process rooms is achieved using sealed containers.

The wash room (room 514) and the clean make-up room (room 516) are classified Zone 1.

The equipment room (room 519) and the cleaning equipment store (room 520) are classed as Zone 2 as materials entering these rooms are substantially free of solvents and process materials capable of generating dusts.

The In-process laboratory (room 518) will not handle large quantities of flammable material and hence is specified as Zone 2.

Sampling of final packed material has the potential to produce a flammable atmosphere. However, regular sampling should not occur in the goods out store (room 702) and hence this area is designated as unclassified.

12.2.2 Sampling Of Gases And Vapours

If materials are used which can produce a toxic atmosphere, a monitoring programme should be carried out. If people are exposed to hazards for long periods instruments which give a continuous reading should be used. Medical checks should be regularly carried out on personnel regularly exposed to potentially harmful substances.

For the measurement of common organic liquid vapours the use of spot reading instruments such as 'Drager Tubes' and day wear 'Diffusion Badges' may be suitable. These instruments can provide valuable information to determine the extent of any solvent vapour problem in a simple and cost effective basis.

Details of monitoring and sampling procedures which Biogal may wish to consider are given in Appendix I.

12.2.3 Breathing Air

These notes are provided as background information for the installation of breathable air systems. Where compressed air is used for breathing, high standards for installation and filtration should be used. Routine maintenance of all equipment is essential.

AIR QUALITY SPECIFICATION

Air supplies should not contain impurities in excess of those stated by a suitable breathing air standard, such as BS4275:1974, given below.

Carbon Monoxide 5 ppm (5.5 mg/m^3)
Carbon Dioxide 500 ppm (900 mg/m^3)
Oil Mist Particulate (0.5 mg/m^3)

Odour and cleanliness - the air must be free from all odour and contamination by dust or metallic particles and should not contain any other toxic or irritating ingredients.

No limit is specified for oil vapour because the vapour pressure of compressor lubricating oils is so low that at temperatures acceptable for breathing air the maximum possible concentration of oil vapour is well below the level of 600-1300 mg/m^3 which can be safely tolerated.

The breathing temperature and humidity must also be specified in order to design the system. A breathing air temperature of 15°-25°C is generally acceptable. The relative humidity of between 25-80% should be used. The breathing of dry air can cause discomfort and in some cases damaging respiratory ailments. The breathing of wet air with a humidity of greater than 80% can also cause discomfort to the user and may also result in slugs of water entering the breathing apparatus due to condensation produced by the cooling of the supply air.

COMPRESSORS

Compressors may be of an Oil Lubricated, Carbon Ring or Water Sealed type. PTFE compressors are not recommended because of the risk of production of offensive gases if rings become overheated. This is despite the fact that the possibility of the compressor actually attaining the temperature level that is dangerous is remote.

The compressor should be installed so that the air intake includes clean fresh air. Inlets should not be exposed to rain, snow, ice, dust fumes or noxious vapours.

INSTALLATION

Correct air line installation practices should be used. Automatic drip leg drains should be used at low points and drain legs, and the operation of these drains checked on a regular basis.

It is preferable to install an independent breathable air distribution system separate from other compressed air systems.

The system should be sized adequately allowing for future changes in operating practice. The requirements for each person depends on the type of breathing apparatus used. A breathing hood, for example, typically requires approximately 200 l/min per person.

ANCILLARY EQUIPMENT

The air is treated centrally in one or more locations to bring the air into specification. Individual filter regulators are used at points of use. The first filtration stage is usually a prefilter. The air then typically enters a specialist coalescing filter to remove oil and water mist. A carbon filter is then used to remove objectionable hydrocarbon vapours.

Filters containing proprietary materials are available for the removal of carbon monoxide. However the inclusion in a system of devices which will remove a particular noxious vapour can give a false sense of security to the user. Such devices need careful monitoring to ensure that they have not reached their life expectancy.

Where the relative humidity content of breathing air is below the recommended value of 25%, at atmospheric pressure due to local meteorological conditions or the inclusion of an air drier within the system, some form of humidifier should be incorporated. Airline lubricators can be successfully utilised as humidifiers, providing the Micro-Fog type is used. The standard Oil-Fog type lubricators (where every drop of fluid that falls from the drip gland is introduced into the air flow) are not suitable, this type of unit causes over

saturation. Micro-Fog lubricators do not introduce free water into the system, by virtue of their design, they only generate water vapour.

At the point of use a filter regulator is installed. The filter removes any pipeline debris. The regulator is adjusted by the user with the use of a flow indicator which may take the form of belt mounted rotameter worn on the person.

In conclusion, the high standards of airline installation, the correct siting of compressor and selection of filters are important. After installation regular inspection and preventative maintenance of all equipment is essential.

12.2.4 Inerting Of Basket Centrifuges

(Whilst not specifically identified in the equipment list, this type of centrifuge is frequently used for general purpose filtration and the following notes are appropriate when solvents are handled.)

GENERAL

A centrifuge has the potential to inflict serious injury to personnel coming into contact with moving parts or hot surfaces, becoming trapped or entangled by it, or being struck by parts of material ejected from it. Process materials can cause scalding, chemical burns or fire and explosions which are discussed further in this section.

Centrifuge doors must not be capable of being opened while the basket is still revolving. Clearances between rotating and stationary parts must be sufficient to prevent contact when the basket and shaft are deflected as a result of unbalanced loads.

Centrifuges will often produce a fine mist within the casing but for a fire or explosion to occur, oxygen within a specified range and an ignition source must be present. In practice flammable vapour/air mixtures must have extremely low ignition energies and so are easy to ignite.

The low flammable limit of a mixture of vapour in air is when the concentration of vapour is too low to support combustion. The upper flammable limit is when the concentration of vapour is too high and hence the concentration of oxygen too low to support combustion.

Within centrifuges, handling certain substances, the average vapour concentration will be above the upper flammable limit for much of the time. Uneven mixing, however, can lead to localised flammable pockets.

HANDLING OF FLAMMABLE MATERIALS

A flammable mixture can be ignited by a flame, a spark, or a hot surface. If the temperature is in the region of 400-600°C autoignition without an ignition source can occur for many materials. This temperature is unlikely to occur within a centrifuge unless a mechanical problem causes a local hotspot. Sparks caused by mechanical contact are almost certain to contain enough energy to ignite a flammable mixture. Static electricity can also produce sparks or sufficient energy. Hydrocarbons have low electrical conductivity and are a particular problem. Filter cake can form an insulting layer so an earthed centrifuge is still at risk. All centrifuges should, however, always be adequately earthed. The operator when digging out a centrifuge can be the source of a static electrical charge particularly when insulated from the earth by, for example, rubber boots. The subject of electrostatics is discussed further in Section 9.6.

For handling flammable materials, the centrifuge casing, lids and doors must be provided with suitable seal and be able to maintain a slight positive pressure without loss of gas or vapour to atmosphere. A suitable general standard is that the loss of internal pressure at constant temperature should not exceed 15% per hour when subject to an initial test pressure of 400 mm wg.

The use of mechanical friction brakes in flammable atmospheres is not recommended unless adequate precautions are taken to prevent the maximum surface temperature exceeding the temperature classification of the substance handled (British Standard 4683). If a direct drive centrifuge is not used, a friction clutch mechanism must be constructed so that no liquid can spill or leak into it. The housing must be continually purged with clean, dry air. If friction brakes are used, they are acceptable if housed in the same air purged housing as the friction clutch.

INERT GAS BLANKETS

The only way of ensuring that a flammable atmosphere does not form in a centrifuge is to reduce the amount of oxygen by purging with inert gas, typically nitrogen.

For most materials the critical oxygen concentration for ignition lies between 10 and 14%. Due to uncertainties of sampling and the high degrees of sampling inside the centrifuge an operating level of not greater than 5% oxygen is recommended.

The means used to regulate the inert gas supply and monitor its continuing presence will vary with the degree of risk and the type of equipment used. The three methods used for monitoring are flow, pressure and oxygen concentration measurement.

Monitoring the flow of inert gas is the simplest system but is the least reliable because air can be drawn into the centrifuge creating an undetected flammable atmosphere. A minimum check of once per shift on oxygen concentration in the gas from the centrifuge is recommended.

Monitoring by pressure is relatively expensive to install but is reliable and can be economical in the consumption of inert gas. The casing is initially vented to a safe place and then the vent valve closed. The flow of inert gas is then regulated by a pressure controller so as to maintain a recommended normal operating pressure of 100 mm wg.

All failures of blanketing, including leaks and oxygen contamination of inert gas supply can only be detected by continuous measurement of the oxygen concentration in the centrifuge. This system is complex and the use of high quality equipment and maintenance is required.

In all the above systems suitable bearing seals should be provided to prevent ingress of process fluid into the bearing space. Inert gas should be applied to the bearing housing so as to prevent the formation of a flammable atmosphere. Care must be taken, however, to prevent blowing lubricant from the bearings causing bearing failure.

Slurry feed and wash supply vessels should have inert gas blankets to prevent air entering the centrifuge, either in solution, or due to vortex entrainment or by running empty.

The centrifuge which may be used in the Biogal development facility is likely to be a type which requires frequent opening for cake discharge and cleaning. The multipurpose nature of this equipment means that it will probably be handling liquids at temperatures at or above their flash points. The centrifuge must therefore be considered to be at

a relatively high level of risk and the recommended method of inert gas blanketing in situations of high risk is monitoring by oxygen concentration.

12.2.5 Electrostatics

Electrostatic charging is caused basically by the electrification of materials through physical contact and separation. The various effects which result from the negative and positive charges so formed include sparks which can constitute fire or explosion hazards. The generation of static electricity cannot be prevented, absolutely, because its intrinsic origins are present at every material interface.

In the context of the Biogal development facility, the possible sources of static electricity include the following:-

- Low conductivity liquids (typically solvents) flowing through pipes and associated fittings.

- Powdered materials flowing through chutes or conveyors.

- Movement of personnel particularly if wearing clothing of silk and/or synthetic fibre and/or when insulated from earth.

- Any movement that involves changes in relative positions between contacting surfaces of dissimilar substances, liquid or solid, one or both of which is a poor conductor of electricity.

Ways of reducing electrostatic hazards in medicinal chemicals handling are outlined below.

HANDLING LIQUIDS

(i) Transfer

All types of flammable liquids must be sampled and the conductivity of the sample measured. If the conductivity of the process fluid is less than 300 pS/m, then any transfer rate within pipelines must be kept to less than 3 m/s but if subsequent free fall or outlet jets occur then even lower rates are necessary.

Where water is entrained in a flammable immiscible non-conducting liquid, velocities must be limited to 1 m/s. Any process liable to disturb water layers on tank bottoms must be avoided. Wherever possible tanks must be fully drained of water bottoms when emptied.

For slurries, multi-phase liquid mixtures or liquid products containing solids, velocities must be limited to 1 m/s. If this is not practical due to settling of solids in the pipeline, then the lowest velocity consistent with satisfactory transfer must be selected.

Ethers and carbon disulphide must be transferred at the slowest rate practicable, the maximum allowable being 0.5 m/s. Esters, ketones and alcohols may be transferred at up to 8 m/s.

For each application a maximum transfer pressure or vacuum must be specified.

Wherever possible, conductive piping must be used for transfer of flammable liquids. The conductive pipe must be securely bonded to earth. Any flexible connections needed in non-permanent plant must be short and as straight as possible. The plant at the flexible pipe terminations must be securely bonded to earth.

Glass pipework is unlikely to become charged electrostatically, particularly if conducting glass is used (specific resistivity 1 Megohm. m). Insulated metal coupling flanges could become charged by induction if high flow rates are allowed. Also any leakage through the gaskets at these points may lead to localised high charges. All such flanges must therefore be interconnected with a robust electrical conductor securely bonded to earth at each end of the pipe run. These connections must be regularly maintained and must be remade whenever they are broken to remove a section of pipe, etc.

Flexible pipe used in transfer system likely to involve frequent dismantling or replacement of the flexible pipe must not contain any metal earthing or reinforcing wires. Those transfer systems likely to remain permanently fixed and which contain unavoidable lengths of non-conducting pipeline must be so constructed that there is a permanently connected robust metal conductor wound spirally with respect to the pipeline and securely bonded to earth at both ends thereof. Anti-static hose can be used for this purpose. The earth continuity must be checked throughout at regular and frequent intervals. Connections must be regularly maintained and must be remade whenever they are broken to remove a section of pipe, etc.

If the use of plastic hose is unavoidable, then wherever possible single lengths must be used. If a hose coupling has to be used, it is preferable to make it metallic and to have the conductor securely fastened to it. Alternatively a plastic coupling could be used, bridged by an electrically conducting cable. In no circumstances should an insulated metal coupling be used.

Carbon-filled (black) polythene hose is non-conducting and should be treated as such.

(ii) Jointed Pipework Systems

All metal backing flanges in non-conducting pipework systems must be bonded together by flat 1/2" copper braid or earthing cable. The bonded system must be connected to earth, preferably at both ends of each pipe run.

All joints must be leak-tight. Since this is necessary for other safety reasons, it should be emphasized.

All metal flange joints with insulating gaskets and all metallic flange joints coupling pipes made of insulating material must have a bonding strip joining the two flanges and each strip must be interconnected and securely bonded to earth.

The resistance to a main earth of any metallic item of plant must be less than 10 ohms.

Ball valves in lines transferring flammable liquids must be of the anti-static type. Stocks of ball valves kept for replacement purposes must be entirely of the anti-static type.

(iii) Filling Vessels

The internal walls of all pipelines must be smooth and free of protrusions. Sharp bends must be avoided. Material flow rate should be steady.

When top filling via a hose coupling into a closed vessel, the flow rate must be kept to a minimum.

If the liquid is flammable, or is being handled in a flame-free area, and is found to have a conductivity not greater than 10 pS/m, then inert blanketing of the vessel prior to filling is essential.

When transferring flammable liquid from a tank by pressurisation, the system must be designed to use inert pressurising gas. The latter must not be allowed to bubble freely through the liquid or transfer pipe.

When transferring flammable liquid into a tank from a drum by vacuum suction, air must not be allowed to bubble freely through the tank contents for prolonged periods. All transfer pipes with earthed spiral used for this duty must terminate in a long earthed nozzle with an integral control cock. The nozzle must be connected to the supply drum to ensure electrical continuity if the latter is metallic, and the drum securely connected to earth.

When transferring material by pumping, the pump must be securely connected to earth. Particular care must be taken when installing new types of pump. This is the recommended preferred method of transfer, rather than pressure or suction transfer. Similarly, when filtering by e.g. a Calmic filter, this must be securely connected to earth.

(iv) Filling Drums

Conductive nozzles must be used, securely connected to earth by an efficient gripping device.

The inlet pipe must extend to the bottom of the drum.

The flow rate must not exceed those recommended above (Transfer).

Metal drums must be securely connected to earth by an efficient gripping device. Durable flexible cables must be used to make earthing connections.

(v) Mixing

The design of jet or propellor mixers must be such as to prevent charged liquid from being carried upward through the liquid surface.

HANDLING SOLIDS

(vi) Chutes

Chutes are not recommended for:

(a) transfer of flammable solids into vessels, or
(b) transfer of solid materials into vessels containing flammable mixtures

If chutes cannot be avoided, they must be made of a conductive material and securely earthed.

The tipping of material into a reaction vessel from a plastic container or drum liner is only permissible if it can be ascertained that the concentration of flammable vapour at the point of entry of the material will not exceed 25% of the lower flammable limit.

(vii) Mixing and Milling

All conductive parts of a mixer or mill handling flammable powders must be earthed.

If the material handled contains flammable solvent, the mixer or mill must be blanketed with inert gas.

(viii) Rotary Driers

Driers must be earthed when installed. Measurements made on rotary cone driers have shown that negligibly small charges are generated by the tumbling of these driers for the mixing of certain powders, so no hazard is likely to exist within them. However, the action of discharging them, particularly via plastic socks, can generate significant charge levels.

(ix) Dust Extraction

Dust extraction machines of the filter bag type handling explosible dusts must be fitted with an explosion relief panel on the filter chamber. These panels must be properly designed to vent any explosion pressure which might be generated to a safe area, preferable prohibited to personnel.

All conductive parts must be securely connected to a main earth.

PERSONNEL

A conductive grid must be fitted round all reactor vessels, etc, on which an operator can stand when charging the later with process chemicals. The grid must be connected to a main earth.

BUILDINGS

Protection against lightning should be implemented as per British Standard Code of Practice CP326 or suitable European Code of Practice.

All buildings containing flammable process materials must be provided with properly grounded earthing strips. Around each floor of a building or an external structure must be run an earth continuity strip. For all normal industrial applications this should be of copper with a minimum cross-sectional area of 0.06 sq.in. (40 sq.mm). This strip must not be drilled through for any purpose other than jointing. PVC protected strip may be used in arduous conditions to protect the conductor from wear and corrosion. The resistance to earth from any point on the strip must be less than 1 ohm.

The continuity strips on the various floors and stagings of each building should be interconnected by a similar conducting strip, which connects via a test link to a drive steel electrode. This should be a solid copper rod fitted with a steel point, such as are used for electrical or lightning conductor earthing. The electrode must be driven into earth by at least 6 feet. The resistance of each earth electrode should be measured by the method described in BS Code of Practice 1013 or other similar European Code of Practice. The resistance must be less than 1 ohm.

Any earthing and bonding conductors should be attached to the earthing continuity strips by soldering, welding or suitable screwed terminations. Chains must not be used.

In no circumstances should any interconnection be made between a static earthing system and a lightning earthing system, except by virtue of the general mass of earth at the buried electrodes.

The resistance to earth from any point on any floor of a building containing flammable solvents must not exceed 1 Megohm.

PLANT

All conductive parts of plant handling flammable liquids must be properly bonded to earth. Each identifiable item of plant or equipment, e.g. pump, still, tank, etc, must be connected to the earth continuity strip by a conductor of the same cross-sectional area. A good conductive joint must be ensured at each end. Equipment should be designed to incorporate a specific earth terminal.

Wheels on portable containers intended for flammable liquids or solids must be of the anti-static variety.

12.2.6 Effluent and Waste

The development unit generates a relatively small quantity of effluent and waste which may be treated in accordance with the notes given below. (See also Section 4.1.2)

- General Plant Aqueous Wastes frcm the wash down of floors, spillages, etc - These pass to the general plant drainage system directly via floor drains, where installed, or via a mop and bucket system where there are no floor drains.

- General Surface Water (rainwater) - This waste passes to conventional storm water drains.

- Domestic effluents from laboratories, toilets and other amenity areas pass to the conventional foul sewer.

12.2.7 Safeguarding of Equipment

For reasons of safety, all moving parts on machines should have adequate guards and interlocks conforming to an appropriate standard. Moving parts needing protection include motors, belts, gears, shafts, couplings, chains, mixers and impellers.

12.3 CONTAINMENT MATTERS

It is emphasized that Biogal do not intend to use genetically manipulated organisms (GMO's) for at least 2-3 years in the new biotechnology development facility. However, it is acknowledged that Biogal may well move to GMO's in the next few years and it has been agreed that the facility should be designed with the eventual use of GMO's in mind from the outset. This FED study reflects this requirement which is noted on different occasions in different sections of this report.

It is appropriate, therefore, to include in this section some notes and guidance on the more important aspects of containment as they affect the basic design of the new facility.

12.3.1 General

The new development facility is designed to handle, in the future, a range of microorganisms and substances to which special attention must be paid from a safety and containment point of view. The organisms and substances may include the following:-

- Bacteria and fungi which may be classified as Class 2 pathogens according to the Health & Safety Executive 1984 regulations for the categorisation of pathogens.

- Genetically manipulated material which is classified as a Category 2 material according to the system of categorisation of the Advisory Committee on Genetic Manipulation (ACGM).

As a result of the above the following generally applies:-

- All materials defined as Class 2 pathogens and Category 2 materials, when handled in the open environment, are handled in Class II Biological Safety Cabinets (see also Ref (3)).

Frequent mention is made in biotechnology of primary and secondary containment which may be defined generally as follows:-

- Primary containment involves the isolation of particular pieces of process equipment within rooms.

- Secondary containment applies to the whole facility level and involves the use of purpose built rooms and other structures designed to prevent the release of biohazards.

Key aspects of primary and secondary containment now follow.

12.3.2 Primary Containment

Guidelines aimed at 'conventional' pathogens do not refer specifically to pilot and production operations where process equipment is involved. Most regulatory authorities large-scales are taken as being of volumes greater than 10l for the main fermentation stage of the process. Working with culture volumes greater than 10l does not automatically

increase the risk asscciated with a pathogen or recombinant organism. However, the larger potential escape volume can give rise to both an increased concentration or organisms and also a longer exposure period.

A typical process which uses a genetically manipulated organism includes certain key items or process equipment. These are:

- Fermenters
- Centrifuge and other cell harvesting equipment
- Cell disrupters
- Ultrafiltration equipment
- Chromatographic equipment

With all these items there is a possibility that leakage could occur and also that contaminated aerosols could be generated. Thus special attention must be paid to the following:

- Pressure relief valves
- Entries into vessels
- Seals or agitators
- Sampling devices
- Drains for steam condensate and cleaning systems
- Seals on vessel lids
- Emergency 'kill' systems
- Exhaust gas filtration and incineration
- Piping connections

The points are covered by the majority of guidelines which in general state that on going from Category 1 to Category 2 steps must be taken to prevent rather than minimise the release of microorganisms from fermenters.

Thus for Category 2 organisms particular attention is paid to the following areas:

- Barriers between cultures and the external environment
- Treatment of exhaust gases
- Sample collection
- Inactivation of organisms before removal from culture vessels
- Seal design
- Inactivation of effluents

Of all the items of process equipment, the two most likely to allow release of a biohazard are fermenters and centrifuges, but these systems inactivate the biohazard and therefore pose no threat.

Fermentation probably poses the biggest threat as, at this stage, organisms are growing at a fast rate and are thus probably at their fittest. It can be argued that, because of the massive aerosols generated, centrifugation poses a bigger threat, although at this stage organisms are often 'past-their-best' and are probably less able to cause disease or pass on their genetic material.

The design features normally considered important for contained fermenter systems (i.e. those designed to prevent release of organisms) are discussed in detail below:

- The use of pressure relief valves should be avoided as they have a tendency to become contaminated with dirty and consequently leak. Rather, a bursting disc system should be used. However, downstream of bursting disc systems, a kill tank should be installed in which any organisms breaking through the pressure relief system due to vessel over pressure are contained and/or killed.

- All entries into vessels, e.g. electrodes, should be sealed with double 'O' rings. A system for the delivery of sterile fluid into the gap between 'O' rings should be provided.

- Top drive agitators or mechanically coupled agitators are preferable to bottom drive systems where culture could possibly leak out of the vessel via the shaft seal. However, modern designs of double mechanical seals are extremely reliable.

- Sampling devices must prevent the release of organisms. To date, the only effective way of achieving this is to have the sample port located inside a suitable microbiological safety cabinet. The development of contained sample valves is being pursued.

- All steam condensate generated from steam used to sterilize vessels, valves, piping or gaps between 'O' rings or steam condensate used to lubricate seals should drain to a suitable 'kill' tank.

- Drains from CIP systems should also go to a 'kill' tank.

- A system for neutralising organisms in spillages should also be included.

- The use of lids on vessels should be avoided. Rather, the vessel should have the upper portion welded to the cylindrical portion. If a lid is used it should be sealed, similar to entry ports, by double 'O' rings with steam barriers.

- A validated exhaust gas filtration system should be employed. This would typically involve two or more 0.2 rated filters in series through which all exhaust gases pass. Downstream of the filter, exhaust gases can also be incinerated to destroy any organism escaping the filters.

- Flanges or pipe joints should be avoided as these are prone to leak due to wear and tear of gaskets. Rather orbital welds should be used where possible. Valves should also be welded into pipes.

12.3.3 Secondary Containment

Secondary containment comprises the following key elements:-

- Layout and building design
- HVAC (heating ventilation and air conditioning)
- Drainage and effluent treatment

These elements are summarised below.

LAYOUT AND BUILDING DESIGN

The approximate areas needed for contained laboratories or a pilot/production plant is calculated and the necessary categorisation of biohazard agreed before a building layout can be established. Where possible, areas dealing with organisms of the same hazard group can be grouped together in a suite so as to be able to utilise common material and personnel decontamination areas. However, in all cases, segregation of areas dealing with different organisms will normally be necessary, if not for containment reasons then usually to comply with good manufacturing practice (GMP) if the product of the process is intended for therapeutic use.

HVAC

In general this refers to all equipment and procedures involved in the maintenance of air purity, temperature, humidity and acceptability for human consumption within a facility.

Typically conditions should be as follows.

A continuous air flow must be maintained into the contained area by one of the following means:

- Extracting the laboratory air through independent ducting to the outside air through a HEPA filter

- Extracting the laboratory air to the outside with a fan and a HEPA filter sited in a wall or window

- A safe variation on these procedures

- Supply and extract flows must be interlocked to prevent positive pressurisation of the room in the event of failure of the extract fan.

All guidelines agree that the atmosphere inside the contained area should be held under negative pressure. This is normally not a problem to maintain. However, in cases where the process housed within the area has to comply with GMP, maintaining the correct air pressures can be difficult.

DRAINAGE AND EFFLUENT TREATMENT

A further problem in the design of buildings and the layout of contained areas is what to do with the wastes which are contaminated with the biohazard.

Containment requirements can be summarised as follows:

- An autoclave for sterilization of waste materials should be situated preferably within the laboratory but one should be readily accessible within the laboratory suite

- All waste materials must be made safe before disposal or removal to the incinerator.

In designing contained areas which are to house large scale operations, provision is normally made for the installation of 'kill' tanks. These would, where possible, be housed in the basement. The 'kill' tanks are used to hold contaminated waste fermenter broths, steam condensate from harvest, sample valves and vessel cleaning waste. The wastes are then normally decontaminated by either heat or chemical means.

Where possible, solid waste is put into suitable containers and sterilized in an autoclave as referred to in the guidelines. Post-sterilization waste is normally incinerated but this can lead to the production of unpleasant odours and, depending on the immediate external environment of the facility, incineration on site may not be practical.

With all methods of waste decontamination it is essential that each process is properly validated to ensure a satisfactory killing of the biohazard.

12.4 SPECIFIC SAFETY ASPECTS

12.4.1 Cabinets and Fume Cupboards

Biological Safety Cabinets

Based on the level of biological hazard predicted, Class II cabinets are generally provided in the appropriate culture areas. These cabinets are open fronted, allowing the work area to be flushed with a unidirectional downward air flow. The air flows are such that laminar flow conditions can be achieved which will assist in preventing product contamination. An inward air flow from the general working area forms an air cushion which minimises the escape of aerosols from the work area. HEPA filters within the system protect the work from contamination. A portion of the air is recirculated whilst the remainder is exhausted via a HEPA filter. The cabinets are designed in accordance with BS5726.

Fume Cupboards

It is anticipated that standard fume cupboards may be used for those general applications in the various laboratories.

Exhaust Ducts

Exhaust ducts from fume cupboards exhaust to atmosphere at a height to be agreed with the local authorities.

12.4.2 Fumigation

All the working areas in the contained area are designed to be f migated. Generally, microbiological safety cabinets are not fumigated separately from the rooms in which they are installed.

The fumigation is carried out using a heater/boiler unit connected to dedicated timer control systems in each of the areas noted above.

The fumigation controls and cycles are similar to those used generally in biotechnology facilities and the following outline sequence is used:-

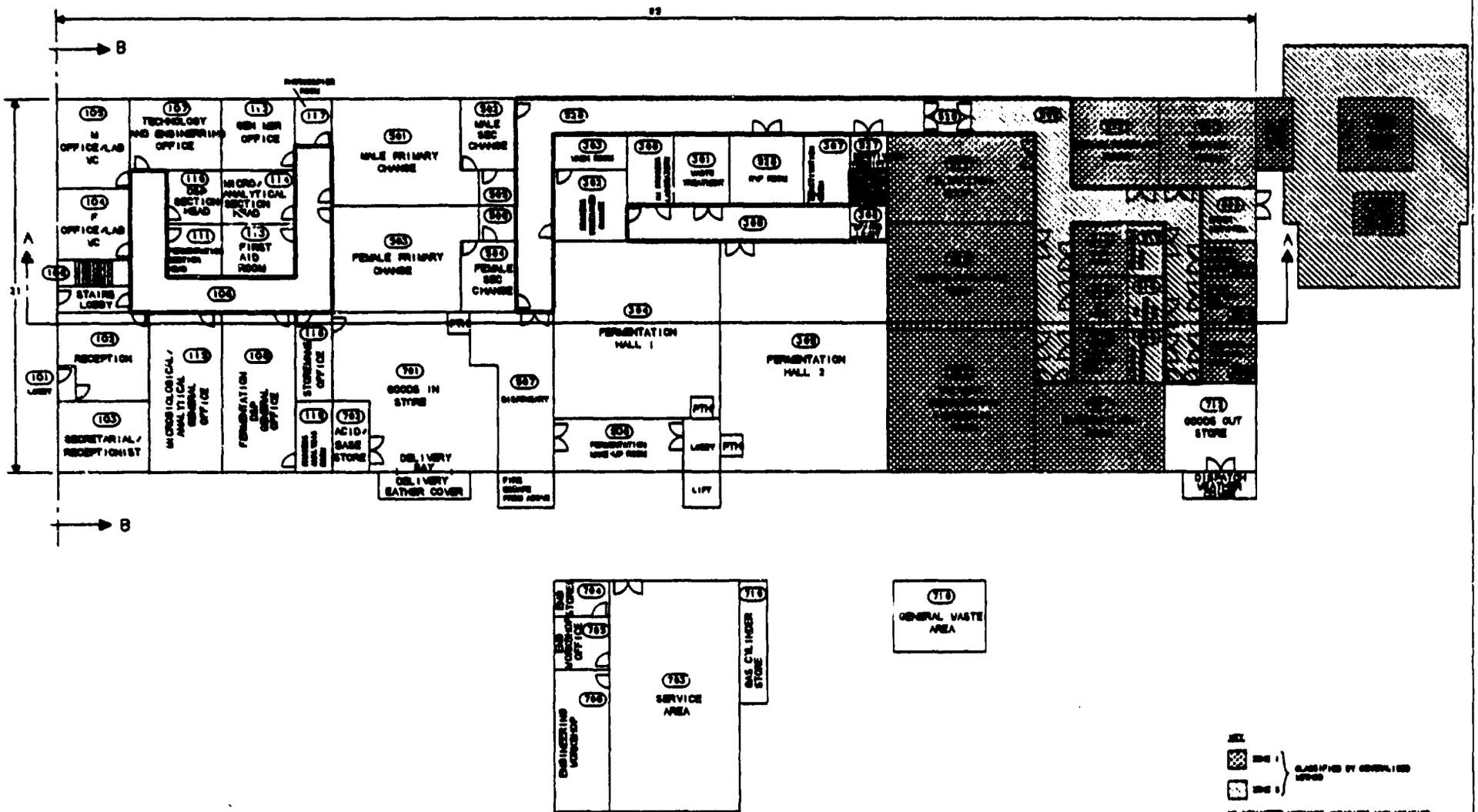
- The system is turned on followed by a 30 minute delay to allow personnel to leave the rooms

- The HVAC is then stopped and the dampers automatically closed to prevent release outside, and the boiler circuit is energised

- The boilers fumigate the rooms for a time period (approx 4 hours) and then the boiler circuit is de-energised

- The HVAC is restarted with an air make-up rate to be advised for a timed period. During this degassing period room pressure differentials are not critical.

- The HVAC returns to normal operation, but facilities are provided for manual override to extend or restart the degassing period if necessary.



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SECTION 13

GMP AND VALIDATION

13 GMP AND VALIDATION

As mentioned in Section 2, the new biotechnology development facility is designed in compliance with current best practices for a pilot plant which, in the near future, may be required to handle GMO's and possibly may be required to produce materials (or intermediates) for clinical trial purposes. 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 new Biogal pilot plant.

13.1 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 FED study, the products made in the development unit are regarded as medicinal chemicals 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 about medicinal chemicals and are intended to give Biogal and the bidding contractors some idea of the levels to which design, installation and operation may have to be taken to secure regulatory authority approval.

13.1.1 Current GMP Regulations

Various USA, UK and EC regulations require that all medicinal 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.

13.1.2 Requirements for GMP

Since the products which in the future could be made in the pilot plant are classed as medicinal chemicals, 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 at the detailed design stage if the plant and equipment eventually installed is to perform as required.

13.1.3 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: (1) quality, safety, and effectiveness must be designed and built into the product; (2) quality cannot be inspected or tested into the finished product; and (3) 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, Biogal should be encouraged to apply those concepts to the maximum extent as far backward in the processing chain as feasible.

13.1.4 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, as the project 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).

13.2 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.

13.2.1 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 new development facility for Biogal, this means that each aspect of the 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 Biogal 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 the 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 the 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.

13.2.2 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 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.

13.2.3 Requirements for Validation

(Note: in the context of this FED study the Purchaser may be Biogal and the Supplier normally is the equipment supplier or engineering contractor, but may also be Biogal's own engineering department.)

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.

(i) 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.

(ii) 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.

(iii) 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 (i) and (ii) will form part of the Supplier's scope of work before take over of the plant. Item (iii) will be carried out following take over of the plant.

SECTION 14

ENGINEERING STANDARDS

14 ENGINEERING STANDARDS

As the development unit may, at some time in the future, produce materials which could be used for clinical trials it is necessary to adopt engineering design and fabrication standards which are appropriate for achieving compliance with GMP regulations.

Reference is made in this section to engineering standards (Appendix II) which are intended to give a general appreciation of the type of fabrication and operational standards which apply to the development facility but it is neither possible nor appropriate to include in this FED study all possible engineering standards which apply. It is ultimately the responsibility of the client (Biogal) either to issue their own engineering standards to the contractor (and/or sub-contractors), or to satisfy themselves that the contractor has his own appropriate and relevant standards which would have to be examined and approved by Biogal (as part of the validation process).

However, GRC Consultants understands that Biogal do not currently have their own in-house engineering standards for the design, fabrication and installation of equipment, pipework, instrumentation, etc. Hence, at some stage, Biogal will have to either develop their own, or agree standards offered by the contractor. As the project for the detailed design, engineering and construction, etc, of the development facility moves to the next stage, this whole subject will have to be addressed by Biogal and appropriate adequate engineering standards and specifications agreed.

Clearly the standards/specifications given in the Appendix are intended as typical examples only and for general information.

For the purposes of this FED study, the following typical standards are included in Appendix II:-

GENERAL SPECIFICATIONS AND STANDARDS: NON-STERILE SERVICE

GENERAL SPECIFICATION AND STANDARDS FOR STERILE SERVICE

PARTICULAR REQUIREMENTS FOR "STERILE ENGINEERING" OF FERMENTERS AND VESSELS

GENERAL SPECIFICATION FOR VESSEL FABRICATION IN AUSTENITIC STAINLESS STEEL

SUPPLEMENTARY REQUIREMENTS FOR VESSEL FABRICATION IN AUSTENITIC STAINLESS STEEL

PIPING SPECIFICATION FOR STERILE DUTIES

The specifications which refer particularly to vessels are also, in parts, relevant to many other items of equipment which are fabricated from austenitic stainless steel. Those clauses of the specification which deal especially with the following topics are highly relevant:-

- Welding
- Materials
- Nozzles
- Internal Finish
- Postweld Heat Treatment
- Radiography
- Inspection and Testing and Reports

SECTION 15

SITE AND/OR PREMISES SELECTION

15 SITE AND/OR PREMISES SELECTION

It is understood that no particular site (or suitable premises) has been identified for the new development facility. The notes given in this section are intended to act as guidelines and strategies for identifying and evaluating potential sites and premises. It is acknowledged that the layout of the new facility, as developed in this FED study, is based on a "greenfield" site with purpose-built buildings, but it is possible that existing premises might be identified which could be adapted to accommodate the new facility. Hence some notes on criteria for identifying premises are also given in this section.

The actual exercise of identifying a possible site, or premises, does not form any part of the Terms of Reference of this FED study, but a methodology for site/premises identification is included.

15.1 GENERAL

Locations for the new facility may be selected in several ways. In many cases the choice of location is dictated by tradition or other circumstances which preclude the need for a selection procedure. The choice of location for a totally new development may appear relatively unconstrained but even in this situation there may be overriding reasons why the facility should be at one location rather than elsewhere. However, if the choice of location is not pre-ordained then there are a large number of factors which can influence location selection.

For the purposes of this study, a number of factors, or features, are proposed as criteria against which the potential premises or sites are assessed. The relative importance of the factors is also discussed. The factors used in this

report are not exhaustive but are perceived as having relevance to this particular study for a "modern, high-tech image, biotechnology based pharmaceutical development facility which, in the future, may use genetically engineered microorganisms".

15.2 METHODOLOGY OF SELECTION PROCESS

An important part of the scope of this study is the identification of possible premises or sites for the new development facility. Not only are there many ways of selecting possibilities, as noted above, but the process of selection can be highly subjective and perceptions of what qualifies as suitable (even ideal) vary with the individuals involved in the selection process. It is appropriate, therefore, to try to approach selection in a more objective way and GRC Consultants, as an impartial party, proposes to use a form of Kepner-Tregoe analysis to identify serious possibilities for premises and sites.

The process basically consists of the following:-

A list is proposed and agreed of features which must be present in any premises or site under consideration. These key features include image, access, security, etc, and a full list is given below in Section 15.5. However, not all features are of equal importance (many, however, may be equally important) hence a further list of importance factors is proposed and agreed.

Information from various sources is then sought based on an agreed preliminary requirement profile.

Each possibility is then 'rated' for its compliance with each key feature on a scale of 1-10. The criteria for rating are described later in Section 15.5.2. At this stage, the rating

is made from a combination of information given in brochures, etc, plus local knowledge of the locations, areas and premises.

For each candidate, its rating for each feature is multiplied by the importance factor of that feature to give a score. The sum of all the scores for each individual candidate is then taken as the overall score for that candidate. The higher the overall score (total), the more attractive the candidate which may be subject to further investigation.

A 'Top Ten' list of candidate sites and premises is compiled and the most promising candidates are viewed.

Following this viewing, the leading candidates may be re-rated and the whole analysis repeated. At this stage, also, importance factors may be reassessed.

This whole process is intended to reduce the subjective nature of selection by individuals and to apply a measure of objectiveness in order to identify candidates for serious investigation by senior management. The process is only one part of the overall exercise of premises/site location and it is acknowledged that other equally important factors apply. Corporate and Board policies, intentions and attitudes obviously affect selection but they may not be quantifiable or appropriate to the technique described above. Nonetheless the technique is a valuable preliminary exercise and the results are usually acceptable to, and understood by, all the interested parties.

15.3 SELECTION CRITERIA IN GENERAL

15.3.1 Vital Selection Criteria

There are a number of criteria which must be satisfied completely otherwise a site cannot be considered at all. These are listed below. Failure to satisfy any one will effectively eliminate a particular site.

Area: This is self evident but the site must have sufficient area available, both for development facility buildings and for ancillaries such as storage, offices, and effluent treatment. Area for future expansion must also be considered.

Permits: These must be available, or obtainable from local (possibly national) authorities for approval/permission to carry out pharmaceutical process pilot plant construction and operation of the processes. Careful attention will have to be paid to the presence of powerful environmental lobbies which may be active in the area of a particular site.

Owner willingness: This again is self evident, but no matter how attractive a site may appear, if the owner of the site, for any reason, does not wish it to be used for the purposes in question, then that site will have to be eliminated.

Government acceptance of possible foreign ownership and repatriation of profits: The stability of any government which is favourably disposed to the new development facility must be assessed and the attitudes of the political opposition considered.

15.3.2 General Selection Criteria

The basis of the methodology, noted in Section 15.2 above, is to identify all the factors which influence site or premises selection. The various individual factors are considered in groups of similar factors. This grouping not only assists in the necessary thought process but also allows for an importance weighting to be given to each group. Six groups are proposed:-

- Raw materials
- Utilities
- Site Facilities
- Personnel
- Political
- Commercial

The following criteria/features are desirable in any site or premises but failure to satisfy any or some of the criteria does not eliminate a particular site or premises since the missing feature/facility could be made available, or an alternative found, albeit at a price.

PROCESS FACTORS

Raw Materials: A local readily available and reliable supply of the key raw materials required. If not, the volume of feedstock materials and their import from other locations will have to be considered.

Process Water: The quality will be important especially if R&D work shows that trace ions or other impurities are important. Depending on its quality, the process water will need various pretreatments (clarification, ion exchange or demineralisation) before use.

Cooling Water: Quality is important, hardness, pH, organic content, etc, if fouling and corrosion are to be avoided. Equally important is the reliability of cooling water supply at the right temperature.

Steam: Steam at low, medium and high pressures will be required for process and general heating. Steam can be supplied either from an adjacent plant or by packaged boiler, hence the choice and availability of fuel is important.

Fuel: The availability of oil, gas, LPG, coal or a combustible waste will be important and could affect the choice of site, hence the cost and security of supply must be closely reviewed.

Electricity: For motor drives, lighting, and heating is needed and will be obtained from the local grid.

Waste Disposal: The availability of means of waste disposal must be considered; be this on site treatment, treatment at a local municipal works or removal by a contractor.

Incineration Facilities: These should be available either locally or included in the plant area, for the disposal of toxic, noxious or otherwise intractable wastes in the event that such wastes are generated.

OTHER FACTORS

Political and Fiscal Factors: Taxation rates, both local and national, may influence site selection.

The availability of national, state and local incentives to inward investment and job creation should also be considered. Capital grants and/or employment subsidies and training grants may be offered.

Ease of obtaining various permits for such items as:-

- Environmental discharges, liquids or gases
- Building Regulations
- Operation permits (permission to operate plant and transport products off site)

Local legislation should not impose unduly onerous conditions on site development, sanitation, waste disposal, noise levels, etc, again it may be prudent to determine the possible extent of influence of local pressure groups.

Trade union influence on local labour is particularly important in order to avoid inter-trade demarcation disputes which could upset the sensible operation of a highly integrated facility.

15.4 SPECIFIC SELECTION CRITERIA FOR SITES

The following factors should be considered when selecting the site (as opposed to existing premises).

Access for construction: The proximity to major roads, railways/railheads must be considered.

Raw material delivery and product distribution: The proximity to major roads, railways/railheads may be considered but because of the relatively low volumes involved, this factor may not be too important.

Access to the site is of less importance to a relatively small scale development facility than to a large scale process with large equipment and very bulky raw materials and products. However, one special factor that may have to be considered is the transport of large vessels from fabrication shops to the site. Generally a diameter of 3.5m is the maximum permitted for road or rail transport.

A cleared and level site is required before construction can begin. If a site is currently occupied by redundant buildings or plant then the costs of removing these must be considered. Similarly, the costs of levelling or infilling a virgin plot must be considered.

Internal roads are required within any site. A serviced or developed site can be expected to have these. Included with internal roads are site ancillaries such as road lighting and drainage.

Site security is required. This may take the form of a boundary fence and a gatehouse as a minimum, right up to the level of sophistication of CCTV and motion detectors around the boundary fence.

Site drainage systems are required. Depending on the process some segregation of drains may be required or desirable.

Pipetracks are required for the distribution of utilities from their point of generation to the process building. If an integrated unit is constructed, minimal pipetracks will be needed. Alternatively, where the utilities are available from an adjoining plot ("over the fence") then new pipetracks will be needed.

A fire fighting system is required. This may take the form of an underground 'wet' main outside the buildings with hydrants at appropriate positions. Also the buildings may need a dry riser fire system and sprinklers in designated areas. Since the largest costs in fire systems are the lagoons, fire pumps and undergrcund ring main, it is advantageous if these can be shared on a developed site.

A site which has roads, security, drainage, pipetracks and fire fighting in place is considered to be a serviced site.

15.5 SPECIFIC SELECTION CRITERIA FOR PREMISES

15.5.1 Key Features

The following features are proposed as being important and by which possible premises may be judged.

- Image (location, environment, surroundings)
- Building condition (age, state of repair)
- Staff amenities
- Building suitability (match to requirements)
- Staff relocation necessity (this applies also to sites)
- Car parking/lorry movements
- Services availability (site infrastructure)
- Security of premises or site
- Incentives (local, regional, national, etc)
- Expansion potential
- Planning permission likelihood
- Local acceptance (pressure groups)

A brief review of each feature now follows.

IMAGE:

It is an undeniable fact that for a modern pharmaceutical company to have credibility it must also have an image. This image is affected by a number of environmental factors which include:-

- visual image; does it look right from the outside
- immediate surroundings; is the immediate neighbourhood pleasant and attractive
- general reputation of the area; does the area have a reputation for crime/vandalism
- approaches; are the approaches equally pleasant and attractive as the immediate surroundings

- proximity to other facilities; is there open space around or is the facility hemmed in

The image of the company and its facility also has an effect on the ability to attract and hold key staff.

BUILDING CONDITION:

A brand new unoccupied building is expected to require little or no immediate improvement to its overall fabric, hence minimal cost is involved.

STAFF AMENITIES:

These include changing rooms, shower facilities, rest rooms, canteen, sports room, creche and all the staff/personnel amenities which create a happy, pleasant working environment within and around the facility.

BUILDING SUITABILITY:

This feature is meant to reflect how closely possible existing premises match the defined needs of the new facility in terms of laboratories, pilot plants, offices, etc. Clearly it is most unlikely that any existing premises can match the requirements exactly but some may be better equipped than others with respect to existing office accommodation or even some laboratories.

STAFF RELOCATION NECESSITY: (Applies also to sites)

In the event that the location of the new facility causes difficult access for key staff, they may need to relocate (or leave) with all that this implies for rehousing, school changes for children, etc.

CAR PARKING/LORRY MOVEMENTS:

There must be adequate and secure car parking for all current (and predicted for the next 3-5 years) staff. Whilst there will not be a significant amount of daily heavy goods traffic the facility must be able easily to accommodate the movements of at least one large transport lorry together with a limited number of local traffic movements (delivery vans, etc).

SERVICES AVAILABILITY:

Whilst the new facility will not be a significant user of power or steam, the facility must be provided with, or have immediate/easy access to, the usual utilities and services such as electricity, gas, telephones, etc, and sewage disposal (both domestic and industrial).

SECURITY:

It is vital that the new facility will be totally secure especially as it is anticipated that some development work may take place with desirable materials. Security may be significantly affected by the local environment.

INCENTIVES:

A range of national, regional and local authority incentives may be available for new enterprises which create new jobs. The extent (and value) of such incentives, particularly those of local authorities, can only be determined on a case-by-case basis with a particular definite proposal.

EXPANSION POTENTIAL:

The new facility may well expand in a phased manner over an initial period of 3-5 years. Clearly, premises must be viewed with such expansion potential in mind.

PLANNING PERMISSION:

The likelihood of receiving (speedily) planning permission for a change of use if existing premises are available, must be assessed but it is highly likely that a prestigious new pharmaceutical development facility will be welcomed by most, if not all, planning authorities in the region.

LOCAL ACCEPTANCE:

This is meant to imply that either local residents or other existing operators in the area have no insuperable objection to the appearance of a pharmaceutical development facility on their doorstep. Acknowledgement must be made of possible local pressure groups which may be anti-pharmaceuticals or anti-biotechnology.

15.5.2 Criteria for Rating Features

It is appropriate to describe briefly how the rating (1-10) for a particular feature for a particular candidate may be determined.

IMAGE:

The highest rating is for a facility set in a "country house estate" surrounded by trees, fields, gardens, etc.

The lowest rating is for inner city housing or industrial land being "reclaimed" but still in poor surroundings.

BUILDING CONDITION:

Highest rating is for an absolutely brand new building, never occupied and ready for immediate entry.

Lowest rating is for old factories awaiting refurbishment.

STAFF AMENITIES:

Highest rating is for full facilities with respect to offices, restaurant/canteen facilities, rest rooms, etc, so well appointed that staff are keen to stay on after hours.

Lowest rating is for the absence of even basic facilities.

BUILDING SUITABILITY:

Highest rating is for a fully equipped biotechnology development facility.

Medium rating is for a well finished warehouse or production factory shell with some integral offices and staff amenities.

Lowest rating is for a shell only which needs fitting out with everything.

STAFF RELOCATION:

This is assessed on the numbers of staff who might need to relocate.

The highest rating is for no-one to move, the mid rating is for about half the staff to move.

The lowest rating is for everyone to have to relocate.

CAR PARKING/LORRY MOVEMENTS:

The highest rating is for unlimited space.

The medium rating is for adequate space only for current needs with little to spare.

The lowest rating implies parking off site or on the street with extremely limited access for lorry movements (off loading in the roadway).

SERVICES AVAILABILITY:

The highest ratings imply that all the necessary utilities and services (quality and quantity) are laid on and readily available.

The lowest ratings mean that everything will have to be provided from scratch.

SECURITY:

The highest rating is for a facility with the complete range of modern security devices, video cameras, infra red passive sensors, totally secure windows, etc.

The lowest ratings imply that people could walk in off the street unhindered, unnoticed and unchecked.

INCENTIVES:

High ratings for the full range of cash and investment incentives.

Low rating means no support and nothing available.

EXPANSION POTENTIAL:

High ratings imply unlimited expansion, certainly 3-4 times the perceived short term needs.

Medium ratings imply at least half as much again as current needs.

Lowest rating means no expansion possible (e.g. mid location terraced unit).

PLANNING PERMISSION:

High rating implies planning permission either already in place or known to be readily available.

It is not known that any planning authority would have any objection to the new development facility but some delays may occur if there is any objection from nearby residential or industrial neighbours.

LOCAL ACCEPTANCE:

Very similar comments as for planning permission but there may be more resistance from local pressure groups which might be anti-pharmaceutical or anti-biotechnology. However, no such groups have yet been identified, but planning permission has not yet been sought, hence the public are not yet aware of the potential development.

High ratings imply total 'open arms' local acceptance.

A lower rating implies possible objections from as yet unidentified local interest or pressure groups.

APPENDICES

I VAPOUR SAMPLING AND MONITORING

II ENGINEERING STANDARDS AND SPECIFICATIONS

APPENDIX I

VAPOUR SAMPLING AND MONITORING

APPENDIX I

VAPOUR SAMPLING AND MONITORING

MONITORING REQUIREMENTS

Monitoring a workplace requires different sampling and analytical techniques for several overall objectives.

Measurement of personnel exposure is best achieved by locating the inlet of the sample device as close as possible to the breathing zone of the individual. Equipment can be in the form of a small pump drawing air through a vapour trap for analysis later. Direct indicating detector tubes or passive dose badges may also be used.

Static monitoring indicates concentration at a fixed position and so does not reflect the personal exposure of operators. The use of direct reading instrumental techniques, or other measurement device is often used for routine process room monitoring.

The identification of airborne contaminants is usually achieved by taking local work environment samples for subsequent qualitative analysis. The amount of important components identified is determined at a later test.

Leak detection is best achieved using direct reading techniques for areas which may contain relatively high concentration of gases or vapours.

COLLECTION OF SAMPLES

Samples are often captured in a non-reactive container or absorbed in liquids or other media for analysis later. Care must be taken that no part of the collection system will absorb the

gas or vapour to be analysed. A collected sample may be analysed over a suitable period of time to determine a consistent result confirming the suitability of the collection vessel.

The simplest collection vessels are syringes and gas bags. Both should be flushed through with the atmosphere before a sample is kept. A hand aspirator or portable pump can be used to fill the bags.

Rigid containers of glass, metal or plastic can also be used to store samples. The containers are filled by evacuation then sampling or by passing the sample through the container for a specified period.

In line bubble trapping is commonly used for reactive gases such as ammonia and sulphur dioxide.

Vapour sorption tubes containing solid sorbents such as charcoal, silica gel, molecular sieve and porous polymer beads are used for a range of contaminants.

Passive samplers (dose badges) containing a sorbent material behind a diffusion gap can be used for personnel and static monitoring.

ANALYSIS OF COLLECTED SAMPLES

Once collected samples may be analysed for more than one substance.

The following table gives a summary of techniques available for the stated classes of compounds.

Compounds	Methods
Organic vapours	Gas chromatography with flame ionisation detectors infrared/ultraviolet
C, H & O compounds	Gas cell spectrometers
Halogenated compounds	Gas chromatography with electron capture or ionisation detectors; microcoulometry
Inorganic gases	Gas chromatography with thermal conductivity detectors
CO & CO_2	IR gas spectrometers
Organosulphur compounds SO_2, H_2S, COS, etc	Gas chromatography with flame photometric detector; microcoulometry
Nitrogen oxides, ozone	Chemiluminescent analysers

DIRECT MEASUREMENT OF SPECIFIC CONTAMINANTS

A detector tube is a glass tube packed with a bed of chemical reagents. A metered volume of air is drawn through the tube producing a colour change. The concentration of contaminant may be read directly via a scale or by reference to a colour chart. These tubes are available for spot reading or with the use of a small continuous pump to give long term results over a shift.

Passive sampler (dose badges) based on diffusion are available which can be read directly, e.g. after the finish of a shift.

Continuous analysers are available in single or multiple point systems usually utilising a central automated infrared/ultraviolet spectrometer or other analytical instrument. Simpler types of autoanalysers exist such as local flammable gas alarms.

INSTRUMENTS FOR THE MEASUREMENT OF GROUPS OF COMPOUNDS

The instruments detailed below can be used locally, or for post sample capture analysis.

Explosimeters are used to detect combustable gases and are based on the changes in resistance of a heated catalyst. Flammable atmospheres may also be detected using solid state detectors based on the changing resistance of a metal oxide film.

Thermal conductivity detectors (cathorometers) are commonly used for leak detection and must be calibrated for each gas.

Flame Ionisation Detectors (FID) can be used to detect some organic vapours without responding to some inorganic vapours. The precision and selectivity may be increased by the use of chromatographic pre separation columns. The detector works by detecting the greater concentration of ions produced in the flame of an organic vapour.

Electrochemical detectors are available in a number of forms and have been incorporated in personal environmental alarms.

Photoionisation detectors measure the ionisation of material by a source of UV light of known excitation energy. Most permanent gases are not ionised by this method reducing problems of background readings. These instruments are not intrinsically safe.

Infrared gas analysers are based on the principle that gas molecules will absorb light of a characteristic wavelength. The instruments are, however, bulk and expensive and although able to measure a wide range of gases many gases absorb energy at the same wavelength. Ultraviolet absorption meters are available but are generally not portable.

Electron capture detectors are based on the detection of electrons production by the ionisation of the gas by a small radioactive isotope. They can detect a limited range of concentration often of halogenated compounds but can be poisoned by high concentration.

Oxygen monitoring can be carried out using the highly specific parametric susceptibility meters. Oxygen and other gases can be measured at low level using volumetric gas absorption devices.

APPENDIX II

ENGINEERING STANDARDS AND SPECIFICATIONS

GENERAL SPECIFICATIONS AND STANDARDS FOR NON STERILE SERVICE

GENERAL SPECIFICATIONS AND STANDARDS FOR STERILE SERVICE

GENERAL SPECIFICATION FOR VESSEL FABRICATION IN AUSTENITIC STAINLESS STEEL

SUPPLEMENTARY REQUIREMENTS FOR VESSEL FABRICATION IN AUSTENITIC STAINLESS STEEL

PARTICULAR REQUIREMENTS FOR 'STERILE ENGINEERING' OF FERMENTERS AND VESSELS

PIPING SPECIFICATION SUMMARIES

PIPING SPECIFCATION FOR STERILE DUTIES

GENERAL SPECIFICATIONS

AND

STANDARDS

FOR

NON STERILE SERVICE

GENERAL SPECIFICATIONS AND STANDARDS
NON STERILE SERVICE

1 PIPE

Generally as per pipework specifications S1, C1 and C2.

All pipelines shall be self draining wherever possible.

2 JOINTS

Generally as per pipework specifications S1, C1 and C2.

3 WELDING

The supplier must have a written SOP for welding and inspection.

Automatic orbital machine TIG welding to be used wherever possible.

Manual TIG welding in other cases.

All welding to be carried out by adequately trained welders, with experience in automatic orbital TIG welding, where appropriate.

Welding procedure will be to the following standards or equivalent:-

BS 4870	Approval testing of welding procedure
BS 4871	Testing of welders

4 VALVES

Generally as per piping specifications C1, C2 and S1.

5 TEMPERATURE TRANSDUCERS

All temperature transducers must be fitted in thermowells.

Thermocouples are acceptable for most duties.

Platinum resistance bulb transducers shall be used for critical duties.

6 TEMPERATURE INDICATORS

All temperature indicators must be fitted in thermowells.

Expansion type thermometers are acceptable.

Mercury in glass thermometers must not be used.

7 FLOW DETECTION/MEASUREMENT

Variable area meters are acceptable.

8 LEVEL MEASUREMENT

Sanitary design instruments and level switches must be used in the CIP system. Suitably protected variable area meters may be used.

9 VESSELS

Pressure vessels shall be designed to BS5500, category 3 or equivalent. (Corrosion allowance nil. Nature and extent of NDT to be proposed by the supplier.)

Other vessels designed to good engineering practice.

Insulated with rockwool preformed sections and clad with dull polished stainless steel, type 304, or polished aluminium.

10 FILTERS

Pharmaceutical grade cartridges and housings are required.

Housings must be fabricated in type 316L stainless steel.

Cartridges are to be of proprietary materials consistent with the requirements of the system.

Cartridges for air filtration shall be hydrophobic, but measures must be taken to ensure that they do not block with condensate.

11 PUMPS

All pumps must be of a self draining design.

12 GASKETS

Gaskets must not contain asbestos. Suitable materials include Viton, compressed non-asbestos fibre in PTFE envelopes or butyl rubber. Solid Teflon gaskets are only acceptable where they are used as standard in proprietary equipment packages.

13 INSPECTION

The supplier to initiate a fully documented programme of inspection of all critical equipment manufactured by sub-contractors/contractors to ensure compliance with specification and supplier's design drawings.

14 EQUIPMENT FINISH

All pipes, instruments and supports in the process hall are to be compatible with the level of finish and design required in the area.

i.e. Appropriate surface finish
No ledges or crevices
Easily cleaned surfaces

15 EQUIPMENT TAGS

Valve and equipment tags (and attachment chains) shall be provided by the Supplier.

GENERAL SPECIFICATIONS

AND

STANDARDS

FOR

STERILE SERVICE

GENERAL SPECIFICATION AND STANDARDS

STERILE SERVICE

1 PIPE

Generally as per pipework specification S2.

Internal finish to be specified by the supplier in line eith regulatory requirements.

All pipelines which are not vertical shall be sloped 1:100 to ensure drainage.

Deadlegs in the pipework must be avoided as far as possible. Where deadlegs are unavoidable they must be restricted to 1.5 pipe diameters. If longer deadlegs are ncessary, these must be approved on a case by case basis by the Purchaser.

All open ends of pipework must be kept clean and covered. This applies to pipe being stored and also to pipe being installed.

2 JOINTS

Generally as per pipework specification S2.

3 WELDING

The contractor must have a written SOP for welding and inspection.

Automatic orbital machine TIG welding to be used wherever possible.

Manual TIG welding in other cases.

All welding to be carried out by fully certified welders, with adequate training in automatic orbital TIG welding.

Welding Procuredure will be to the following standards:-

BS 4870 Approval testing of welding procedure
BS 4871 Testing of welders

The weld testing and sampling will be carried out by the performance of one test weld for each size that each welder will be welding that session, prior to work commencing. The test weld pieces are to be identified and logged prior to inspection and retention by the Purchaser.

Weld quality control may be confirmed by using a borescope to visually inspect the inner weld surface of selected welds.

All welds must be uniquely identified in the field and be indelibly marked, as well as on piping GA's, piping isometrics and day welding isometrics. All welds shall be logged with the following:-

- identifying number
- welder
- machine parameters
- date
- time
- inspection details
- inspection result
- corrective action

In order to produce the clean square joint which is required to achieve a top quality weld it is advisable to use a G+F cutting machine. All swarf and burrs must be removed and the area of the tube/fitting which is to be welded should be cleaned with scotch pad or similar.

Before tack welding the argon purge should be introduced. To ensure that all oxygen has been displaced from inside the tube an oxygen analyzer must be used before welding commences.

A borescope can be used for visual inspection of the internal weld profile, this is carried out at the customers request.

A hydraulic test is to be carried out using distilled water. The pressure and period is to be as per the customers details.

4 PASSIVATION

All stainless steel systems will be cleaned and passivated by the supplier with a dilute nitric acid solution prior to commissioning.

5 PRESSURE RELIEF

Stainless steel/nickel/PTFE composite bursting discs are to be used for pressure relief.

Vacuum break valves will not be allowed.

6 VALVES

Generally as per pipework specification S2.

Saunders type AFP sanitary diaphragm valves, fabricated in 316L stainless steel are preferred.

Diaphragms and seals shall be capable of periodic CIP with a caustic solution at 80°C and of period sterilisation with steam at 121°C.
EPDM (Saunders type 325) is the preferred diaphragm material for valves with a working temperature below 121°C. PTFE faced VITON (Saunders type 215/226) is preferred for working temperatures above 121°C.

Valves must be installed so that they are internally self draining.

The valve design must ensure that there is a clear indication of the valve status (open/closed) at all times.

7 HOSES

PTFE with stainless steel (304) overbraid. Where appropriate, silicon rubber covered hoses can be used.

Design rating must match that of the pipeline with the most severe design conditions to which it can be attached.

Ends to be IDF fittings, with the same nominal OD as the hose.

Convoluted hoses, if used, to have minimal profile to ensure good drainage.

8 PRESSURE GAUGES

Pressure gauges shall be of sanitary design and diaphragm seals must be used.

9 TEMPERATURE TRANSDUCERS

All temperature transducers must be fitted in thermowells or Ingold ports.

Platinum resistance bulb transducers shall be used for critical duties, otherwise thermocouples are acceptable.

Surface mounted thermocouples shall be used to detect the temperature of equipment during steam sterilisation.

10 TEMPERATURE INDICATORS

All temperature indicators must be fitted in thermowells or Ingold ports.

Mercury in glass thermometers must not be used.

Temperature sensitive stickers or paint/crayons may be used to indicate the temperature of external surfaces during steam sterilisation.

11 FLOW DETECTION/MEASUREMENT

Non-intrusive instruments must be used, e.g. ultrasonic.

12 LEVEL MEASUREMENT

Non-intrusive or sanitary design instruments and level switches must be used.

13 PRESSURE VESSELS

Pressure vessels shall be designed to BS5500, category 3 or equivalent. (Corrosion allowance nil. Nature and extent of NDT to be proposed by the supplier.)

Sterile vessels shall be designed to withstand all of the following working conditions.

- Steam at 1.5 Bar g and 121°C
- Full Vacuum
- The hydrostatic head with the vessel full

Vessels shall be constructed in 316L type stainless steel.

The internal finish shall be electropolished. All welds must be ground smooth before polishing.

The external finish should be dull polished (welds ground smooth) only where visible; otherwise the surface should be wire brushed clean.

Insulated with rockwool preformed sections and clad with dull polished stainless steel, type 304, or polished aluminium.

14 FILTERS

Sanitary or pharmaceutical grade cartridges and housings are required.

Housings must be fabricated in type 316L stainless steel.

Cartridges are to be of proprietary materials consistent with the requirements of the system.

Cartridges for air filtration shall be hydrophobic, but measures must be taken to ensure that they do not block with condensate.

15 GASKETS

Gaskets must not contain asbestos. Suitable materials include viton, compressed non-asbestos fibre in PTFE envelopes or butyl rubber. Solid Teflon gaskets are only acceptable where they are used as standard in proprietary equipment packages.

16 INSPECTION

The Supplier to initiate a fully documented programme of inspection of all critical equipment manufactured by sub-contractors/contractors to ensure compliance with specification and Supplier's design drawings.

17 EQUIPMENT FINISH

All pipes, instruments and supports in the process hall are to be compatible with the level of finish and design required in the area.

i.e. Appropriate surface finish
No ledges or crevices
Easily cleaned surfaces

18 EQUIPMENT TAGS

Valve and equipment tags (and attachment chains) shall be provided by the Supplier.

GENERAL SPECIFICATION

FOR

VESSEL FABRICATION

IN

AUSTENITIC STAINLESS STEEL

1 GENERAL

1.1 SCOPE

This specification, together with the Purchaser's design drawings and standards, covers the requirements for design, materials, fabrication, erection, inspection, testing, and shipping of fusion-welded vessels designed for internal pressures exceeding 15 psig, and for external pressures. All requirements of the Codes for pressure vessels (see below), shall be followed, whether or not the vessel is to be code stamped.

All conflicts between the requirements of this specification, design drawings, specified codes, and local or national regulations and/or insurance requirements shall be called to the Purchaser's attention without delay. Where requirements on the drawings conflict with this specification, the drawings shall take precedence.

1.2 CODES AND STANDARD

(Latest issue, including all addenda, revisions or supplements thereto).

The following Codes, or their internationally recognized equivalents, shall be used.

ASME Boiler and Pressure Vessel Code, Section VIII, Division I (will be referred to as ASME Code), and Section II and Section IX.

ANSI B16.5 Steel Pipe Flanges and Flanged Fittings.

BS 5500.

1.3 BIDS

Quotations shall be made in accordance with the requirements of this specification. Quotation on any other basis will be considered as an "alternate", and all exceptions should be considered.

Cost of all inspections required by Code, inspection agencies or local regulatory bodies shall be included in the quoted price.

Bidders must be prepared to include one (1) copy each of all Welding Procedure Specifications and Qualifications intended for use in the fabrication of items being quoted.

Each such welding procedure shall be qualified in accordance with the provisions of Section IX of the ASME Code.

2 DESIGN BASIS

2.1 Company's design drawings will specify the conditions of design and show the shape, dimensions, material specifications, and thicknesses for all primary parts and certain constructional details; however, these drawings are not suitable for shop fabrication, and are not to be used as such by the Vendor, without special permission to add the necessary fabrication details. in addition, the Company will furnish all related standard specifications, standard drawings, etc, as required for the design and construction of the vessel.

2.2 Copies of all detail fabrication drawings and calculations shall be submitted to the Company for approvals, comments, and record purposes.

Vendor's responsibility remains for design, mechanical performance, and details. The submittal of these documents does not in any way relieve the Fabricator of his responsibility for the correctness or for the compliance of such details with specifications, standard drawings or purchase order.

2.3 Fabricator's certified detail drawings shall show the Company's complete purchaser order and item number, weld locations and details (including welding grooves), design data and material specifications, and the location and wording of Code and Purchaser's stamping.

2.4 Welding Procedure Qualifications and Welding Performance Qualifications are to be submitted and approved before any welding is performed. Welding rods, electrodes and filler metals, automatic or manual, shall deposit a composition corresponding to the material being welded. Welding rods, electrodes and filler metals shall meet ASME Boiler and Pressure Vessel Code, Section II, Part C, Material Specification's requirements. Welds that are not made in accordance with approved, qualified procedure specifications are subject to rejection. Purchaser shall be notified of any changes made to essential variables of the welding procedure.

2.5 Bills of Materials and Shop Layout Drawings will be considered as records only, and will be reviewed, but not necessarily approved.

2.6 All final vendor record drawings shall be signed "Certified Correct" by an authorized representative of the Vendor.

2.7 The number of Fabricator's drawings required will be given on the Purchaser Order or Requisition. Each show drawing shall be checked and signed before it will be accepted for approval.

2.8 Corrosion allowance, on removable internal parts, shall be one-half of the specified corrosion allowance applied to all exposed surfaces. Corrosion allowance, on non-removable internal non-pressure parts, shall be the same as the vessel corrosion allowance applied to all exposed surfaces of pressure parts.

2.9 Shop drawings shall have the tray supports, nozzles and support clips numbered and lettered identically with the Company's vessel drawings.

2.10 The vessel Fabricator shall show the location of all circumferential and longitudinal welded joints on the shop drawings submitted for approval.

2.11 All coils are to be fabricated, assembled, and erected per code for Pressure Piping, ANSI B31.3 or internationally recognized equivalent.

3 RESPONSIBILITIES

3.1 Conformance to the latest codes and legal requirements is the responsibility of the vessel Fabricator. The Company co-operates with all fabricators regarding these requirements, and will make every effort to assist in obtaining the latest and most accurate information.

3.2 Where the fabrication to a code is specified, it shall be the Fabricator's responsibility to fabricate in strict accordance with the code. Should any feature of the Purchaser's design violate the intent or not meet the requirements of the code, the Fabricator is to bring such points to the attention of the Purchaser without delay.

All vessels that are required to be "code stamped" shall be inspected by a "qualified", authorised insurance company representative.

3.3 It shall be the Fabricator's responsibility to obtain, if required, the approval of the regulatory bodies having jurisdiction in the locality of installation.

3.4 Where the type of construction offered by the Fabricator is of a proprietary nature, the Fabricator's published fabrication specification, subject to acceptance by the

Purchaser, may be used as the basis of fabrication. It shall be the Fabricator's responsibility, however, to obtain approval of the local authorities and/or insuring agencies. Three (3) copies of these approvals shall be furnished to the Purchaser, prior to shipment of the vessel, showing adequate data for maintenance and repair.

3.5 All vessels shall be furnished complete, as shown on the Company's Design Drawings and Standards, or as required by the Purchase Order, and as herein noted, and shall include all necessary bolts, nuts, gaskets and all internals and internal piping.

3.6 The vessel Fabricator shall furnish and install the following clips, and other items, which are welded to the outside surface of the vessel or skirt:

Clips for ladders, platforms, pipe supports, and guides, as specified by the Purchaser.

Vessel davit complete, when called on Purchaser's drawings.

Lifting devices for erection (all vessels over 20 tons weight, and all columns more than 20m overall height).

Insulation supports and welding studs or blank nuts for fireproofing, as specified by the Purchaser.

Other special brackets, ladders, platforms, etc, as detailed on Purchaser's drawings.

4 FABRICATION

4.1 MATERIALS

Material of construction for vessel parts shall confirm to the Specification given in Section II of the ASME Boiler and Pressure Vessel Code or other governing codes. Alloy plate and pipe shall be stamped with the mill, heat, slab and SA specification numbers, and shall be included in the code material certifications. The exact grades of materials for different parts of the vessel are to be agreed with the Company but, in general, all stainless steel parts of the vessel, except where specifically detailed on the Company's drawings, shall be fabricated from a fully softened and descaled austenitic stainless steel of either the 18/8/Ti or 18/8/3M type.

Large carbon steel attachments, such as jacket closures, support lugs, legs, platform or pipe support brackets, etc, shall not be directly welded to vessels built of solid alloy plate less than 3/8" thick, but shall be welded to an

intermediate alloy pad of the same thickness as the shell, extending 2" in each direction beyond the extremities of the attachment. Such pads shall be continuously welded to the vessel.

Support skirts of vertical vessels built of solid alloy plate shall not be welded directly to the bottom head. An alloy ring of the same thickness as the skirt and approximately 4" long shall be provided on the head for attachment of the carbon steel skirt.

4.2 NOZZLES

Where nozzle flanges are within the scope of ANSI B16.5, flanges conforming to this standard shall be used. For flanges outside the scope of this standard, special design shall be submitted. Special designs shall be in accordance with the ASME Code, Section VIII. Unless otherwise noted, bolt holes are to straddle natural vessel centrelines.

Rolled Plate nozzle necks and reinforcing pads shall be the same material as specified for the vessel shell or head to which they are attached.

The minimum corroded thickness of nozzle necks, manholes, and handholes in all sizes up to 24" shall be the lesser of the minimum thickness of standard weight pipe or the corroded required thickness of the vessel wall. The specified vessel corrosion allowance shall be added to these thicknesses to arrive at the fabricated minimum thicknesses. Where corrosion allowance in the neck can be provided, without going to a pipe wall thickness greater than 160, the nozzle shall be forged or built-up welding neck.

Blind flanges may be forgings or made from plate and blind flanges may be alloy clad to extremity of gasket contact surface. Detail of facing is subject to the Company's approval.

All nozzles or connections shall be flush inside, except as shown on the drawing. All inside sharp edges shall be rounded.

Bolting and service gaskets shall be furnished by the vessel vendor for the following connections: manways, blinds, handholes, agitator flanges and all studded pads.

4.3 INTERNALS

Pipe or tubing for heating or cooling coils shall be seamless drawn.

Internal flanges, if unavoidable, shall have bolts and nuts of the same type material as the flanges.

4.4 WELDING

All welding shall be performed by "qualified" welders.

No welding shall be performed unless the initial metal temperatures are above 15°C. Preheating shall be employed in accordance with Appendix R of the ASME Code.

Preparation for double butt welding of shells, heads, and plates shall include edge bevels on all thicknesses greater than 1/4".
Shell and head joints shall be full preparation, double welded butt joints. For joints inaccessible from the inside, alternate methods of welding, where full penetration and fusion can be achieved from one side, may be submitted for approval.

Permanent back-up rings or strips may be used only at approved inaccessible closing joints less than 24" in diameter.

Nozzles and couplings shall be welded to shell and heads with full penetration welds. Compliance with Code must be maintained and calculations showing the strength of attachment shall be submitted, if requested.

Weld sizes for internal and external attachments shall satisfy structural and corrosion requirements.

4.5 INTERNAL FINISH

Weld spatter, welding scale, loose mill scale, and excessive weld deposits shall be removed.

Completed welds shall be reasonably smooth, ripple-free, and free of undercutting, cavities or depressions in which vessel contents may lodge.

Interior finish shall be as specified by the Company.

All surfaces exposed to vessel contents, its vapours or condensate, shall be free of gouges, deep scratches, pits, crakes, weld craters or other surface defects.

4.6 POSTWELD HEAT TREATMENT

Postweld heat treatment, when specified, shall be done in accordance with the requirements of the ASME Code.

No welding, hammering, pressing or forming shall be performed directly on a vessel wall after it has been postweld heat treated, without prior written approval of the Purchaser.

5 RADIOGRAPHY

Welded vessels, when specified, shall be radiographed in accordance with a Code to agreed with the Company.

Welded joints belonging to categories A or B, Paragraph UW-3, of the ASME Code shall not be positioned to pass under a reinforcing pad where possible. If this is unavoidable, the joint under the pad shall be ground flush and radiographed for its entire covered length, plus 1" on each side.

6 MAGNETIC PARTICLE AND LIQUID PENETRANT EXAMINATIONS

Vessels or parts, when specified, shall be examined in accordance with the ASME Code, Appendix IV through VIII.

7 ULTRASONIC EXAMINATION OF WELDS

Procedures for the examination of welds, when specified, shall be in accordance with the ASME Code, Appendix U.

8 TOLERANCE

Vessel and tower fabrication tolerances shall be in accordance with a Standard to be agreed with the Company.

9 INSPECTION, TESTING AND REPORTS

9.1 The Company will inspect and test all work performed, and all materials used by the Vendor or Sub-Vendor in fabricating equipment covered by the Purchase Order. Successive step-dated fabrication schedules shall be submitted to the Company for determining the intermediate inspections to be performed on the fabrication and assembly of all vessels. All vessels shall be inspected in accordance with the latest issue of the drawings and referenced Engineering Standards.

The above noted inspections will include the inspections of materials and review of mill test certificates, impact test reports, etc, before the start of fabrication.

9.2 The Company's inspector or agent shall be granted full access to sections of the Vendor's plant engaged in such fabrication, and permitted the use of such facilities as are necessary to perform the inspection. Vendor shall advise the Company, at least five working days in advance, of the date of intermediate inspection, non-destructive testing, and final inspection.

9.3 Vessel shall be tested with all dip pipes, coils, agitator assemblies, sight glasses, valves, blind flanges, and any other equipment that is part of the Purchase Order, and is bolted to effect a penetration into the vessel.

9.4 Vessel shall be tested with the same type of gasket as the service gaskets. Pressure bolting supplied with the vessel shall be used for testing.

9.5 Before shipment is made, all internals are to be installed in the vessel and checked for fit-up. After inspection is made, the internals, without the proper support, shall be removed and packed, with proper identification, for shipment with the vessel. This inspection shall be carried out by the Company's Inspector.

9.6 Vessel shall be tested in accordance with the requirements of the drawing, sketch or requisition as a minimum requirement, which may include the testing of the specified corrosion allowance thickness. Vessel and test water temperatures should be at 15°C minimum.

9.7 Vessels are to be hydrostatically tested at 1 1/2 times the MAWP new and cold. Vendor shall furnish the Company with copies, as specified on Purchase Order of Manufacturer's Data Reports, mill test reports, and/or material certificates for all major components identified with heat numbers corresponding to actual vessel parts, graphs of stress relieving operation, if performed, and hydrostatic test; and pencil rubbing of nameplate and vessel stamping. All shall be furnished in booklet form at the time of final Company inspection, before shipping the vessel.

9.8 Radiographic films shall be kept on file by the Vendor for a minimum period of one year after the shipment of the vessel.

9.9 Whenever sandblasting or metallic grit blasting is specified, it shall be performed after the pressure testing.

9.10 A magnetic particle examination shall be performed and shall be witnessed by the Company Inspector, on the continuous fillet welds at the skirt to head or shell attachment, and at both sides of the continuous fillet welds on the compression ring or chair to skirt attachment.

10 CLEANING AND PAINTING

10.1 Each vessel shall be thoroughly cleaned inside and outside, and shall be free from grease, weld spatter, scale, slag, rust, and all other foreign matter.

10.2 Vessel exterior surfaces shall not be painted, unless otherwise specified. If shop painting is specified, the surfaces shall be prepared, and the paint applied in accordance with the instructions furnished by the Company.

10.3 The inside surface of all austenitic stainless steel vessels shall be degreased and followed by immersion or swabbing treatment with 10 wt. % aqueous citric acid solution at 70-82°C for at least 15 minutes, and further followed by 80°C clean, hot water rinse.

11 SHIPMENT

11.1 The Company standard nameplate shell be permanently attached to all vessels, adjacent to the Manufacturer's nameplate, before shipment. The nameplate will be furnished to the Vendor by the Company.

11.2 All flanged or studded openings shall be protected by bolted-on wooden or non-metallic-covers. All threaded openings shall be closed with watertight pipe plugs or thread protector caps. Test holes, in reinforcing pads and in slip-on flanges, shall be plugged with heavy grease.

11.3 The vessel Fabricator shall be responsible for loading, bracking, and anchoring vessels, or vessel sections, to prevent any damage during shipment. Anchoring , bracing, and loading diagram shall be inspected by the Company, if so requested. For large or heavy vessels, the Vendor shall submit a loading diagram for review and comment. This loading diagram shall have been approved by the Vendor's carrier.

11.4 The vessel Fabricator shall determine and indicate that completed item can be shipped to the job site. Where clearances for shipping are required, no changes shall be made, unless written approval has been obtained from the Company.

11.5 Agitator drive assemblies, etc, shall be dismounted and shipped separately and must bear proper identification.

SUPPLEMENTARY REQUIREMENTS

FOR

VESSEL FABRICATION

IN

AUSTENITIC STAINLESS STEEL

1 GENERAL

This specification is for the guidance of vendors employed on the fabrication of stainless steel vessels for the Company. This must be closely adhered to and should any departure be deemed necessary by the vendor the Company's written approval must be obtained. Acceptance of any order or contract placed subject to this specification shall be regarded as an acceptance of all its conditions by the vendor.

2 DRAWINGS AND DESIGN

The vessel shall in general conform to the Company's relevant drawings, but the vendor shall be at liberty to suggest minor alterations, except where specifically restricted by this specification, in order to utilize existing tools or working procedures. Four copies of the final working drawings in detail must therefore be supplied by the vendor before the commencement of work, and after approval by the Company must be strictly adhered to, except at the express direction of and cost to the Company.

Nevertheless, the vendor shall be required to check the design to ensure that in his opinion the vessel will satisfactorily withstand the pressure or vacuum or physical load specified. Suggestions for any improvement in design will be welcomed.

3 MATERIAL

All stainless steel parts of the vessel, except where specifically excepted on the drawing, shall be fabricated from a fully softened and descaled austenitic steel of either the 18/8/Ti or the 18/8/3Mo type.

All such material shall be certified and it shall be the vendor's responsibility to establish the identity of such material with the certificate(s) and to retain such certification for delivery to the Company upon completion of the contract. (See under Section 8, Certification, below).

In case of doubt a sample of the material, preferably weighing not less than 50 gm, should be sent to the Company for analysis.

4 WELDING ELECTRODES

Permitted electrodes for metal-arc welding are:-

For 18/8/Ti Steels	For 18/8/3Mo Steels
Murex - Nicrex ND	Rockweld - Chromac MM
Rockweld - Chromac C	
Quasi-Arc - Chromac 2	

or equivalent, approved by the Company.

For the welding of mild steel parts to stainless (where permitted - see Section 6, Manufacture and Workmanship), Chromac MM electrodes may be used in all cases.

For inert-gas welding the filler wire shall be of similar composition to the parent metal.

5 RECORD PADS

Unless stated otherwise the following shall apply:-

Each vessel shall be provided with two adjacent stainless steel plates, 100mm x 75mm, to be described as the Test Record Pad and the Cast Record Pad, welded preferably to the shell wrapper, in a prominent position to be indicated on the drawing, on which shall be stamped the following details:-

Test Record Pad

Maker's name and Works order number
Code
Test Date
Internal Test Pressure in bar g
Internal Working Pressure in bar g
Internal Vacuum
Jacket Test Pressure in bar g
Jacket Working Pressure in bar g
Weight (tonnes)
Item No

Note: Suitable abbreviations may be used, e.g. Int. T.P. for Internal Test Pressure.

Cast Record Pad

Cast numbers of all major items of stainless steel such as shell wrapper, dished ends, curb-ring, run-off pad, agitator, etc and batch numbers of all stainless steel welding electrodes.

Plant Number Plates

In addition, a blank polished plate, 100mm x 75mm, shall be secured over the Cast Record Pad by four stainless steel screws at the corners, to be used by the Company as a Plant number plate.

6 MANUFACTURE AND WORKMANSHIP

6.1 WELDING

The welding of stainless steel parts shall be carried out manually by the Metallic Arc or TIC processes. Other processes shall be used only by special agreement with the Company, except that flash-butt welding of curbs or flanged-rings is permitted.

Welds shall be deposited in a uniform and workmanlike manner, free from gasholes, slag inclusions and undercutting, with substantially flat or slightly convex head, using the maker's recommended current density and as short an arc as practicable.

All longitudinal and circumferential seams shall comprise double-sided butt welds, except in the case of thin sections where sufficient penetration can be achieved from TIC single-sided butt welds to ensure a flush surface after subsequent grinding. Plate-edge preparation and the gap between plates shall be such as to ensure good penetration, and where necessary plate edges shall be beveled to an included angle of not less then 70°.

After welding one side of a butt weld, the reverse side shall be thoroughly cleaned and the root of the Vee chipped back to sound metal before the sealing run is deposited. For multi-pass welds thorough cleaning and de-slagging between passes is mandatory.

6.2 FINISH

External welds shall be dressed clean and free from spatter and sharp snags. Plate surfaces, both internally and externally, shall be left in the descaled condition unless grinding or polishing is stipulated on the order, but shall be thoroughly cleaned and free from spatter, rust contamination, or crevices.

All traces of weld-staining and residual scale shall be removed by the application to the affected areas of a proprietary descaling liquid or paste, followed by thorough washing to remove all traces of the descaling medium.

6.3 PRESSING AND ROLLING

Dished and flanged ends may be produced by hot pressing, hot rotary pressing (spinning) or cold dishing in a press followed by cold flange-rolling.

Rolling of curbs may be done either hot or cold.

In all cases, Clauses 6.4 to 6.6 will apply.

6.4 HOT WORKING OF STAINLESS STEEL

Hot working shall be carried out within the temperature range 900°C to 1150°C. Pyrometric control of the heating furnace is essential.

Precautions shall be taken to prevent contamination, particularly carbon pick-up, in the furnace, including the use of a suitable temporary muffle if necessary.

The Company shall be at liberty to require subsequent heat treatment if it is deemed desirable.

6.5 COLD WORKING OF STAINLESS STEEL

Cold working which could result in the production of substantial residual stresses shall be followed by heat treatment as under Clause 6.6 below.

6.6 HEAT TREATMENT OF STAINLESS STEEL

Where heat treatment is required, this shall consist of "soaking" at 1050°C for 1/2 hour per 25mm of thickness, followed by cooling in still air, all scale subsequently being removed by chemical descaling as under Clause 6.2 above or by scurfing.

The Company must be satisfied that the Vendor's furnace facilities are adequate for the purpose, and if they are unacceptable, the Company shall be at liberty to require the sub-contracting of the heat treatment to an approved specialist firm.

7 TESTING

The vessel(s) shall be tested on completion of manufacture as follows:-

7.1 Pressure vessels shall be treated hydrostatically at twice the working pressure, the pressure being maintained for a minimum of 1 hour. In certain cases it may be necessary to apply a lower test pressure; this shall be subject to negotiation with the Company.

7.2 Vessels subject to both pressure and vacuum duties shall be tested hydrostatically at 2 bar g or double the working pressure, whichever is the higher, and in the case of the exterior of a jacketed vessel, the test pressure shall be based on the net working pressure differential between the shell and the jacket.

8 CERTIFICATION

The documentation to be included in the vessel "dossier" is to be agreed with the Company.

9 SUB-LETTING

No part of the fabrication work, including the manufacture of dished and flanged ends shall be sub-let without notification to the Company, who reserve the right to withhold approval of a sub-contractor. In all cases it shall be the Vendor's responsibility to ensure that the sub-contractor adheres to the provisions of this specification.

PARTICULAR REQUIREMENTS

FOR

"STERILE ENGINEERING"

OF

FERMENTERS & VESSELS

1 GENERAL

This document covers requirements for sterile equipment and is to be used as an addendum to the vessel specifications for the contract concerned.

The general requirements for sterile equipment are that they shall be biologically leakproof and sterilisable with saturated steam.

2 DESIGN CODES

The mechanical design, construction, inspection and testing of fabricated equipment shall be to the requirements of the design codes specified for the items concerned. For further inspection and testing requirements see Section 5.

3 STERILISATION

Before start-up, or in the event of infection of the process fluid, the equipment will be drained and sterilised with saturated steam. In order to achieve sterilisation, all internal surfaces of equipment designated as sterile must be heated to the required sterilisation temperature and held at that temperature for the required period. It is essential that the following points are incorporated into the design to make this possible.

3.1 DRAINAGE

Areas which cannot be drained will be slow to heat and, therefore, must be avoided:-

All sterile equipment must be fully and freely self-draining and self-venting.

Where the process requires drain and vent connections, they must be positioned at, or as near as possible to, the lowest and highest points of the enclosed space.

As far as possible there must be no pockets, traps or places where pools of fluid would be left after draining. Where this cannot be achieved, the number of pools must be kept to a minimum, the surface area must be small and the depth not more then 5mm. Any such area must be fully detailed and the acceptability of them must be discussed with, and approved by, the Company.

Internal void spaces which would be slow to drain, and into which the sterilising steam would not flow, are not acceptable.

Horizontal surfaces on either the shell or internals must be avoided. A positive slope of at least 1/30, and preferably greater, shall be used. When attachments to the inside of the shell are necessary, eg to support internal fittings, vertically oriented brackets not more than 50mm thick shall be used.

The bores of all pads must be tapered at an angle of 30° to the pad axis so that they drain freely into the vessel. Whenever possible pads shall be positioned in the vertical parts of the shell and not in the top and bottom dished heads.

Bellows shall not be used.

A special internal finish is not required although some internal dressing of welds may be necessary for testing/inspection procedures.

3.2 ATTACHMENTS TO SHELLS

Poorly designed attachments to the shell could make thermal insulation less effective and attachments which form heat sinks must be avoided:-

There shall be no unnecessary attachments to the shell although lagging supports are permissible. Stiffening rings must not be used in vacuum design. Access platforms shall be supported from adjacent steelwork and not from the vessel.

Neither davits nor hinges may be fitted to manways. The manway cover shall have a tapped hole into which an eyebolt can be fitted and the cover removed by a lifting device remote from the vessel.

Vertical vessels shall be supported on skirts. If the 'as built' thickness of the skirt is greater than 0.5 x (vessel corroded thickness + 7mm) then a limpet coil welded to the skirt will be required to enable heat to be applied directly to the skirt by the use of steam. Insulation for all skirts shall extend down the skirt for a minimum 500mm.

Welded-on lifting attachments will be removed (by others) after erection but up to 50mm may be left attached to the vessel. This must be considered by the fabricator in the design of these attachments.

Internal and external shell attachments must be at least 300mm apart.

4 LEAKAGE

To ensure that sterile conditions can be maintained over long periods, it is essential that there are no biological leakage paths to atmosphere and, in the case of internal coils inside vessels, to the fluid on the non-sterile side. The following requirements are necessary to ensure this:-

Bolted, flanged connections shall not be used except where absolutely unavoidable such as for manways, instrument connections and agitator mounting pads.

Where bolted, flanged connections are used, these must be of a grooved flange type with a rubber 'O' ring. Details and surface finishes are to be agreed with the Company.

All nozzles for external connections should protrude 250mm from the shell and shall terminate with a preparation suitable for butt welding to the connecting pipework. Nozzles shall finish flush with the inside surface of the shell except where an internal extension to the nozzle is required for process reasons.

All nozzles, pads and other connections through the shell shall have full penetration welds which, where possible, shall be welded from both sides.

All attachments to the shell either inside or outside shall be by continuous full penetration welds. Crevices are not permitted. Shell reinforcement is to be provided, where necessary, by means of insert plates with full penetration butt welds. Fillet welded doubling plate reinforcement shall not be used.

5 INSPECTION AND TESTING

It is vital that equipment complies with every detail of the manufacturing specification. Failure to achieve this standard may well result in the equipment, and in consequence the whole plant, being literally inoperable.

General Inspection Requirements

In accordance with the appropriate design code, 100% NDT shall be applied to all welds prior to hydrotest. Radiography shall be used where practicable, otherwise NDT methods appropriate to the detail being tested shall be used. For attachment welds, surface crack detection is acceptable. It is emphasized that, where the term "all welds" is used in this specification, it means literally "all welds", pressure containing and attachment, internal and external.

For those welds where inspection by radiography or ultrasonics is impractical, the prepared cut edges of the plant shall be checked by dye penetrant for laminations (magnaflux for carbon steel).

Upon completion of all weld checks, the vessel shall be hydraulically tested in accordance with the manufacturing code.

Following hydraulic test dye penetrant crack detection (magnaflux for carbon steel) shall be applied to all welds to ensure that cracks have not propagated in the course of the test. On large items, the Company may relax this requirement to "all stress concentrations", such areas to be agreed with the Vendor in writing.

Following the hydraulic test, a Helium test may be required. The Company shall decide upon the necessity for this following receipt of the design details. In such cases the requirements of Section 6 will apply.

6 DEGREASING OF EQUIPMENT AND PIPEWORK PRIOR TO HELIUM TESTING

6.1 GENERAL

This section covers degreasing requirements for sterile equipment prior to Helium testing, and shall be used as an addendum to the equipment and piping specifications for the contract concerned. The detailed requirements for specific items will be specified in the testing, fabrication and erection supplement.

All personnel in the degreasing area are required to wear clean, oil and grease free overalls and gloves before commencing work. All tools must be thoroughly cleaned before use, including slings, chains, etc.

6.2 DEGREASING METHOD

The equipment or piping to be degreased shall be degreased internally or externally using one or a combination of the following methods:-

(i) Steam clean incorporating the use of a non-caustic emulsified detergent, eg Lissapol.

(ii) Using a solvent cleaner, eg Genklene or Triclone, and either fully immersing the item in a mildly agitated container or circulating solvent through the item. All air must be released and a time period of 30 minutes allowed.

After completion of (i) and/or (ii) above, the unit shall be completely drained, and washed as detailed in Section 6.3.

6.3 WASHING

External Surfaces

One of the following three methods shall be used (in order of preference):-

(i) Wash with chloride-free water (less than 1 ppm chlorides) and hot air dry.

(ii) Wash with Town's water, followed by a final wash with chloride-free water and hot air dry.

(iii) Wash with Town's water, and thoroughly dry by swabbing and wiping. The vessel must not be dried by either still air or a heated current of air.

Internal Surfaces

One of the following two methods shall be used (in order of preference:-

(i) Wash with chloride-free water (less than 1 ppm chlorides) and hot air dry.

(ii) Wash with Town's water, followed by a final wash with chloride-free water and hot air dry.

All openings shall be capped and sealed, or, if the item is small, sealed in polyethylene sheet.

6.4 CHEMICALS

The chemicals mentioned in Section 6.2 are the preferred chemicals for degreasing. If any other chemicals are proposed, approval of samples by the Company is required before commencement of degreasing.

7 HELIUM LEAK TESTING

7.1 GENERAL REQUIREMENTS

Sterile equipment and pipes are to be leak tested with a 50/50 Helium/air mixture at 3 bar to ensure that welds and joints are leak tight. Sensing of leaks is done by means of a Helium mass spectrometer. All items are to be degreased inside and outside prior to Helium testing. All items with 12mm thick welds or less are to be Helium tested at the maker's works and the tested joints marked.

Equipment will pass the test if leakage is less than 10^{-7} atm cc/sec.

All equipment and complete components such as instruments, valves, pipe lengths, etc, shall be pressure tested at the maker's works.

Conventional hydraulic tests shall be performed at the maker's works.

7.2 TESTING METHODS

Before testing, the test piece shall be pressurized to 3.0 bar g, or evacuated to a pressure of 10mm Hg in order to remove water trapped in minute cracks.

There are two methods of Helium leak testing:-

Pressurisation of the test piece with the chosen gas/air mixture at 3 bar pressure. The outside surface is probed for leaks using the detector or the test piece is enclosed in a plastic bag with a sample taken from the bag.

The probe is connected to the inside of test piece which is then evacuated. Helium is then sprayed on possible leakage points around the outside of the unit.

PIPING SPECIFICATION

SUMMARIES

PIPING SPECIFICATION

Designation	C1
Duty	COOLING TOWER WATER (NON PROCESS AREAS) HEATING STEAM DRAINS (PLANT ROOM) REFRIGERATED WATER TOWNS WATER (NON PROCESS AREAS) CONDENSATE (PLANT ROOM & AMENITIES)

Max Working Pressure	6 Bar g
Max Working Temperature	165oC
Pipe	
Material	Carbon Steel
Rating	150 lb ASA
Fittings	Welded
Unions	Socket Weld
Connections	Screwed
Gaskets	Compressed non-asbestos
Valves	As table below

DUTY	SIZES (mm)	MATERIAL	TYPE	ENDS
Shut-off/Isolation	15,25	Bronze	Gate	Screwed
	40,50,80,100	Cast Iron	Gate	Flanged
Regulation	15,25	Bronze	Globe	Screwed
	40,50,80,100	Cast Iron	Globe	Flanged
Check	15,25	Bronze	Lift	Screwed
	40,50,80,100	Cast Iron	Swing	Flanged

Note: In the context of this specification, 15mm is equivalent to 1/2" imperial.

Rev: 1 Date: 23/03/92

PIPING SPECIFICATION

Designation	C2
Duty	TOWNS WATER PLANT AIR INSTRUMENT AIR (see note) COOLING TOWER WATER (PROCESS AREAS)

Max Working Pressure	7 Bar g
Max Working Temperature	50oC
Pipe	
Material	Galvanised Carbon Steel
Rating	150 lb ASA
Fittings	Screwed or welded
Unions	Screwed
Connections	Screwed
Jointing	PTFE tape
Gasket	Compressed non-asbestos
Valves	As table below

DUTY	SIZES (mm)	MATERIAL	TYPE	ENDS
Shut-off/Isolation	15,25	Bronze/SS/ Galvanised	Ball/Gate	Screwed
	40,50,80,100	Cast Iron	Gate	Flanged
Regulation	15,25	Bronze	Globe	Screwed
	40,50,80,100	Cast Iron	Globe	Flanged
Check	15,25	Bronze	Lift	Screwed
	40,50,80,100	Cast Iron	Swing	Flanged

Note: In the context of this specification, 15mm is equivalent to 1/2" imperial.

INSTRUMENT AIR - local supply to be nylon with push fit connectors and ss or brass valves
- main distribution lines to be galvanised carbon steel

PIPING SPECIFICATION

Designation	S1
Duty	PROCESS (Non-sterile) CONDENSATE (PROCESS AREAS)

Max Working Pressure	5 Bar g
Max Working Temperature	121oC
Pipe	
Material	Stainless Steel 304 or 316
Rating	OD Tube or Schedule 10 pipe
Finish	Descaled
Fittings	Welded or screwed
Unions	Screwed
Equipment connections	Screwed
Gaskets	Viton
Valves	As table below

DUTY	SIZES (mm)	MATERIAL	TYPE	ENDS
Shut-off/Isolation	15,20,25	SS 304/316	Ball, Diaphragm Butterfly	Screwed/ Welded
	40,50	SS 304/316	Ball Diaphragm Butterfly	Flanged
Regulation	15,20,25	SS 304	Globe	Screwed
	40,50	SS 304	Globe	Flanged
Check	15,20,25	SS 304	Spring	Screwed
	40,50	SS 304	Lift	Flanged

Steam traps: Spirax Sarco BTM7 for condensate from vessels
Spirax Sarco BTD-5ZL for condensate from lines.

Note: In the context of this specification, 15mm is equivalent to 1/2" imperial.

PIPING SPECIFICATION

Designation	S2
Duty	PROCESS STERILE CLEAN/STERILISING STEAM

Max Working Pressure	5 Bar g
Max Working Temperature	127oC
Pipe	
Material	Austenitic Stainless Steel to the requirements of ASTM A270 type 316L
Rating	Seamless OD Tube
Finish	Descaled internally, polished externally
Fittings	Welded where possible, all to the requirements of ASTM A270 type 316L
Unions (15mm, 20mm)	316L Triclamp
Unions (25mm, 40mm, 50mm)	316L Triclamp
Hose ends	316L Triclamp
Gaskets	EPDM
Valves	As table below

DUTY	SIZES (mm)	MATERIAL	TYPE	ENDS
Shut-off/Isolation	15,20	SS 316L	Diaphragm	Welded
	25,40,50	SS 316L	Diaphragm	Welded
Regulation	15,20	SS 316L	Diaphragm	Welded
	25,40,50	SS 316L	Diaphragm	Welded

Note: All valves to be Saunders type AFP valves with 214/226 type diaphragms (PTFE/viton backing). Satin (320 grit) internal finish, vacu-blast (120 grit) external finish. Cast iron bonnets with white epoxy coating.

Note: In the context of this specification, 15mm is equivalent to 1/2" imperial.

PIPING SPECIFICATION

Designation	S3
Duty	WATER FOR INJECTION FINAL PRODUCT
Max Working Pressure	10 bar g
Max Working Temperature	135°C
Pipes & Fittings Material	316L stainless steel. Biobore (by Stainless Fittings Ltd) or equivalent
Rating	16 SWG OD Tube (up to 3") 14 SWG OD Tube (4")
Internal Finish	Smooth, free of pits, crevices and scratches, 20 micro-inch maximum surface finish for pipe, 26 micro-inch max for fittings Any weld seam must be entirely eradicated Clean, free of embedded grease, washed, ends suitably capped to maintain cleanliness
External Finish	Satin finish
Fittings	All welded where possible, otherwise triclamp Suitable for orbital welding
Tolerance	To ASTMA-270 or better
Cast numbers	All pipe and fittings to be from the same (or minimum number) of cast numbers All items to be cast marked and certified
Gaskets	EPDM (FDA approved)
Valves up to 2"	Welded diaphragm Saunders type AFP (or equivalent) with PTFE/Viton (type 214/226) diaphragms. Satin internal finish, vacublast external finish.
Valves above 2"	Welded hygienic butterfly valve, EPDM seals.

PIPE SUPPORT SPECIFICATION

APPLICATION: TO SUPPORT S2 AND S3 SPECIFICATION PIPEWORK

DUTY: WATER FOR INJECTION
CLEAN STEAM
PROCESS STERILE

PRINCIPLE: Stainless steel pipe holder with a suitable rubber or plastic insert to prevent direct contact between the pipe and the pipe support. This is to prevent cold spots in the pipe when it is being steam sterilised.

PIPE HOLDER: 304 stainless steel with hinged holder and either a knurled nut or a wing nut to enable the support to be easily dismantled and cleaned.

INSERT: Food grade approved rubber/plastic suitable for outside pipe temperatures of 120°C. For pipes outside clean rooms (e.g. in service voids, plant rooms, etc) food grade approved material is not mandatory. White inserts are preferred in clean rooms.

SUPPORTS: Pipe supports are to be positioned to prevent pipework sagging between supports. All pipes which are not vertical shall be sloped at least 1:100 to ensure drainage. The supports must take into account the expansion of pipework during steam sterilisation at 120 to 130°C.

TYPICAL SUPPLIERS:

- Alfa-Laval Flow Equipment type LKRHD pipe support with nitrile rubber insert
- Stainless Fittings Ltd
- APV Baker Ltd
- Defontaine white silicone, or black EPDM (bored out for sizes other than 1/2 inch OD)

PIPING SPECIFICATION

FOR

STERILE DUTIES

PIPING SPECIFICATION:

STERILE DUTIES

1. GENERAL DATA

Max working pressure: 5 Bar g
Max working temperature: 121°C

1.1 PIPE

Material:
Stainless steel, types 304(L) and 316(L) are acceptable. Certain acid or chloride containing streams may need special grades of stainless steel and these must be agreed with the Company.

Rating:
OD of tube

Finish:
Descaled

Note:
Seamless pipe is preferred, but where seam welded pipe only is available, then the seam must have a cold worked internal surface, with 100% radiographic and dye penetrant examination.

Flanges:
Where essential, must be at least ANSI 300 lb weld neck and bending moments at the flange are to be a minimum in relation to the piping system. The inner corner of the flange edges for sterile service shall be nominally square edged to minimize crevices which could adversely affect operation.

Fittings:
Welded

Unions:
(15mm, 20mm) ILC, as manufactured by Dairy Pipelines Ltd, or agreed alternative.

(25mm, 40mm, 50mm) IDF to BS4825 or equivalent.

Connections:
Welded.

1.2 VALVES

For sterilising steam temperatures of up to 120°C valves will be diaphragm type Saunders AFP (or equivalent), with food grade butyl rubber diaphragms (Saunders EPDM 325 grade or equivalent) and butt weld ends. "Saunders" diaphragm valves are available up to 8" diameter though at the present time both 6" and 8" are specials. For larger sizes, butterfly valves shall be used. Where large differential pressures are required the size of the diaphragm valves may be limited. The "Saunders" diaphragm valves will have vacu-blast internal and external finish with clean white bonnets.

Process fluid valves which will be used are diaphragm (up to 4") and butterfly for larger sizes. However, 6" and 8" diaphragm valves are available as specials and are preferred.

Flanged valves are not recommended. Although PTFE ball valves will withstand a temperature of 160°C, these valves are not recommended as the design of the valve internals gives rise to a greater sterile risk because of hold up.

All valves in sterile systems shall be self-draining. With some valve designs this may limit their installation with respect to horizontal, vertical or angled orientation.

The following general features shall apply for valves (see also Section 2):-

- no internal crevices leading to enclosed voids
- clean flow lines having no or at least minimal pockets
- self-draining into pipeline
- single seat for nominal shut-off
- body connections for welding in-line
- easy maintenance of seat or diaphragm from outside pipeline

1.3 INSTALLATION

All butt weld construction shall be used and argon root welds shall be used to provide a smooth internal finish, flanges being permitted only by a special concession from the Company.

All valves, except top entry diaphragm valves, shall be installed with 6" long and 1/2" thick weld pups, to permit cutting and re-welding, for maintenance and replacement.

All sterile lines are to be insulated with resin bonded mineral wool, and clad with aluminium for indoor applications.

All steam condensate lines to slope in the direction of the flow.
All steam lines, where possible, to slope against the vapour flow.
Unavoidable low points may be trapped directly to the condensate collection system but separately routed in each case.

Restriction orifices to be provided at the end of steam headers discharging to a condensate system, to purge any accumulation of inerts to a contaminated condensate system.

All branches on process pipelines are to be as short as possible. "Dead Legs" in sterile pipes are <u>not</u> permitted.

Steam sterilising connections into horizontal process lines to be on the horizontal centre line of the process pipe. Drain branches to be positioned conventionally on the vertical centre line, and below the process pipe. Any areas which could form pools during steam sterilisation are to be avoided.

No pipe support are to be welded to sterile systems. All pipe supports are to be clamped around the special insulated support segments. Connections between the pipe supports and steelwork are to be further insulated with 10mm thick pads.

1.4 INSPECTION AND TESTING

100% radiographic examination together with dye penetrant testing is required for all butt welds, and any welds exposed to the process media (see relaxation, Clause 2.18).

All piping systems are to be Helium leak tested. (See document, Particular Requirements for 'Sterile Engineering' of Fermenter and Vessels.

1.5 GASKETS

Viton/EPDM

1.6 SPECIAL PIPING ITEMS

All special piping items must be capable of withstanding sterilising steam conditions.

No flanged items are permitted, butt weld ends only.

Smooth bore internals are required, with no gaps, threads, slots, etc.

All items must be self-draining and self-venting.

2 GENERAL NOTES

2.1 Swage nipples may be used for sizes 1" and smaller, but only when absolutely necessary.

2.2 Root pass of all butt welds and nozzles welds are to be made by the GTAW process with Argon purge inside of the pipe. Automatic "Orbital" welding to be used wherever practicable.

2.3 Every sterile pipe shall be self-venting and self-draining. All "horizontal" pipe must slope as required by the ELD's (slope 1:10). For CIP systems, piping to slope down from steam inlet to condensate outlet. No dead legs, pockets, or air traps permitted. (Note: CIP - Clean In Place, SIP - Steam In Place).

2.4 No vents and drains to be added for testing purposes, follow ELD's exactly.

2.5 Flanges are not permitted, except when approved by the Company.

2.6 No dead legs or pockets are permitted.

2.7 Pipe systems to be leak tested after erection, using air, and all soft joints checked with soapy water (diaphragm seals, gaskets, etc.). Leak test to be carried out after first thermal cycle (Steam out).

2.8 Thermally insulated pipe supports must be used. No metal to metal contact between pipe and support is permitted.

2.9 The following certified documents from steel manufactures are required:

a. Mill report or check analysis
b. Test report of the non-destructive test

2.10 Piping material with same heat numbers shall be identified with a colour code information. This is required for the automatic preprogrammed welding.

2.11 Ends of stainless steel pipe valves, and fittings, shall be capped to protect them against dirt and damage.

2.12 After cleaning components, ends for welding shall not be touched by skin (fingers) and shall be carefully handled with white gloves to avoid contamination.

2.13 All welding shall preferably be done using Automatic Orbital Welding.

2.14 All field closure welds shall be borescoped where possible. A random borescope check shall be made for all shop fabricated welds. All welds shall be free from pits, craters, ridges, inclusions of foreign materials and linear indications. Welds found with such defects shall be repaired or removed.

2.15 Inspection of all welds shall be performed by personnel qualified under ASME Code, Section V, Par. T-150, Article 1, or international equivalent.

2.16 All valves must be installed to allow full self draining.

2.17 On-site welds must be minimized. Fabrication under clean, controlled, conditions in fabrication shop must be maximized.

2.18 Where this specification is used for Sterilising Steam/Condensate only, the following relaxations apply:

a. 5% Radiography required
b. Borescoping of welds is not required
c. Nozzle connections may be used in lieu of vessolets/sweepolets

2.19 Internal surfaces of all pipe valves and fittings must be smooth, grease free, clean, and free from any damage or repair, and supplied with plastic and caps.

3 WELDING

3.1 PROCESS

This document covers the gas tungsten arc welding of austenitic stainless steel using automatic orbital tube welding machines (preferred) or manual GTAW equipment.

Terms used in this document shall be defined in conformance with ASME Code, Section IX, Appendix I; AWS A3.0, Terms and Conditions; or international equivalent and as specified herein. The term "piping" shall include all components of the weldment.

3.2 GENERAL REQUIREMENTS

Manual GTAW welders using these procedures shall be qualified in accordance with ASME Code, Section IX or international equivalent.

Automatic welding machine operators shall be qualified by making acceptable test welds on sample materials. Test welds shall be made on 2 inch Type 316L material in both the 2G and 5G positions.
Tack welding of the components must be accomplished in such a manner as to not cause any deleterious effect on the completed weld or interior surfaces of the piping or fitting. Tacks should be as light as possible to reduce excessive heat. Tacks should not penetrate to the inner surface, and the same back-up purge cycle as the production weld required is necessary when tack welding.

After the tack welding has been completed the fit-up shall be checked for poor alignment or excessive gap (.010 maximum gap).

All tack welds shall be performed by qualified welders and meet the same requirements as the production weld. Cracked or improper tack welds shall be rejected.

3.3 MATERIALS

The material to be welded shall be austenitic stainless steel type P, number 8 or other internationally recognized equivalent.

All pipe and fittings shall have complete weld penetration.

Welding electrode to be used shall be a pointed 2% thoriated tungsten electrode.

The electrode shall be replaced if contaminated.

The tungsten tip-to-work, or arc gap, is an important variable; a smaller arc will produce a more stable arc and deeper penetration.

Welding grade argon gas shall be used inside the pipe for back-up purge and shall be 99.996% minimum purity. Ladish type gas cups shall be used to assure positive blanket of gas on the piping I.D.

A welding grade mixture of 95-(argon), 5-(hydrogen) is to be used for the torch gas.

3.4 WELD JOINT PREPARATION AND FIT-UP

It is essential that the two surfaces to be joined are clean, circular, square and match properly.

Preparing of the weld end for butt welds shall be performed by machining. (Cutting facility is part of automatic welding equipment).

The machining method or base metal preparation shall leave the weld end with smooth surfaces, free from notches, burrs, or other harmful irregularities.

Any cut-off operation using an abrasive wheel must be followed by a facing operation sufficient to remove abrasive dust and then be abraded with a stainless steel wire brush on either side to remove oxide.

The ends to be welded should be cleaned with a suitable non-residual solvent such as 111 TCE (111 Trichloroethylene), stored in a capped can. Foreign material should be removed to prevent oxidation or porosity in the completed weld.

Tools used for weld joint and preparation, fabrication, and installation shall be stainless steel or approved alloy steel, cleaned free of oil, grease and other contamination residues before they are used. All tools will be colour coded to be used on stainless steel. Non sulphur based cutting oil may be used provided all traces of such oil are completely removed from both the interior and exterior surfaces of the tubing prior to welding.

All joints shall be dried with the use of approved solvent or by the use of hot air heaters to eliminate moisture.

No welding shall be done when surfaces to be welded are wet.

The welding equipment shall be set up by the designated subcontract welding supervisor. The inspector at his option will check that all the settings comply with the master programme.

At the start of each day and after any lengthy shut-down period, each operator shall make acceptable test welds on plain pipe. These pieces shall be identified and kept by the welding inspector. Test welds shall be made for each automatic welding machine, each type of material and each size of piping to be welded that day.

The welder shall check for alignment and excessive gap (.010 max) and that the electrode is centered over the butt joint.

3.5 POSITION

The butt welding shall be accomplished in the 2G and 5G positions. The 2G position pipe with its axis fixed vertical and the weld butt in a horizontal plane. The 5G position pipe with its axis fixed horizontally and the weld butt in a vertical plane.

3.6 PREHEATING TEMPERATURE

In general, no preheating shall be required. The minimum base material temperature shall not be less that 10°C prior to welding.

If the ambient temperature is less than 10°C, the material shall be heated by using electrical resistance induction units or other approved methods that will provide uniform heating over the entire pre-heat area. No fuel gas fired torches are permitted for any heat treatment.

Preheat temperature shall be checked with contact pyrometer approximately 1 inch to 2 inches from the butt edge, if the ambient temperature is below 5°C.

3.7 HEAT TREATMENT

Postweld heat treatment shall not be required.

3.8 ELECTRICAL CHARACTERISTICS

Current shall be continuous DC or pulsed DC and shall be as specified on the applicable welding schedule. The base material shall be on the positive side of the line (straight polarity).

3.9 WELDING PROCEDURE

The welding technique, such as weld deposition sequence, welding programme settings, electrode positioning, etc, shall be as shown in the applicable welding schedules.

3.10 PROGRAMMER CONTROL SETTINGS

Programmer settings shall be those as approved per calibration requirements, with an allowable 10% deviation.

3.11 WELD REPAIR

A weld repair is required when, through examination, it is determined that an unacceptable defect exists, and that the defect is correctable. The first repair may be a reweld over one existing cycle.

The allowable defects which may be repaired are porosity and pin-holes.

All welds with cracks shall be considered a reject and removed including the heat affected zone.
The pipe ends shall be prepared in the proper manner and a new weld performed that will be subjected to all the standard tests.

3.12 WELD SAMPLES

Witnessed weld samples shall be made using the machine welding programmes. All weld samples shall be made in the 5G and 2G position and shall be inspected by the Company.

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 92/030, Project Biogal, Notes of Visits/Meetings 23-27 February 1992

(3) Commission of European Communities

"Proposal for a Regulatory Framework for the use of Genetically Modified Organisms" COM(88)160

Part 1: Council Directive on the Contained Use of Genetically Modified Micro-organisms

(4) UNIDO Contract 92/030, Good Manufacturing Practice Audit of Biotechnology Pilot Plants of the Biogal Pharmaceutical Company (First Interim Report) May 1992