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GRC Consultants

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(1 of 3)

QUALITY CONTROL AUDIT

AND

GOOD MANUFACTURING PRACTICE CRITIQUE

OF

SMALL SCALE PRODUCTION UNIT

OF

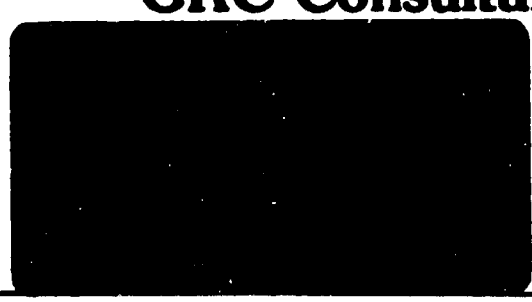
ALKALOIDA

UNIDO CONTRACT 92/031

G E GUIDOBONI
NOVEMBER 1992

This report has been prepared for the United Nations Industrial Development Organisation (UNIDO) for the project TF/HUN/90/907 "Technical assistance for upgrading the DSP section of the small scale multi product medicinal chemical plant"

GRC Consultants



Partners G E GUIDOBONI, P D RUSSELL, J G CHALLENGER C H BROOKS

SYNOPSIS

This report presents the results of a broad Quality Control (QC) and Good Manufacturing Practice (GMP) audit of these functions at the Tiszavasvari plant of the Alkaloida company in general, but with particular reference to the proposed multiproduct small scale production unit for pharmaceutical chemicals.

The concept and implications of VALIDATION of the proposed unit are discussed, particularly as they affect technical and design documentation.

The report also contains a 'critique' of the current design and part construction of the small scale production unit, especially from a GMP point of view. A number of design and construction features are identified for further discussion and possible improvement.

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SECTION 1

INTRODUCTION

1 INTRODUCTION

Towards the end of 1989, the Government of the United Kingdom announced that it was to establish a Know-How Fund (UK/KHF) for Hungary to assist selected major production companies in the preparation of short to medium term programmes for upgrading and expanding research and development as well as improving the existing production facilities, first of all in the pharmaceutical, fine chemical, food and biotechnology sector of 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 first Alkaloida 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 was scheduled to begin at the end of February 1992. However, before the contract was started, it became evident that the client, Alkaloida, was desirous of reformulating the objectives of the project in order to change the technical content of certain key aspects. The discussion and agreement of this reformulation was the subject of the project kick-off meeting and the key points are noted below.

- By means of a GMP audit and FED study, GRC Consultants would advise Alkaloida of actions necessary to upgrade the downstream processing (DSP) section of the small scale, multiproduct medicinal chemical manufacturing plant, which currently is under construction, to meet the GMP standards and facilities approval requirements of the EC and USA.

- For the purposes of the project, it was agreed that the DSP unit noted above is understood to be one of the secondary pharmaceutical production plants of Alkaloida and this unit would be the focus of the GMP audit and FED study, rather than the company wide practices and facilities noted in paragraph 2 above.

- It was agreed that whilst the original objectives had been reformulated, the changes did not have any significant consequences on either the total amount of work to be carried out by GRC Consultants or on the overall timescale of the project.

- It was agreed, however, that the reformulation did require more work by GRC Consultants in the early stages of the project in order to make the report more relevant to Alkaloida's immediate needs.

- It was agreed that the DSP unit was now designed as a small scale production unit, not a pilot plant, and Alkaloida intends to use the medicinal chemicals made in the DSP unit for clinical trials.

- An extremely important implication of the statement above regarding end use of the products is that the whole of the design, construction, installation, commissioning and operation of the DSP unit for BPC's must be VALIDATED, with all that this implies, to the satisfaction of, and approved by, foreign inspectors for compliance with GMP standards.

- Furthermore, it must be appreciated that as far as GMP regulations and inspections are concerned, the upper floor of the small scale production unit is an integral part of the facility for the production of bulk pharmaceutical chemicals and its design, construction, installation, commissioning and operation must also be validated.

The report has, therefore, been prepared to reflect and comply with the above agreed requirements and consists essentially of two main subjects.

The first subject concerns GMP and Quality Control matters as they are currently practiced in Alkaloida in a very general and company wide way.

Whilst it was recognised that this general GMP/QC audit was purposely broad and general in scope, it would be more appropriate to focus' the audit on the DSP plant noted above by preparing a critique of the design and construction to date of the DSP, particularly with all the implications of GMP and Validation in mind. Hence, the second main subject of this interim report concerns design and construction aspects of the DSP.

Of necessity, this report is therefore expanded in content (from that intended by the original project terms of reference). Topics covered briefly in this report are developed in the FED study which contains process, equipment, mechanical and layout material, together with appropriate outline engineering standards/specifications, in sufficient detail to invite contractors to bid for the detailed design, supply, construction and installation (all validated) of the works needed to complete the partly constructed DSP facility.

SECTION 2

GOOD MANUFACTURING PRACTICE (GMP)

2 GOOD MANUFACTURING PRACTICE (GMP)

As mentioned in the Introduction, the DSP unit is designated as a small scale unit for the preparation of bulk medicinal chemicals for use in clinical trials. Hence the unit must be designed, installed and operated to GMP standards in 'approved' facilities. It was also noted that this has significant implications and it is therefore appropriate to review, in this section, key aspects of GMP as they will affect the Alkaloida DSP.

2.1 GENERAL

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 (QC, see also Section 4).

The basic principles of GMP require that plant and buildings, such as the DSP 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 report, the products made in the DSP 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 and EC inspectors about BPC's and are intended to give some idea of the levels to which design, installation and operation may have to be taken to secure regulatory authority approval.

2.2 BACKGROUND

There are basic differences between the processes used for the production of medicinal chemicals and the processes used for the production of finished drug products. Medicinal chemicals usually are made by chemical synthesis, by recombinant DNA technology, by fermentation, or by recovery from natural materials. On the other hand, finished drug products are usually the result of a formulation from bulk materials whose quality can be measured against fixed specifications.

In almost every case in the production of medicinal chemicals the starting materials, or derivatives of the starting materials, undergo some significant chemical change. Impurities, contaminants, carriers, vehicles, inerts, diluents, and/or unwanted crystalline or molecular forms which may be present in the raw materials are largely removed by various treatments in the production process. Purification is the ultimate objective and is effected by various chemical, physical, and/or biological processing steps. The effectiveness of these steps is in turn confirmed by various chemical, biological, and physical tests of the medicinal chemicals.

In contrast, in finished drug production, the quality of the drug ingredients (the components), and the care exercised in handling them, somewhat predetermines the purity of the finished drug product. Purification steps usually are not involved.

The use of precision automatic, mechanical, or electronic control and recording equipment and of automatic processing equipment is even more likely to be found in a medicinal chemicals plant than in a finished drug product plant. Use of such equipment is appropriate when adequate inspection, calibration and maintenance procedures are utilised.

Production equipment and operations vary widely depending on the type of medicinal chemicals in production, the scale of production, and the type of operation (batch vs continuous). In general, the environmental conditions, equipment, and operational techniques employed are those associated with the chemical industry rather than the finished drug product industry. Chemical processes frequently are performed in closed systems, which tend to provide protection against contamination, even when the reaction vessels are not enclosed in buildings. However, this does not preclude the introduction of contaminants from equipment, materials used to protect equipment, corrosion, cleaning, and personnel and their clothes.

It is appropriate to consider the type of system (open or closed), form of the material (wet or dry), and use of the equipment and/or area (multipurpose or dedicated). "Closed" systems in chemical plants are often not closed when they are being charged and/or when the final product is being emptied. Also, the same reaction vessels are frequently used for different reactants.

Other factors to be considered include:-

- Degree of exposure of the material to adverse environmental conditions
- Potential for cross-contamination from any source
- Relative ease and thoroughness of clean-up
- Sterile vs non-sterile operations

In the production of medicinal chemicals, the recycling of process liquors, and recovery from waste streams which have been tested and meet appropriate standards often are necessary for quality, economic and environmental reasons. In addition, the production of some medicinal chemicals involves processes in which chemical and biochemical mechanisms have not been fully understood and scientifically documented. Therefore,

the methods and procedures for materials accountability will often differ from those applicable to the manufacture of dosage form drug products.

The producer of medicinal chemicals must recognise the need for appropriate evaluation of raw materials before their introduction into the process. In addition, as chemical processing proceeds, a chain of documentation should be established which at the minimum includes a written process and appropriate production records, records of raw materials used, records of initial and subsequent batch numbers, records of the critical processing steps accomplished, and intermediate test results with appropriate standards. As the end of the process is approached, the completeness of the records and of the material accountability should increase, and the latter finishing steps should be thoroughly documented and conducted under appropriate conditions to avoid contamination and mix-ups.

2.3 STATUS OF BULK PHARMACEUTICAL DRUGS

Medicinal chemicals are components of drug products and the manufacture of medicinal chemicals is therefore carried out in accordance with the concepts of GMP. The manufacturers of inactive ingredients may not be required to register with the FDA, but they are not exempt from complying with GMP concepts, and they are not exempt from inspection.

The question of when an industrial chemical becomes a medicinal chemical is complex and criteria such as the following are used to identify a chemical as a medicinal chemical:

- when there is no other recognised non-drug commercial use for the product

- when it reaches the point in its synthesis that it is known that the end product will be used in a drug product

- when the manufacturing facility can be identified as a manufacturer for the pharmaceutical industry

- when the manufacturer sells the drug or offers it for sale to a pharmaceutical firm for use in a drug product

It is reasonable to expect GMP concepts to come into play at that point where a starting material enters a biological or chemical synthesis or series of process steps, where it is known that the end product will be a medicinal chemical.

2.4 CURRENT GMP REGULATIONS

Various USA and EC regulations require that all drugs 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 Act.

2.5 SCOPE

These notes are applicable to all medicinal chemicals produced in the USA and EC. They are also applicable to medicinal chemicals produced in foreign countries intended to be exported to the USA or EC. These notes are to provide guidance for medicinal chemicals, which are eventually to become sterile and apply to:-

- Human drugs
- Veterinary drugs
- Biologics

These notes also apply when the medicinal chemical is:

- A drug of animal origin
- A drug of botanical origin
- An inactive ingredient as appropriate
- A component not appearing in the finished drug product
- A bulk intended for use in placebos

These notes apply to the complete facility, the entire process, all equipment, components, the system of records and documentation, and the entire quality assurance, process control and release system.

2.6 GENERAL GUIDANCE

Although strict observance of high standards of GMP, approaching or equalling those expected for finished drug products, may be expected in some types of bulk 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. A drug master file with a process flow chart should be available for the process.

As briefly discussed in Section 2.. Background, the documentation system required for the early steps in the process must provide a chain of documentation but need not necessarily be as comprehensive as in the later parts of the process.

Further aspects of documentation are noted in Section 3.

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

Aspects of GMP, as they apply to the Alkaloida DSP, are discussed further in Section 7 of this report.

SECTION 3

DOCUMENTATION AND VALIDATION

3.1 DOCUMENTATION

3.1.1 Documentation Master Plan

3.1.2 Documentation of Standard Operating Procedures (SOP)

3.2 VALIDATION

3.2.1 Validation Planning

3.2.2 Project Validation Requirements

3 DOCUMENTATION AND VALIDATION

As mentioned in Sections 1 and 2, the concepts of, and requirements for documentation and validation are extremely important as they relate to the Alkaloida DSP which is to be used to make clinical trials materials and products for sale. The DSP is, therefore, to be an 'approvable' facility and the significance of documentation and validation is outlined in the sections which follow.

3.1 DOCUMENTATION

The first stage in the project organisation, culminating in the installation and erection of an 'approvable' plant is the development of a documentation master plan. This master plan defines the project stages and explains to working groups within the company and external personnel, what GMP type documentation is required in each area of operation. The master plan also provides sample forms to ensure uniform documentation where possible throughout the company. Initially the plan identifies the areas of documentation to be developed.

The documentation, as defined by the documentation master plan, provides a record of the work done in relation to the new plant, and of the approval of the results of that work. Hence the documentation master plan defines the work to be done from original plant concept, through a series of internal stage approvals, to include documentation required during regular plant operation. It is developed as early as possible since a mass of unstructured documentation provides difficulties for the report generators, reviewers and retrievers including regulatory authority inspectors. The development of the master plan is continuous and more detail is added to the structure of each section of the master plan from time to time.

A system for approving these changes must be instigated.

3.1.1 Documentation Master Plan

The importance of the documentation master plan and its relation to the overall project has been noted earlier. Some related concepts are detailed here and the master plan is discussed further.

The most important feature of the master plan is that it is clear, logical and thorough. The plan can be considered to be a catalogue and filing system for plant documentation.

The benefits of the early implementation of a documentation master plan include:

- The development of a more accurate appreciation of work required in each aspect of the project leading to better resource management.

- Development of documentation master plan leads to better project management and so less duplication of the same work.

- The documentation master plan forms an integral part of the project plan.

- The shortcomings of the project can be identified early, so preventing abortive work on a non-feasible plant.

- Examining what documentation is required can identify gaps in a project.

Alkaloida should consider the implementation of a master plan and also perform a review of documentation on this project to date.

3.1.2 Documentation of Standard Operating Procedures (SOP)

An important concept in Pharmaceutical Good Manufacturing Practice is the Standard Operating Procedure. It consists of a set of documents which cover the who, what, when and how of activities relating to the plant and personnel which could affect product quality. They cover work from the purchase of starting materials, through cleaning and operation of plant, culminating in the procedure for recalling faulty batches. It is advantageous to have a list of SOP to be written well in advance of commissioning, in order to plan writing duties and workforce training.

SOP's also must be validated and the significance of validation is outlined in Section 3.2 which follows.

3.2 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.

3.2.1 Validation Planning

Whist the concept of formal validation was introduced for the production of sterile dosage forms only, it is now required for most stages in pharmaceutical 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 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.

3.2.2 Project Validation Requirements

(Note: in the context of this report the Purchaser may be Alkaloida and the Supplier normally is the equipment supplier or engineering contractor, but may also be Alkaloida'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 (including CIP and sterilization sequences) 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 4

CURRENT QC/GMP IN ALKALOIDA

4 CURRENT QC/GMP IN ALKALOIDA

4.1 GENERAL

As mentioned in the Introduction, one of the first activities to be carried out for this study was to review/audit the current approach of Alkaloida to the structure and operation of systems for Quality Control (QC) and Good Manufacturing Practice (GMP). The importance of QC and GMP cannot be overemphasized if Alkaloida are desirous of entering and competing in the Western European, North American and other potentially lucrative world markets, with their existing or newly developed products.

GRC Consultants understands that Alkaloida does have a few products which are made in 'FDA inspected' plant, hence the company must already have an appreciation of the general requirements for GMP as they relate to 'approvable' facilities.

The nature of GMP has been described in Section 2 and the following notes on QC are appropriate before reviewing the current status of GMP and QC in Alkaloida.

'QUALITY CONTROL' is a collection of activities, including design analysis and statistical sampling with inspection for defects, designed to ensure adequate quality in manufactured products. The QC department which performs this function does not control the quality of the product in the strictest sense (this is the responsibility of the production department) but monitors the quality of the product 'as a fact'.

'QUALITY ASSURANCE (QA)' is an overall, company wide concept that ensures the establishment of certain criteria before production, the control of certain key factors during production, and the evaluation of certain results after production.

The relationship between QA, QC and GMP may be expressed as:-

QA = GMP + [OTHER PRODUCT FACTORS]

where GMP = QC + [MANUFACTURING]

where OTHER PRODUCT FACTORS = Product Design and Product Development

Hence it is clear that for the purposes of this study, GMP and QC must have a significant and dominant presence in the overall organisation and structure of the Alkaloida company.

4.2 NATIONAL ORGANISATION

In Hungary the conditions of production of pharmaceuticals are regulated by 'Good Practices in the Manufacture and Quality Control of Drugs (WHO 1975)' and the 'Basic Standards' and other guidelines of the 'Pharmaceutical Inspection Convention' (PIC), which Hungary joined in 1976, and published by the Hungarian Institute of Pharmacy. This Institute is responsible for approving the appointment, within a company, of the QC Manager on a 'once and for all' basis and does not reapprove or review the appointment on a regular basis. The Institute only approves the appointment of the QC Manager but not that of any other staff within the QC function.

4.3 ALKALOIDA AND QUALITY ASSURANCE

Currently Alkaloida only have a QC function organised and operating; there is as yet no formal QA function. However, Alkaloida currently are using a Hungarian consultancy company to carry out an overall QA audit of the existing company wide operations and this consulting firm will report its findings to the Alkaloida Board during 1992.

It is intended to establish a Quality Assurance Council, to publish a company wide QA Manual and to set up local QA groups/teams in various company departments.

Alkaloida are aiming to have these functions in place by early 1993 and intend to apply for ISO9001 and BS5750 approval.

4.4 ALKALOIDA AND QUALITY CONTROL

The following notes should be read in conjunction with the attached diagram.

The General Manager is the Board Director responsible for the QC function within Alkaloida. The Manager of the QC Department reports in a management function to the General Manager. However, the QC Department Manager is the ultimate technical authority within Alkaloida on all matters relating to QC.

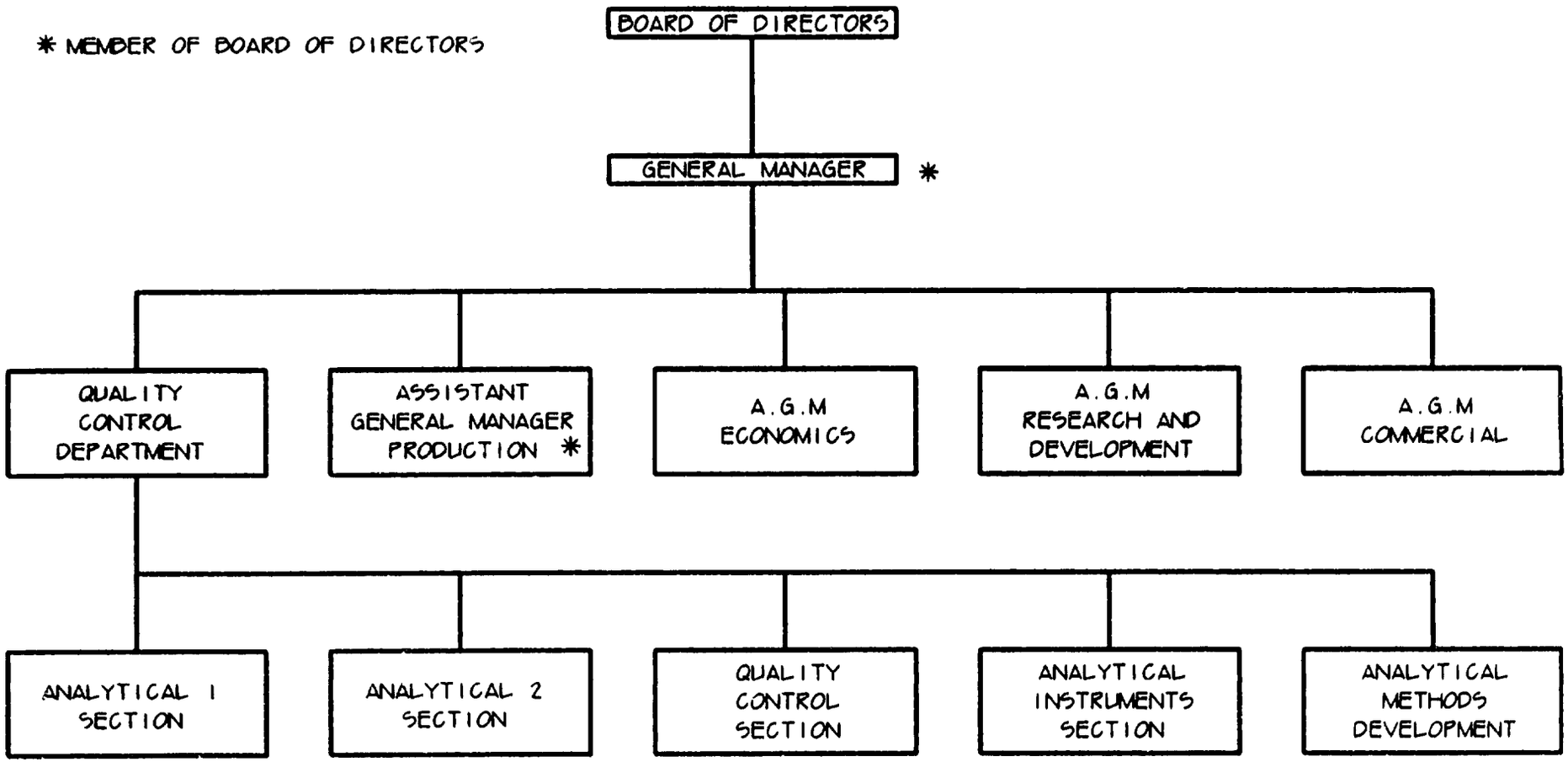
The QC Department is responsible for the quality of raw materials and for the release of products. This department also prepares 'Alkaloida House Standards' which are applied compulsorily throughout the factory.

The QC Department is organised into 5 sections with responsibilities as outlined below:-

Section 1 - Analytical 1

Responsible for the analysis of incoming materials to Hungarian and local standards but not to Pharmacopoeia standards. Materials include intermediates made by Alkaloida and chemical finished products which are sold on to other companies as intermediates for finished materials.

* MEMBER OF BOARD OF DIRECTORS



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PROJECT: ALKALOIDA

TITLE: OVERALL ORGANISATION

DATE: APRIL '92

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Section 2 - Analytical 2

Responsible for the analysis of all incoming materials according to Pharmacopoeia standards. Also responsible for all pharmaceutical finished products and all pharmaceutical active substances.

Section 3 - Quality Control

Responsible for the quality control of packaging materials, labels, stoppers, closures, etc, and all other components. Also responsible for taking and carrying out analysis of research samples. This section also checks production records, checks analytical results, checks production methods and compiles and releases certificates of analysis.

This group is also responsible for the taking of all production and other samples within the factory. Only this group is authorised and trained to take production samples which they pass to the other section within the analytical department for analysis.

Section 4 - Analytical Instruments

This group is responsible for carrying out those analyses which require the use of instruments such as HLPC, GLC, etc. This group is also responsible for the analysis of the 'pesticide' group of compounds made by Alkaloida.

Section 5 - Analytical Methods Department

This group is responsible for the development of new, and improvement of existing analytical methods and techniques.

The group is responsible for the analyses required during drug development and during drug registration processes. The group also carries out stability trials and checks the compatability of packaging materials with products.

4.5 ALKALOIDA AND GMP

Alkaloida have in place a factory GMP committee which is required by the Hungarian Institute of Pharmacy and is a self auditing body. It is under the general direction of the Assistant General Manager (Production) and has a permanent secretary who is the quality control department manager. The committee consists of some 9 persons from various departments, together with the Chairman and the secretary. The key departments represented on the committee are as follows:

Head of Despatch Department
Head of Chemical Technology Department
Head of Warehouse and Stores
Head of Maintenance
Head of Production
Head of Pharmaceutical Development

Currently there is no representation from any engineering or design department. The only engineering input to the committee is via the Head of Maintenance.

The committee is mainly self auditing and makes plans at the beginning of a year for the work to be carried out. At approximately 1-2 month intervals the committee carries out production audits of the various units. It checks a particular department against GMP requirements and each audit takes approximately half a day, depending on the area.

It carries out two kinds of audits:

(1) a council audit in which the whole committee takes part, and
(2) a member audit carried out by two members, one of which is the head of the department being audited, the second member being independent.

At the end of the audit the team makes a report which identifies problems, makes recommendations, take decisions and issues instructions to carry out repairs and modifications, etc. The report itself is issued to all the audit members, to the General Manager, Assistant General Manager, the Department Head and other people who need to know the results.

If a Department Head is instructed to carry out a repair and modification but lack of financial resources prohibits an immediate response, the Department Head refers the matter to the Assistant General Manager (Production) for resolution.

Currently the permanent secretary of the committee (QC Department Manager) is responsible for progressing the actions and instructions from the GMP committee. It is understood that the existing GMP committee will be absorbed eventually into the new Quality Assurance Council which is being established (see item 4.3 above). It is also noted that (in May 1992) the chairman of the GMP Committee is the Assistant General Manager, Production, but this is not considered generally to be good practice since the permanent secretary is also subordinate to the Assistant General Manager, Production.

4.6 OBSERVATIONS

During the course of the audit of the existing QC/GMP systems, GRC Consultants was able to review overall documentation procedures, the organisation and operation of the main warehouse and despatch area, and the organisation and operation of the Analytical Laboratories of the QC Department.

4.6.1 Overall Organisation and Management

(See also sections 4.3 - 4.5 above)

It is noted that the QC Department Manager is not a qualified pharmacist. This is slightly surprising but is acceptable to the Hungarian Institute of Pharmacy. It is also noted that 2 of the 5 QC Department section heads have formal pharmaceutical qualifications.

4.6.2 Personnel and Training

It is noted that out of a total staff of about 114 in the QC Department 14 are qualified to Degree/PhD level, 84 are classed as technicians and 16 are classed as skilled workers. It is acknowledged that the qualified senior staff have appropriate and relevant degrees, and it is assumed that the technicians are adequately trained.

4.6.3 Procedures and Records

Generally these are 'paper' based and appropriate for the various functions. It is noted that on the last FDA inspection, some points were made by the inspector regarding documentation. (They have been subsequently actioned by Alkaloida).

It is also noted that Alkaloida are currently investigating (jointly with several other Hungarian pharmaceutical companies) the possibilities for a computer data based QC/QA system. They are aware of the needs for and the difficulties of VALIDATION of such a computer based system and advice/support on this topic is needed.

4.6.4 Rodent Elimination Programme

Alkaloida operate such a programme on a company wide basis. A specialist company is sub-contracted to organise and execute this programme which includes a regular inspection and visit every 6 months.

4.6.5 Recall and Complaints Procedure

Company wide procedures are in place for both of these topics and experience suggests that they are adequate. Computers are used to store and retrieve data on every batch of finished product and purchased material.

4.6.6 Warehousing

As part of the audit, a visit was made to the main warehouse and despatch building and the following points are noted:-

- Finished products in packs in cartons on pallets were observed, virtually out in the open on a loading ramp, with no overwraps to protect either the cartons individually, or the pallets overall, from the weather.

- The quarantining of labels, packaging materials and other components is achieved by a system of colour coding by stick-on labels (yellow on receipt, green cleared for use). This is a common practice with traditional pharmaceuticals and is both appropriate and acceptable.

- Special areas are set aside as large locked cages, for the receipt and temporary storage of materials which arrive either during the night or when the warehouse is not fully manned.

- The warehouse overall is relatively old and shows some signs of a lack of maintenance. The building is not air conditioned as such but is maintained at a reasonable temperature by traditional heating methods.

- Throughout the building, the floors appeared to be relatively soft asphalt finished and were clearly heavily rutted, presumably by the passage of trolley wheels, etc. This was a poor feature and the ability to keep the floors clean to an adequate standard must be questioned.

- There were no obvious high security measures in place to prevent/control the movement of personnel, particularly at the ground floor level.

4.6.7 Analytical Laboratories

These laboratories appeared bright, clean, airy and well organised. They are equipped with a wide range of analytical instruments, some new, some old and traditional.

The main sub-sections, Analytical 1 and 2, occupy totally different floors within the same building, and this arrangement effectively prevents the mixing of samples, etc.

The long term sample storage facilities are extensive and secure.

The overall impression was formed that the Analytical Laboratories are entirely adequate for current operations with Alkaloida.

SECTION 5

THE MULTI PRODUCT UNIT TECHNICAL DESCRIPTION

5.1 OVERVIEW

5.2 UPPER FLOOR

- 5.2.1 General
- 5.2.2 Personnel and Material Flows
- 5.2.3 Equipment List

5.3 GROUND FLOOR DOWNSTREAM PROCESSING

- 5.3.1 General
- 5.3.2 Personnel and Material Flows
- 5.3.3 Equipment List
- 5.3.4 Room List

5.4 SERVICES

- 5.4.1 General Services
- 5.4.2 HVAC

5.5 CURRENT STATUS

- 5.5.1 Equipment
- 5.5.2 Premises
- 5.5.3 HVAC

5 TECHNICAL DESCRIPTION

5.1 OVERVIEW

The Multiproduct Unit will be designed on a multitonne per annum basis. It will be designed to meet European/American current GMP requirements and will be located in the empty part of an existing building.

The plant is located on two floors. The upper floor will be the synthesis and primary separations area. Slurry will be transferred from this area via a single pipe to the downstream processing area on the ground floor. The finished bulk pharmaceutical chemicals will be despatched from the ground floor after quality control release.

Reference to the upper floor is included for completeness only and is not the subject of this study.

5.2 UPPER FLOOR

5.2.1 General

A raised control room overlooks the main process hall. Two smaller enclosed suites exist on this level, the filter room and the dangerous process room.

For distillation and crystallization LAMPART pressure vessels will be used with associated ancillary equipment. Two Pfaudler pressure vessels will be used in the dangerous process area.

There will be two pressure filters and a 2000l extractor.

Computerised process control is expected to be used for several items of equipment.

5.2.2 Personnel and Material Flows

Raw materials in sacks, wooden pallets or drums will be transferred to the upper floor by lift or chain grab. Liquids will be handled by 500l mobile tanks, drums or 2 m^3 external tanks.

2-3 men will work on this floor and will enter via the stairs. They will change on the ground floor using a changing room adjacent to the lift and which is totally independent of the DSP changing facilities. There are three emergency exits on this level.

5.2.3 Equipment List

The main process equipment is shown below, ancillary equipment is not listed.

Note: The equipment numbers are taken from Alkaloida drawings, etc.

Main Process Hall

7A01	400l Lampart pressure vessel
7A04	630l Lampart pressure vessel
7A05	1000l Lampart pressure vessel
7A06	1600l Lampart pressure vessel
7A08	2500l Lampart pressure vessel
7A09	1600l Lampart pressure vessel
7X01	2000l Extractor

Dangerous Process Suite

7A02	630l Pfaudler pressure vessel
7A03	630l Pfaudler pressure vessel
7F01	300l Lampart pressure filter

Filter Room

7A07 16001 Lampart pressure vessel

7F02 3001 Lampart pressure filter

5.3 GROUND FLOOR DOWNSTREAM PROCESSING

5.3.1 General

Final product separation, drying, milling, sieving and product dispatch will occur on this level.

The layout is given in Drg. 92/005/102 attached to the end of this section.

The steel floor of the upper level will be airtight providing a barrier between the two floors. A fire retardant suspended ceiling will be installed on the lower level.

Two types of vacuum drier are provided for flexibility.

5.3.2 Personnel and Material Flows

Packing material will enter the goods in receipt room via the main entrance lobby. Here it will be checked and cleaned and passed through to the cleared 'goods-in' room.

Process material will be passed from the upper floor via a single pipe.

In process material will be transferred in 50-1001 stainless steel vessels.

Finished bulk pharmaceutical material will exit the building via the sampling room. Quality control personnel will sample and then authorise transfer to the cleared finished product store if the chemical is within specifications. The material is then available for transport from the building.

4-5 men will work on this level and will enter the building via a two stage changing suite.

5.3.3 Equipment List

The main process equipment is shown below. Ancillary equipment is not listed.

3F01	1000l stainless steel submerged tank
3F02	1000l stainless steel submerged tank
3F03	1000l stainless steel submerged tank
4F01	2 m^2 Nutsche Filter
6M01	500 kg Balance
4H01	400 kg Capacity Cone Blender
4T01	200 kg Capacity Horizontal Drum Drier
4F02	0.7 m^2 Basket Centrifuge
4H02	Hammer Mill
4T02	200 kg Capacity Tray Drier

5.3.4 Room List

No.	Description
1	Entrance Lobby
2	Lobby
3	Common Dressing Room
4	Ingoing Clean Dressing Room
5	Lobby

6	Outgoing Clean Dressing Room
7	Shower
8	Toilet
9	Lobby
10	Goods In Receipt
11	Cleared Goods In
12	Main Corridor
12A	Fire Hydrant Cupboard
13	Process Store
14	Filter Room
15	Wash-up Room
16	Laboratory
17	Drying Room A
18	Service Room A
19	Drying Room B
20	Blending and Packing Room
21	General Store
22	Sampling Room
23	Cleared Finished Products Store
24	Service Room B

5.4 SERVICES

5.4.1 General Services

The building already has the following services in place and these will be used as necessary in the Multiproduct Unit.

Steam/Condensate System (6 bar)
Cooling Water System
Chilled Water System (brine)
Nitrogen (6 and 3 bar)
Compressed Air
Process Water

Dedicated vacuum pumps to service the Multiproduct Unit are situated on the 1st floor service area. The vacuum driers on the ground floor have local vacuum pumps and ancillary equipment.

5.4.2 Heating Ventilation and Air Conditioning (HVAC)

On the 1st floor heating appears to be achieved entirely by the use of radiators. The air extraction and supply system has been designed in-house to provide 10-15 room changes an hour.

On the ground floor it is proposed to provide heating partially by radiators and partially by the air supply system.

5.5 CURRENT STATUS

5.5.1 Equipment

Centrifuge 4F02 has been bought from Giovanola. All other equipment is in the quotation or negotiation stage.

Some equipment has been designed in-house and is planned to be fabricated by local fabricators or in-house.

5.5.2 Premises

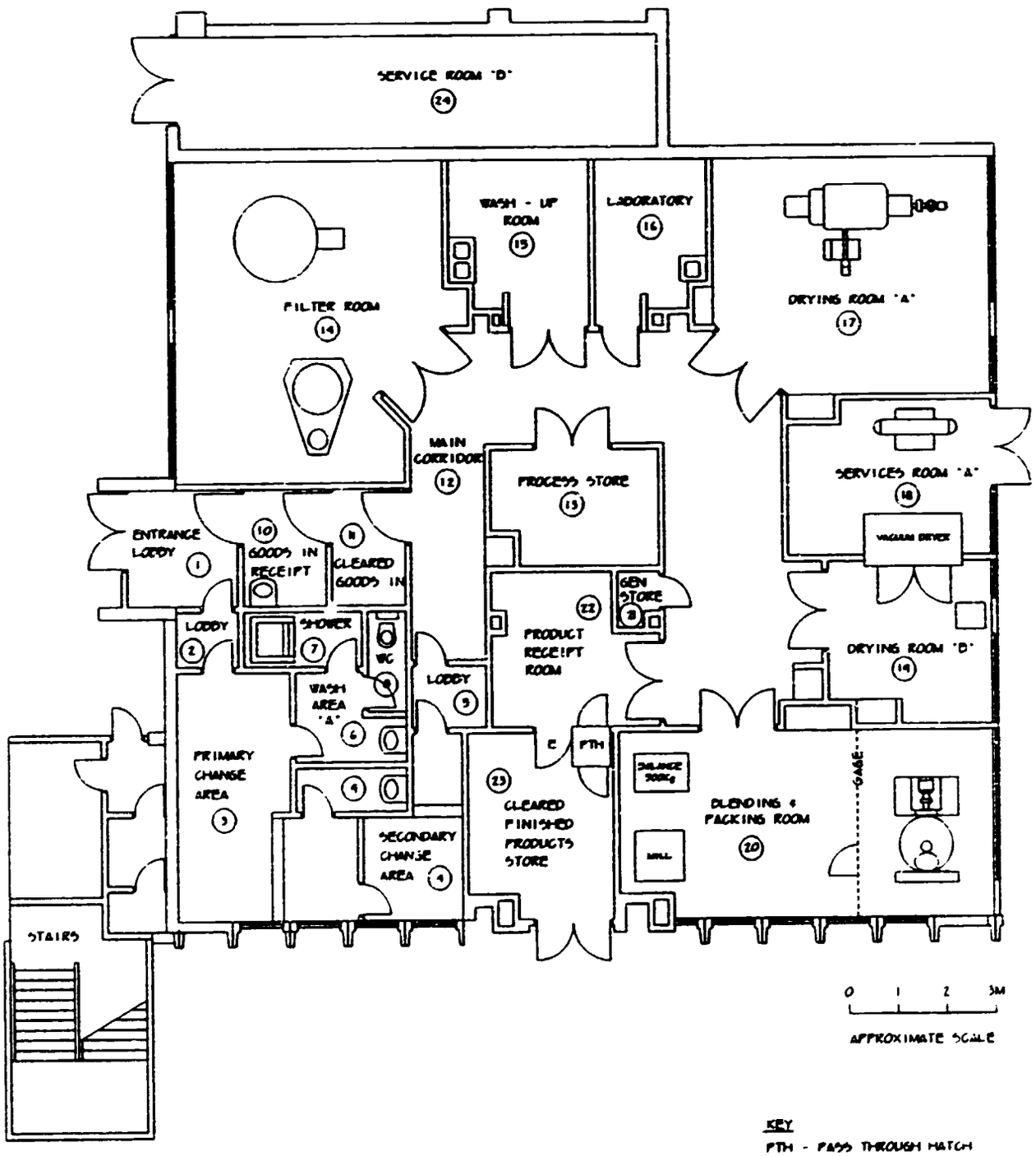
The building shell is complete as it forms part of an already established building.

The ground floor internal wall blockwork is virtually complete for the proposed layout (see Drg 92/005/102). The two process rooms have been constructed on the 1st floor.

The floors and drainage on the ground floor are substantially complete. The walls on the ground floor have a rough cement finish.

5.5.3 Heating, Ventilation and Air Conditioning System (HVAC)

The heating, ventilation and air conditioning system for the ground floor has been designed by a specialist company, Kipszer. GRC Consultants understands that the design of the HVAC system has been carried out according to certain GMP standards, but it is not known by GRC Consultants to date to which standards these refer. Since it is vitally important that the HVAC system is designed to approvable USA/EC GMP standards, the whole subject of the design of the HVAC system will be examined in further detail in the Front End Design study. It appears that the upstairs ventilation system is totally separate and has been designed in house.



GRC CONSULTANTS GROSVENOR HOUSE 70 HIGH STREET ALTON HANTS GU34 1DH TEL 0420 88847 FAX 0420 88447	CLIENT UNIDO, P O BOX 300, A-1400 VIENNA AUSTRIA FAX 2-?156 DATE MAY 1 '91 SCALE N/A DIMENSIONS IN METRES	PROJECT ALKALOIDA I TF/HUN/90/907	TITLE GROUND FLOOR ROOM LAYOUT DRAWING NUMBER 92/005/A02 REVISION D

SECTION 6

CRITIQUE OF DESIGN/CONSTRUCTION OF MPU DOWNSTREAM AREA

6 CRITIQUE OF DESIGN/CONSTRUCTION OF MPU DOWNSTREAM AREA

6.1 INTRODUCTION

The purpose of this section is to identify potential problems in the design of the new Alkaloida Multi Product Unit Ground Floor Finishing Area. It is based on information available to GRC Consultants at the time of writing.

6.2 DOCUMENTATION

GRC Consultants have received the document 'Technical Description of Multipurpose Pilot Plant of Alkaloida, Sept 1991' together with an equipment list and a set of drawings.

The Technical Description gives a good overview of the plant but must be supported by more detailed documentation before the plant is built.

It is noted that there is no Quality Control Approval on the GRC Consultants copy of the Technical Description. At some stage in the plant design, co-ordination with QC and subsequent approval must occur.

GRC Consultants have no documents giving process details or the subsequent use of this information to form the basis of the plant design.

The Technical Description contains no room cleanliness classification information, air change rates or room finish specification.

There is no evidence of the development of a documentation master plan (see Section 3.1).

There are no details of personnel involved in the project or their qualifications. There are no details of planned medical examination procedures or training programmes or records of past programmes.

The staffing structures, working time arrangements and draft job descriptions are not detailed.

There are no records of required utilities and services quality details (for materials such as rinse water, nitrogen for pressure transfer, etc) or quality of services available. This is an important consideration which may lead to the requirement for additional service equipment.

6.3 EQUIPMENT

It appears from the documentation that no automated Cleaning in Place (CIP) systems are proposed. For this type of multiproduct plant the use of a centralised automated cleaning in place system is recommended.

The filter room contains three lined tanks (set below floor level) for process fluid use. From Alkaloida Drg. T3522 it appears that the fluid is extracted from these tanks by means of a dip leg connected to a pump. It appears that the design inherently prevents the complete drainage of these tanks. The reproducible cleanability of these tanks is therefore in question and hence their use is not good practice.

It is assumed that no wheeled vessel, such as IR02 which is kept outside, will enter the ground floor plant.

6.4 SERVICES

6.4.1 Drainage

The MPU shares the same common drainage as the Iminodibenzl (IDB) plant in the adjacent part of the building. The IDB drain passes under the MPU, and MPU floor drains are piped directly into this drain. There is a local liquid seal incorporated into the drain grating to protect the MPU for vapours and aerosols from the common drain, originating from the IDB plant or perhaps other areas of the Alkaloida site. The loss of the water seal by evaporation or removal of the drain cover for cleaning obviously leaves the plant vulnerable to various sources of contamination.

The drainage system is far from ideal. A better drainage arrangement would be to pipe the drainage from the MPU to an intermediate tank before joining the main drainage. This arrangement would also allow the use of an intermediate solvent trap if necessary.

A ground floor drainage grating/rodding point is located in the cleared finished product room immediately prior to despatch as shown on Alkaloida Drg. T3523. This arrangement gives serious concerns for contamination of the final product by vapour and aerosols from the main drain. The cover for this rodding point must be sealed shut semi-permanently. Consideration should be given to the relocation of this rodding point.

Floor drains exist in many of the areas on the ground floor. The need for these drains should be reviewed with respect to the cleaning regimes proposed in each of the areas.

It is assumed that the foul drainage from the WC and Change Area will be piped away and processed separately from the general process drains.

6.4.2 Heating

It appears from Alkaloida Drgs. EG-2413 and EG-2415 that the heating system is proposed to be a hot water system with radiators. This is not considered to be good practice. Heating is more satisfactorily achieved using the heating, ventilation and air conditioning system.

The use of a hot water radiator system can lead to many problems including contaminating water leaks, encouraged by thermal cycling, and the difficulties of effective cleaning behind the radiators. To introduce unnecessary equipment into the workplace is against the principles of GMP.

6.4.3 Safety Showers

It is understood by GRC Consultants that safety showers will be placed above all exit doors in processing areas. The exact placement, reasons for and method of operation of these showers are unclear at the present time. More information is required before detailed comment is made.

It may be noted that any showers not specifically required for safety or other reasons should be removed. Unnecessary showers may drip, causing possible contamination problems and also producing a potentially hazardous wet area.

6.4.4 Heating, Ventilation and Air Conditioning (HVAC)

The MPU is situated adjacent to the IDB production unit in the same building. The IDB unit is known to emit certain organic vapours. The inlet to the HVAC must be situated well away from the source of these emissions. An activated carbon filter has been specified on the inlet of the HVAC system but

the capacity and efficiency of this filter is unknown. The extent of the possible intake of emissions from another plant must be assessed and quantified on site.

The specification of individual room quality classification, including recommended air changes, will be performed as part of the front end design. The capacities, extract positions, filter positions and filter efficiencies of the HVAC system can then be reviewed and comments made as appropriate.

6.4.5 Other Services

Various services are shared between the MPU Downstream Processing area and the rest of the Alkaloida site. This in itself is not objectionable provided that common services which may affect product quality have adequate protection from contamination originating elsewhere on the site and the quality is assured by regular Quality Control testing.

There is no indication of a central breathing air system for use with breathing hoods or suits. It should be noted that breathing apparatus may be required for protection from toxins or asphyxiation. Particular areas of concern include the manual handling of solvent wet cake, e.g as cake is manually removed from a centrifuge.

The types and quality of water available and the positioning of offtakes need clarifying.

6.5 PREMISES

The glass explosion relief panels in the process areas have gaps between the glass panels. Special care must be taken to minimise these gaps using an inert sealant. This must be done to minimise contaminant traps and also minimise ingress of outside environmental contamination.

Opening windows are present. These must be permanently sealed closed and preferably replaced with a simpler design which is easier to clean and does not contain unnecessary ledges.

6.6 LAYOUT

6.6.1 General

The overall layout, materials and personnel flows are reasonably linear which gives an acceptable first impression.

It is assumed that negligible raw materials, apart from packing and laboratory materials, will be used on the ground floor. It is therefore, as the design in Alkaloida Drg. T3523 shows, not necessary to have a separate raw material weighing area.

The milling and blending operations occur in the same room. Ideally these will be located in separate areas but this arrangement should be acceptable when operating on a single product. Consideration should be given to the use of air flow to minimise particulates from the milling operating settling on the blending equipment and vice versa.

The wash-up room appears small and does not appear to have a segregated drying area, to protect clean items from possible contaminating aerosols.

The use of interlocked pass through hatches should be considered for the passing of material into the plant and products out of the plant. The use of hatches can reduce contamination and physically prevent unauthorised personnel movement but may mean additional emergency exits are required.

From Alkaloida Drg. T3523 it appears that above the goods in and goods out doors there is no covering to prevent accidental contamination, by rain, etc, of goods moving between lorries and the building.

It is assumed that all product entering the ground floor downstream processing area will do so via a single line and there will be no transport of materials in containers from the upper floor via the lift or stairs.

There is no specific rejected raw material store. However the use of a segregated area and an efficient labelling system will probably be sufficient to accommodate this requirement.

There appear to be no internal windows in the proposed layout. Wherever practical, good quality, ledge free internal windows should be used for reasons of safety and operator comfort.

6.6.2 Changing Areas

The general scheme for changing to enter the process area, as suggested by the existing proposed change room layout, is as follows:-

The process worker enters the building in his street clothes and enters the Primary Change via the building lobby and air lock. In the Primary Change area he changes into his work wear and proceeds to the Ingoing Clean Change area. He changes into a coverall suit and steps over the clean bench and the passes into the process area via an air lock.

The process worker exits the process area via an air lock into the outgoing change area where he removes his suit and coverall. He then goes through to the primary change area where he changes out of his work wear into his street wear, and exits the building via the air lock and lobby.

The above changing regime requires a fresh change of overclothes each time the clean area is entered. This is normally achieved by the supply of four suits a day.

If the plant is used for the processing of one product at a time this expensive changing regime will probably not be necessary and a simpler operation may be used.

GRC Consultants believes that the layout of the changing rooms and associated facilities requires further development which will show significant changes to the current design. However, it is unlikely the rooms surrounding the changing room area will be affected significantly by this design development.

The outgoing change area contains a shower which is open to the general change area. To prevent the dispersal of shower generated aerosols into the outgoing clean change area, a solid door should be used between the shower room and changing area.

Air extraction in the shower and WC should be used to produce a negative pressure with respect to the outgoing change area.

6.6.3 Product Sampling

A plan of the proposed ground floor layout is given as drawing 92/005/102 included in this report.

GRC Consultants understands that only an authorised member of the quality control staff can take the final sample of the finished bulk pharmaceutical chemical. It is further understood that the member of QC staff will enter the building via the cleared finish products store and take the sample in the product sampling room. This person will then exit the way he came in through the cleared finished products room.

For a product to be sampled in the product sampling room, the product itself must for a time be exposed to air in an open container. It is the opinion of GRC Consultants that the product sampling room must therefore be considered part of the clean area of this facility. No person, whether QC or production, may enter any part of the clean area without adhering to a strict changing protocol similar to that used by production staff.

The direct exposure of product to a member of QC staff wearing outdoor clothes and possibly using sampling tools carried here from elsewhere is not consistent with GMP. This person would not only be a source of personal and environmental contamination, but also of contamination from any other product he has sampled since his last clothing change.

The sampling requirements, company sampling protocols, design of the product store rooms and the method of entry of QC staff into the building need further detailed discussion.

All the points raised in the foregoing sections have been discussed with Alkaloida and results of the discussions are incorporated in the Front End Design Study for the SSMPU.

SECTION 7

EC REGULATIONS AND THE SSMPU

7 EC REGULATIONS AND THE SSMPU

In this section, the EC Regulations for Quality Assurance in the manufacture of medicinal products are applied to the concept of the SSMPU and comments are on the relevance, or otherwise, of the various Regulations to the SSMPU. A copy of the EC Regulations is included at the end of this section and the headings in italics used below are those used in the Regulations.

1. Quality Management

These clauses concern:-

- Quality Assurance (QA)
- Good Manufacturing Practice (GMP)
- Quality Control (QC)

in a very general way and apply primarily to the organisation and management of the QC Department. Hence they do not apply strictly to the design and operation of the SSMPU.

2. Personnel

These clauses concern:-

- General Matters
- Key Personnel
- Training
- Personal Hygiene

and all of the clauses apply to the SSMPU except for:

2.10 Special Hazards
2.20 Sterile Preparations

3. Premises and Equipment

These are the key clauses which apply to the SSMPU and all of them apply except clauses 3.26 to 3.29 inclusive, since these concern primarily the Quality Control Laboratories, etc, which are not an integral part of the SSMPU.

Clause 3.30 does not apply since it concerns rest and refreshment rooms (not part of the SSMPU).

Clause 3.33, Animal Houses, clearly does not apply to the SSMPU.

4. Documentation

Whilst all the clauses in the whole of this section are valid, they do not relate, as such, to the technical/engineering design of the SSMPU and relate essentially to the responsibility of Production Management.

5. Production

As with the previous section, all of these clauses are relevant but not directly related to the design of the SSMPU. However, some clauses are to some extent more relevant as follows:-

5.10 Protection from microbial and other contamination
5.11 Dusts
5.14 Pipelines correctly connected
5.16 Restricted access
5.18 Cross contamination

6. Quality Control

These clauses are concerned with sampling, specifications and testing, and as such are not directly related to the technical/engineering design of the SSMPU. However, see Section 8 for a discussion of QA/QC matters.

7. Contract Manufacture and Analysis

These clauses, as such, do not apply to the SSMPU.

8. Complaints and Product Recall

These clauses refer to procedural matters and, as such, are not directly related to engineering design.

9. Self Inspection

These clauses are not directly applicable to the design of the SSMPU.

Supplementary Guidelines: Manufacture of Sterile Medicinal Products

The products from the SSMPU are not sterile, hence none of the clauses in this supplementary section apply as such to the SSMPU.

INTRODUCTION

The Pharmaceutical Industry in EEC Member States maintains high standards of Quality Assurance in the development, manufacture and control of medicinal products. A system of Marketing Authorization issued by Member States ensures that all medicinal products are assessed by a Competent Authority to ensure compliance with the contemporary standards of safety, quality and efficacy. A system of Manufacturing Authorizations ensures that licensed products are only manufactured by licensed manufacturers, whose activities are regularly inspected by the Competent Authorities. Manufacturing Authorizations are required by all pharmaceutical manufacturers in EEC whether the products are sold in EEC or exported.

In order to further encourage the removal of barriers to trade in medicinal products and to promote uniformity in licensing decision, the Commission proposed, the Member States agreed that this EEC Guide to Good Manufacturing Practice for Medicinal Products should be prepared to provide a common, agreed basis throughout EEC for maintaining good manufacturing practices in the Pharmaceutical Industry. It will be used in assessing applications for Manufacturing Authorizations and as a basis for inspection of manufacturers of medicinal products.

This Guide explains and details the principles of Good Manufacturing Practice. These principles and more detailed guidelines are applicable to all operations which require the authorization referred to in Article 16 of Directive 75/319/EEC. They are also relevant for all other large scale pharmaceutical manufacturing processes, such as in hospitals, for the preparation of products for use in clinical trials, and for wholesaling, where applicable.

This Guide is presented in chapters, each headed by a principle. Chapter 1 on Quality Management outlines the fundamental concept of Quality Assurance as applied to the manufacture of medicinal products. Thereafter each chapter has a principle outlining the Quality Assurance objectives of that chapter and a text which provides sufficient detail for manufacturers to be made aware of the essential matters to be considered when implementing the principle. A glossary of some terms used in this Guide has been incorporated after the Introduction. The current text of Chapter IV of Directive 75/319/EEC dealing with manufacture of medicinal products in annexed at the end of the Guide.

In addition to the general matters of Good Manufacturing Practice outlined in the chapters of this first edition, supplementary guidelines on 'Sterile Products' have been incorporated. The purpose of the supplemental guidelines, and further guidelines on other subjects which will appear in the near future, is to provide detail about specific areas of activity which may not necessarily apply to all manufacturers.

This Guide is not intended to cover security aspects for the personnel engaged in manufacture; those are governed by other provisions of Community or national law.

Throughout the Guide it is assumed that the requirements of the Market Authorization relating to the safety, quality and efficacy of the products are systematically incorporated into all the manufacturing, control and release for sale arrangements of the holder of the Manufacturing Authorization.

This Guide has been written with the intention that it should replace national guidelines or other relevant GMP requirements. It is recognized that there are acceptable methods, other than those described in this Guide, which are capable of achieving the principles of the Guide. This Guide is not intended to place any restraint upon the development of new concepts or new technologies, which have been validated and provide a level of Quality Assurance at least equivalent to those set in this Guide.

This Guide will be regularly revised and updated amendments are envisaged.

GLOSSARY

Definitions given below apply to the words as used in this Guide. They may have different meanings in other contexts.

Air-Lock An enclosed space with two or more doors, and which is interposed between two or more rooms, e.g. of differing class of cleanliness, for the purpose of controlling the air-flow between those rooms when they need to be entered. An air-lock is designed for and used by either people or goods.

Batch (or Lot) A defined quantity of starting material, packaging material or product processed in one process or series of processes so that it could be expected to be homogeneous.

Note: To complete certain states of manufacture, it may be necessary to divide a batch into a number of subbatches, which are later brought together to form a final homogeneous batch. In the case of continuous manufacture, the batch must correspond to a defined fraction of the production, characterized by its intended homogeneity.

For control of the finished product, the following definition has been given in Directive 75/318/EEC: 'For the control of the finished product, a batch of a proprietary medicinal product comprises all the units of a pharmaceutical form which are made from the same initial mass of material and have undergone a single series of manufacturing operations or a single sterilization operation or, in the case of a continuous production process, all the units manufactured in a given period of time'.

Batch Number (or Lot Number) A distinctive combination of numbers and/or letters which specifically identifies a batch.

Bulk Product Any product which has completed all processing stages up to, but not including, final packaging.

Calibration The set of operations which establish, under specified conditions, the relationship between values indicated by a measuring instrument or measuring system, or values represented by a material measure, and the corresponding known values of a reference standard.

Clean Area An area with defined environmental control of particulate and microbial contamination, constructed and used in such a way as to reduce the introduction, generation and retention of contaminants within the area. Note: The different degrees of environmental control are defined in the Supplementary Guidelines for the Manufacture of sterile medicinal products.

Gross Contamination Contamination of a starting material or of a product with another material or product.

Finished Product A medicinal product which has undergone all stages of production, including packaging in its final container.

In-Process Control Checks performed during production in order to monitor and if necessary to adjust the process to ensure that the product conforms to its specification. The control of the environment or equipment may also be regarded as a part of in-process control.

Intermediate Product Partly processed material which must undergo further manufacturing steps before it becomes a bulk product.

Manufacture All operations of purchase of materials and products, Production, Quality Control, release, storage, distribution of medicinal products and the related controls.

Manufacturer Holder of a Manufacturing Authorization as described in Article 16 of Directive 75/319/EEC.

Medicinal Product Any substance or combination of substances presented for treating or preventing disease in human beings or animals.

Any substances or combination of substances which may be administered to human beings or animals with a view to making a medical diagnosis or to restoring, correcting or modifying physiological functions in human beings or in animals is likewise considered a medicinal product.

Packaging All operations, including filling and labelling, which a bulk product has to undergo in order to become a finished product.

Note: Sterile filling would not normally be regarded as part of packaging, the bulk product being the filled, but not finally packaged, primary containers.

Packaging Material Any material employed in the packaging of a medicinal product, excluding any outer packaging used for transportation or shipment. Packaging materials are referred to as primary or secondary according to whether or not they are intended to be in direct contact with the product.

Procedures Description of the operations to be carried out, the precautions to be taken and measures to be applied directly or indirectly related to the manufacture of a medicinal product.

Production All operations involved in the preparation of a medicinal product, from receipt of materials, through processing and packaging, to its completion as a finished product.

Qualification Action of proving that any equipment works correctly and actually leads to the expected results. The word *validation* is sometimes widened to incorporate the concept of qualification.

Quality Control See Chapter 1.

Quarantine The status of starting or packaging materials, intermediate, bulk or finished products isolated physically or by other effective means whilst awaiting a decision on their release or refusal.

Reconciliation A comparison, making due allowance for normal variation, between the amount of product or materials theoretically and actually produced or used.

Record See Chapter 4.

Recovery The introduction of all or part of previous batches of the required quality into another batch at a defined stage of manufacture.

Reprocessing The reworking of all or part of a batch of product of an unacceptable quality from a defined stage of production so that its quality may be rendered acceptable by one or more additional operations.

Return Sending back to the manufacturer or distributor of a medicinal product which may or may not present a quality defect.

Specification See Chapter 4.

Starting Material Any substance used in the production of a medicinal product, but excluding packaging materials.

Sterility Sterility is the absence of living organisms. The conditions of the sterility test are given in the European Pharmacopoeia.

Validation Action of proving, in accordance with the principles of Good Manufacturing Practice, that any procedure, process, equipment, material, activity or system actually leads to the expected results (see also qualification).

1 QUALITY MANAGEMENT

Principle

The holder of a Manufacturing Authorization must manufacture medicinal products so as to ensure that they are fit for their intended use, comply with the requirements of the Marketing Authorization and do not place patients at risk due to inadequate safety, quality or efficacy. The attainment of this quality objective is the responsibility of senior management and requires the participation and commitment by staff in many different departments and at all levels within the company, the company's suppliers and the distributors. To achieve the quality objective reliably there must be a comprehensively designed and correctly implemented system of Quality Assurance incorporating Good Manufacturing Practice and thus Quality Control. It should be fully documented and its effectiveness monitored. All parts of the Quality Assurance system should be adequately resourced with competent personnel, and suitable and sufficient premises, equipment and facilities. There are additional legal responsibilities for the holder of the Manufacturing Authorization and for the Qualified Person(s).

1.1 The basic concepts of Quality Assurance, Good Manufacturing Practice and Quality Control are inter-related. They are described here in order to emphasize their relationships and their fundamental importance to the production and control of medicinal products.

Quality Assurance

1.2 Quality Assurance is a wide ranging concept which covers all matters which individually or collectively influence the quality of a product. It is the sum total of the organized arrangements made with the object of ensuring that medicinal products are of the quality required for their intended use. Quality Assurance therefore incorporates Good Manufacturing Practice plus other factors outside the scope of this Guide.

The system of Quality Assurance appropriate for the manufacture of medicinal products should ensure that:

i medicinal products are designed and developed in a way that takes account of the requirements of Good Manufacturing Practice and Good Laboratory Practice;

ii production and control operations are clearly specified and Good Manufacturing Practice adopted;

iii managerial responsibilities are clearly specified;

iv arrangements are made for the manufacture, supply and use of the correct starting and packaging materials;

v all necessary controls on intermediate products, and any other in-process controls and validations are carried out;

vi the finished product is correctly processed and checked, according to the defined procedures;

vii medicinal products are not sold or supplied before a Qualified Person has certified that each production batch has been processed and controlled in accordance with the requirements of the Marketing Authorization and any other regulations relevant to the production, control and release of medicinal products;

viii satisfactory arrangements exist to ensure, as far as possible, that the medicinal products are stored, distributed and subsequently handled so that quality is maintained throughout their shelf life;

ix there is a procedure for Self-Inspection and/or quality audit which regularly appraises the effectiveness an applicability of the Quality Assurance system.

Good Manufacturing Practice for Medicinal Products (GMP)

1.3 Good Manufacturing Practice is that part of Quality Assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the Marketing Authorization.

Good Manufacturing Practice is concerned with both production and quality control. The basic requirements of GMP are that:

i all manufacturing processes are clearly defined, systematically reviewed in the light of experience and shown to be capable of consistently manufacturing medicinal products of the required quality and complying with their specifications;

ii critical steps of manufacturing processes and significant changes to the process are validated;

iii all necessary facilities for GMP are provided including:

a. appropriately qualified and trained personnel;

b. adequate premises and space;

c. suitable equipment and services;

d. correct materials, containers and labels;

e. approved procedures and instructions;

f. suitable storage and transport;

iv instructions and procedures are written in an instructional form in clear and unambiguous language, specifically applicable to the facilities provided;

v operators are trained to carry out procedures correctly;

vi records are made, manually and/or by recording instruments, during manufacture which demonstrate that all the steps required by the defined procedures and instructions were in fact taken and that the quantity and quality of the product was as expected. Any significant deviations are fully recorded and investigated;

vii records of manufacture including distribution which enable the complete history of a batch to be traced, are retained in a comprehensible and accessible form;

viii the distribution (wholesaling) of the products minimizes any risk to their quality;

ix a system is available to recall any batch or product, from sale or supply;

x complaints about marketed products are examined, the causes of quality defects investigated and appropriate measures taken in respect to the defective products and to prevent reoccurrence.

QUALITY CONTROL

1.4 Quality Control is that part of Good Manufacturing Practice which is concerned with sampling, specifications and testing, and with the organization, documentation and release procedures which ensure that the necessary and relevant tests are actually carried out and that materials are not released for use, nor products released for sale or supply, until their quality has been judged to be satisfactory.

The basic requirements of Quality Control are that:

i adequate facilities, trained personnel and approved procedures are available for sampling, inspecting and testing starting materials, packaging materials, intermediate, bulk, and finished products, and where appropriate for monitoring environmental conditions for GMP purposes;

ii samples of starting materials, packaging materials, intermediate products, bulk products and finished products are taken by personnel and by methods approved by Quality Control;

iii test methods are validated;

iv records are made, manually and/or by recording instruments which demonstrate that all the required sampling, inspecting and testing procedures were actually carried out. Any deviations are fully recorded and investigated;

v the finished products contain active ingredients complying with the qualitative and quantitative composition of the Marketing Authorization, is of the purity required, and is enclosed within its proper container and correctly labelled;

vi records are made of the results of inspection and that testing of materials, intermediate, bulk, and finished products is formally assessed against specification. Product assessment includes a review and evaluation of relevant production documentation and an assessment of deviations from specified procedures;

vii sufficient reference samples of starting materials and products are retained to permit future examination of the product if necessary and that the product is retained in its final pack unless exceptionally large packs are produced.

2 PERSONNEL

Principle

The establishment and maintenance of a satisfactory system of quality assurance and the correct manufacture of medicines relies upon people. For this reason there must be sufficient qualified personnel to carry out all the tasks which are the responsibility of the manufacturer. Individual responsibilities should be clearly understood by the individuals and recorded. All personnel should be aware of the principles of Good Manufacturing Practice that affect them and receive initial and continuing training, including hygiene instructions, relevant to their needs.

General

2.1 The manufacturer should have an adequate number of personnel with the necessary qualifications and practical experience. The responsibilities placed on any one individual should not be so extensive as to present any risk to quality.

2.2 The manufacturer must have an organization chart. People in responsible situations should have specific duties recorded in written job descriptions and adequate authority to carry out their responsibilities. Their duties may be delegated to designated deputies of a satisfactory qualification level. There should be no gaps or unexplained overlaps in the responsibilities of those personnel concerned with application of Good Manufacturing Practice.

Key Personnel

2.3 Key Personnel includes the head of Production, the head of Quality Control, and if at least one of these persons is not responsible for the duties described in Article 22 of Directive 75/319/EEC, the Qualified Person(s) designated for the purpose. Normally key posts should be occupied by full-time personnel. The heads of Production and Quality Control must be independent from each other. In large organizations, it may be necessary to delegate some of the functions listed in 2.5, 2.6 and 2.7.

2.4 The duties of the Qualified Person(s) are fully described in Article 22 of Directive 75/319/EEC, and can be summarized as follows:

(a) for medicinal products manufactured within the European Community, a Qualified Person must ensure that each batch has been produced and tested/checked in accordance with the directives and the marketing authorization (*);

(b) for medicinal products manufactured outside the European Community, a Qualified Person must ensure that each imported batch has undergone, in the importing country, the testing specified in paragraph 1 (b) of Article 22;

(c) a Qualified Person must certify in a register or equivalent document, as operations are carried out and before any release that each production batch satisfies the provisions of Article 22.

The persons responsible for these duties must meet the qualification requirements laid down in Article 23 of the same Directive, they shall be permanently and continuously at the disposal of the holder of the Manufacturing Authorization to carry out their responsibilities. Their responsibilities may be delegated, but only to other Qualified Person(s).

2.5 The head of the Production Department generally has the following responsibilities:

i to ensure that products are processed and stored according to the appropriate documentation in order to obtain the required quality;

ii to approve the instructions relating to production operations and to ensure their strict implementation;

iii to ensure that the production records are evaluated and signed by an authorized person before they are sent to the Quality Control Department;

iv to check the maintenance of his department, premises and equipment;

v to ensure that the appropriate validations are done;

vi to ensure that the required initial and continuing training of his department personnel is carried out and adapted according to need.

2.6 The head of the Quality Control Department generally has the following responsibilities:

i to approve or reject, as he sees fit, starting materials, packaging materials, and intermediate, bulk and finished products;

ii to evaluate batch records;

iii to ensure that all necessary testing is carried out;

iv to approve specifications, sampling instructions, test methods and other Quality Control procedures;

(*) According to Directive 75/319/EEC and the Ruling (Case 247/81) of the Court of Justice of the European Communities, medicinal products which have been properly controlled in the EEC by a Qualified Person must not be recontrolled or rechecked in any other Member State of the Community.

v to approve and monitor the contract analysts;

vi to check the maintenance of his department, premises and equipment;

vii to ensure that the appropriate validations are done;

viii to ensure that the required initial and continuing training of his department personnel is carried out and adapted according to need.

Other duties of the Quality Control Department are summarized in Chapter 6.

2.7 The heads of Production and Quality Control generally have some shared, or jointly exercised, responsibilities relating to quality. These may include, with respect to national regulations:

- the authorization of written procedures and other documents, including amendments;
- the monitoring and control of the manufacturing environment;
- plant hygiene;
- process validation;
- training;
- the approval and monitoring of suppliers of materials;
- the approval and monitoring of contract manufacturers;
- the designation and monitoring of storage conditions for materials and products;
- the retention of records;
- the monitoring of compliance with the requirements of Good Manufacturing Practice;
- The inspection, investigation, and taking of samples, in order to monitor factors which may affect product quality.

Training

2.8 The manufacturer should provide training for all the personnel whose duties take them into production areas or into control laboratories (including the technical, maintenance and cleaning personnel), and for other personnel whose activities could affect the quality of the product.

2.9 Besides the basic training on the theory and practice of Good Manufacturing Practice, newly recruited personnel should receive training appropriate to the duties assigned to them. Continuing training should also be given, and its practical effectiveness should be periodically assessed. Training programs should be available, approved by either the head of Production or the head of Quality Control, as appropriate. Training records should be kept.

2.10 Personnel working in areas where contamination is a hazard, e.g. clean areas or areas where highly active, toxic, infectious or sensitizing materials are handled, should be given specific training.

2.11 Visitors or untrained personnel should, preferably, not be taken into the production and quality control areas. If this is unavoidable, they should be given information in advance, particularly about personal hygiene and the prescribed protective clothing. They should be closely supervised.

2.12 The concept of Quality Assurance and all the measures capable of improving its understanding and implementation should be fully discussed during the training sessions.

Personnel Hygiene

2.13 Detailed hygiene programmes should be established and adapted to the different needs within the factory. They should include procedures relating to the health, hygiene practices and clothing of personnel. These procedures should be understood and followed in a very strict way by every person whose duties take him into the production are control areas. Hygiene programmes should be promoted by management and widely discussed during training sessions.

2.14 Steps should be taken to ensure as far as is practicable that no person affected by an infectious disease or having open lesions on the exposed surface of the body is engaged in the manufacture of pharmaceutical products.

2.15 All personnel should receive medical examination upon recruitment. It must be the manufacturer's responsibility that there are instructions ensuring that health conditions that can be of importance come to its knowledge. After the first medical examination, examinations should be carried out when necessary for the work and personal health.

2.16 Every person entering the manufacturing areas should wear protective garments appropriate to the operations to be carried out.

2.17 Eating, drinking, chewing or smoking, or the storage of food, drink, smoking materials or personal medication in the production and storage areas should be prohibited. In general, any unhygienic practice within the manufacturing areas or in any other area where the product might be adversely affected, should be forbidden.

2.18 Direct contact should be avoided between the operator's hands and the exposed product as well as with any part of the equipment that comes into contact with the products.

2.19 Personnel should be instructed to use the hand-washing facilities.

2.20 Any specific requirements for the manufacture of special groups of products, for example sterile preparations, are covered in the Supplementary Guidelines.

3 PREMISES AND EQUIPMENT

PRINCIPLE

Premises and equipment must be located, designed, constructed, adapted and maintained to suite the operations to be carried out. Their layout and design must aim to minimize the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination, build up of dust or dirt and, in general, any adverse effect on the quality of products.

PREMISES

General

3.1 Premises should be situated in an environment which, when considered together with measures to protect the manufacture, presents minimal risk of causing contamination of materials or products.

3.2 Premises should be carefully maintained, ensuring that repair and maintenance operations do not present any hazard to the quality of products. They should be cleaned and, where applicable, disinfected according to detailed written procedures.

3.3 Lighting, temperature, humidity and ventilation should be appropriate and such that they do not adversely affect, directly or indirectly, either the medicinal products during their manufacture and storage, or the accurate functioning of equipment.

3.4 Premises should be designed and equipped so as to afford maximum protection against the entry of insects or other animals.

3.5 Steps should be taken in order to prevent unauthorized people from coming in. Production, storage and quality control areas should not be used as a right of way be personnel who do not work in them.

Production Area

3.6 In order to minimize the risk of a serious medical hazard due to cross-contamination, dedicated and self contained facilities must be available for the production of particular drugs, such as highly sensitizing materials (e.g. penicillins) or biological preparations (e.g. from live micro-organisms). The production of certain additional products, such as certain highly active drugs and non-medical products should not be conducted in the same facilities. For those products, in exceptional cases, the principle of campaign working in the same facilities can be accepted provided that specific precautions are taken and the necessary validations are made. The manufacture of technical poisons, such as pesticides and herbicides, should not be allowed in premises used for the manufacture of medicinal products.

3.7 Premises should preferably be laid out in such a way as to allow the production to take place in areas connected in a logical order corresponding to the sequence of the operations and to the requisite cleanliness levels.

3.8 The adequacy of the working and in-process storage space should permit the orderly and logical positioning of equipment and materials so as to minimize the risk of confusion between different medicinal products or their components, to avoid cross-contamination and to minimize the risk of omission or wrong application of any of the manufacturing or control steps.

3.9 Where starting and primary packaging materials, intermediate or bulk products are exposed to the environment,interior surfaces (walls, floors and ceilings) should be smooth, free from cracks and open joints, and should not shed particulate matter and should permit easy and effective cleaning and, if necessary, disinfection.

3.10 Pipe work, light fittings, ventilation points and other services should be designed and sited to avoid the creation of recesses which are difficult to clean. As far as possible, for maintenance purposes, they should be accessible from outside the manufacturing areas.

3.11 Drains should be of adequate size, and have trapped gullies. Open channels should be avoided where possible, but if necessary, they should be shallow to facilitate cleaning and disinfection.

3.12 Production areas should be effectively ventilated, with air control facilities (including temperature and, where necessary, humidity and filtration) appropriate both to the products handled, to the operations undertaken within them and to the external environment.

3.13 Weighing of starting materials usually should be carried out in a separate weighing room designed for that use.

3.14 In cases where dust is generated (e.g. during sampling, weighing, mixing and processing operations, packaging of dry products) specific provisions should be taken to avoid cross-contamination and facilities cleaning.

3.15 Premises for the packaging of medicinal products should be specifically designed and laid out so as to avoid mix-ups or cross-contamination.

3.16 Production areas should be well lit, particularly where visual on-line controls are carried out.

3.17 In-process controls may be done within the production area provided they do not carry any risk for the production.

Storage Areas

3.18 Storage areas should be of sufficient capacity to allow orderly storage of the various categories of materials and products: starting and packaging materials, intermediate, bulk and finished products, products in quarantine, released, rejected, returned or recalled.

3.19 Storage areas should be designed or adapted to ensure good storage conditions. In particular, they should be clean and dry and maintained within acceptable temperature limits. Where special storage conditions are required (e.g. temperature, humidity) these should be provided, checked and monitored.

3.20 Receiving and dispatch bays should protect materials and products from the weather. Reception areas should be designed and equipped to allow containers of incoming materials to be cleaned where necessary before storage.

3.21 Where quarantine status is ensured by storage in separate areas, these areas must be clearly marked and their access restricted to authorized personnel. Any system replacing the physical quarantine should give equivalent security.

3.22 There should normally be a separate sampling area for starting materials. If sampling is performed in the storage area, it should be conducted in such a way as to prevent contamination or cross-contamination.

3.23 Segregated areas should be provided for the storage of rejected, recalled or returned materials or products.

3.24 Highly active materials or products should be stored in safe and secure areas.

3.25 Printed packaging materials are considered critical to the conformity of the medicinal product and special attention should be paid to the safe and secure storage of these materials.

Quality Control Areas

3.26 Normally, Quality Control laboratories should be separated from production areas. This is particularly important for laboratories for the control of biologicals, microbiologicals and radioisotopes, which should also be separated from each other.

3.27 Control laboratories should be designed to suit the operations to be carried out in them. Sufficient space should be given to avoid mix-ups and cross-contamination. There should be adequate suitable storage space for samples and records.

3.28 Separate rooms may be necessary to protect sensitive instruments from vibration, electrical interference, humidity, etc.

3.29 Special requirements are needed in laboratories handling particular substances, such as biological or radioactive samples.

Ancillary Areas

3.30 Rest and refreshment rooms should be separate from other areas.

3.31 Facilities for changing clothes, and for washing and toilet purposes should be easily accessible and appropriate for the number of users. Toilets should not directly communicate with production or storage areas.

3.32 Maintenance workshops should be as far as possible be separated from production areas. Whenever parts and tools are stored in the production area, they should be kept in rooms or lockers reserved for that use.

3.33 Animal houses should be well isolated from other areas, with separate entrance (animal access) and air handling facilities.

Equipment

3.34 Manufacturing equipment should be designated, located and maintained to suit its intended purpose.

3.35 Repair and maintenance operations should not present any hazard to the quality of the products.

3.36 Manufacturing equipment should be designed so that it can be easily and thoroughly cleaned. It should be cleaned according to detailed and written procedures and stored only in a clean and dry condition.

3.37 Washing and cleaning equipment should be chosen and used in order not to be a source of contamination.

3.38 Equipment should be installed in such a way as to prevent any risk of error or of contamination.

3.39 Production equipment should not present any hazard to the products. The part of the production equipment that come into contact with the product must not be reactive, additive or absorptive to such an extent that it will affect the quality of the product and thus present any hazard.

3.40 Balances and measuring equipment of an appropriate range and precision should be available for production and control operations.

3.41 Measuring, weighing, recording and control equipment should be calibrated and checked at defined intervals by appropriate methods. Adequate records of such tests should be maintained.

3.42 Fixed pipe work should be clearly labelled to indicate the contents and, where applicable, the direction of flow.

3.43 Distilled, deionized, and where applicable, other water pipes should be sanitized according to written procedures that detail the action limited for microbiological contamination and the measures to be taken.

3.44 Defective equipment should, if possible, be removed from production and quality control areas, or at least be clearly labelled as defective.

4 DOCUMENTATION

Principle

Good documentation constitutes an essential part of the quality assurance system. Clearly written documentation prevents errors from spoken communication and permits tracing of batch history. Specifications, Manufacturing Formulae and Instructions, procedures, and records must be free from errors and available in writing. The legibility of documents is of primordial importance.

General

4.1 *Specifications* describe in detail the requirements with which the products or materials used or obtained during manufacture have to conform. They serve as a basis for quality evaluation.

Manufacturing Formulae, Processing and Packaging Instructions state all the starting materials used and lay down all processing and packaging operations.

Procedures give directions for performing certain operations like cleaning, clothing, environmental control, sampling, testing equipment operations.

Records provide a history of each batch of product, including its distribution, and also of all other relevant circumstances pertinent for the quality of the final product.

4.2 Documents should be designed, prepared, reviewed and distributed with care. They should comply with the relevant parts of the manufacturing and marketing authorization dossiers.

4.3 Documents should be approved, signed and dated by appropriate and authorized persons.

4.4 Documents should have unambiguous contents; title, nature and purpose should be clearly stated. They should be laid out in an orderly fashion and be easy to check. Reproduced documents should be clear and legible. The reproduction of working documents from master documents must not allow any error to be introduced through the reproduction process.

4.5 Documents should be regularly reviewed and kept up-to-date. When a document has been revised, systems should be operated to prevent inadvertent use of superseded documents.

4.6 Documents should not be handwritten; although, where documents require the entry of data, these entries may be made in clear, legible indelible handwriting. Sufficient space should be provided for such entries.

4.7 Any alteration made to the entry on a document should be signed and dated; the alteration should permit the reading of the original information. Where appropriate, the reason for the alteration should be recorded.

4.8 The records should be made or completed at the time each action is taken and in such a way that all significant activities concerning the manufacture of medicinal products are traceable. They should be retained for at least one year after the expiry date of the finished product.

4.9 Data may be recorded by electronic data processing systems, photographic or other reliable means, but detailed procedures relating to the system in use should be available and the accuracy of the records should be checked. If documentation is handled by electronic data processing methods, only authorized persons should be able to enter or modify data in the computer and there should be a record of changes and deletions; access should be restricted by passwords or other means and the result of entry of critical data should be independently checked. Batch records electronically stored should be protected by back-up transfer on magnetic tape, microfilm, paper or other means. It is particularly important that, during the period of retention, the data are readily available.

Documents Required

4.10 Specifications

There should be appropriately authorized and dated specifications for starting and packaging materials, and finished products; where appropriate, they should be also available for intermediate or bulk products.

Specifications for starting and packaging materials

4.11 Specifications for starting and primary or printed packaging materials should include, if applicable:

a) a description of the materials, including:
   - the designated name and the internal code reference;
   - the reference, if any, to a pharmacopoeial monograph;
   - the approved suppliers and, if possible, the original producer of the products.
   - a specimen of printed materials;

b) directions for sampling and testing or reference to procedures;

c) qualitative and quantitative requirements with acceptance limits;

d) storage conditions and precautions;

e) the maximum period of storage before re-examination.

Specifications for intermediate and bulk products

4.12 Specifications for intermediate and bulk products should be available if these are purchased or dispatched, or if data obtained from intermediate products are used for the evaluation of the finished product. The specifications should be similar to specifications for starting materials or for finished products, as appropriate.

Specifications for finished products

4.13 Specifications for finished products should include:

a) the designated name of the product and the code reference where applicable;

b) the formula or a reference to;

c) a description of the pharmaceutical form and package details;

d) directions for sampling and testing or a reference to procedures;

e) the qualitative and quantitative requirements, with the acceptance limits;

f) the storage conditions and precautions, where applicable;

g) the shelf-life.

Manufacturing Formula and Processing Instructions

Formally authorized Manufacturing Formula and Processing Instructions should exist for each product and batch size to be manufactured. They are often combined in one document.

4.14 The Manufacturing Formula should include:

a) the name of the product, with a product reference code relating to its specification;

b) a description of the pharmaceutical form, strength of the product and batch size;

c) a list of all starting materials to be used, with the amount of each, described using the designated name and a reference which is unique to that material; mention should be made of any substance that may disappear in the course of processing;

d) a statement of the expected final yield with the acceptable limits, and of relevant intermediate yields, where applicable.

4.15 The Processing Instructions should include:

a) a statement of the processing location and the principal equipment to be used;

b) the methods, or reference to the methods, to be used for preparing the critical equipment (e.g. cleaning,assembling, calibrating, sterilizing);

c) detailed stepwise processing instructions (e.g. checks on materials, pretreatments, sequence for adding materials, mixing times, temperatures);

d) the instructions for any in-process controls with their limits;

e) where necessary, the requirements for bulk storage of the products; including the container, labelling and special storage conditions where applicable;

f) any special precautions to be observed.

Packaging Instructions

4.16 There should be formally authorized Packaging Instructions for each product for pack size and type. These normally include, or have a reference to, the following:

a) name of the product;

b) description of its pharmaceutical form, and strength where applicable;

c) the pack size expressed in terms of the number, weight or volume of the product in the final container;

d) a complete list of all the packaging materials required for a standard batch size, including quantities,sizes and types, with the code or reference number relating to the specifications of each packaging material;

e) where appropriate, an example or reproduction of the relevant printed packaging materials, and specimens indicating where to apply batch number references, and shelf life of the product;

f) special precautions to be observed, including a careful examination of the area and equipment in order to ascertain the line clearance before operations begin;

g) a description of the packaging operation,including any significant subsidiary operations, and equipment to be used;

h) details of in-process controls with instructions for sampling and acceptance limits.

Batch Processing Records

4.17 A Batch Processing Record should be kept for each batch processed. It should be based on the relevant parts of the currently approved Manufacturing Formula and Processing Instructions. The method of preparation of such records should be designed to avoid transcription errors. The record should carry the number of the batch being manufactured.

Before any processing begins, there should be recorded checks that the equipment and work station are clear of previous products, documents of materials not required for the planned process, and that equipment is clean and suitable for use.

During processing, the following information should be recorded at the time each action is taken and, after completion, the record should be dated and signed in agreement by the person responsible for the processing operations:

a) the name of the product;

b) dates and times of commencement, of significant intermediate stages and of completion of production;

c) name of the person responsible for each stage of production;

d) initials of the operator of different significant steps of production and, where appropriate, of the person who checked each of these operations (e.g. weighing);

e) the batch number and/or analytical control number as well as the quantities of each starting material actually weighed (including the batch number and amount of any recovered or reprocessing material added);

f) any relevant processing operation or event and major equipment used;

g) a record of the in-process controls and the initials of the person(s) carrying them out, and the results obtained;

h) the amount of product obtained at different and pertinent stages of manufacture (yield);

i) notes on special problems including details, with signed authorization, for any deviation from the Manufacturing Formula and Processing Instructions.

Batch Packaging Records

4.18 A batch Packaging Record should be kept for each batch or part batch processed. It should be based on the relevant parts of the Packaging Instructions and the method of preparation of such records should be designed to avoid transcription errors. The record should carry the batch number and the quantity of bulk product to be packed, as well as the batch number and the planned quantity of finished product that will be obtained.

Before any packaging operation begins, there should be recorded checks that the equipment and work station are clear of previous products, documents or materials not required for the planned packaging operations, and that equipment is clean and suitable for use.

The following information should be entered at the time each action is taken, and after completion, the record should be dated and signed in agreement by the person(s) responsible for the packaging operations:

a) the name of the product;

b) the date(s) and times of the packaging operations;

c) the name of the responsible person carrying out the packaging operation;

d) the initials of the operators of the different significant steps;

e) records of checks for identity and conformity with the packaging instructions including the results of in-process controls;

f) details of the packaging operations carried out, including references to equipment and the packaging lines used;

g) whenever possible, samples of printed packaging materials used, including specimens of the batch coding, expiry dating and any additional overprinting;

h) notes on any special problems including details for any deviation from the Packaging Instructions with written authorization by an appropriate person.

i) the quantities and reference number or identification of all printed packaging materials and bulk product issued, used, destroyed or returned to stock and the quantities of obtained product, in order to provide for an adequate reconciliation.

Procedures and Records

Receipt

4.19 There should be written procedures and records for the receipt of each delivery of each starting and primary and printed packaging material.

4.20 The records of the receipts should include:

a) the name of the material on the delivery note and the containers;

b) the "in-house" name and/or code of material (if different from a);

c) date of receipt;

d) supplier's name and, if possible, manufacturer's name;

e) manufacturer's batch or reference number;

f) total quantity, and number of containers received;

g) the batch number assigned after receipt;

h) any relevant comment (e.g. state of the containers).

4.21 There should be written procedures for the internal labelling, quarantine and storage of starting materials, packaging materials and other materials, as appropriate.

Sampling

4.22 There should be written procedures for sampling, which include the person(s) authorized to take samples, the methods and equipment to be used, the amounts to be taken and any precautions to be observed to avoid contamination of the material or any deterioration in its quality (see 6.13).

Testing

4.23 There should be written procedures for testing materials and products at different stages of manufacture, describing the methods and equipment to be used. The tests performed should be recorded (see 6.17).

Other

4.24 Written release and rejection procedures should be available for materials and products, and in particular for the release for sale of the finished product by the qualified person(s) in accordance with the requirements of Article 22 of Direction 75/319/EEC.

4.25 Records should be maintained of the distribution of each batch of a product in order to facilitate the recall of the batch if necessary (see Chapter 8).

4.26 There should be written procedures and the associated records of actions taken or conclusions reached, where appropriate, for:

- validation;
- equipment assembly and calibration;
- maintenance, cleaning and sanitation;
- personnel matters including training, clothing, hygiene;
- environmental monitoring;
- pest control;
- complaints;
- recalls;
- returns.

4.27 Clear operating directions should be available for major items of manufacturing and test equipment.

4.28 Major or critical equipment should be accompanied by log books recording, as appropriate, any validations, calibrations, maintenance, cleaning or repair operations, including the dates and identity of people who carried these operations out.

4.29 The use of major or critical equipment and the areas where the products have been processed should be appropriately recorded in chronological order.

5 PRODUCTION

Principle

Production operations must follow clearly defined procedures; they must comply with the principles of Good Manufacturing Practice in order to obtain products of the requisite quality and in accordance with their manufacturing and marketing authorization.

General

5.1 Production should be performed and supervised by competent people.

5.2 All handling of materials and products, such as receipt and quarantine, sampling, storage, labelling, dispensing, processing, packaging and distribution should be done in accordance with written procedures or instructions and, where necessary, recorded.

5.3 All incoming materials should be checked to ensure that the consignment corresponds to the order. Containers should be cleaned where necessary and labelled with the prescribed data.

5.4 Damage to containers and any other problem which might adversely affect the quality of a material should be investigated, recorded and reported to the Quality Control Department.

5.5 Incoming materials and finished products should be physically or administratively quarantined immediately after receipt or processing, until they have been released for use or distribution.

5.6 Intermediate and bulk products as such should be handled on receipt as though they were starting materials.

5.7 All materials and products should be stored under the appropriate conditions established by the manufacturer and in an orderly fashion to permit batch segregation and stock rotation.

5.8 Checks on yields, and reconciliation of quantities, should be carried out as necessary to ensure that there are no discrepancies outside acceptable limits.

5.9 Operations on different products should not be carried out simultaneously or consecutively in the same room unless there is no risk of mix-up or cross-contamination.

5.10 At every stage of processing, products and materials should be protected from microbial and other contamination.

5.11 When working with dry materials and products, special precautions should be taken to prevent the generation and dissemination of dust. This applies particularly to the handling of highly active or sensitizing materials.

5.12 At all times during processing, all materials, bulk containers, major items of equipment and where appropriate rooms used should be labelled or otherwise identified with an indication of the product or material being processed, its strength (where applicable) and batch number. Where applicable, this indication should also mention the stage of production.

5.13 Labels applied to container, equipment or premises should be clear, unambiguous and in the company's agreed format. It is often helpful in addition to the wording on the labels or use colors to indicate status (for example, quarantined, accepted, rejected, clean.....)

5.14 Checks should be carried out to ensure that pipelines and other pieces of equipment used for the transportation of some products from one area to another are connected in a correct manner.

5.15 Any deviation from instructions or procedures should be avoided as far as possible. If deviations occur,they should be approved in writing by a competent person, with the involvement of the Quality Control Department when appropriate.

5.16 Access to production premises should be restricted to authorized personnel.

5.17 Normally, the production of non-medicinal products should be avoided in areas and with the equipment destined for the production of medicinal products.

Prevention of cross-contamination

5.18 Contamination of a starting material or of a product by another material or product has to be avoided. This risk of accidental cross-contamination arises from the uncontrolled release of dust, grease, vapors, sprays or organisms from materials and products in process, from residues in equipment, and from operator's clothing. The significance of this risk varies with the type of contaminant and of product being contaminated. Among the most hazardous contaminants are highly sensitizing materials, biological preparations such as living organisms, some hormones, cytotoxics, and other highly active materials. Products in which contamination is likely to be most significant are those administered by injection, those given in large doses and/or a long time.

5.19 Cross-contamination should be avoided by appropriate technical or organizational measures, for example:

a) production in segregated areas (required such as penicillins, live vaccines, live bacterial preparations and some other biologicals), or by campaign (separation in time) followed by appropriate cleaning;

b) providing appropriate air-locks and air extraction;

c) minimizing the risk of contamination caused by recirculation or re-entry of untreated or insufficiently treated air;

d) keeping protective clothing inside areas where products with special risk of cross-contamination are processed;

e) using cleaning and decontamination procedures of known effectiveness, as ineffective cleaning of equipment is a common source of cross-contamination;

f) using "closed systems" of production;

g) testing for residues and use of cleaning status labels on equipment.

5.20 Measures to prevent cross-contamination and their effectiveness should be checked periodically according to set procedures.

Validation

5.21 Validation studies should reinforce Good Manufacturing Practice and be conducted in accordance with defined procedures. Result and conclusions should be recorded.

5.22 When any new manufacturing formula or method or preparation is adopted, steps should be taken to demonstrate its suitability for routine processing. The defined process, using the materials and equipment specified, should be shown to yield a product consistently of the required quality.

5.23 Significant amendments to the manufacturing process, including any change in equipment or materials, which may affect product quality and/or the reproducibility of the process should be validated.

5.24 Processes and procedures should undergo periodic critical revalidation to ensure that they remain capable of achieving the intended results.

Starting Materials

5.25 The purchase of starting materials is an important operation which should involve staff who have a particular and thorough knowledge of the suppliers.

5.26 Starting materials should only be purchased from approved suppliers named in the relevant specification and, where possible, directly from the producer. It is recommended that the specifications established by the manufacturer for the starting materials be discussed with the suppliers. It is of benefit that all aspects of the production and control of the starting material in question, including handling, labelling and packaging requirements, as well as complaints and rejection procedures are discussed with the manufacturer and the supplier.

5.27 For each delivery, the containers should be checked for integrity of package and seal and for correspondence between the delivery note and the supplier's labels.

5.28 If one material delivery is made up of different batches, each batch must be considered as separate for sampling, testing and release.

5.29 Starting materials in the storage area should be appropriately labelled (see Chapter 5, item 13). Labels should bear at least the following information:

- the designated name of the product and the internal code reference where applicable;
- a batch number given at receipt;
- where appropriate, the status of the contents (e.g. in quarantine, on test, released, rejected);
- where appropriate, an expiry date or a date beyond which retesting is necessary.

When fully computerized storage systems are used, all above information should not necessarily be in a legible form on the label.

5.30 There should be appropriate procedures or measures to assure the identity of the contents of each container of starting material. Bulk containers from which samples have been drawn should be identified (see Chapter 6, item 13).

5.31 Only starting materials which have been released by the Quality Control Department and which are within their shelf life should be used.

5.32 Starting materials should only be dispensed by designated persons, following a written procedure, to ensure that the correct materials are accurately weighed or measured into clean and properly labelled containers.

5.33 Each dispensed material and its weight or volume should be independently checked and the check recorded.

5.34 Materials dispensed for each batch should be kept together and conspicuously labelled as such.

Processing operations: intermediate and bulk products

5.35 Before any processing operation is started, steps should be taken to ensure that the work area and equipment are clean and free from any starting materials, products, product residues or documents not required for the current operation.

5.36 Intermediate and bulk products should be kept under appropriate conditions.

5.37 Critical processes should be validated (see *"Validation"* in this Chapter).

5.38 Any necessary in-process controls and environmental controls should be carried out and recorded.

5.39 Any significant deviation from the expected yield should be recorded and investigated.

Packaging Materials

5.40 The purchase, handling and control of primary and printed packaging materials shall be accorded attention similar to that given to starting materials.

5.41 Particular attention should be paid to printed materials. They should be stored in adequately secure conditions such as to exclude unauthorized access. Cut labels and other loose printed materials should be stored and transported in separate closed containers so as to avoid mix-ups. Packaging materials should be issued for use only by authorized personnel following an approved and documented procedure.

5.42 Each delivery or batch of printed or primary packaging material should be given a specific reference number or identification mark.

5.43 Outdated or obsolete primary packaging material or printed packaging material should be destroyed and this disposal recorded.

Packaging operations

5.44 When setting up a program for the packaging operations, particular attention should be given to minimizing the risk of cross-contamination, mix-ups or substitutions. Different products should not be packaged in close proximity unless there is physical segregation.

5.45 Before packaging operations are begun, steps should be taken to ensure that the work area, packaging lines, printing machines and other equipment are clean and free from any products, materials or documents previously used, if these are not required for the current operation. The line-clearance should be performed according to an appropriate check-list.

5.46 The name and batch number of the product being handled should be displayed at each packaging station or line.

5.47 All products and packaging materials to be used should be checked on delivery to the packaging department for quantity, identity and conformity with the Packaging Instructions.

5.48 Containers for filling should be clean before filling. Attention should be given to avoiding and removing any contaminants such as glass fragments and metal particles.

5.49 Normally, filling and sealing should be followed as quickly as possible by labelling. If it is not the case, appropriate procedures should be applied to ensure that no mix-ups or mislabelling can occur.

5.50 The correct performance of any printing operation (for example code numbers, expiry dates) to be done separately or in the course of the packaging should be checked and recorded. Attention should be paid to printing by hand which should be re-checked at regular intervals.

5.51 Special care should be taken when using cut-labels and when over-printing is carried out off-line. Roll-feed labels are normally preferable to cut-labels, in helping to avoid mix-ups.

5.52 Checks should be made to ensure that any electronic codes readers, label counters or similar devices are operating correctly.

5.53 Printed and embossed information on packaging materials should be distinct and resistant to fading or erasing.

5.54 On-line control of the product during packaging should include at least checking the following:

a) general appearance of the packages;

b) whether the packages are complete;

c) whether the correct products and packaging materials are used;

d) whether any over-printing is correct;

e) correct functioning of line monitors.

Samples taken away from the packaging line should not be returned.

5.55 Products which have been involved in an unusual event should only be reintroduced into the process after special inspection, investigation and approval by authorized personnel. Detailed record should be kept of this operation.

5.56 Any significant or unusual discrepancy observed during reconciliation of the amount of bulk product and printed packaging materials and the number of units produced should be investigated and satisfactorily accounted for before release.

5.57 Upon completion of a packaging operation, any unused batch-coded packaging materials should be destroyed and the destruction recorded. A documented procedure should be followed if encoded printed materials are returned to stock.

Finished products

5.58 Finished products should be held in quarantine until their final release under conditions established by the manufacturer.

5.59 The evaluation of finished products and documentation which is necessary before release of product for sale are described in Chapter 6 (Quality Control).

5.60 After release, finished products should be stored as usable stock under conditions established by the manufacturer.

Rejected, recovered and returned materials

5.61 Rejected materials and products should be clearly marked as such as stored separately in restricted areas. They should either be returned to the suppliers or, where appropriate, reprocessed or destroyed. Whatever action is taken should be approved and recorded by authorized personnel.

5.62 The reprocessing of rejected products should be exceptional. It is only permitted if the quality of the final product is not affected, if the specifications are met and if it is done in accordance with a defined and authorized procedure after evaluation of the risks involved. Record should be kept of the reprocessing.

5.63 The introduction of all or part of earlier batches, conforming to the required quality, into a batch of the same product at a defined stage of manufacture should be authorized beforehand. This recovery should be carried out in accordance with a defined procedure after evaluation of the risks involved, including any possible effect on shelf life. The recovery should be recorded.

5.64 The need for additional testing of any finished product which has been reprocessed, or into which a recovered product has been incorporated, should be considered by the Quality Control Department.

5.65 Products returned from the market and which have left the control of the manufacturer should be destroyed unless without doubt their quality is satisfactory; they may be considered for re-sale, relabelling or bulking with a subsequent batch only after they have been critically assessed by the Quality Control Department in accordance with a written procedure. The nature of the product, any special storage conditions it requires, its condition and history, and the time elapsed since it was issued should all be taken into account in this assessment. Where any doubt arises over the quality of the product, it should no be considered suitable for re-issue or re-use, although basic chemical re-processing to recover active ingredient may be possible. Any action taken should be appropriately recorded.

6 QUALITY CONTROL

Principle

Quality Control is concerned with sampling, specifications and testing as well as the organization, documentation and release procedures which ensure that the necessary and relevant tests are carried out, and that materials are not released for use,not products released for sale or supply, until their quality has been judged satisfactory. Quality Control is not confined to laboratory operations, but must be involved in all decisions which may concern the quality of the product. The independence of Quality Control from Production is considered fundamental to the satisfactory operation of Quality Control (see also Chapter 1).

General

6.1 Each holder of a manufacturing authorization should have a Quality Control Department. This department should be independent from other departments, and under the authority of a person with appropriate qualification and experience, who has one or several control laboratories at his disposal. Adequate resources must be available to ensure that all the Quality Control arrangements are effectively and reliably carried out.

6.2 The principle duties of the head of Quality Control are summarized in Chapter 2. The Quality Control Department as a whole will also have other duties, such as to establish, validate and implement all quality control procedures, keep the reference samples of materials and products, ensure the correct labelling of containers of materials and products, ensure the monitoring of the stability of the products, participate in the investigation of complaints related to the quality of the product, etc. All these operations should be carried out in accordance with written procedures and, where necessary, recorded.

6.3 Finished product assessment should embrace all relevant factors, including production condition, results of in-process testing, a review of manufacturing (including packaging) documentation, compliance with Finished Product Specification and examination of the final finished pack.

6.4 Quality Control personnel should have access to production areas for sampling and investigation as appropriate.

Good Quality Laboratory Practice

6.5 Control laboratory premises and equipment should meet the general and specific requirements for Quality Control areas given in Chapter 3.

6.6 The personnel, premises, and equipment in the laboratories should be appropriate to the tasks imposed by the nature and the scale of the manufacturing operations. The use of outside laboratories, in conformity with the principles detailed in Chapter 7, Contract Analysis, can be accepted for particular reasons, but this should be stated in the Quality Control records.

Documentation

6.7 Laboratory documentation should follow the principles given in Chapter 4. An important part of this documentation deals with Quality Control and the following details should be readily available to the Quality Control Department:

- specifications;
- sampling procedures;
- testing procedures and records (including analytical worksheets and/or laboratory notebooks);
- analytical reports and/or certificates;
- data from environmental monitoring, where required;
- validation records of test methods, where applicable;
- procedures for and records of the calibration of instruments and maintenance of equipment.

6.8 Any Quality Control documentation relating to a batch record should be retained for one year after the expiry date of the batch and at least 5 years after the certification referred to in article 22.2 of Directive 75/319/EEC.

6.9 For some kinds of data (e.g. analytical tests results, yields, environmental controls.....) it is recommended that records in a manner permitting trend evaluation be kept.

6.10 In addition to the information which is part of the batch record, other original data such as laboratory notebooks and/or records should be retained and readily available.

Sampling

6.11 The sample taking should be done in accordance with approved written procedures that describe:

- the method of sampling;
- the equipment to be used;
- the amount of the sample to be taken;
- instructions for any required sub-division of the sample;
- the type and condition of the sample container to be used;
- the identification of containers sampled;

— any special precautions to be observed, especially with regard to the sampling of sterile or noxious materials;

— instructions for the cleaning and storage of sampling equipment.

6.12 Reference samples should be representative of the batch of materials or products from which they are taken. Other samples may also be taken to monitor the most stressed part of a process (e.g. beginning or end of a process).

6.13 Sample containers should bear a label indicating the contents, with the batch number, the date of sampling and the containers from which the samples have been drawn.

6.14 Reference samples from each batch of finished products should be retained till one year after the expiry date. Finished products should usually be kept in their final packaging and stored under the recommended conditions. Samples of starting materials (other than solvents, gases and water) should be retained for a minimum of two years if their stability allows. Reference samples of materials and products should be of a size sufficient to permit at least a full re-examination.

Testing

6.15 Analytical methods should be validated. All testing operations described in the marketing authorization should be carried out according to the approved methods.

6.16 The results obtained should be recorded and checked to make sure that they are consistent with each other. Any calculations should be critically examined.

6.17 The tests performed should be recorded and the records should include at least the following data:

a) name of the material or product, where applicable, dosage form;

b) batch number and, where appropriate, the manufacturer and/or supplier;

c) references to the relevant specification and testing procedures;

d) test results, including observations and calculations, and reference to any certificates of analysis;

e) dates of testing;

f) initials of the persons who performed the testing;

g) initials of the persons who verified the testing and the calculations, where appropriate;

h) a clear statement of release or rejection (or other status decision) and the dated signature of the designated responsible person.

6.18 All the in-process controls, even those made in the production areas by production personnel, should be done according to methods approved by Quality Control and the results recorded.

6.19 Special attention should be given to the quality of laboratory reagents, volumetric glassware and solutions, reference standards and culture media. They should be prepared in accordance with written procedures.

6.20 Laboratory reagents intended for prolonged use should be marked with the preparation data and the signature of the person who prepared them. The expiry date of unstable reagents and culture media should be indicated on the label, together with specific storage conditions. In addition, for volumetric solutions, the last date of standardization and the last current factor should be indicated.

6.21 Where necessary, the date of receipt of any substance used for testing operations (e.g. reagents and reference standards) should be indicated on the container. Instructions for use and storage should be followed. In certain cases it may be necessary to carry out an identification test and/or other testing of reagent materials upon receipt or before use.

6.22 Animals used for testing components, materials or products, should where appropriate, be quarantined before use. They should be maintained and controlled in a manner that assures their suitability for the intended use. They should be identified, and adequate records should be maintained, showing the history of their use.

7 CONTRACT MANUFACTURE AND ANALYSIS

Principle

Contract manufacture and analysis must be correctly defined, agreed and controlled in order to avoid misunderstandings which could result in a product or work of unsatisfactory quality. There must be a written contract between the Contract Giver and the Contract Acceptor which clearly established the duties of each party. The contract must clearly state the way in which the Qualified Person releasing each batch of product for sale exercises his full responsibility.

Note: This chapter deals with the responsibilities of manufacturers towards the Competent Authorities of the Member States with respect to the granting of marketing and manufacturing authorizations. It is not intended in any way to affect the respective liability of contract acceptors and contract givers to consumers: this is governed by other provisions of Community and national law.

General

7.1 There should be a written contract covering the manufacture and/or analysis arranged under contract and any technical arrangements made in connection with it.

7.2 All arrangements for contract manufacture and analysis including any proposed changes in technical or other arrangements should be in accordance with the marketing authorization for the product concerned.

The Contract Giver

7.3 The Contract Giver is responsible for assessing the competence of the Contract Acceptor to carry out successfully the work required and for ensuring by means of the contract that the principles of GMP described in this Guide are followed.

7.4 The Contract Giver should provide the Contract Acceptor with all the information necessary to carry out the contracted operations correctly in accordance with the marketing authorization and any other legal requirements. The Contract Giver should ensure that the Contract Acceptor is fully aware of any problems associated with the product or the work which might pose a hazard to his premises, equipment, personnel, other materials or other products.

7.5 The Contract Giver should ensure that all processed products and materials delivered to him by the Contract Acceptor comply with their specifications or that the products have been released by a Qualified Person.

The Contract Acceptor

7.6 The Contract Acceptor must have adequate premises and equipment, knowledge and expertise, and competent personnel to carry out satisfactorily the work ordered by the Contract Giver. Contract manufacture may be undertaken only by a manufacturer who is the holder of a manufacturing authorization.

7.7 The Contract Acceptor should ensure that all products or materials delivered to him are suitable for their intended purpose.

7.8 The Contract Acceptor should ensure that all products or materials delivered to him are suitable for their intended purpose.

7.8 The Contract Acceptor should not pass to a third party any of the work entrusted to him under the contract without the Contract Giver's prior evaluation and approval of the arrangements. Arrangements made between the Contract Acceptor and any third party should ensure that the manufacturing and analytical information is made available in the same way as the original Contract Giver and Contract Acceptor.

7.9 The Contract Acceptor should refrain from any activity which may adversely affect the quality of the product manufactured and/or analyzed for the Contract Giver.

The Contract

7.10 A Contract should be drawn up between the Contract Giver and the Contract Acceptor which specifies their respective responsibilities relating to the manufacture and control of the product. Technical aspects of the contract should be drawn up by competent persons suitably

knowledgeable in pharmaceutical technology, analysis and Good Manufacturing Practice. All arrangements for manufacture and analysis must be in accordance with the marketing authorization and agreed by both parties.

7.11 The contract should specify the way in which the Quality Person releasing the batch for sale ensures that each batch has been manufactured and checked for compliance with the requirements of Marketing Authorization.

7.12 The contract should describe clearly who is responsible for purchasing materials, testing and releasing materials, undertaken production and quality controls, including in-process control, and who has responsibility for sampling and analysis. In the case of contract analysis, the contract should state whether or not the Contract Acceptor should take samples at the premises of the manufacturer.

7.13 Manufacturing, analytical and distribution records, and reference samples should be kept by, or be available to, the Contract Giver. Any records relevant to assessing the quality of a product in the event of complaints or a suspected defect must be accessible and specified in the defect/recall procedures of the Contract Giver.

7.14 The contract should permit the Contract Giver to visit the facilities of the Contract Acceptor.

7.15 In case of contract analysis, the contract Acceptor should understand that he is subject to inspection by the competent Authorities.

8 COMPLAINTS AND PRODUCT RECALL

Principle

All complaints and other information concerning potentially defective products must be carefully reviewed according to written procedures. In order to provide for all contingencies, and in accordance with Article 28 of Directive 75/319/EEC, a system should be designed to recall, if necessary, promptly and effectively products known or suspected to be defective from the market.

Complaints

8.1 A person responsible for handling the complaints and deciding the measures to be taken should be designated together with sufficient supporting staff to assist him. If this person is different to the Qualified Person, the latter should be made aware of any compliant, investigation or recall.

8.2 There should be written procedures describing the action to be taken including the need to consider a recall, in the case of a complaint concerning a possible product defect.

8.3 Any complaint concerning a product defect should be recorded with all the original details and thoroughly investigated. The person responsible for Quality Control should normally be involved in the study of such problems.

8.4 In a product defect is discovered or suspected in a batch, consideration should be given to whether other batches should be checked in order to determine whether they are also affected. In particular, other batches which may contain reworks of the defective batch should be investigated.

8.5 All the decision and measures taken as a result of a complaint should be recorded and referenced to the corresponding batch records.

8.6 Complaints records should be regularly reviewed for any indication of specific or recurring problems requiring attention and possibly the recall of marketed products.

8.7 The Competent Authorities should be informed if a manufacturer is considering action following possibly faulty manufacture, product deterioration, or any other serious quality problems with a product.

Recalls

8.8 A person responsible for execution and coordination of recalls should be designated as well as sufficient staff to handle all the aspects of the recalls with the appropriate degree of urgency. This responsible person should normally be independent of the sales and marketing organization. If this person is different to the Quality Person the latter should be made aware of any recall operation.

8.9 There should be established written procedures, regularly checked and updated with necessary, in order to organize any recall activity.

8.10 Recall operations should be capable of being initiated promptly and at any time.

8.11 All Competent Authorities of all countries to which products may have been distributed should be promptly informed if products are intended to be recalled because they are, or are suspect of being defective.

8.12 The distribution records should be readily available to the person(s) responsible for recalls, and contain sufficient information on wholesalers and directly supplied customers (with addresses, phone numbers inside or outside working hours, batches and amounts delivered), including for exported products and medical samples.

8.13 Recalled products should be identified and stored separately in a secure area while awaiting a decision on their fate.

8.14 The progress of the recall process should be recorded and a final report issued, including a reconciliation between the delivered and recovered quantities of the products.

8.15 The effectiveness of the arrangements for recalls should be evaluated from time to time.

9 SELF INSPECTION

Principle

Self Inspection should be conducted in order to monitor the implementation and the respect of Good Manufacturing Practice principles and to propose necessary corrective measures.

9.1 Personnel matters, premises, equipment, documentation, production, quality control, distribution of the medicinal products, arrangements for dealing with complaints and recalls, and self inspection, should be examined at intervals following a pre-arranged program in order to verify their conformity with the principles of Quality Assurance.

9.2 Self inspections should be conducted in an independent and detailed way be designated competent person(s) from the company. Independent audits by external experts may also be useful.

9.3 All self inspections should be recorded. Reports should contain all the observations made during the inspections, and, where applicable, proposals for corrective measures. Statements on the actions subsequently taken should also be recorded.

SUPPLEMENTARY GUIDELINES

MANUFACTURE OF STERILE MEDICINAL PRODUCTS

Principle

Manufacture of sterile preparations needs special requirements to minimize risks of microbiological contamination, and of particulate and pyrogen contamination. Much depends on the skill, training and attitudes of the personnel involved. Quality Assurance bears a particularly great importance, and this manufacture must strictly follow carefully established and validated methods of preparation and procedures.

Note: These guides do not take the place of the corresponding chapters of the Guide, but only stress the specific points for the manufacture of sterile preparations.

General

1. Production of sterile preparations should be carried out in clean areas who entry should be though airlocks for personnel or for goods. Clean areas should be maintained to an appropriate cleanliness standard and supplied with air which has passed through filters of an appropriate efficiency.
2. The various operations of component preparation, product preparation, filling and sterilization should be carried out in separate areas within the clean area.

3. Clean areas for production of sterile products are classified according to the required characteristics of the air, in grades A, B, C and D. The air characteristics are given in the table below.

4. Each manufacturing operation requires an appropriate air cleanliness level in order to minimize the risks of particulate or microbial contamination of the product or materials being handled. Items 5 and 6 give the minimum air-grades required for different *manufacturing* operations. The particulate and microbiological conditions given in the table should be maintained in the zone immediately surrounding the product whenever the product is exposed to the environment. The conditions should be achieved throughout the background environment where unmanned, and recovered after a short "clean-up" period.

   The utilization of absolute barrier technology and automated systems to minimize human interventions in processing areas can produce significant advantages in assurance of sterility of manufactured products. When such techniques are used, the recommendations in the Supplementary Guidelines, particularly those relating to air quality and monitoring still apply with appropriate interpretation of the terms "work station" and "environment".

   Manufacturing operations are here divided into two categories, first those where the preparation is terminally sterilized, sealed in its final container, and second those which must be conducted in an aseptic way at some or all stages.

Terminally sterilized products

5. Preparation of solutions should be done in a grade C environment in order to give low microbial and particulate counts, suitable for filtration and sterilization. It could be allowed in a grade D environment, provided additional steps are taken in order to minimize the contamination, such as the use of closed vessels.

   Filling large volume parenteral should be done under laminar air flow work station, in a grade C environment. The same condition are recommended for small volume parenteral.

   Preparation and filling of ointments, creams, suspensions and emulsions should generally be done in a grade C environment before terminal sterilization.

Aseptic preparations

6. Handling of starting materials should be done in a grade C environment, if sterile filtered later in the process, if not, in a grade A zone with a grade B background.

   Preparation of solutions which are to be sterile filtered during the process should be done in a grade C environment; if not filtered, it should be done in a grade A environment with a grade B background.

   Handling and filling of aseptically prepared products including small and large volume parenteral, should be done in a grade A environment, with a grade B background.

   Preparation and filling of ointments, creams, suspensions and emulsions should be done in a grade A environment, background of grade B, if the preparation occurs in open container and without filtration.

Personnel

7. Only the minimum number of personnel required should be present in clean areas; this is particularly important during aseptic processes. Inspections and controls should be conducted from outside the areas as far as possible.

8. All personnel (including those concerned with cleaning and maintenance) employed in such areas should receive regular training and disciplines relevant to the correct manufacture of sterile products, including reference to hygiene and to the basic elements of microbiology. When outside staff who have not received such training (e.g. building or maintenance contractors) need to be brought in, particular care should be taken over their supervision.

9. Staff who have been engaged in the processing of animal tissue materials or of cultures of micro-organisms other than those used in the current manufacturing process should not enter sterile-product areas unless rigorous and clearly defined decontamination procedures have been followed.

AIR CLASSIFICATION SYSTEM FOR MANUFACTURE OF STERILE PRODUCTS

Grade	Max. permitted number of particles per m³ equal to or above:		Max. permitted No. of viable micro-organisms per m³
	0.5 μm	5 μm	
A Laminar air flow work station	3,500	none	less than 1*
B	3,500	none	5*
C	350,000	2,000	100
D	3,500,000	20,000	500

Notes: Laminar air flow systems should provide an homogeneous air speed of 0.30 m/s for vertical flow and 0.45 m/s for horizontal flow.

In order to reach the B, C and D air grades, the number of air changes should generally be higher than 20 per hour in a room with a good air flow pattern and appropriate HEPA filters.

Low values involved here* are only reliable when a large number of air samples are taken.

The guidance given for the maximum permitted number of particles corresponds approximately to the US Federal Standard 209C as follows: Class 100 (Grades A and B), Class 10 000 (grade C) and Class 100 000 (grade D).

It is accepted that it may not always be possible to demonstrate conformity with particulate standards at the point of fill when filling is in progress, due to generation of particles or droplets from the product itself.

10. High standards of personal hygiene and cleanliness are essential, and personnel involved in the manufacture of sterile preparations should be instructed to report any condition which may cause the shedding of abnormal numbers or types of contaminants; periodic health checks for such conditions are desirable. Actions to be taken about personnel who could be introducing undue microbiological hazard should be decided by a designated competent person.
11. Outdoor clothing should not be brought into the clean areas, and personnel entering the changing rooms should already be clad in standard factory protective garments. Changing and washing should follow a written procedure.
12. The clothing and its quality has to be adapted to the process and the working place, and worn in such a way as to protect the product from contamination.
13. Wristwatches and jewelry should not be worn in clean areas and cosmetics which can shed particles should not be used.
14. Clothing should be appropriate to the air grade of the area where the personnel will be working. The description of clothing required for each grade is given below:

    Grade D: Hair and, where appropriate, beard should be covered. A general protective clothing and appropriate shoes or overshoes should be worn. Appropriate measures should be taken to avoid any contamination coming from outside the clean area.

    Grade C: Hair and, where appropriate, beard should be covered. A single or two-piece trouser suit, gathered at the wrists and with high neck and appropriate shoes or overshoes should be worn. They should virtually shed no fibers or particulate matter.

    Grade B: A headgear should totally enclose hair and, where appropriate beard; it should be tucked into the neck of the suit; a face mask should be worn to prevent the shedding of droplets; sterilized non powdered rubber gloves and sterilized or disinfected footwear should be worn; trousers-bottoms should be tucked inside the footwear as well as garment sleeves into the gloves. The protective clothing should shed virtually no fibers or particulate matter and retain particles shed by the body.
15. For every worker in a grade B room, clean sterilized protective garments should be provided at each work session, or at least once a day if monitoring results justify this. Gloves should be regularly disinfected during operations and masks and gloves should be changed at least at every working session. The use of disposable clothing may be necessary in certain circumstances.
16. Clean area clothing should be laundered or cleaned in such a way that it does not gather additional particulate contaminants which can later be shed. Separate laundry facilities for such clothing are desirable. Damaging fibers by inappropriate cleaning or sterilization may increase the risk of shedding of particles. Washing and sterilization operations should follow written procedures.

Premises

17. In clean areas, all exposed surfaces should be smooth, impervious and unbroken in order to minimize the shedding or accumulation of particles or microorganisms and to permit the repeated application of cleaning agents, and disinfectants where used.
18. To reduce accumulation of dust and to facilitate cleaning there should be no uncleanable recesses and a minimum of projecting ledges, shelves cupboards and equipment. Doors should be carefully designed to avoid those uncleanable recesses; sliding doors are undesirable for this reason.
19. False ceilings should be sealed to prevent contamination from the space above them.
20. Pipes and ducts should be installed so that they do not create recesses which are difficult to clean.
21. Sinks and drains should be avoided wherever possible and should be excluded from areas where aseptic operations are done. Where installed they should be designed, located and maintained so as to minimize risks of microbial contamination; they should be fitted with effective, easily cleanable traps and with air breaks to prevent back-flow. Any floor channel should be open, shallow and easily cleanable and be connected to drains outside the area in a manner which prevents ingress of microbial contaminants.
22. Changing rooms should be designed as airlocks and used to provide separation of the different stages of changing and so minimize microbial and particulate contamination of protective clothing. They should be effectively flushed with filtered air. The use of separate changing rooms for entering and leaving clean areas is sometimes desired. Hand washing facilities should be provided only in the changing rooms.
23. Airlock doors should not be opened simultaneously. An interlocking system or a visual and/or audible warning system should be operated to prevent the opening of more than one door.

Equipment

24. A filtered air supply should maintain a positive pressure relative to surrounding areas under all operational conditions and flush the area effectively. Moreover, particular attention should be paid to the protection of the zone of greatest risk, that is, the immediate environment to which a product and cleaned components which contact the product are exposed. The various recommendations regarding air supplies and pressure differentials may need to be modified where it becomes necessary to contain some materials, e.g. pathogenic, highly toxic, radioactive or live viral or bacterial materials or products. Decontamination facilities and treatment of air leaving a clean area may be necessary for some operations.
25. It should be demonstrated that air-flow patterns do not present a contamination risk, e.g. care should be taken to ensure that air-flows do not distribute particles from a particles-generating person, operation, or machine to a zone of higher product risk.
26. A warning system should be included to indicate failure in the air supply. An indicator of pressure difference should be fitted between areas where this difference is important and the pressure differences should be regularly recorded.
27. A conveyor belt should not pass through a partition between a clean area B and a processing area of lower air cleanliness, unless the belt itself is continually sterilized (e.g. in a sterilizing tunnel).
28. As far as possible equipment fittings and services should be designed and installed so that operations, maintenance and repairs can be carried out outside the clean area. If sterilization is required, it should be carried out after complete reassembly wherever possible.
29. When equipment maintenance has been carried out within the clean area, the area should be cleaned, and disinfected where appropriate, before processing recommences if the required standards of clean lines and/or asepsis have not been maintained during the work.
30. All equipment including sterilizers, air filtration systems, water treatment systems including stills should be subject to planned maintenance and validation; their use following maintenance work should be approved by the Quality Control.
31. Water treatment plants should be designed, constructed and maintained so as to ensure the reliable production of water of an appropriate quality. They should not be operated beyond their designated capacity. Water should be produced, stored and distributed in a manner which prevents microbial growth, for example by constant circulation at temperature above 70 degrees C.

Sanitation

32. The sanitation of clean areas is particularly important. They should be cleaned frequently and thoroughly in accordance with a written program approved by the Quality Control Department. Where disinfectants are used, more than one type should be employed. Monitoring should be regularly undertaken in order to detect the development of resistant strains.

33. Disinfectants and detergents should be monitored for microbial contamination: dilutions should be kept in previously cleaned containers and should not be stored for long periods unless sterilized. Partly emptied containers should not be topped up.

34. Fumigation of clean areas may be useful for reducing microbiological contamination in inaccessible places.

35. Clean areas should be monitored at planned intervals during operations by means of in microbial counts; where aseptic operations are performed, monitoring should be frequent and the results considered when determining batch approval. Additional monitoring is sometimes also desirable outside production operations, e.g. after validation of systems, cleaning, fumigation.

Processing

36. Precautions to minimize contamination should be taken during all processing stages including the stages before sterilization.

37. Preparations of microbiological origin should not be made or filled in areas used for the processing or other medicinal products; however, vaccines of dead organisms or of bacterial extracts may be filled, after inactivation, in the same premises as other sterile medicinal products.

38. Aseptic processes or significant modifications should be validated by using a sterile nutrient medium for simulating the process to be performed. That validation should be repeated at defined intervals.

39. Care should be taken that validations do not hazard the processes.

40. Water sources, water treatment equipment and treated water should be monitored regularly for chemicals, biological contamination and, as appropriate, for endotoxins. Records should be maintained of the results of the monitoring and of any action taken.

41. Activities in clean areas and especially when aseptic operations are in progress should be kept to a minimum and movement of personnel should be controlled and methodical, to avoid excessive shedding of particles and organisms due to over-vigorous activity. The ambient temperature and humidity should not be uncomfortably high because of the nature of the garments worn.

42. Microbiological contamination of starting materials should be minimal. The bioburden should be monitored before sterilization. Specifications should include requirements for microbiological quality when the need for this has been indicated by monitoring.

43. Containers and materials liable to generate fibers should be minimized in clean areas and avoided completely when aseptic work is in progress.

44. Components, containers and equipment should be handled after the final cleaning process in such a way that they are not recontaminated.

45. The interval between the washing and drying and the sterilization of components, containers and equipment as well as between the sterilization and their use should be as short as possible and subject to a time-limit appropriate to the storage conditions.

46. The time between the start of the preparation of a solution and its sterilization or filtration through a bacteria-retaining filter should be as short as possible. There should be a set maximum permissible for each product that takes into account its composition and the prescribed method of storage.

47. The microbiological contamination of products should be minimal prior to sterilization. There should be a working limit on contamination immediately before sterilization which is related to the efficiency of the method to be used and the risk of pyrogens. All solutions, in particular large volume infusion fluids, should be passed through a micro-organism retaining filter, if possible immediately before filling.

48. Components, containers, equipment and any other article required in a clean areas where aseptic work is in progress should be sterilized and passed into the area through double ended sterilizers sealed into the wall, or by a procedure which achieves the same end of not introducing contamination.

49. The efficacy of any new procedure should be validated, and the validation repeated at regular intervals thereafter, or, when any significant change is made in the process or equipment.

Sterilization

50. All sterilization processes should be validated. Particular attention should be given when the adopted sterilization method is not described in the current edition of the European Pharmacopoeia, or when it is used for a preparation which is not a simple aqueous or oily solution. Where possible and practicable, heat sterilization is the method of choice. In any case, the sterilization process must be in accordance with the marketing and manufacturing authorizations.

51. Before any sterilization process is adopted its suitability for the product and its efficacy in achieving the desired sterilizing conditions in all parts of each type of load to be processed should be demonstrated. This work should be repeated at scheduled intervals, at least annually, and whenever significant modifications have been made to the equipment. Records should be kept of the results.

52. For effective sterilization the whole of the material must be subjected to the required treatment and the process should be designed to ensure that this is achieved.

53. Biological indicators should be considered only as an addition method for monitoring the sterilization. If they are used, strict precautions should be taken to avoid transferring microbial contamination from them.

54. There should be a clean means of differentiating products which have not been sterilized from those which have. Each basket, tray or other carrier of products or components should be clearly labelled with the material name, its batch number and an indication of whether or not it has been sterilized. Indicators such as autoclave tape may be used, where appropriate, to indicate whether or not a lot (or sub-lot) has passed through a sterilization process, buy they do not give a reliable indication that the lot is, in fact, sterile.

Sterilization by heat

55. Each heat sterilization cycle should be recorded on a time/temperature chart with a suitably large scale or by other appropriate equipment with suitable accuracy and precision. The temperature should be recorded from a probe at the coolest part of the load or loaded chamber, this point having been determined during the validation, and preferably also checked against the second independent temperature probe located at the same position. The Chart, or a photocopy thereof, should form part of the batch record. Chemical or biological indicators may also be used, but should not take the place of physical controls.

56. Sufficient time must be allowed for the whole of the load to reach the required temperature before measurement of the sterilizing time-period is commenced. This time must be determined for each type of load to be processed.

57. After the high temperature phase of a heat sterilization cycle, precautions should be taken against contamination of a sterilized load during cooling. Any cooling fluid or gas in contact with the product should be sterilized, unless it can be shown that any leaking container would not be approved for use.

Moist Heat

58. Both temperature and pressure should be used to monitor the process. The temperature recorder should normally be independent of the controller, and there should be an independent temperature indicator, the reading from which is routinely checked against the chart recorder during the

sterilization period. For sterilizers fitted with a drain at the bottom of the chamber, it may also be necessary to record the temperature at this position, throughout the sterilization period. There should be regular leak tests on the chamber when a vacuum phase is part of the cycle.

59. The items to be sterilized, other than products in sealed containers, should be wrapped in a material which allows removal of air and penetration of steam but which prevents recontamination after sterilization. All parts of the load should be in contact with water or saturated steam at the required temperature for the required time.

60. Care should be taken to ensure that steam used for sterilization is of suitable quality and does not contain additives at a level which could cause contamination of product or equipment.

Dry Heat

61. The process used should include air circulation within the chamber and the maintenance of a positive pressure to prevent the entry of non-sterile air. In case air should be supplied, it should be passed through a micro-organisms retaining filter. Where this process is also intended to remove pyrogens, challenge tests using endotoxins may be required as part of the validation.

Sterilization by radiation

62. Radiation sterilization is used mainly for the sterilization of heat sensitive materials and products. Many medicinal products and some packaging materials are radiation-sensitive, so this method is permissible only when the absence of deleterious effects on the product has been confirmed experimentally. Ultraviolet irradiation is not normally an acceptable method of sterilization.

63. During the sterilization procedure the radiation dose would be measured. For this purpose, dosimetry indicators which are independent of dose rate should be used, giving a quantative measurement of the dose received by the product itself. Dosimeters should be inserted in the load in sufficient number, and close enough together to ensure that there is always a dosimeter in the chamber. Where plastic dosimeters are used they should be used within the time-limit of their calibration. Dosimeter absorbances should be read within a short period after exposure to radiation. Biological indicators may only be used as an additional control. Radiation-sensitive color disks may also be used to differentiate between packages which have been subjected to irradiation and those which have not; they are not indicators of successful sterilization. The information obtained should constitute part of the batch record.

64. Validation procedures should ensure that the effects of variations in density of the packages are considered.

65. Materials handling procedures should prevent mix-up between irradiated and non-irradiated materials. Each package should carry a radiation sensitive indicator to show whether or not it has been subjected to a radiation treatment.

66. The total radiation dose should be administered within a predetermined timespan.

Sterilization with ethylene oxide

67. This method should only be used when no other method is practicable. During process validation it should be shown that there is no damaging effect on the product and that the conditions and time allowed for degassing are such as to reduce any residual gas and reaction products to defined acceptable limits for the type of product or material.

68. Direct contact between gas and microbial cells is essential; precautions should be taken to avoid the presence of organisms likely to be enclosed in material such as crystals or dried protein. The nature and quantity of packaging materials can significantly affect the process.

69. Before exposure to the gas, materials should be brought into equilibrium with the humidity and temperature required by the process. The time required for this should be balanced against the opposing need to minimize the time before sterilization.

70. Each sterilization cycle should be monitored with suitable biological indicators, using the appropriate number of test pieces distributed throughout the load. The information so obtained should form part of the batch record.

71. Biological indicators should be stored and used according to the manufacturers instructions, and their performance checked by positive controls.

72. For sterilization cycle, records should be made of the time taken to complete the cycle, of the pressure, temperature and humidity within the chamber during the process and of the gas concentration. The pressure and temperature should be recorded throughout the cycle on a chart. The record(s) should form part of the batch record.

73. After sterilization, the load should be stored in a controlled manner under ventilated conditions to allow residual gas and reaction products to reduce to the defined level. This process should be validated.

Filtration of medicinal products which cannot be sterilized in their final container

74. Filtration alone is not considered sufficient when sterilization in the final container is practicable. With regard to methods currently available, steam sterilization is to be preferred. If this product cannot be sterilized in the final container, solutions or liquids can be filtered through a sterile filter of nominal pore size of 0.22 micron (or less), or with at least equivalent micro-organism retaining properties, into a previously sterilized container. Such filters can remove bacteria and molds, but not all viruses or mycoplasmas. Consideration should be given to complementing the filtration process with some degree of heat treatment.

75. Due to the potential additional risks of the filtration method as compared with other sterilization processes, a second filtration via a further sterilized micro-organism retaining filter, immediately prior to filling, may be advisable. The final sterile filtration should be carried out as close as possible to the filling point.

76. Fibers-shedding filter should not be used.

77. The integrity of the filter should be checked by an appropriate method such as bubble point test immediately after each use (it may also be useful to test the filter in this way before use). The time taken to filter a known volume of bulk solution and the pressure difference to be used across the filter should be determined during validation and any significant differences from this should be noted and investigated. Results of these checks should be recorded in the batch record.

78. The same filter should not be used for more than one working day unless such use has been validated.

79. The filter should not affect the product by removal of ingredients from it or release of substances into it.

Finishing of sterile products

80. Container should be closed by appropriately validated methods. Samples should be checked for integrity according to appropriate procedures.

81. Containers sealed under vacuum should be sampled and the samples tested for maintenance of that vacuum after an appropriate, pre-determined period.

82. Filled containers of parenteral products should be inspected individually. When inspection is done visually, it should be done under suitable and controlled conditions of illumination and background. Operators doing the inspection should pass regular eye-sight checks, with spectacles if worn, and be allowed frequent breaks from inspection. Where other methods of inspection are used, the process should be validated and the performance of the equipment checked at intervals.

Quality Control

83. The sterility test applied to the finished product should only be regarded as the last in a series of controlled measures by which sterility is assured.

84. Samples taken for sterility testing should be representative of the whole of the batch, but should in particular include samples taken from parts of the batch considered to be most at risk of contamination, e.g.:

    a) for products which has been filled aseptically, samples should include containers filled at the beginning and end of the batch and after any significant interruption of work;

    b) for products which have been heat sterilized in their final containers, consideration should be given to taking samples from the potentially coolest part of the load.

85. For injectable products, consideration should be given to monitoring the water and the intermediate and finished product for endotoxins, according the European Pharmacopoeia method, and after validation for each type of product. For large volume infusion solutions such monitoring of water or intermediates should always be done in addition to any tests required by the marketing authorization on the finished product. When a sample fails the test, the cause or failure should be investigated and remedial action taken where necessary.

SECTION 8

SUGGESTIONS FOR QC FOR THE SSMPU

8.1 GENERAL

8.2 MASTER DOCUMENTS

- 8.2.1 Product Authorisation
- 8.2.2 Master Formula
- 8.2.3 Master Manufacturing Instructions
- 8.2.4 Master Packaging Instructions
- 8.2.5 Specifications
- 8.2.6 Test Methods
- 8.2.7 Sampling Procedures

8.3 BATCH RECORDS

8.4 AUDITS

8 SUGGESTIONS FOR QC FOR THE SSMPU

The Terms of Reference for the second Alkaloida project (2) call for information on the practical use of a quality control system for the SSMPU. It is felt that it would be much more appropriate to include this information in this study report rather than in the Front End Design study which is a document much more concerned with technical, engineering design and processing matters.

The notes and suggestions which follow are for guidance only but do reflect the approach to QA/QC being adopted by companies in the USA and Western Europe. It is appreciated that not every suggestion is directly applicable to the SSMPU, and all the following material must be reviewed by Alkaloida in the light of their own current, and proposed, practices for QA/QC and adapted specifically for use in the SSMPU.

8.1 GENERAL

The development and introduction of a new medicinal chemical into Alkaloida's existing range of products needs a significant amount of planning. Co-ordination of manufacturing operations in the SSMPU requires some system of "time/event" scheduling so that every "event" in the life of a 'product' as it passes through the SSMPU is co-ordinated for obvious reasons. Hence all departments involved in manufacturing and QC in the SSMPU should have their systems, procedures, training programmes and documentation in place and ready for when the SSMPU comes into operation.

In the context of this report, the notes which follow are concerned mainly with documentation matters since many of the other functions are already available from Alkaloida's existing organisation and practices. The following key topics are therefore discussed and suggestions offered:-

- Master Documents
- Batch Records
- Standard Procedures

8.2 MASTER DOCUMENTS

Within the overall Quality Assurance concept there are certain requirements, or specifications, in a quality control system which have to be met in order to be certain that materials are sampled, tested and evaluated against predetermined specifications. Master documents are prepared in advance of production and define the requirements mentioned above.

Basically seven master documents are identified for each in-process item and finished product.

Product Authorisation
Master Formula
Master Manufacturing Instructions
Master Packaging Instructions
* Specifications
* Test Methods
* Sampling Procedure

Items marked * apply in particular to labels, packaging materials and raw materials.

8.2.1 Product Authorisation

The following information is specified by the Product Authorisation master document:-

- Product Name: (usually the trade name and its generic name)

- Production Identification Number: (applies uniquely to a specific product formulation and to a specific SSMPU manufacturing process)
* Dosage: (weight of active ingredient per unit dose)
* Dosage Form: (tablet, capsule, syrup, etc)
* Container/Closure System: (bottle/cap combination)
* Size: (number of units per container)
* Expiration Date
- Manufacturing Site
- Date of Approval
- Approval Signatures (as many as required)

It is appropriate to note that the SSMPU will be used to produce medicinal chemicals in the 'bulk form' only. The bulk material is sent to other parts of the Alkaloida factory for transformation into finished product. Hence those items above marked * will not necessarily apply to the SSMPU.

8.2.2 Master Formula

This is basically a list of ingredients, weight basis, which are used to make the final dosage form. Hence it does not apply, as such, to the SSMPU which only makes the bulk active ingredient.

8.2.3 Master Manufacturing Instructions

These basically are the recipe for the manufacture of the final drug product, hence are not strictly applicable to the SSMPU.

8.2.4 Master Packaging Instructions

These apply to the final dosage form and do not apply to the SSMPU.

8.2.5 Specifications

In the context of the SSMPU, specifications refer basically to raw materials, in-process items and the final bulk active materials. The specifications should include:-

- Identification: item name, number, description
- Tests: list of tests to be conducted on the material
- Limits: quantitative limits to enable the analyst to determine if the item meets the specification
- Approvals: date and signature of authorising person

8.2.6 Test Method

This applies particularly in the SSMPU to the test methods for the raw materials and the final active bulk medicinal chemical.

The methods are many and varied and include the following:-

- Title
- Summary of Method
- List of Equipment Needed
- List of Reagents Needed
- Detailed Procedure
- Calculations
- References

8.2.7 Sampling Procedures

Alkaloida's QC department has a group which is responsible for sampling and sample taking, and has perfectly adequate procedures. However, it is appropriate to note that the sampling procedures should include information on the following:-

- Title
- Scope
- Preparation for Sampling
- Sample Size
- Sampling Procedure
- Sample Retention Protocol

8.3 BATCH RECORDS

Batch records are used to record the results of QC tests and to ensure that the exact manufacturing instructions have properly been followed for every batch of product. The batch production record is a document, or set of documents, that confirms and records the satisfactory completion of each significant step in the manufacturing (and packaging operation which is not applicable to the SSMPU).

The main features of the batch record are similar to those of the master production documents (sections 8.2.3 and 4) and include:

- Identification: the product name, product identification number, (dosage, dosage form) together with the batch number and the expiration date

- Documentation: this includes an accurate reproduction of the master production document and all the necessary forms and documents listing dates, times, people, equipment, weights

and measures, samplings, inspections, actual yields, in-process checks, recording charts, to make certain the instructions were followed exactly

- Notations: any deviations from the master production documents must be noted, including the reasons for the deviations

- Approvals: signatures are required of the personnel performing the significant operations, signatures of the personnel reviewing and confirming those operations, and signatures of the quality control personnel who have reviewed the completed batch record

When a batch of material is received in the quality control department for testing, it is necessary to have a set of documents that constitute the batch record, along with a set to record the fact that the batch was received, sampled, tested, and released in accordance with the master documents. The batch record consists of the following:

- receiving report
- quarantine report
- sampling frequency
- sample taken
- resample request
- testing frequency
- certificate of analysis
- disposition
- certificate of disposal
- stickers

The quality control department's archives should retain copies of the master quality control documents and copies of the batch records for every batch, in addition to log sheets,

records of results, and other miscellaneous items. The GMPs require period review of these records as an added measure of control.

It may be noted from section 4.6.3 that Alkaloida currently use a system for procedures and records based on "paperwork" and that the system has been subjected satisfactorily to FDA inspection. Hence it is evident that Alkaloida should have no difficulty in setting up a batch record system for the SSMPU.

For information purposes only, examples of typical batch record sheets, as they might apply to the SSMPU, for the items noted above are included in this section.

8.4 AUDITS

An important feature of an overall QA programme is the use of audits for the formal and methodical examination/review of the manufacturing operations, including engineering and maintenance, the process, and the quality control functions. Manufacturing and control operations are audited to ensure compliance with both internal company policies and GMP regulations. The audit is useful for ensuring completion and accuracy of documentation, and it quickly provides plant management with information needed to take corrective actions.

An audit report is drawn up and then reviewed by department heads before its issuance. It is then management's responsibility to institute a programme to correct any deficiencies noted. A nominated responsible department should follow up at definite intervals to ensure that corrective measures are implemented.

The auditors may also visit outside vendors and contractors to make certain their operations comply with both regulatory requirements and company policies. Also, aud[illegible]

facility may be made by investigators from the regulatory agencies. It is the responsibility of the company's audit department to provide an escort for the outside investigator, to accompany him or her during the inspection of the plant site, to write a report of the investigation, and to make sure the required corrective actions are taken.

RECEIVING DEPARTMENT: RECEIVING REPORT

ITEM NAME: | ITEM NUMBER:

INSTRUCTIONS:
1. Make out a separate Receiving Report for each supplier's Lot Number.
2. Send copies of the Receiving Report to:
   - ☐ Purchasing
   - ☐ Quality Control
   - ☐ Receiving Department Files
   - ☐ Raw Material Inventory Control
3. Transfer Raw Material immediately to quarantined storage.

SUPPLIER: _____

SUPPLIER LOT NO.: _____

PURCHASE ORDER NO.: _____

RECEIVING NO.: _____

RECEIVED BY: _____

DATE RECEIVED: _____

CARRIER: _____

QUANTITY RECEIVED: _____

NUMBER OF CONTAINERS: _____

ASSIGNED BATCH NO. (Must be stamped on each container) _____

REMARKS: _____

PREPARED BY:	APPROVED:	SUPERSEDES:	EFF. DATE:	PAGE_OF_

RECEIVING REPORT

QUALITY CONTROL: QUARANTINE REPORT

ITEM NAME: | ITEM NUMBER:

LOT NUMBER	QUANTITY RECEIVED	PLACED IN QUARANTINE (DATE)	DISPOSITION SHEET RECEIVED	RELEASED FROM QUARANTINE (DATE)

PREPARED BY:	APPROVED:	SUPERSEDES:	EFF. DATE:	PAGE OF

QUARANTINE REPORT

QUALITY CONTROL: SAMPLE TAKEN

ITEM NAME:	BATCH NUMBER:	ITEM NUMBER:

INSTRUCTIONS:
1. Take Receiving Report to Quarantine Area.
2. Sample Raw Materials.
3. Label each Sample.
4. Note any discrepancies in the Remarks Section.
5. Send copies of Sample Taken form to:
   - ☐ Sample Expeditor
   - ☐ File 1 Copy

RECEIVING REPORT ATTACHED: _____

SAMPLED BY: _____

DATE SAMPLED: _____

SAMPLING METHOD NO.: _____

QUANTITY TAKEN:

FOR LABORATORY _____

FOR RETAINED SAMPLES _____

FOR IDENTIFICATION _____

REMARKS: _____

NUMBER OF CONTAINERS SAMPLED: _____

PREPARED BY:	APPROVED:	SUPERSEDES:	EFF. DATE:	PAGE_OF_

SAMPLE TAKEN

QUALITY CONTROL TEST RESULTS: CERTIFICATE OF ANALYSIS

ITEM NAME:	BATCH NUMBER:	ITEM NUMBER:

TEST	SPECIFICATION	RESULTS	METHOD

ANALYST: _____

DATE: _____

NOTEBOOK NUMBER: _____

REVIEWED BY: _____

DATE: _____

RECOMMENDATION:
- ☐ ACCEPTED FOR USE PRIOR TO_____, MUST BE RETESTED AFTER THIS DATE.
- ☐ RESAMPLE REQUESTED
- ☐ INFORMATION ONLY
- ☐ REJECTED

PREPARED BY:	APPROVED:	SUPERSEDES:	EFF. DATE.:	PAGE_OF_

CERTIFICATE OF ANALYSIS

SECTION 9

CONCLUSIONS AND RECOMMENDATIONS

9 CONCLUSIONS AND RECOMMENDATIONS

- The organisation and operation of the Quality Control function, on a company wide basis at Alkaloida, is essentially traditional and based largely on paperwork documentation.

- The QC function is probably adequate for some traditional pharmaceutical products but a much greater in depth audit is needed to determine if the existing QC function could match the ever more stringent requirements of the US/EC authorities, especially where 'sterile' products are concerned.

- The requirements for compliance with current USA/EC Good Manufacturing Practice (GMP), as applied to the pharmaceutical products which Alkaloida wish to make in the multi product small scale production unit (currently under construction), are becoming increasingly severe. Certain aspects of the design and part construction of the small scale production unit may not satisfy the requirements and need to be reviewed/assessed.

- Where VALIDATION is concerned (a key feature of GMP), there are many aspects of the design and construction of the small scale production unit which give rise for concern, particularly regarding design and construction documentation.

- It is recommended that Alkaloida begin a wide ranging review and appraisal of its QC function and approach to GMP for the proposed small scale production unit, in the light of this audit report and Front End Design study.

- It would also be appropriate to review this report with any report which GRC Consultants understands is being prepared by the Hungarian consultant on a Quality Assurance programme for Alkaloida.

- It is also recommended that decisions regarding any modifications to the current design of the small scale production unit should be made when the Front End Design study is complete and its implications discussed and agreed.

REFERENCES

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

(2) TF/HUN/90/910 - Upgrading of Quality Assurance and Good Manufacturing Practices in the Multipurpose Medicinal Chemical Pilot Plant of Alkaloida - Contract No. 92/114

GRC Consultants

20023
(2 of 3)

FRONT END DESIGN STUDY

FOR

SMALL SCALE MULTI PRODUCT UNIT (SSMPU)

FOR

THE ALKALOIDA COMPANY, TISZAVASVARI

VOLUME I

G E GUIDOBONI

DECEMBER 1992

UNIDO CONTRACT 92/031
92/114

This report has been prepared for the United Nations Industrial Development Organisation (UNIDO) for the projects:-

- TF/HUN/90/907 "Technical Assistance for Upgrading the DSP Section of the Small Scale Multi Product Medicinal Chemical Plant of Alkaloida".
- TF/HUN/90/910 "Upgrading of Quality Assurance and Good Manufacturing Practices in the Multipurpose Medicinal Chemical Pilot Plant of Alkaloida".

CONTENTS

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GRC Consultants wishes to acknowledge the co-operation and support of many of the Alkaloida staff at Tiszavasvari 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 engineering, technical and quality control departments, without whose understanding and help, this FED would not be as comprehensive as it is.

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 first Alkaloida 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 downstream processing (DSP) section of the small scale multi product medicinal chemical plant of Alkaloida at Tiszavasvari, for which a building has already been selected by Alkaloida and in which some preliminary construction work (internal walls) has been carried out.

However, in June 1992 the Hungarian Government selected a second Alkaloida project which was to complement and support the first project noted above.

The Terms of Reference for this second project included a Front End Design (FED) study for a plant to carry out the synthesis stages which precede the DSP section of the unit noted above in the first project.

Work began on this second project in July 1992 (3) in parallel with the first project begun in February. However, because the two 'separate' projects clearly were inextricably linked it soon became obvious that the two separate Front End Design studies would inevitably contain a number of sections which would be very similar (almost identical) in a number of ways. The concept of combining the two separate FED's into a single unified project document was discussed by the project team (GRC Consultants/Alkaloida) and the UNIDO responsible officer at the project meetings in July 1992 (4) and it was unanimously agreed that it was eminently sensible and highly appropriate to produce a single consolidated FED study which would include both the upstream synthesis and downstream processing (finishing) stages of the project.

The results of the consolidated 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 Alkaloida 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 Alkaloida 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 ALKALOIDA

2.3 STUDY CONTENTS

2 SCOPE OF STUDY

This study is concerned with the preparation of a Front End Design (FED) for the synthesis and downstream processing (DSP) areas of the small scale multi purpose medicinal chemicals unit, abbreviated to SSMPU, which Alkaloida plan to complete at their site at Tiszavasvari 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 GMP requirements typically of the USA, UK and the EC. However, it is clearly understood that since Alkaloida have already selected a building, have carried out some design work in-house, and have begun some construction work, GRC Consultants freedom to design "from scratch" is restricted in certain areas. The design presented in this FED study report takes into account, as far as possible, the chosen location and the design work already carried out by Alkaloida, but where GRC Consultants has identified any aspect of design, by others, which could compromise compliance with GMP, then note of the feature is made and GRC Consultants recommendations are clearly stated.

With further regard to this point, reference may be made to the GMP critique of the Alkaloida plans (5).

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 ALKALOIDA

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

- Nature of Facility: The basic function of the facility which is the subject of this FED study, is the preparation of medicinal chemical products, in the dry powder form, from a starting material which generally is a crystal or precipitate slurry (in a solvent) which is prepared in the synthesis section of the multi product unit.

- Nature of Products: The SSMPU is an integrated unit in which it is intended to make a variety of medicinal products for sale within Hungary and for export. Because of this, the products will have to be made under strict GMP conditions and the facility will have to be validated and inspected by the appropriate approving authorities, e.g. FDA for the USA, or Medicines Control Agency (MCA) in the UK, or in accordance with EC Directives - Rules Governing Medicinal Products in the European Community.

- Status of Project: It is appropriate to note that Alkaloida have already chosen an existing building in which to house the SSMPU and have carried out a certain amount of basic design work in-house. They have also begun some construction work (internal walls) in the unit. The fact that a building has already been chosen to house the SSMPU means that the FED study is automatically constrained to some extent where layout is concerned.

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, Basis of Design; contains data used for calculation purposes and the source of the data is noted. 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 4, Equipment; the equipment list identifies each key item of process equipment and contains basic parameters such as size, material of construction and notes of any special features. Alkaloida have already ordered or designed (for local fabrication) some equipment items.

- Section 5, Utilities and Services; contains information on the type of utilities and services needed by the SSMPU and the outline distribution pattern of the services throughout the facility.

- Section 6, Instrumentation, Control and Electrics; the philosophy of the control strategy is outlined and preliminary details given of the instrumentation requirements of the various equipment items.

- Section 7, Layout; is concerned with the flow of people and materials and this section describes the layout of the facility both in terms of equipment within the rooms, and the rooms within the building. It is emphasized that the layout is somewhat constrained by the facts that Alkaloida have already chosen a building to house the SSMPU and have already carried out some design and preliminary construction work within the chosen building.

- Section 8, Building Design; contains preliminary technical and mechanical descriptions of the more important aspects of building design such as Heating, Ventilation and Air Conditioning (HVAC). These specifications are for information and guidance only at this stage.

- Section 9, Safety/Environment; contains information on aspects of safety which arise from the potentially hazardous nature of the solvents used and the dry powder products made in the facility. Since solvents are used in various parts of the process, mention is made of the implication of

solvents for electrical equipment and operator safety. The handling and treatment of effluents and emissions is also discussed.

- Section 10, GMP and Validation; contains information particularly about the needs for validation of the facility since this is a topic which must be recognised by any future bidding contractor as vitally important to the successful realisation of a SSMPU for medicinal chemicals.

- Section 11, Standards; contains preliminary engineering standards which give an idea of the level of engineering which is required for a facility of this nature.

- Section 12, Capital Cost Estimates; provides an estimate for the main components of the capital investment required to achieve an approvable SSMPU.

SECTION 3

BASIS OF DESIGN

3 BASIS OF DESIGN

The basis of design is the core information from which this Front End Design of the SSMPU has been developed.

Fundamental data (non confidential) which have been obtained from Alkaloida are presented. Example process descriptions are given and a process materials balance is presented as a method of estimating process losses.

3.1 BASIC DATA

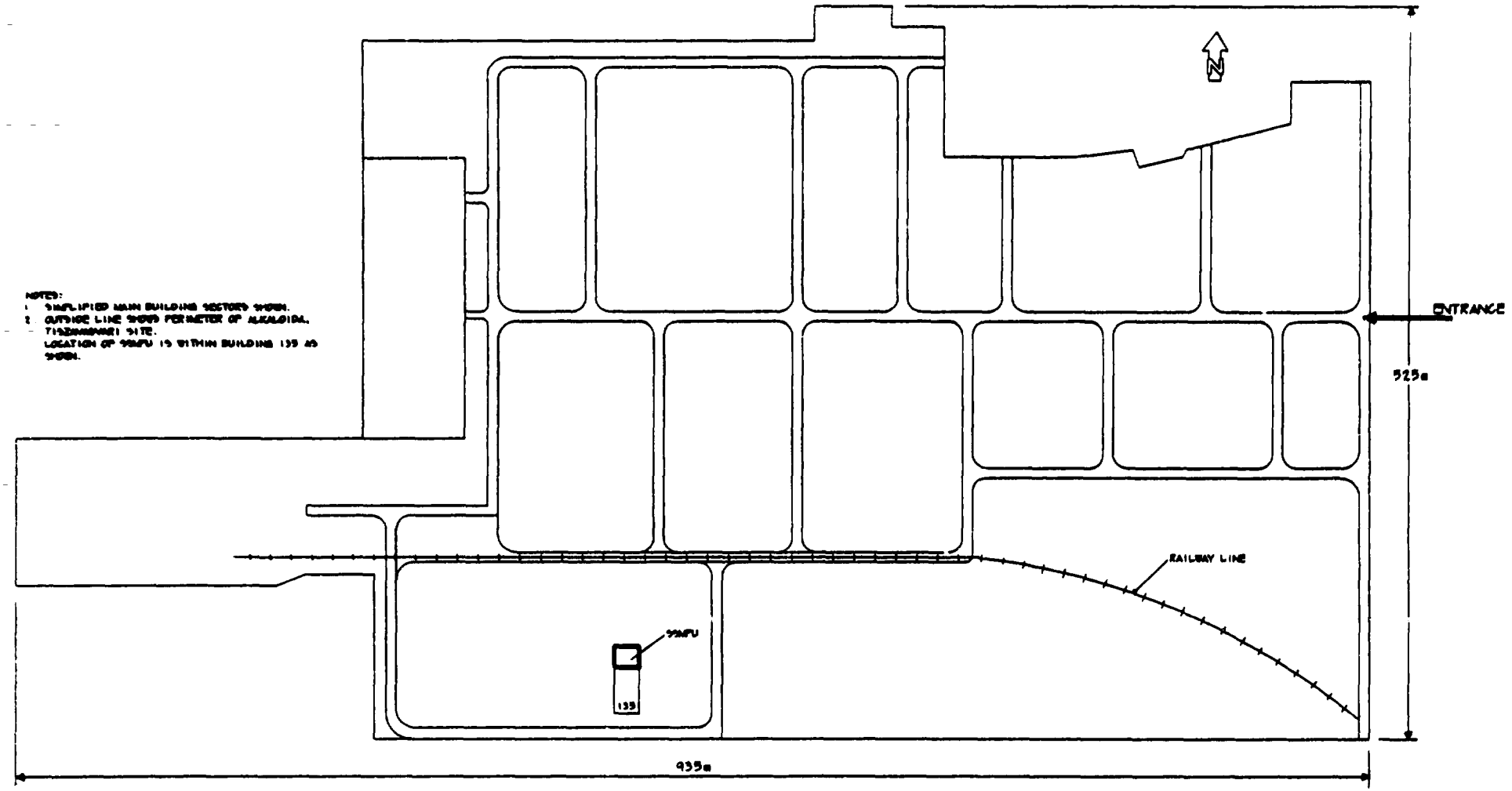
The new plant is a small-scale, multiproduct medicinal chemical manufacturing unit which is the subject of this report and is designed to meet the Good Manufacturing Practices (GMP) requirements of the EC and USA.

A site for the new plant has been allocated in an empty part of an already operational production building on the Alkaloida Tiszavasvari site, Building 135. The location of this building on the Alkaloida site is given in the simplified overall Alkaloida site layout drg. 92/005/116. A more detailed layout of the local area is given in drg. 92/005/115 Local Site Layout. The position of the SSMPU within Building 135 is indicated.

The overall plant is on two levels, the 1st floor synthesis suite and the ground floor DSP facility.

The 1st floor contains synthesis, extraction, distillation and separation equipment.

The ground floor contains the DSP area for which the process equipment requirements have been defined by Alkaloida.



NOTES:
1. SIMPLIFIED MAIN BUILDING SECTORS SHOWN.
2. OUTSIDE LINE SHOWS PERIMETER OF ALKALOIDA, TISZAVASVARI SITE.
   LOCATION OF 99MPU IS WITHIN BUILDING 139 AS SHOWN.

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APPRD JD						
DRAWN CS			ISSUED FOR REPORT	B	5/7/92	
			ISSUED FOR REPORT	A	24/7/92	
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DIMENSIONS IN: N/A

PROJECT
ALKALOIDA I
TF/HUN/90/907

TITLE
ALKALOIDA
TISZAVASVARI
OVERALL SITE LAYOUT

DRAWING NUMBER
92/005/116

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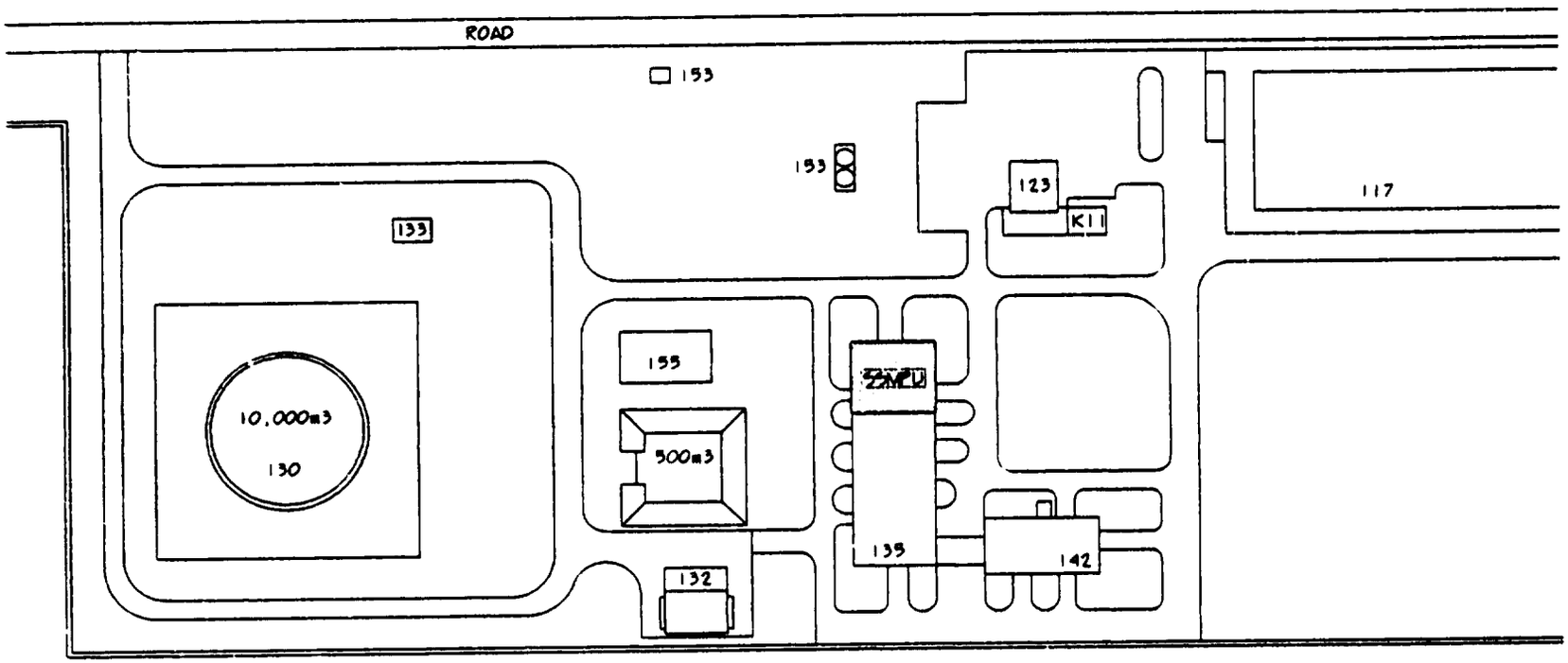

NOTE
NUMBERS ARE BUILDING REFERENCES

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APPRD JD							DATE: APRIL 1992
DRAWN CS			ISSUED FOR REPORT	A	25/6/92		SCALE: 1:1000
			MODIFICATION	ISSUE	DATE		DIMENSIONS IN: N/A

PROJECT: ALKALOIDA I TF/HUN/90/907	TITLE: ALKALOIDA TISZAVASVARI SITE LAYOUT	
	DRAWING NUMBER: 92/005/115	REV: A

The ground floor has an area approximately the same size as the 1st floor, 256m^2, and is located directly below it. The preliminary layouts of both the ground and first floor areas have been developed by Alkaloida engineers and some internal wall construction has been carried out.

Service rooms are present on the ground and 1st floors of approximately 24 and 42 m^2 respectively. Provisionally the 1st floor service area has been set aside for HVAC equipment.

The synthesis plant is operated continuously with 4 people per shift.

The downstream processing plant is, however, operated by 4-5 men in one shift per day. A batch size of 100-200kg of dry powder is planned to be produced every 2 days.

It is understood that the plant handles a variety of solvents and that the powders produced are potentially explosive.

One of the most important basic features of the SSMPU which must be appreciated (since it is absolutely fundamental to the design of the SSMPU within the context of this FED study) is the fact that the unit is designed to accommodate the production of one product for at least the first 2-3 years of its operating life. The product name is confidential and will hereafter be called Example Pharmaceutical Chemical (EPC). The equipment needed for EPC will be installed and piped-up according to the precise operating requirements. However, some additional process equipment will also be installed, but not piped-up initially, to give the SSMPU a degree of flexibility (by means of pipework addition and/or reconfiguration) to accommodate other processes after the initial 2-3 period of EPC production.

A possible second process scheme has been discussed, GRC Consultants/Alkaloida, and outline information has been made available. This is confidential and is not included in this FED study. However, the information was used by GRC Consultants in the development of the design of the SSMPU in such a way that the later reconfiguration of pipework could be carried out without a major reconstruction of the whole SSMPU. It is emphasized, however, that the anticipation of flexibility, etc, for later processes in no way affects the design of the SSMPU for its primary and most important task of producing EPC.

There is also a second important basic feature of the design of the SSMPU which must be appreciated within the Terms of Reference for the combined FED studies. The designs and specifications developed for, and presented in, this FED study are based on GRC Consultants experience of, and expertise with, similar medicinal chemical production units in Western Europe and North America. Hence the approach to process design, safety and good operating practices is that which would be used for the design/specification of an equivalent facility in the UK. This inevitably means that, on occasions, during project progress meetings and reviews of Alkaloida's own preliminary designs, GRC Consultants process design and engineering specifications will differ from those of Alkaloida (using Hungarian norms, etc). However, for the purposes of this FED study, where the emphasis has always been understood and agreed to base the design on current "Western" Good Manufacturing (and Safe Operating) Practice, GRC Consultants norms and standards have been used. It is fully appreciated that in some cases this may lead to relatively more "expensive" designs/specifications but these matters can be discussed and resolved at the design stage of the project.

3.2 PROCESS DESCRIPTION

GRC Consultants has been provided with process information by Alkaloida for the first product, EPC, and the descriptions which follow should be read in conjunction with the outline Process Block Diagram and the Equipment Flow Diagrams. Since the overall process is conveniently divided into two distinct stages, synthesis and downstream processing, it is appropriate to describe these stages separately.

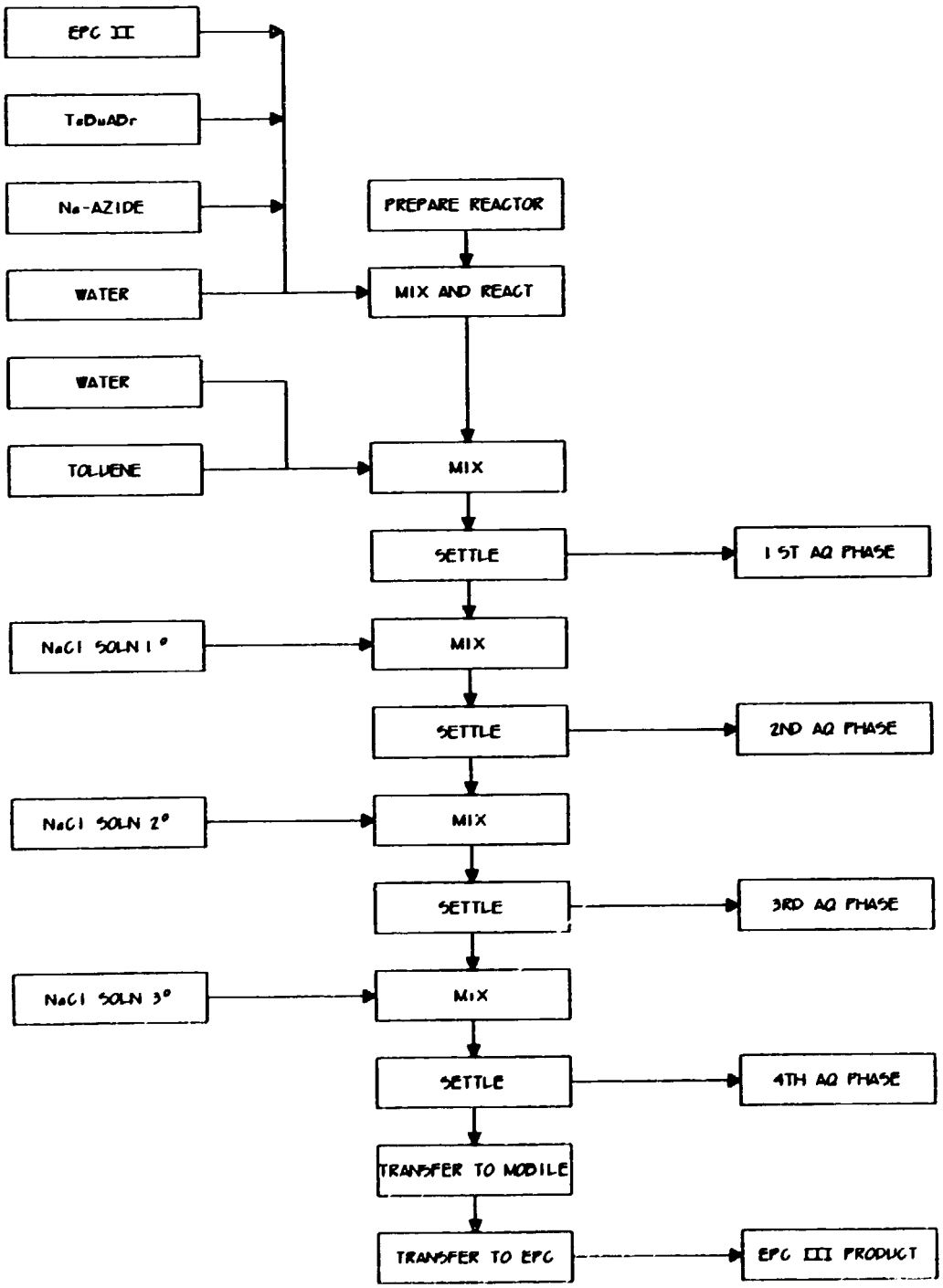
3.2.1 Synthesis

The processes performed in the synthesis suite of this facility are Stage 3, Stage 5 and Deazidation and Waste Water Neutralisation which are shown in Process Block Diagrams 92/013/221, 92/013/222 and 92/013/223 respectively. The process block diagrams are for reasons of confidentiality reproduced in the report in shortened form. The full versions are produced in the confidential technical annex.

Stages I, II and IV of the EPC process are performed elsewhere on site and the raw materials are transferred to the SSMPU for stages III and V. Stage V produces the raw material for the downstream processing part of the SSMPU. Stages III and V and the associated deazidation and waste water neutralisation are described below.

Stage 3 reacts EPC II, produced elsewhere on site, with sodium azide and several solvent/water extractions are performed to produce EPC III. The reactants for the azidation in stage 3 are fed into the reactor including a significant amount of solid powder EPC II. When the reaction has taken place toluene and water are added and mixed into the solution. The mixture is settled and the aqueous phase is discarded. The resulting organic phase is washed three times with brine (NaCl solution). This is achieved each time by mixing the aqueous

DRG No. 92/013/221A



PROCESS BLOCK DIAGRAM STAGE 3 - SHORTENED FORM

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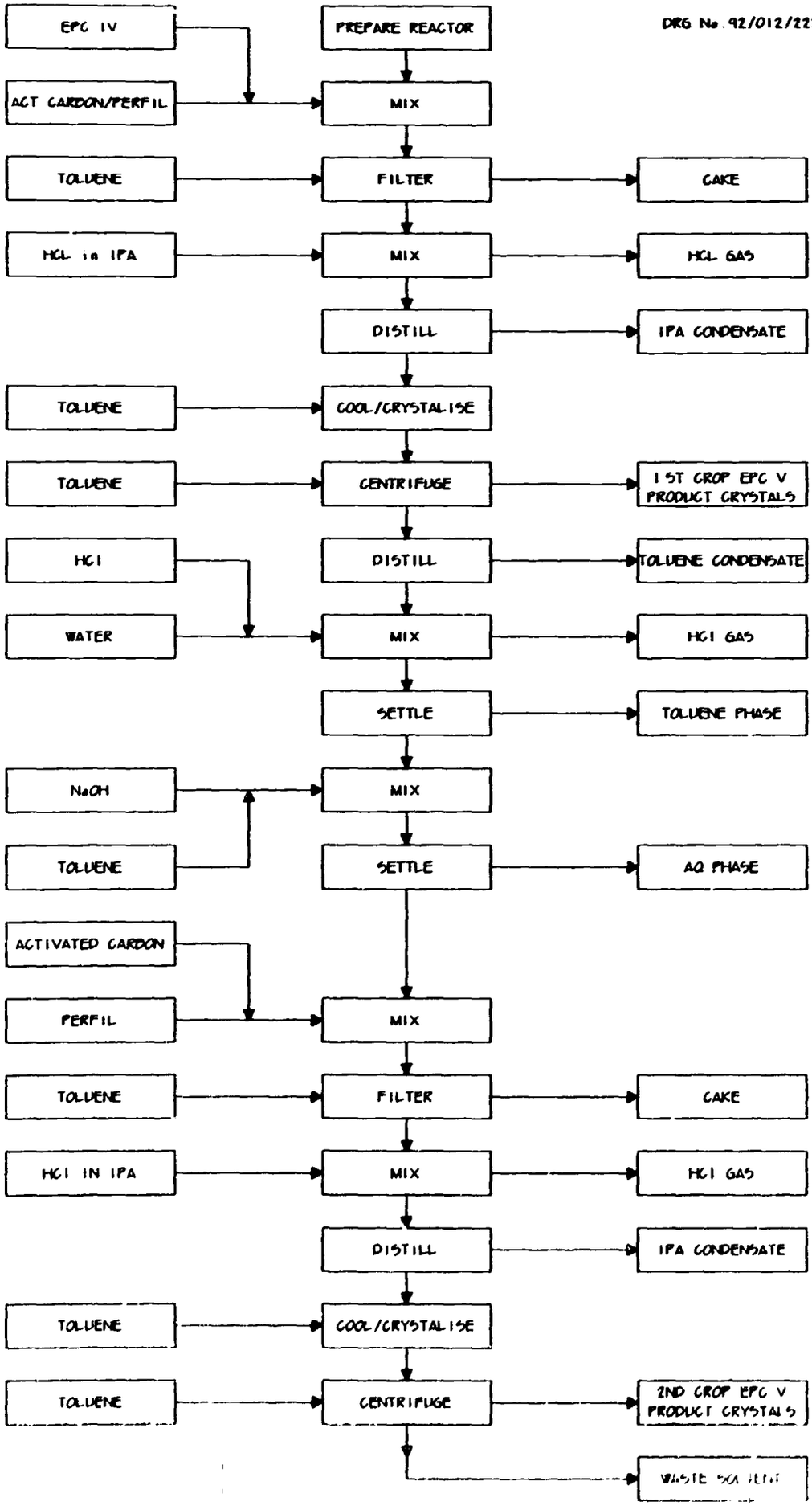
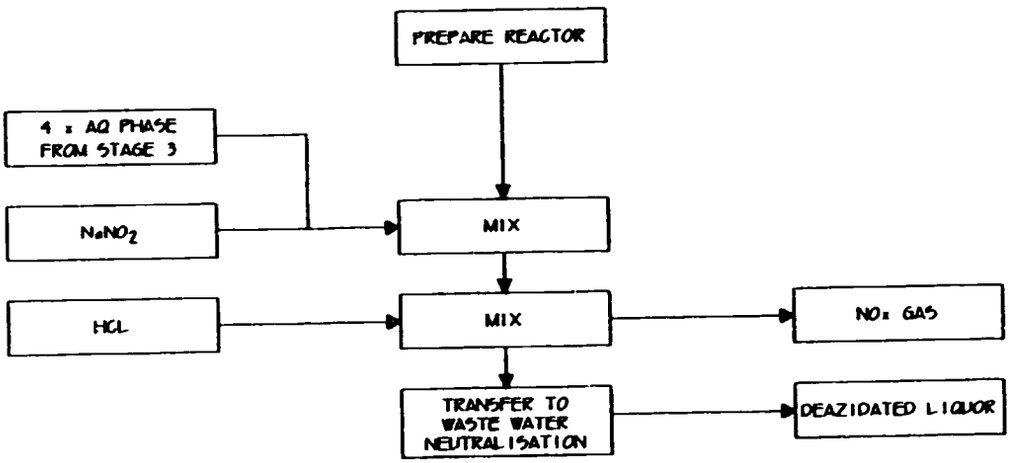


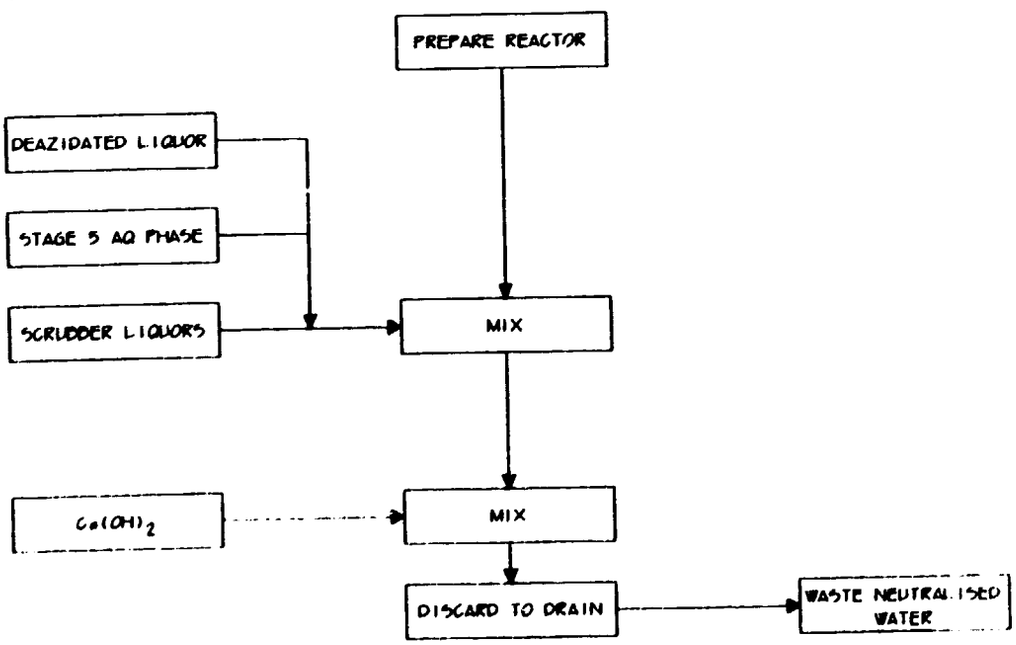
PROCESS BLOCK DIAGRAM STAGE 5 - SHORTENED FORM

DRG No. 92/013/223A

DEAZIDATION



WASTE WATER NEUTRALISATION



PROCESS BLOCK DIAGRAM - SHORTENED FORM
DEAZIDATION AND WASTE WATER NEUTRALISATION

brine solution into the organic phase, allowing to settle and discarding the aqueous phase once the organic/aqueous phase separation has occurred.

The resulting organic solution of EPC III is transferred to a mobile tank for transport to stage IV processing elsewhere on site.

Stage 4 processing produces EPC IV which forms the raw material for stage 5. EPC IV is mixed with activated carbon and the filter aid perfil and subsequently filtered producing an activated carbon cake which is transported away for incineration. The resulting clarified solution is reacted with HCl in IPA with the evolution of HCl gas which is removed by scrubbing of the reactor exit gases. The reaction mixture is then distilled producing an Isopropyl Alcohol condensate transported to on site solvent recovery.

Toluene is added to the residual liquor from the distillation and the resulting mixture cooled producing a crystal slurry. This slurry is centrifuged with a toluene wash to produce the first crop of EPC IV crystals which are processed further in the downstream processing section of the SSMPU.

The clarified liquor produced by the centrifugation is further processed as described below to produce a second crop of EPC IV crystals.

The liquor is first distilled producing a toluene condensate which is transported away to solvent recovery elsewhere on site. HCl and water is added to the residual liquor producing HCl gas which is scrubbed in the usual manner. The liquid mixture is agitated and allowed to settle, the toluene phase being discarded for solvent recovery. Sodium hydroxide and toluene are added to the aqueous phase and again mixed and settled. This time the aqueous phase is discarded to waste water neutralisation.

The organic phase is for a second time mixed with activated carbon and filtered, with a toluene cake wash. The clarified liquor is reacted with HCl in IPA and distilled producing IPA condensate which is transported away for solvent recovery.

Toluene is added to the residual liquor and the resultant mixture cooled, producing a crystalline slurry. This slurry is centrifuged incorporating a toluene wash producing waste solvent for incineration and a second crop of EPC V crystals for further processing in downstream processing.

Two crystal crops have now been produced and stage 5 is complete.

In stage 3 and stage 5 a number of waste aqueous streams are produced and these must be treated before disposal into the site drainage system. The deazidation and waste water neutralisation processes do not strictly have to be part of the GMP facility as they are purely waste treatment and have no influence on final product quality. However these processes will be substantially performed in the synthesis suite and as such will be required to adhere to GMP principles and are described below.

Stage 3 produces 4 batches of aqueous waste which will undergo deazidation. The waste is mixed with sodium nitrate and hydrochloric acid evolving NOx gas which is diverted to a scrubber. The resulting deazidated liquor is transferred to waste water neutralisation.

In waste water neutralisation aqueous liquors from deazidation, stage 5 and the process scrubbers are treated with calcium hydroxide and on reaching the required pH are discarded to drain.

3.2.2 Downstream Processing (DSP)

The DSP stages of the SSMPU are significantly different to the synthesis reactions described in the previous section. DSP operations are very much more concerned with individual unit operations generally carried out in dedicated rooms. Also, since the SSMPU is intended to be multiproduct by nature, for the purposes of this FED study two typical generic process routes (both suitable for EPC production) for DSP are described below:-

PROCESS 1

To be read with reference to the Equipment Flow Diagram 92/005/214 and the process block diagrams, drawings no. 92/005/208 to 92/005/211.

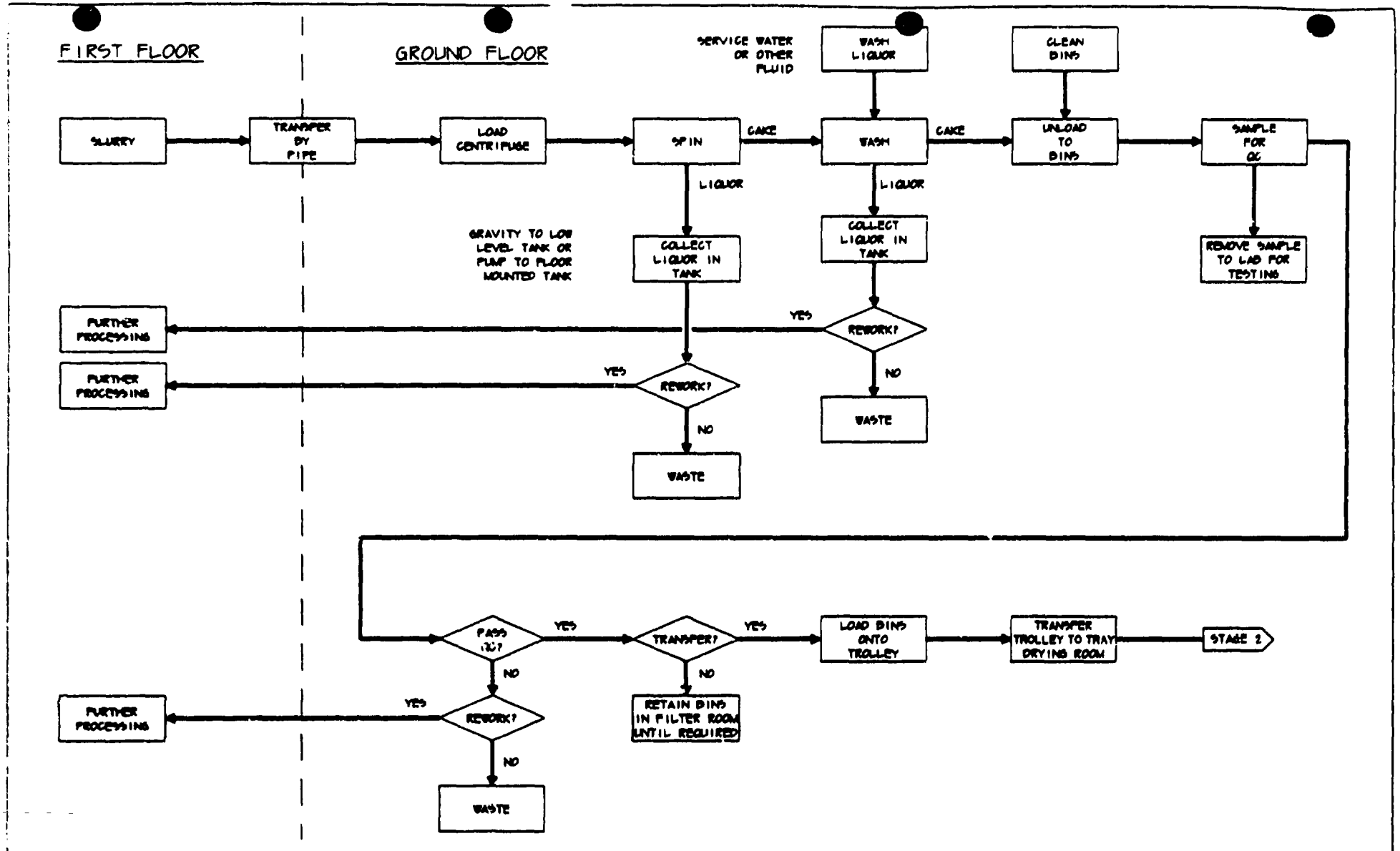
For convenience, the process is split into four discrete stages as follows:

Stage 1	Centrifugation
Stage 2	Drying
Stage 3	Milling and Sieving
Stage 4	Blending and Packing

Stage 1: Centrifuging

Slurry is fed from the 1st floor to the ground floor via a connecting pipe. The slurry is piped directly to the rotating basket type centrifuge, operating in batches.

The feed vessel on the 1st floor is under continuous agitation to prevent any settling of the slurry.



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PROJECT
ALKALOIDA I
TF/HUN/90/907

TITLE
PROCESS 1 . STAGE 1 :
CENTRIFUGATION

DRAWING NUMBER
92/005/208

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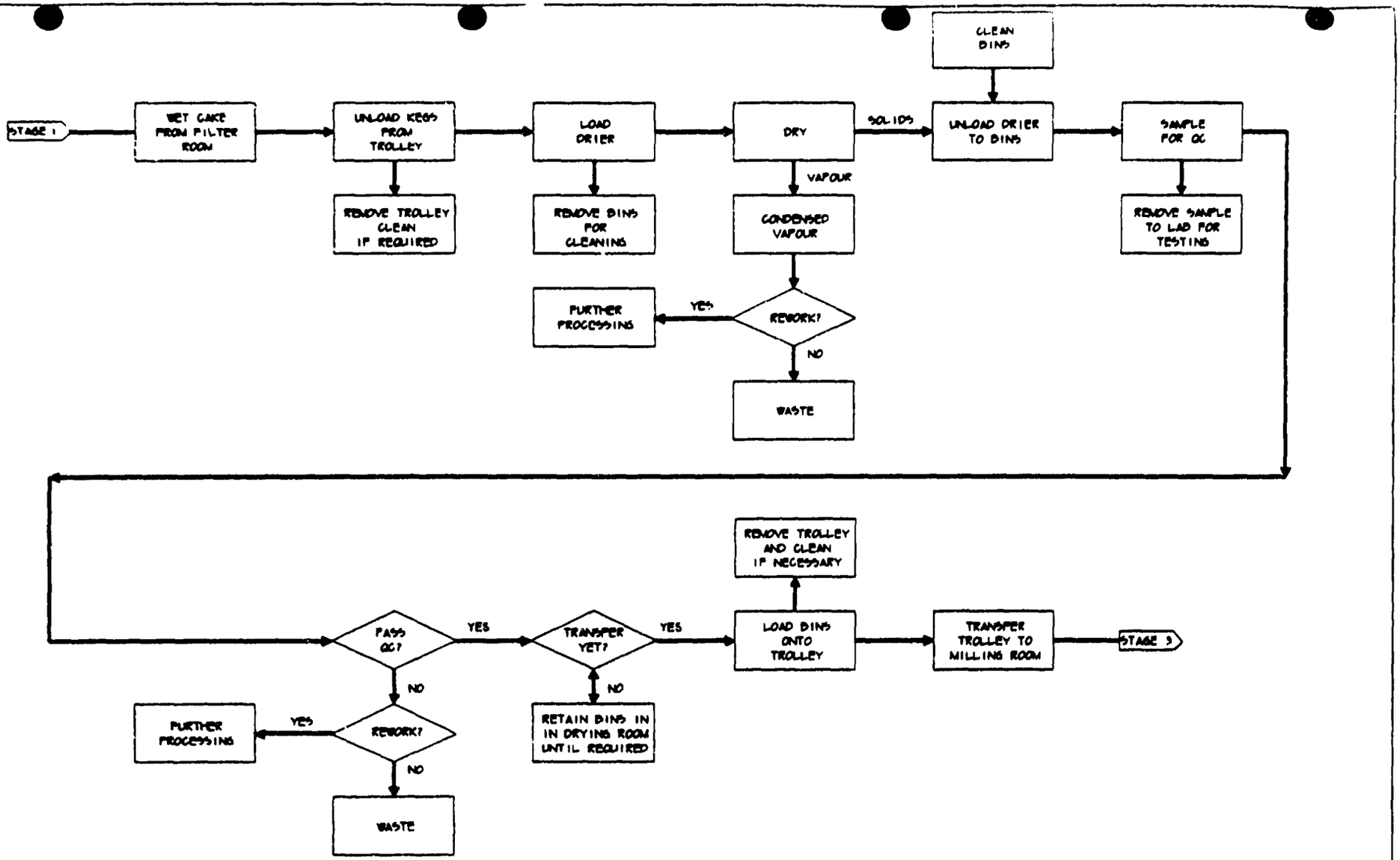

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PROJECT
ALKALOIDA I
TF/HUN/90/907

TITLE
PROCESS 1 STAGE 2:
DRYING

DRAWING NUMBER
92/005/209

REV
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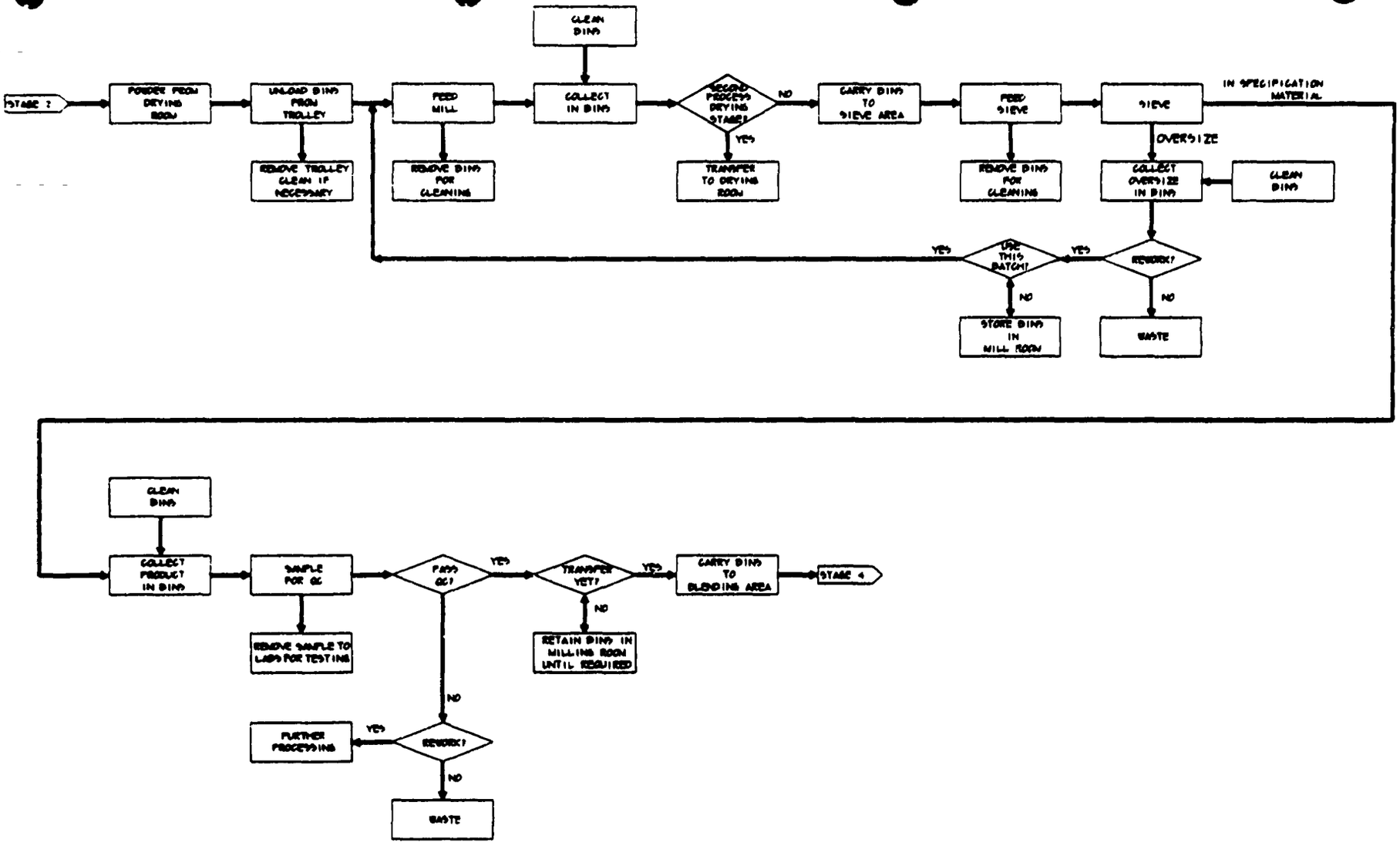

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PROJECT
ALKALOIDA I
TF/HUN/90/907

TITLE
PROCESS 1 STAGE 3:-
MILLING AND SEIVING

DRAWING NUMBER
92005/210

REV
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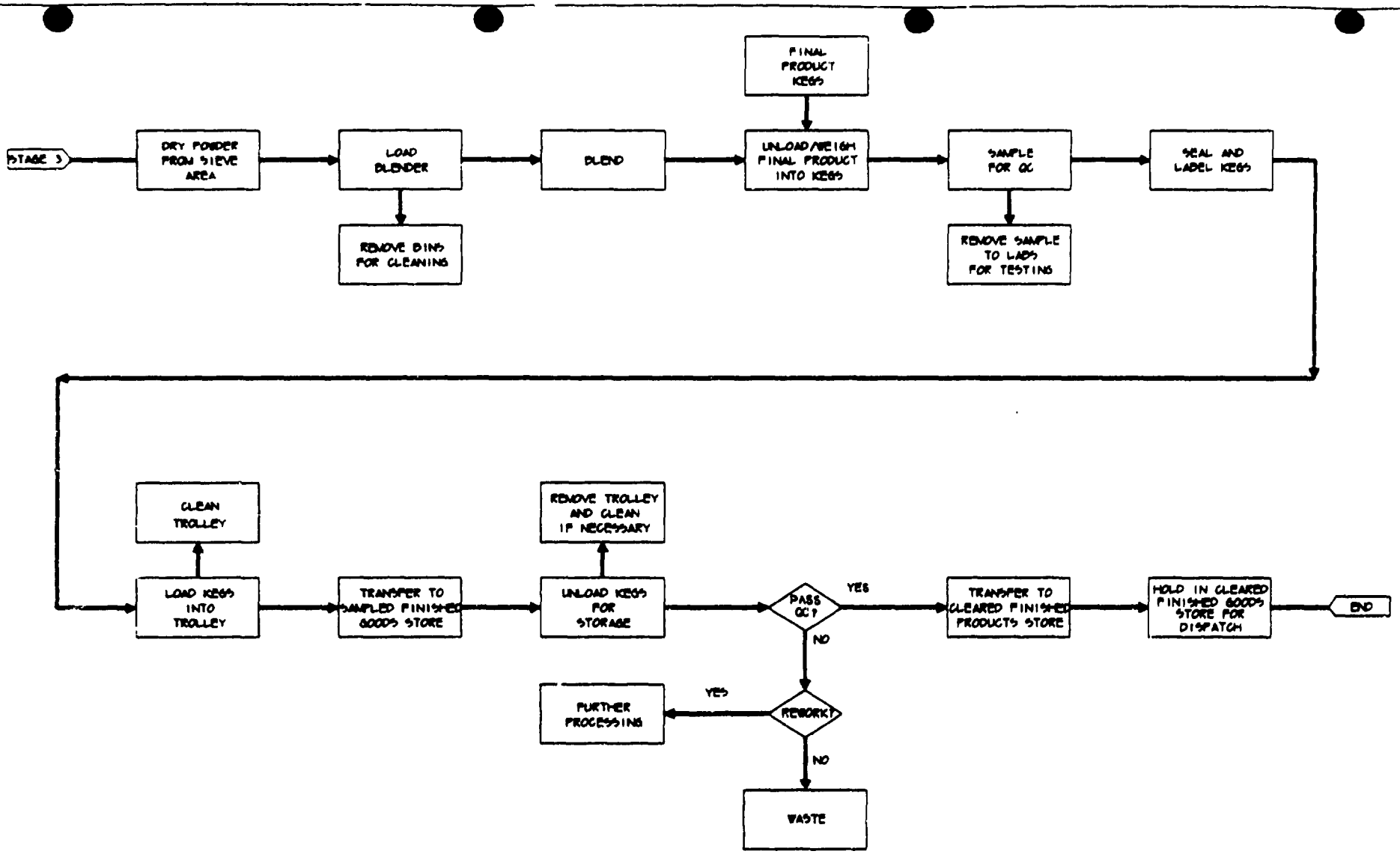

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PROJECT
ALKALOIDA I
TF/HUN/90/907

TITLE
PROCESS 1. STAGE 4
BLENDING & PACKING

DRAWING NUMBER: 92/005/211
REV: A

The liquor from the first centrifuge spin is collected in a tank for reworking elsewhere or disposal. The cake left in the centrifuge is now washed with rinse liquor and spun again. This rinse liquor is collected in a tank for reworking elsewhere or disposal. The wet cake is then removed manually from the centrifuge into a wheeled bin.

A number of centrifuge batches may be required to complete a whole process batch.

At this stage a sample is taken and sent to quality control for analysis.

Stage 2: Drying

The wheeled bin and cake are then transferred to the drying room where the wet cake is loaded manually onto trays which are placed in the tray drier. After the drying cycle is complete the trays are removed and the dried solids unloaded into clean wheeled bins. A sample is taken at this stage for quality control testing.

The liquor collected in the drier condenser is recycled for later use in the synthesis area on the first floor, or disposed of as waste.

Stage 3: Milling and Sieving

The wheeled bin and cake are transferred to the milling and packing room. The dry powder is fed through the mill and collected in clean bins.

The powder may now undergo a size classification stage by passing through a series of sieves.

Stage 4: Blending and Packing

Material of the correct size specification is sampled for quality control. The powder is then loaded into a double cone blender for mixing. Once the blending cycle is complete the material is unloaded into containers and sampled for quality control analysis.

The dry finished powder is then packed, weighed and sealed into its container and is transferred to the 'product receipt' store awaiting quality control results before transfer to the 'cleared finished products' store.

From the finished product store the material is dispatched for sale or further processing elsewhere on the site.

PROCESS 2

To be read with reference to Equipment Flow Diagram 92/005/214.

Process 2 is similar to process 1 and has the same unit operations but uses different equipment for two of these unit operations.

For the final separation stage (the first stage of the downstream processing) a pressure filter is used instead of a centrifugal type filter.

The other change is that the filter cake is dried in a horizontal paddle type vacuum dryer instead of a vacuum tray dryer.

All other operations remain the same.

3.3 PROCESS MASS BALANCE

3.3.1 Synthesis

A process mass balance has been prepared for the EPC synthesis process but because it contains actual process data it cannot be reproduced. It is included in full in the confidential annex.

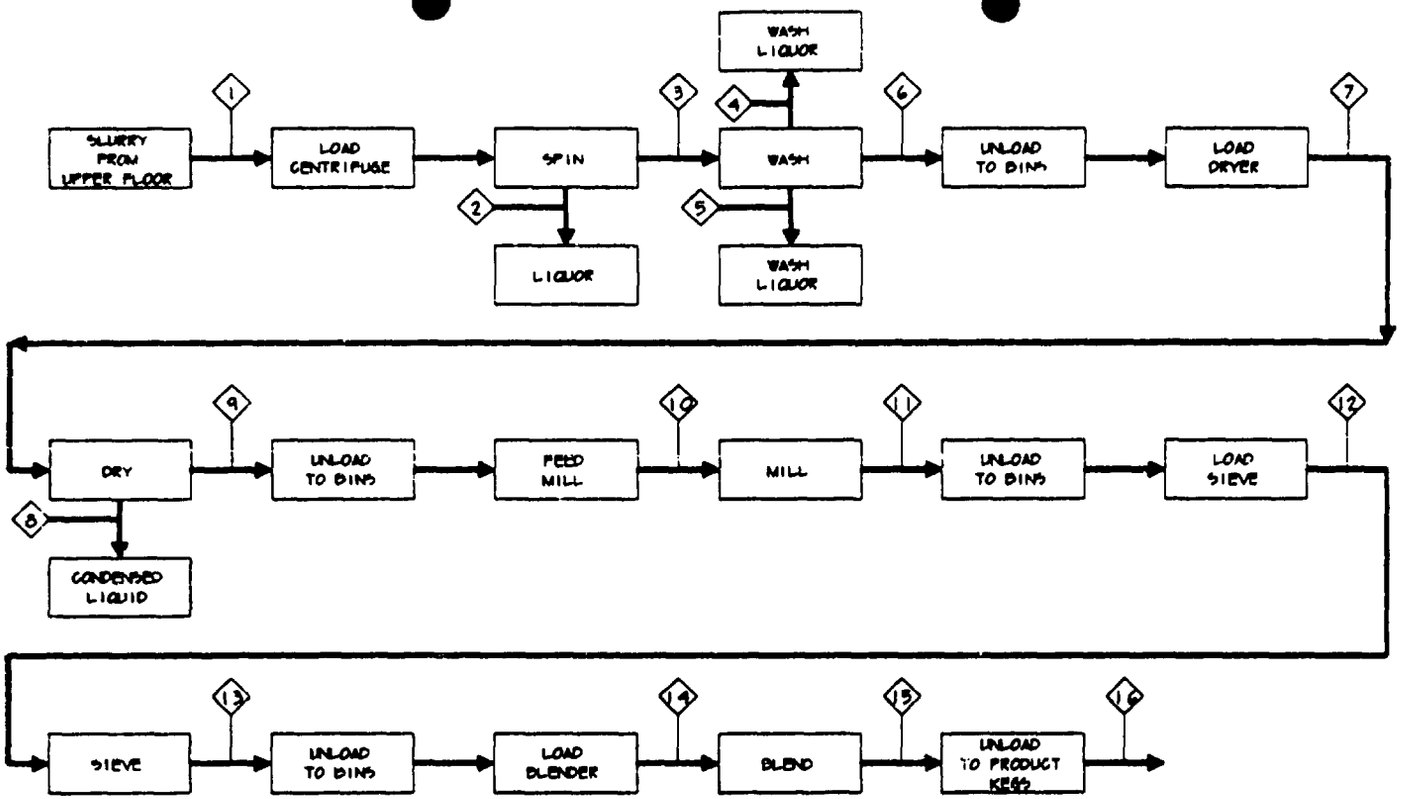
The mass balance for downstream processing contains only example data not related to any particular Alkaloida process and is therefore included for illustration purposes in the main body of this report.

3.3.2 Downstream Processing

A process mass balance is presented for process 1, (drg. no. 92/005/212) and is used to identify overall losses in this type of process.

The loss figures, shown in the tabulation, have been estimated by GRC Consultants and are agreed as typical for these types of unit operations.

Operation	Loss % weight/weight
Centrifugation 1st Stage	5% product lost in liquor stream
Centrifugation Wash Stage	1% product lost in liquor stream
Bin transfer between equipment	2.5%
Tray vacuum drying	0% lost through vacuum line
Milling	1% atmospheric losses
Sieving	1% atmospheric losses
Blender	0% lost



STREAM / MATERIAL	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
SOLID	100.0	5.0	95.0	0	1.0	94.0	91.7	0	91.7	89.4	88.5	86.3	85.4	83.3	83.3	82.5
PROCESS LIQUOR	566.7	250.0	316.7	0	285.0	31.7	30.9	30.9	0	0	0	0	0	0	0	0
WASH LIQUOR	0	0	0	500.0	218.4	281.4	274.6	274.6	0	0	0	0	0	0	0	0
TOTAL	666.7	305.0	411.7	500.0	504.4	407.3	397.1	305.5	91.7	89.4	88.5	86.3	85.4	83.3	83.3	82.5

ALL WEIGHTS IN Kg

BASIS:- 100Kg SOLIDS
566.7Kg PROCESS LIQUOR

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TF/HUN/90/907

TITLE
PROCESS I
EXAMPLE MASS BALANCE

DRAWING NUMBER 92005/212
REV A

The 'bin transfer between equipment' figure is the material loss in unloading one item of equipment into bins and loading the next item of equipment. The lost material is left in the first piece of equipment, in the bin or is lost by spillage.

It can be seen from the mass balance that an overall recovery of about 80% is expected for the downstream plant.

3.4 MATERIALS MOVEMENTS

3.4.1 Synthesis

Two tables are prepared for this section and are included in the main report in an abridged form. Full versions of these tables are included in the confidential technical annex.

Table 3.4.1, the materials movement table, is included to clarify materials movement throughout the process.

The materials entering and leaving each major item of equipment are shown as well as the method of transfer between items of equipment. The table forms the basis for equipment entry nozzle definition and transfer pipework design.

The materials movement summary table 3.4.2 gives a broad overview of materials entering and leaving the plant for each batch produced. This information may be used for costing purposes, and for calculating site storage and waste disposal requirements. It can be seen that the process wastes are dealt with on site largely by recycling or where this is not possible, incineration.

EQUIPMENT			MATERIALS IN		
	Function	Crop	Input	Source	Measured by
7A02	Main azidation reactor/Extractor		S EPC II	Hopper connected above vessel	Pre-weighed
			S TeBuABr	Hopper port	Pre-weighed
			S Na Azide	Hopper connected above vessel	Pre-weighed
			L Water	Water Head Tank GRC/9801	Through Batc
			L Toluene	7H02 Header 9E01	9E01 Level
			L NaCl Soln	7A01	Not Measure
			L Reflux Return	7A02 Condenser	Not Measure
9H02	Vessel 7A02 reflux condenser		G Reflux Vapour	7A02	Not measure
7A01	Brine make-up reactor for 7A02		L Tap Water	Water Head Tank GRC/9801	Batch Meter
			S NaCl	Transfer container	Pre-Weighe
9E01	Toluene header for vessel 7A02		L Toluene	Toluene tank GRC/V4	9E01 Level
GRC/V1	7A02 Aqueous phase measuring vessel		L Aq Phase	7A02	GRC/V1 Lev
7A07	Carbon decolorisation reactor/filter feed	1	L EPC IV	6KD4	7A07 Load
		1	L Toluene	Toluene tank GRC/V4	7A07 Load
		1	S Act.Carbon	Hopper port	Pre-weigh
		1	S Perfil	Hopper port	Pre-weigh
		1	L recycld liqour	7F02	Not measur
		2	L Proc Flow	7X01	7A07 Load
		2	L Toluene	Toluene tank GRC/V4	7A07 Load
		2	S Act.Carbon	Hopper port	Pre-weighe
		2	S Perfil	Hopper port	Pre-weighe
		2	L recycld liqour	7F02	Not measu
7F02	Carbon decolorisation pressure filter	1	L liq for recycle	7A07	Rotameter
		1	M Proc Flow	7A07	Rotameter
		1	L Filtr Wash	7A07	Rotameter
		2	L liq for recycle	7A07	Rotameter
		2	M Proc Flow	7A07	Rotameter
		2	L Filtr Wash	7A07	Rotameter
7A08	Reactor/Evaporatr/Crystalisr/Centrifuge feed	1	L Proc Flow	7F02	Not measu
		1	L HCl in IPA	8E05	8E05 Lev
		2	L Proc Flow	7F02	Not measu
		2	L HCl in IPA	8E05	8E05 Lev
8E05	HCl in IPA Header for 7A08	1	L HCl in IPA	HCl in IPA tank 2T03	8E05 Lev
		2	L HCl in IPA	HCl in IPA tank 2T03	8E05 Lev

Table 3.-.1
Materials Movement Table
Part 1 of 4

MATERIALS IN				MATERIALS OUT			
	Source	Measured by	Method of transfer	Output	Destination	Measured by	Method of transfer
	Hopper connected above vessel	Pre-weighed in hopper	Gravity	G Reflux Vapour	9R02	Not Measured	Rsg Vap
	Hopper port	Pre-weighed in container	Manual	L Aq phase	GRC/V1	GRC/V1 Level ind	Gravity
	Hopper connected above vessel	Pre-weighed in hopper	Gravity	L EPC 111	V1	Scale on V1	Gravity
	Water Head Tank GRC/9B01	Through Batch Meter	Gravity				
	7R02 Header 9E01	9E01 Level Ind	Gravity				
	7A01	Not Measured	Pressure				
urn	7A02 Condenser	Not Measured	Gravity				
our	7A02	Not measured	Rsg Vap	L Condensed Liquid	7A02	Not Measured	Gravity
	Water Head Tank GRC/9B01	Batch Meter	Gravity	L NaCl Soln	7A02	Not Measured	Pressure
	Transfer container	Pre-Weighed in container	Manual				
	Toluene tank GRC/V4	9E01 Level Ind	Pump 1S01	L Toluene	7A02	9E01 Level Ind	Gravity
	7A02	GRC/V1 Level Ind	Pump 1S01	L Aq Phase	7A04	GRC/V1 Level Ind	Pump 6S03
	6K04	7A07 Load cells	Pump GRC/P1	L Liquor for recycle	4F02	Rotameter/No Total	Pump GRC/P2
	Toluene tank GRC/V4	7A07 Load cells	Pump 1S01	M Process Flow	4F02	Rotameter/No Total	Pump GRC/P2
n	Hopper port	Pre-weighed in container	Manual	L Filter Wash	4F02	Rotameter/No Total	Pump GRC/P2
	Hopper port	Pre-weighed in container	Manual				
iquor	7F02	Not measured	Pump GRC/P3				
	7X01	7A07 Load cells	Pressure	L Liquor for recycle	4F02	Rotameter/No Total	Pump GRC/P2
	Toluene tank GRC/V4	7A07 Load cells	Pump 1S01	M Process Flow	4F02	Rotameter/No Total	Pump GRC/P2
	Hopper port	Pre-weighed in container	Manual	L Filter Wash	4F02	Rotameter/No Total	Pump GRC/P2
	Hopper port	Pre-weighed in container	Manual				
iour	7F02	Not measured	Pump GRC/P3				
ycle	7A07	Rotameter/No Total	Pump GRC/P2	L Recycled Liquor	7A07	Not Measured	Pump GRC/P3
	7A07	Rotameter/No Total	Pump GRC/P2	L Proc Flow	7A08	Not measured	Pump GRC/P3
n	7A07	Rotameter/No Total	Pump GRC/P2	M Cake	GRC/T01	Weighed	Gravity
ycle	7A07	Rotameter/No Total	Pump GRC/P2	L Recycled Liquor	7A07	Not Measured	Pump GRC/P3
	7A07	Rotameter/No Total	Pump GRC/P2	L Proc Flow	7A08	Not Measured	Pump GRC/P3
n	7A07	Rotameter/No Total	Pump GRC/P2	M Cake	GRC/T01	Weighed	Gravity
	7F02	Not measured	Pump GRC/P3	G HCl gas	HX2	Not Measured	7L02 Fan
	8E05	8E05 Level Ind	Pump 6S08	G IPA vapour	HX2	Not Measured	7L02 Fan
				M Proc Flow	C1	Not Measured	Gravity
	7F02	Not measured	Pump GRC/P3	G HCl gas	HX2	Not Measured	7L02 Fan
A	8E05	8E05 Level Ind	Pump 6S08	G IPA vapour	HX2	Not Measured	7L02 Fan
				M Proc Flow	C1	Not Measured	Gravity
	HCl in IPA tank 2T03	8E05 Level Ind	Pump 1S04	L HCl in IPA	7A08	8E05 Level Ind	Pump 6S08
	HCl in IPA tank 2T03	8E05 Level Ind	Pump 1S04	L HCl in IPA	7A08	8E05 Level Ind	Pump 6S08

SECTION 3

EQUIPMENT			MATERIALS IN		
	Function	Crop	Input	Source	Measured by
9W08	Vessel V3 condenser	1	G IPA Vapour	7A08	Not measured
		2	G IPA Vapour	7A08	Not measured
8E03	IPA distilate receiver (from 7A08)	1	L Cnd=sd IPA	9W08	8E03 level indicator
		2	L Cnd=sd IPA	9W08	8E03 level indicator
6E03	HCl Scrubber 7L02 recirculation liquor tank 1	1	L NaOH Soln	8E02	8E02 Level Ind
			L Scrub liq return	7L02	Not measured
		2	6E03 not used in the 2nd crop process		
6E04	HCl Scrubber 7L02 recirculation liquor tank 2	1	6E04 not used in the 1st crop process		
		2	L NaOH Soln	8E02	8E02 Level Ind
			L Scrub liq return	7L02	Not measured
8E02	NaOH Dilution Header	1	L NaOH	NaOH tank 2T01	8E02 Level Ind
			L Water	Water Head Tank GRC/9W01	8E02 Level Ind
		2	L NaOH	NaOH tank 2T01	8E02 Level Ind
			L Water	Water Head Tank GRC/9W01	8E02 Level Ind
			L NaOH	NaOH tank 2T01	8E02 Level Ind
			L Water	Water Head Tank GRC/9W01	8E02 Level Ind
7L02	HCl Scrubber Column	1	L Scrub Liq	6E03	Rotameter/No Total
			G HCl Vapour	9W08	Flo M Dev/No Total
		2	L Scrub Liq	6E04	Rotameter/No Total
			G HCl Vap	9W09	Flo M Dev/No Total
			G HCl Vapour	9W08	Flo M Dev/No Total
4F01	Centrifuge	1	M proc flow	7A08	Not Measured
			L Wash Liq	Toluene tank GRC/V4	Batch Meter
		2	M proc flow	7A08	Not Measured
			L Toluene	Toluene tank GRC/V4	Batch Meter
GRC/V6	Centrifuge liquor receipt tank 1	1	L Proc Flow	4F01	Not Measured
		2	L Proc Flow	4F01	Not Measured

Table 3.4.1
Materials Movement Table
Part 2 of 4

MATERIALS IN			MATERIALS OUT			
Source	Measured by	Method of transfer	Output	Destination	Measured by	Method of transfer
:08	Not measured	Fan 9V02	G vapour free of IPA L Cntmtd IPA	7L02 8E03	Not Measured 8E03 Level Ind	Fan 9V02
:08	Not measured	Fan 9V02	G vapour free of IPA L Cntmtd IPA	7L02 8E03	Not Measured 8E03 Level Ind	Fan 9V02
:W08	8E03 level indicator	Gravity	L Cntmtd IPA	1R01	1R01 level Ind	Gravity
:08	8E03 level indicator	Gravity	L Cntmtd IPA	1R01	1R01 level Ind	Gravity
:E02 :L02	8E02 Level Ind Not measured	Gravity Gravity	L Scrubbing liquor L Waste liq	7L02 2A01	Rotameter/No Total 2A01 Level Ind	Pump 6S01 Pump 6S01
e 2nd crop process			6E03 not used in the 2nd crop process			
e 1st crop process			6E04 not used in the 1st crop process			
3E02 n 7L02	8E02 Level Ind Not measured	Gravity Gravity	L Scrubbing liquor L Waste liq	7L02 2A01	Rotameter/No Total 2A01 Level Ind	Pump 6S01 Pump 6S01
NaOH tank 2T01 Water Head Tank GRC/9B01	8E02 Level Ind 8E02 Level Ind	Pump 1S02 Gravity	L NaOH Soln	6E03	8E02 Level Ind	Gravity
NaOH tank 2T01 Water Head Tank GRC/9B01	8E02 Level Ind 8E02 Level Ind	Pump 1S02 Gravity	L NaOH Soln	6E04	8E02 Level Ind	Gravity
NaOH tank 2T01 Water Head Tank GRC/9B01	8E02 Level Ind 8E02 Level Ind	Pump 1S02 Gravity	L NaOH Soln L NaOH Soln	6E01 6E02	8E02 Level Ind 8E02 Level Ind	Gravity Gravity
5E03 9W08	Rotameter/No Total Flo M Dev/No Total	Pump 6S01 Fan 9V02	L Srubbing liquor G Scrubbed Gas	6E03 Vent	Not measured Not Measured	Gravity Fan 9V02
5E04 9W09 9W08	Rotameter/No Total Flo M Dev/No Total Flo M Dev/No Total	Pump 6S01 Fan 9V02 Fan 9V02	L Srubbing liquor G Scrubbed Gas G Scrubbed Gas	6E04 Vent Vent	Not measured Not Measured Not Measured	Gravity Fan 9V02 Fan 9V02
7A08 Toluene tank GRC/V4	Not Measured Batch Meter	Gravity Gravity	L Proc Flow M Hex V Prodct	GRC /V6 /V7 GRC/V2	Not Measured Weigh Scales	Pump GRC/P4 Manual
7A08 Toluene tank GRC/V4	Not Measured Batch Meter	Gravity Pump 1S01	L For Burning M EPC V Product	GRC/V6 GRC/V2	Not Measured Weigh Scales	Pump GRC/P4 Manual
4F01	Not Measured	Pump GRC/P4	L Proc Flow	7A09	Not Measured	Pump 3S01/I
4F01	Not Measured	Pump GRC/P4	L Proc Flow	GRC/MV1	GRC/MV1 Level Ind	Pump 3S01/II

SECTION 2

EQUIPMENT			MATERIALS IN		
	Function	Crop	Input	Source	Measured by
GRC/V7	Centrifuge liquor receipt tank 2	1	797Kg L Proc Flow	4F01	Not Measured
		2	GRC/V7 not used in 2nd crop process		
7A09	Evaporator		L Proc Flow	GRC /V6 /V7	Not Measured
9W09	9A09 Condenser		G Tol. Vap	7A09	Not Measured
GRC/V3	9W09 Condensate receiver		L Conc Tol.	9W09	GRC/V3 Level Ind
7A06	Reactor/Extractor		L Proc Flow	7A09	Not measured
			L Tap Water	Water Head Tank GRC/9B01	Batch meter
			L HCl Acid	Header 8E01	8E01 Level Ind
8E01	HCl Acid Header for 7A05 and 7A06		L HCl Acid	HCl Acid tank 2T02	8E01 Level Ind
7X01	Extractor		L Proc Flow	7A06	Not Measured
			L NaOH	Header 8E03	8E03 Level Ind
			L Toluene	Toluene tank GRC/V4	Batch Meter
9E03	NaOH Header for 7X01		L Conc NaOH	Conc NaOH tank 2T01	9E03 Level Ind
7A04	Deazidation reactor 1 - Sodium Nitrate addition		L Aq Waste	7A02	Not Measured
			S Na Nitrate	Hopper connected above vessel	Pre-Weighed in hopper
7A05	Deazidation reactor 2 - HCl addition		L Aq Waste	7A05	Not Measured
			L HCl Acid	Header 8E01	8E01 Level Ind
2A01	Waste water neutralisation tank		L Aq Waste	7A05	2A01 Level Ind
			L Waste liq	6E01	2A01 Level Ind
			L Waste liq	6E02	2A01 Level Ind
			L Waste liq	6E03	2A01 Level Ind
			L Aq Waste	7X01	2A01 Level Ind
			L Waste liq	6E04	2A01 Level Ind
			L Ca Hydrox	Hopper connected above vessel	Pre-Weighed hopper
6E01	NOx scrubber 7L01 recirculation liquor tank 1		L Dilute NaOH	8E02	8E02 Level Ind
			L Scrub liq return	7L01	Not measured
6E02	NOx scrubber 7L01 recirculation liquor tank 2		L Dilute NaOH	8E02	8E02 Level Ind
			L Scrub liq return	7L01	Not measured
7L01	NOx scrubber		G NOx Vapour	7A04	Flo M Dev/No Total
			L Srubbing liquor	V15	Rotameter/No Total

SECTION 1

Table 3.4.1
Materials Movement Table
Part 3 of 4

MATERIALS IN			MATERIALS OUT			
Source	Measured by	Method of transfer	Output	Destination	Measured by	Method of transfer
:1	Not Measured	Pump GRC/P4	L Proc Flow	7A09	Not Measured	Pump 3S01/I
a crop process			GRC/V7 not used in 2nd crop process			
: /V6 /V7	Not Measured	Pump 3S01/I	G Toluene Vap	9B09	Not Measured	Rsg Vap
			L Proc Flow	7A06	Not Measured	Pump 6S09
09	Not Measured	Rsg Vap	L Cont. Tol	GRC/V3	GRC/V3 Level Ind	Gravity
			G Vapour free of Tol	Vent	Not Measured	Rsg Vap
09	GRC/V3 Level Ind	Gravity	L Cont Tol	IR02	GRC/V3 Level Ind	Pump 6S09
09	Not measured	Pressure	G HCl Vapour	7L02	Not Measured	Fan 9V02
ter Head Tank GRC/9B01	Batch meter	Gravity	L Cont. Tol	GRC/RV2	Not Measured	Gravity
eader 8E01	8E01 Level Ind	Gravity	L Proc Flow	7X01	Not Measured	Pressure
: Acid tank 2T02	8E01 Level Ind	Pump 1S03	L HCl Acid	7A06	8E01 Level Ind	Gravity
			L HCl Acid	7A05	8E01 Level Ind	Gravity
06	Not Measured	Pressure	L Aq Waste	2A01	Not Measured	Gravity
eader 8E03	8E03 Level Ind	Gravity	L Proc Flow	7A07	7A07 Load Cells	Pressure
oluene tank GRC/V4	Batch Meter	Pump 1S01				
Conc NaOH tank 2T01	9E03 Level Ind	Pump 1S02	L Conc NaOH	7X01	9E03 Level Ind	Gravity
02	Not Measured	Gravity	L Aq Waste	7A05	Not Measured	Pressure
opper connected above vessel	Pre-Weighed in hopper	Gravity	G NOx Vapour	7L01	Flow Meas Device	Fan 9V01
05	Not Measured	Gravity	L Aq Waste	2A02	Not Measured	Gravity
eader 8E01	8E01 Level Ind	Gravity				
05	2A01 Level Ind	Gravity	L Waste Water	Drain	Not Measured	Gravity
01	2A01 Level Ind	Pump 6S05				
02	2A01 Level Ind	Pump 6S05				
03	2A01 Level Ind	Pump 6S01				
01	2A01 Level Ind	Gravity				
04	2A01 Level Ind	Pump 6S01				
opper connected above vessel	Pre-Weighed hopper	Gravity				
E02	8E02 Level Ind	Gravity	L Scrubbing liquor	7L02	Rotameter/No Total	Pump 6S05
L01	Not measured	Gravity	L Waste liq	2A02	2A02 Level Ind	Pump 6S05
E02	8E02 Level Ind	Gravity	L Scrubbing liquor	7L02	Rotameter/No Total	Pump 6S05
L01	Not measured	Gravity	L Waste liq	2A02	2A02 Level Ind	Pump 6S05
A04	Flo M Dev/No Total	Fan 9V01	L Srubbing liquor	6E01	Not Measured	Gravity
15	Rotameter/No Total	Pump 6S05	G Scrubbed Gas	Vent	Not Measured	Fan 9V01

SECTION 2

EQUIPMENT			MATERIALS IN		
	Function	Crop	Input	Source	Measured by
	Wheeled vessels				
6KD6	EPC IV wheeled vessel for transfer to this plant		From EPC IV plant	-	
6KB1	EPC III wheeled vessel for Transfer to EPC IV plant		L EPC III	7A02	6K01 Vessel Scale
IR01	IPA Recovery Vessels on wheeled trailer	1	L Conc IPA	8E03	1R01 Level Ind
		2	L Conc IPA	8E03	1R01 Level Ind
IR02	Toluene condensate recovery wheeled vessel		L Conc Tol	GRC/V3	GRC/V3 Level Ind
GRC/RV2	Toluene recovery wheeled vessel		L Conc Tol	7A06	GRC/RV4 Lev Indica
GRC/RV1	Centrifuge Waste Liquor wheeled vessel for incineration		L Proc Flow	GRC/V6	GRC/RV1 Level Ind
	Raw Material Tanks Note that total volumes per batch are given below				
2T01	Conc NaOH storage tank		Filled from equipment external to plant		
2T02	Conc HCl Acid storage tank		Filled from equipment external to plant		
2T03	HCl In IPA storage tank		Filled from equipment external to plant		
GRC/V4	Toluene storage tank		Filled from equipment external to plant		
GRC/WB01	Water Head Tank		Filled from water ring main		

Abbreviations
Rsg Vap - Rising Vapour
Ind - Indicator
Proc Flow - Process Flow
Flo M Dev - Flow Measuring Device
Tol - Toluene
Cont - Contaminated
Na - Sodium
Ca - Calcium
Hydrox - Hydroxide
G - Gas phase
L - Liquid phase
S - Solid phase
M - Mixed liquid/solid phase

Table 3.4.1
Materials Movement Table
Part 4 of 4

MATERIALS IN			MATERIALS OUT			
Source	Measured by	Method of transfer	Output	Destination	Measured by	Method of transfer
			L EPC IV	7A07	7A07 load cells	Pump GRC/P1
	6X01 Vessel Scale	Gravity	To EPC IV Plant for further processing			
:2	1R01 Level Ind	6S07	To Solvent recycle plant for further processing			
:3	1R01 Level Ind	6S07	To Solvent recycle plant for further processing			
:3	GRC/V3 Level Ind	Pump 6S09	To Solvent recycle plant for further processing			
C/V3	GRC/MV4 Lev Indicator	Gravity	To Solvent recycle plant for further processing			
6	GRC/MV1 Level Ind	Pump 3S01/II	To incineration plant for disposal			
/V6						
		Pump 1S02	L Conc NaOH	9E03	9E03 Level Ind	Pump 1S02
t external to plant		Pump 1S02	L Conc NaOH	8E02	8E02 Level Ind	Pump 1S02
		Pump 1S03	L HCl Acid	8E01	8E01 Level Ind	Pump 1S03
t external to plant		Pump 1S04	L HCl in IPA	7A08	7A08 Level Ind	Pump 1S04
t external to plant		Pump 1S01	L Toluene	9E01	9E01 Level Ind	Pump 1S01
t external to plant		Pump 1S01	L Toluene	7X01	Batch Meter	Pump 1S01
		Pump 1S01	L Toluene	7A07	7A07 Load cells	Gravity
		Not in Plant	L Water	7A01	Batch Meter	Gravity
ing main			L Water	7A02	Batch Meter	Gravity
			L Water	7A06	Batch Meter	Gravity
			L Water	8E02	Batch Meter	Gravity

Table 3.4.2
Materials Movement Summary

Material Out	Transfered By		Destination
		Gases	
Scrubbed Gas	Vent	Vents from HCl and NOx scrubbers	High Level atmospheric vent
		Liquids	
EPC III	4K01	EPC III wheeled vessel	EPC IV plant for further processing
Contaminated IPA	IB01	IPA Recovery Vessels on wheeled trailer	Site solvent recovery plant
Contaminated Toluene	IB02	Toluene condensate recovery wheeled vessel	Site solvent recovery plant
Contaminated Toluene	GRC/RV2	Toluene recovery wheeled vessel	Site solvent recovery plant
Process Flow	GRC/RV1	Centrifuge Waste Liquor wheeled vessel for incineration	Site incineration plant
Waste Water	Drain	Process Drain	Site process drainage system
		Solids	
Wet Filter cake	GRC/T01	Wheeled bin	Site incineration Plant
Wet EPC V Product	GRC/T02	Wheeled bin	Downstream plant for further processing

Material In	Recieved For Use In Plant By		Source
		Liquids	
EPC IV	6K04	EPC IV wheeled vessel for transfer to this plant	EPC IV plant
Concentrated NaOH	2T01	Conc NaOH storage tank	Wheeled vessel from site NaOH distribution
Hydrochloric Acid	2T02	Conc HCl Acid storage tank	Barrels from site storage
HCl in IPA	2T03	HCl in IPA storage tank	Barrels from site storage
Toluene	GRC/V4	Toluene storage tank	Wheeled vessel from site Toluene distribution
Water	GRC/V801	Water Head Tank	Site water ring main
		Solids	
Sodium Azide	7A02	Azidation reactor	Container from local storage and dispensory
TeBuNBr			Container from local storage and dispensory
EPC II			Container from EPC II plant
Perfil	7A07	Carbon decolorisation reactor/filter feed	Container from local storage and dispensory
Activated Carbon			Container from local storage and dispensory
Sodium Nitrate	7A04	Deazidation reactor 1	Container from local storage and dispensory
Calcium Hydroxide	2A01	Waste water neutralisation tank	Container from local storage and dispensory

3.4.2 Downstream Processing

Materials movement in DSP will be in a linear fashion operated in a batchwise manner. For these reasons no materials movement details for the EPC process are considered necessary at this stage.

3.5 EQUIPMENT UTILISATION SCHEDULES

3.5.1 Synthesis

Process timings have been developed by GRC to determine an order of plant capacity. The following tables and charts illustrate the techniques of using process turnings and serve as a starting point from which Alkaloida, using their process expertise, may refine this data in order to obtain a more accurate estimate. It should be noted that the plant capacity is limited by the synthesis suite capacity and so a detailed analysis of this part of the process is undertaken.

Tables 3.5.1 to 3.5.4 inclusive detail the process in the form of a timetable. Each row represents a time 'slice' beginning at the time shown in the time column and lasting a time duration shown in the dT column. The equipment used in this time slice is denoted in the various equipment columns by an asterisk and the operation carried out is summarised in the description column.

Drgs. 92/013/301 to 92/013/305 are drawn from the data presented in these tables. These timecharts show equipment utilisation over time with equipment presently being used shown as horizontal lines on the chart.

Table 3.5.1
Equipment Utilisation Timetable
Stage 3

Time	7A02	9H02	7A01	GRC-V1	7A04	6K01	dT	Description
0.00	*						0.50	Add EPC II,TeBuABr,Sodium Azide,Water to 7A02
0.50	*	*					0.50	Heat ,Start agitator,Heat to reflux
1.00	*	*					12.00	Reflux for 12 hours
13.00	*	*					0.50	Add tap water,toluene,agitate
13.50	*		*				1.00	Settle for 1 hour, make up NaOH soln in 7A01
14.50	*		*	*	*		0.50	Transfer 1st lower aq. phase to GRC/V1 then 7A04
15.00	*		*	*	*		0.25	Transfer 1st NaCl soln to 7A02 from 7A01, Mix phases
15.25	*		*	*	*		1.00	Settle for 1 hour
16.25	*		*	*	*		0.50	Transfer 2nd lower aq. phase to GRC/V1 then 7A04
16.75	*		*	*	*		0.25	Transfer 2nd NaCl soln to 7A02 from 7A01, Mix phases
[illegible]00	*		*	*	*		1.00	Settle for 1 hour
18.00	*		*	*	*		0.50	Transfer 3rd lower aq. phase to GRC/V1 then 7A04
18.50	*		*	*	*		0.25	Transfer 3rd NaCl soln to 7A02 from 7A01, Mix phases
18.75	*			*	*		1.00	Settle for 1 hour
19.75	*			*	*		0.50	Transfer 4th lower aq. phase to GRC/V1 then 7A04
20.25	*			*	*	*	0.50	Transfer EPC III product to Mobile 6K01
20.75						*		Mobile 6K01 ready for transfer to EPC IV plant

Table 3.5.2
Equipment Utilisation Timetable
Stage 5

Time	6K04	7F02	7A07	8E03	7A08	6E03	6E04	1R01	2A01	4GRC/V6	7GRC/V6	7GRC/V7	9GRC/V3	7A09	1R02	7X01	7GRC/MV2	dT	Description
0.00	*	*																0.50	Transfer from wheeled vessel 6K04 to vessel 7A07
0.50		*																0.50	Add Activated carbon and Perfil to 7A07
1.00		*																1.00	Mix for 1 hour with heating
2.00		*	*	*														0.50	Transfer to filter 7F02
2.50		*	*	*														0.50	Allow filter process to finish and cake to drain
3.00		*	*	*														0.50	Rinse 7A07 with toluene transfer to filter to wash cake
3.50			*	*	*	*	*	*										0.50	Allow filter proc to finish and drain cake: prepare scrubber
4.00			*	*	*	*	*	*										1.00	Add HCl in IPA to 7A08 mix and cool: Unload cake from 7F02
5.00				*	*	*	*	*										2.00	heat 7A08 to 103 deg c ,condensing IPA into 8E03
7.00				*	*	*	*	*										0.50	Add toluene to 7A08 ,mix and cool
7.50				*			*		*	*								0.50	Pump scrubber liquor from 6E03 to 7A04: Transfer 8E03 to 1R01
8.00				*														6.00	Crystalise for 6 hours
14.00				*							*	*						1.00	Feed to centrifuge by gravity, 1st batch collected in GRC/V6
15.00				*							*	*						1.00	2nd batch centrifugation collected in GRC/V6
16.00				*							*	*	*	*				0.50	3rd batch centrifugation to GRC/V7: GRC/V6 pumped to 7A09
16.50				*							*	*	*	*	*			0.50	1st batch evaporation in 7A09: distillate collected in GRC/V3
17.00				*							*	*	*	*	*			0.50	4th batch centrifugation collected in GRC/V7
17.50				*							*	*	*	*	*	*		0.50	1st batch evap. finished:GRC/V3 to 1R02: 7A09 pumped to 7A06
18.00											*	*	*	*	*	*		0.50	5th batch centrifugation to GRC/V6: GRC/V7 pumped to 7A09
18.50											*	*		*	*	*		0.50	2nd batch evaporation in 7A09: distillate collected in GRC/V3
19.00											*	*		*	*	*		0.50	6th batch centrifugation collected in GRC/V6
19.50											*	*		*	*	*		0.50	2nd batch evaporation finished:GRC/V3 to 1R02: 7A09 to 7A06
20.00												*		*	*	*		0.50	6th batch centrifugation finished: GRC/V6 pumped to 7A09
20.50														*	*	*		1.00	3rd batch evap. started in 7A09: distillate collected in GRC/V3
21.50					*	*								*	*	*		0.50	3rd batch evap. done: GRC/V3 to IR02: 7A09 to 7A06: prep scrub
22.00					*	*									*	*		1.00	Add HCl and water to evaporation residues in 7A06 and mix
23.00					*	*									*	*		1.00	Allow 7A06 contents to settle forming 2 phases
24.00					*	*									*	*	*	0.50	Transfer 7A06 lower Aq. phase to 7X01: Toluene phase to GRC/MV2
24.50					*	*										*		0.50	Add NaOH and Toluene and mix
25.00					*	*										*		1.00	Allow 7X01 contents to settle forming 2 phases
26.00	*				*	*		*								*		0.50	Tranfer aq. phase to 2A01: Transfer toluene phase to 7A07
26.50	*				*	*												0.50	Add Activated carbon and Perfil to 7A07
27.00	*				*	*												1.00	Mix for 1 hour and heat
28.00	*	*	*		*	*												0.50	Pump to filter 7F02
28.50	*	*	*		*	*												0.50	Allow filter process to finish and cake to drain
29.00	*	*	*		*	*												0.50	Rinse 7A07 with toluene transfer to filter to wash cake
29.50	*	*	*	*	*	*												0.50	Allow filter process to finish and cake to drain: prep. scrub.
30.00			*	*	*	*												1.00	Add HCl in IPA to 7A08 mix and cool: Unload cake from 7F02
31.00				*	*	*												2.00	heat 7A08 ,condensing IPA into 8E03
33.00				*	*	*												0.50	Add toluene to 7A08 ,mix and cool
33.50				*			*		*									0.50	Pump scrubber liquor from 6E04 to 2A01
34.00				*														6.00	Crystalise for 6 hours
40.00				*							*	*						1.00	Feed to centrifuge by gravity, liquor collected in GRC/V6
41.00				*							*	*					*	0.50	Unload cake to for drying: GRC/V6 to GRC/MV1 for incineration
41.50																	*		Process Complete

Table 3.5.3
Equipment Utilisation Timetable
Deazidation

Stage 3 Timing	7A02	7A04	7A05	7L01	6E01	6E02	2A01	dT	Description
14.50	*	*						0.50	Transfer 1st aq. phase from 7A02 to 7A04
15.00	*	*							Transfer finished
16.25	*	*						0.50	Transfer 2nd aq. phase from 7A02 to 7A04
16.75	*	*							Transfer finished
18.00	*	*						0.50	Transfer 3rd aq. phase from 7A02 to 7A04
18.50	*	*							Transfer finished
19.75	*	*						0.50	Transfer 4th aq. phase from 7A02 to 7A04
20.25		*		*	*	*		0.50	Add Na Nitrate to 7A04: Prepare scrub 7L01
20.75		*	*	*	*	*		0.50	Transfer 7A04 to 7A05
21.25			*	*	*	*		1.00	Add HCl to 7A05
22.25			*	*	*	*	*	0.50	Transfer 7A05 to 2A01
22.75				*	*	*	*	0.50	Pump 6E01/6E02 scrubbing liquor to 2A01
23.25							*		Deazidation complete

Table 3.5.4
Equipment Utilisation Timetable
Waste Water Neutralisation

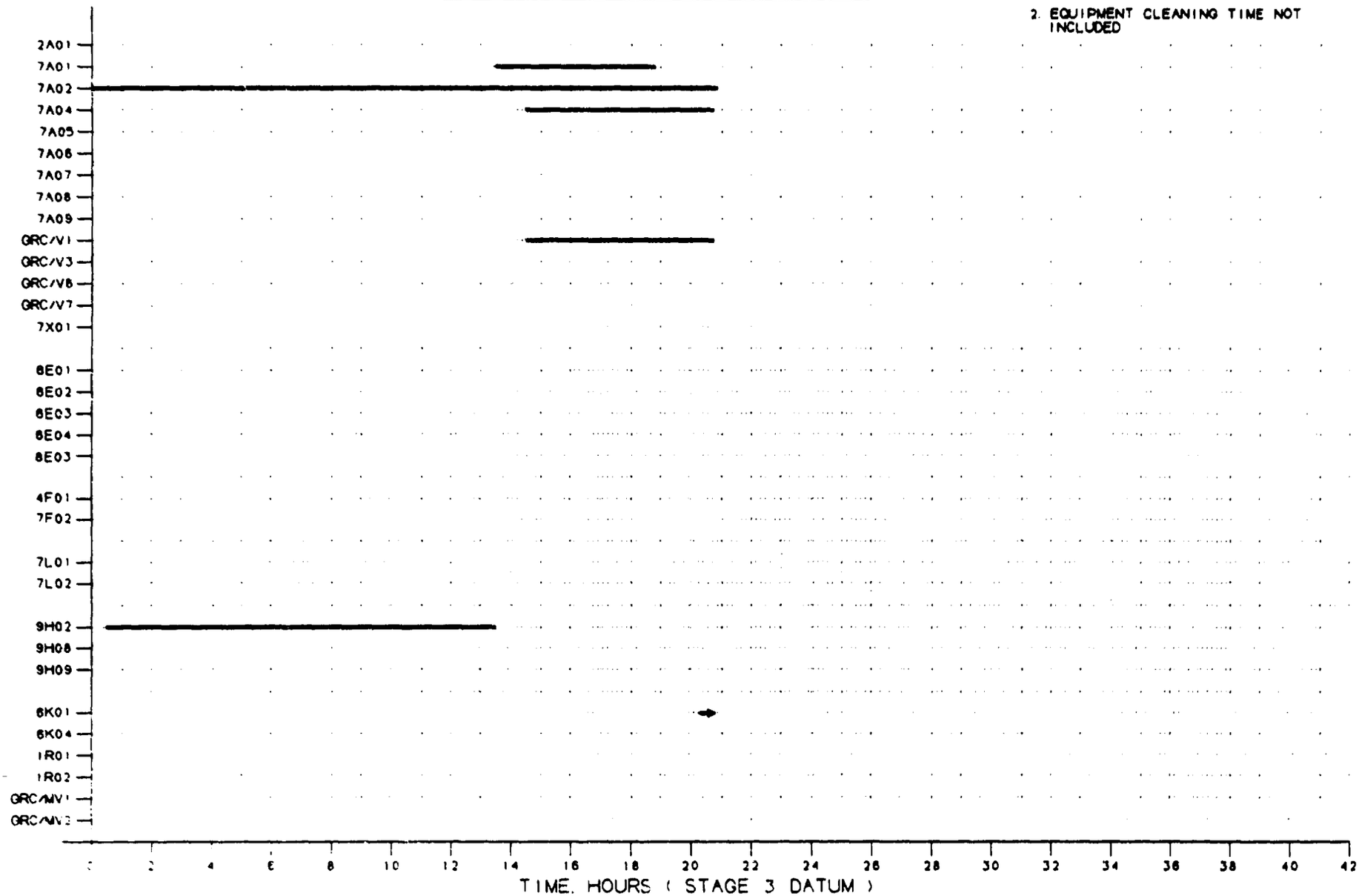
Stage 3 Timing	Stage 5 Timing	7A05	2A01	6E01	6E02	6E03	7X01	6E04	dT	Description
20.50		*	*						0.50	Transfer liquor, post deoxidation, from 7A05 to 2A01
21.00			*	*	*				0.50	Pump scrubber liquor from 6E01/6E02 to 2A01
21.50			*						0.50	Transfer complete
	7.50		*			*			0.50	Pump scrubber liquor from 6E03 to 2A01
	8.00		*							Transfer complete
	26.00		*				*		0.50	Transfer 7X01 to 2A01
	26.50		*							Transfer complete
	33.50		*					*	0.50	Pump scrubber liquor from 6E04 to 2A01
	34.00		*						1.00	Add Ca Hydroxide to 2A01 with agitation
	35.00		*						0.50	2A01 ran to drain by gravity
	35.50									Waste water neutralisation complete

DRG No 92013/3018

STAGE 3

EQUIPMENT UTILISATION TIMECHART

1. ARROW INDICATES EQUIPMENT STILL IN PROCESS USE AFTER STAGE COMPLETE
2. EQUIPMENT CLEANING TIME NOT INCLUDED

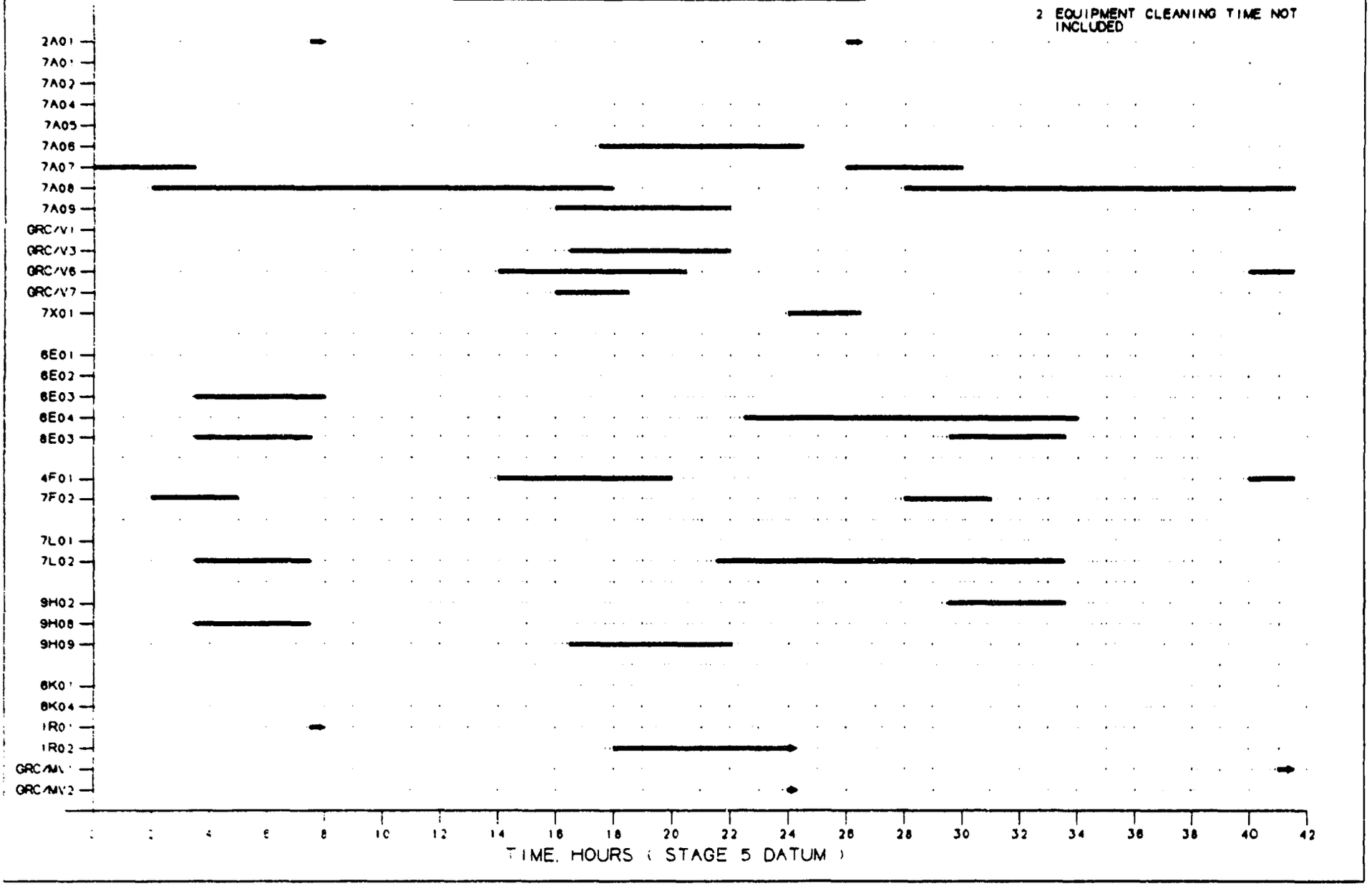


STAGE 5

EQUIPMENT UTILISATION TIMECHART

DRG No 82013/3058

1. ARROW INDICATES EQUIPMENT STILL IN PROCESS USE AFTER STAGE COMPLETE
2. EQUIPMENT CLEANING TIME NOT INCLUDED

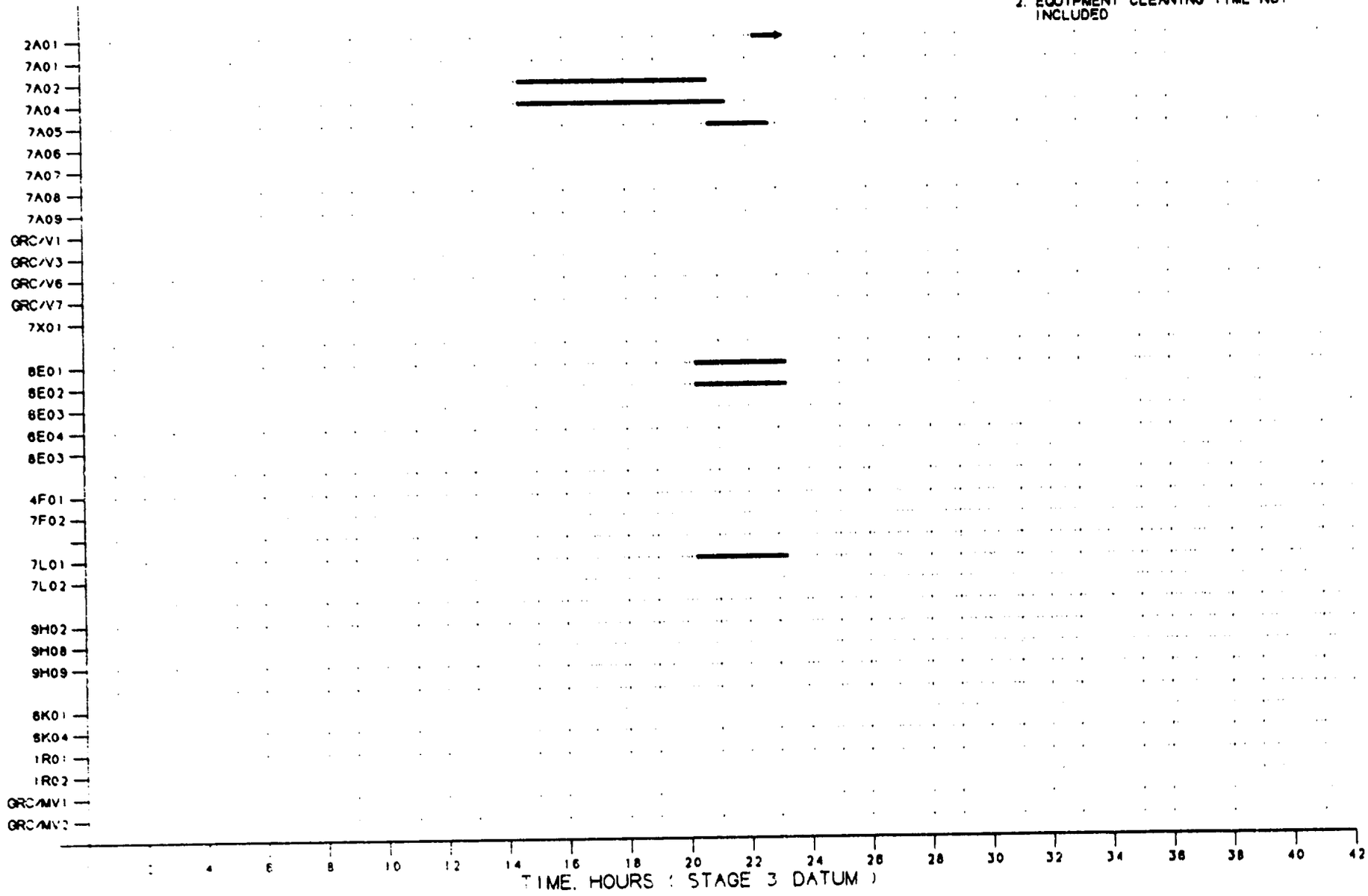


DRG No 82013/304B

DEAZIDATION

EQUIPMENT UTILISATION TIMECHART

1. ARROW INDICATES EQUIPMENT STILL IN PROCESS USE AFTER STAGE COMPLETE
2. EQUIPMENT CLEANING TIME NOT INCLUDED

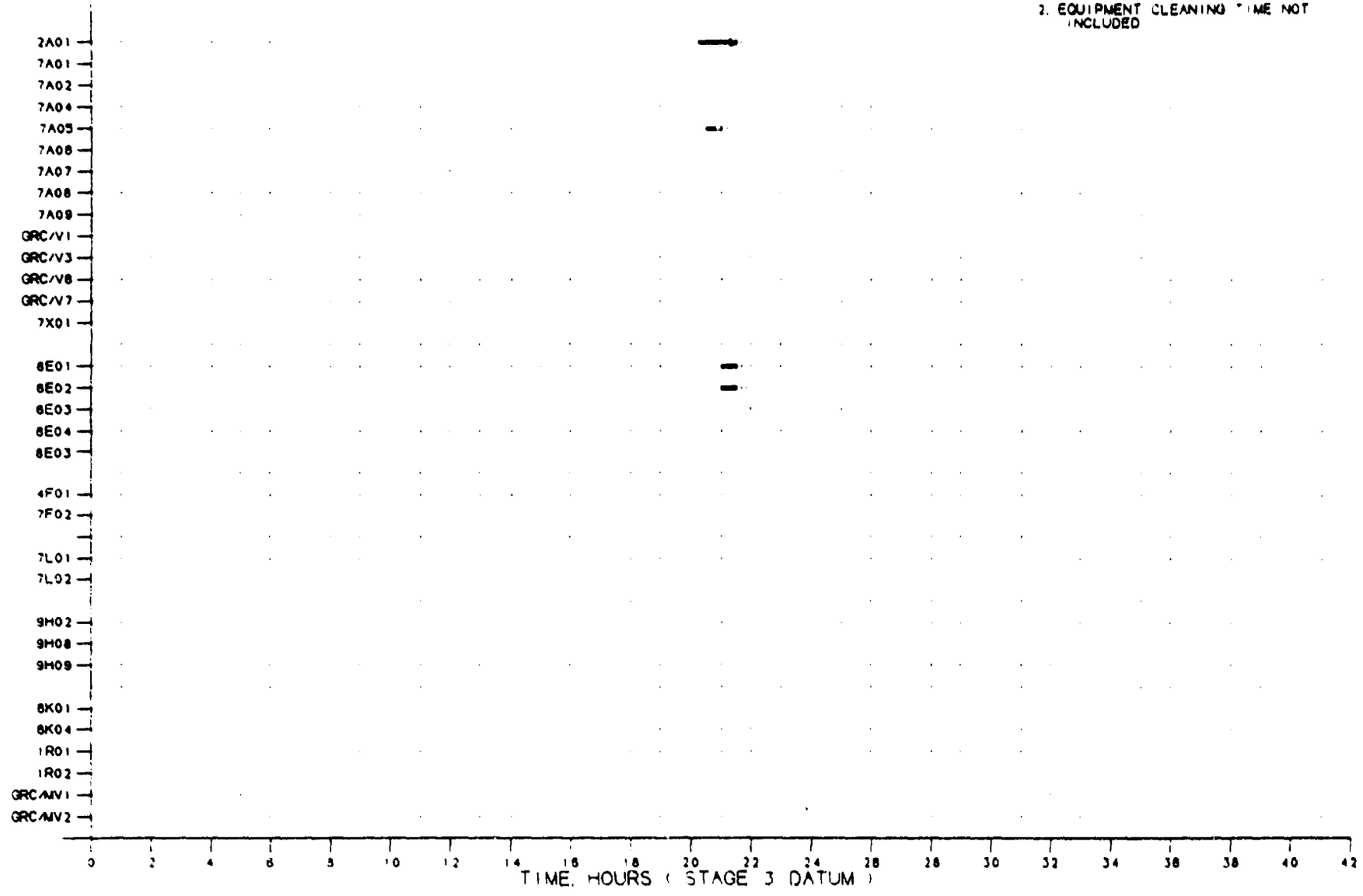


WASTE WATER NEUTRALISATION - STAGE 3

EQUIPMENT UTILISATION TIMECHART

DRG No 92013/3038

1. ARROW INDICATES EQUIPMENT STILL IN PROCESS USE AFTER STAGE COMPLETE
2. EQUIPMENT CLEANING TIME NOT INCLUDED

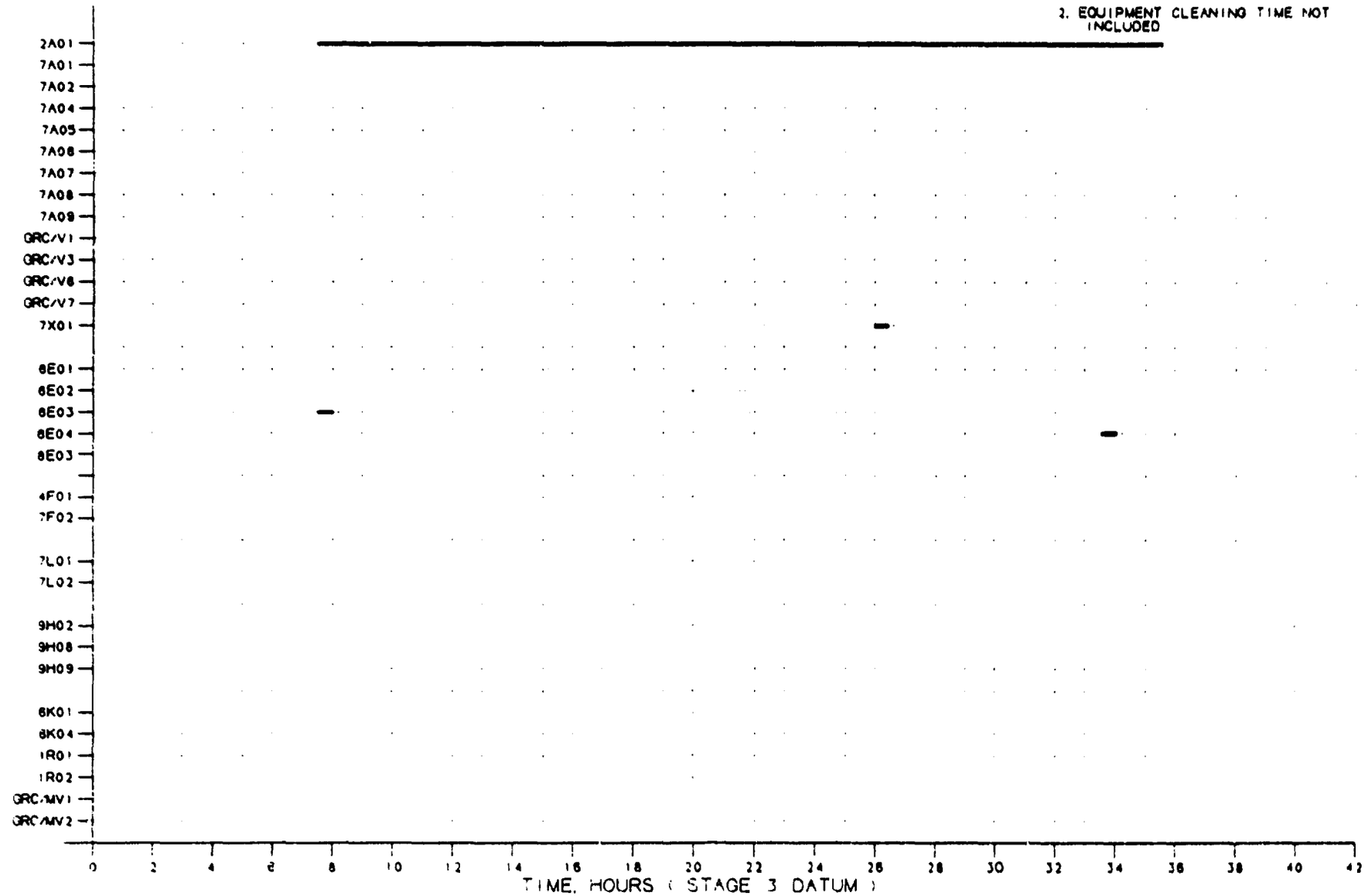


WASTE WATER NEUTRALISATION - STAGE 5

EQUIPMENT UTILISATION TIMECHART

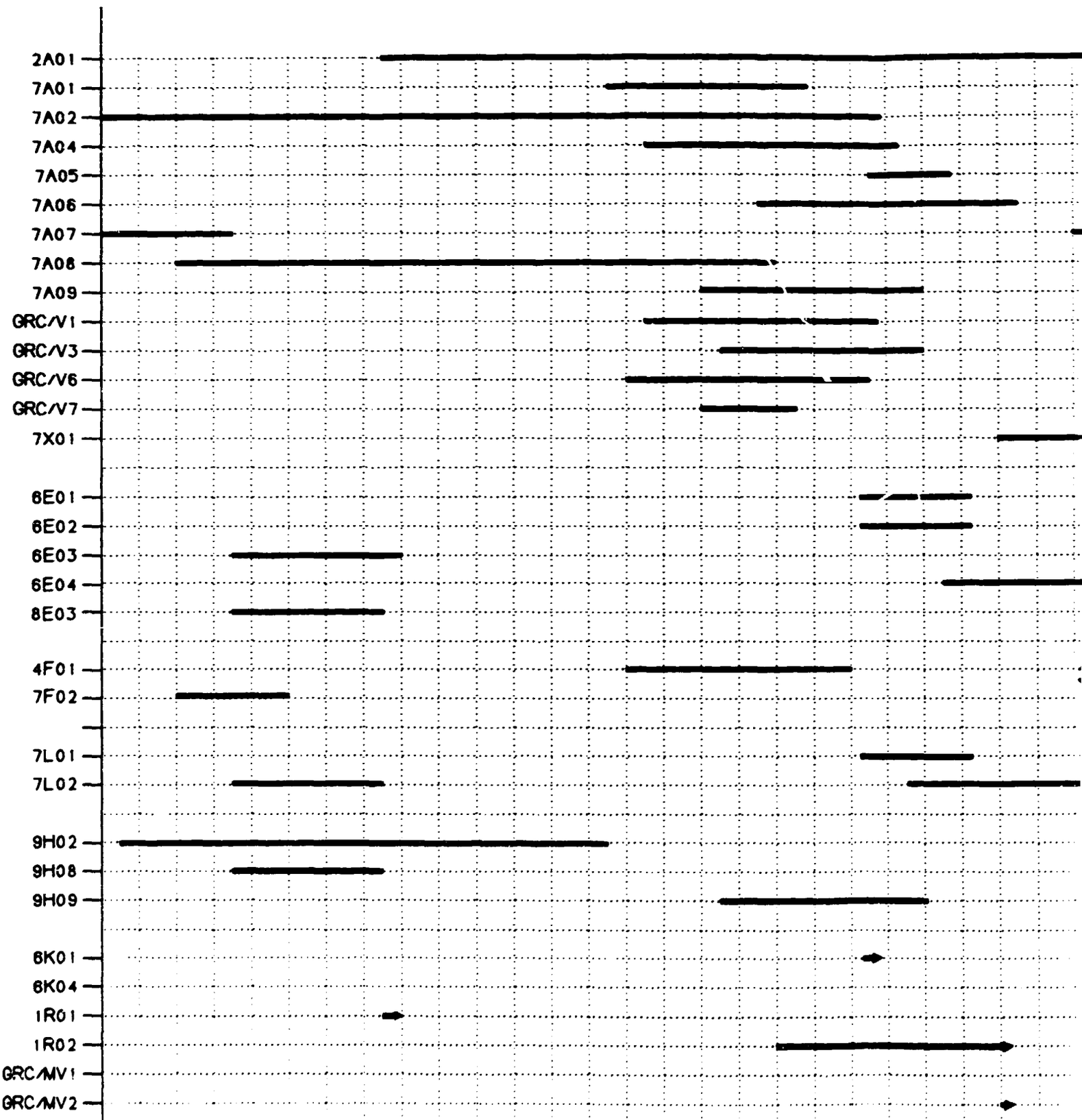
DRG No 82013/302B

1. ARROW INDICATES EQUIPMENT STILL IN PROCESS USE AFTER STAGE COMPLETE
2. EQUIPMENT CLEANING TIME NOT INCLUDED



EPC PROCESS

OVERALL EQUIPMENT UTILISATION TIMEC



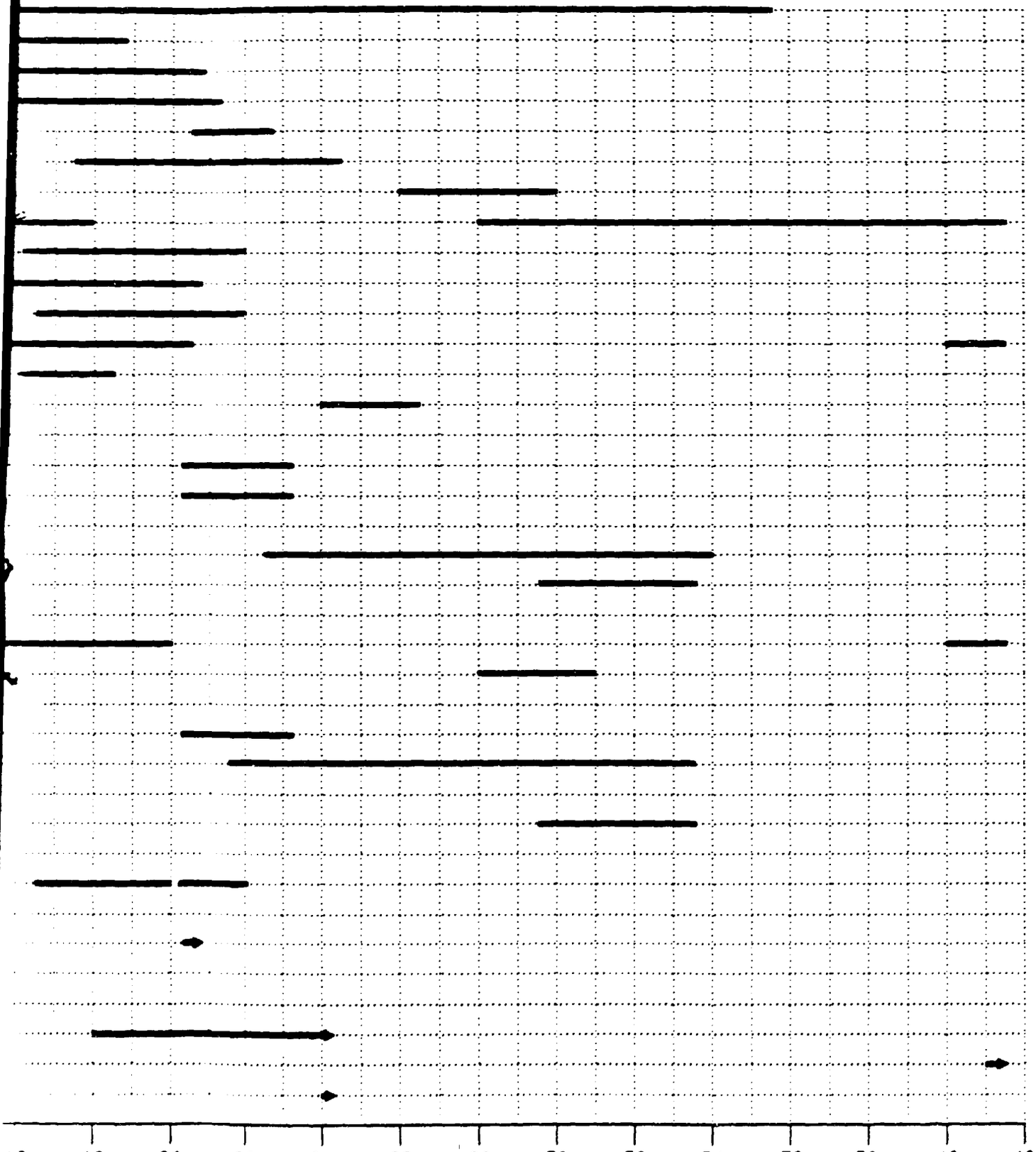
SECTION 1

DRG No 92013/306B

EPC PROCESS

PMENT UTILISATION TIMECHART

1. EQUIPMENT CLEANING TIME NOT INCLUDED
2. STAGES 3 & 5 STARTED SIMULTANEOUSLY



SECTION 2

From the process description it can be seen that EPC stages 3 and 5 are distinct processes and each may be carried out independently of each other. In order to draw the overall equipment utilisation timechart drg. 92/013/306 it has been assumed that stages 3 and 5 will begin concurrently.

The overall equipment utilisation timetable may be used to illustrate the degree of equipment usage throughout the process and clearly show where certain equipment has the potential to be reused in various stages of the process. However, since this plant is to be connected for use on other processes in the future, all equipment is considered essential.

The charts also identify points of time where a lot of equipment is being used concurrently and are useful to give an early indication of required manning levels.

From the timetables it can be seen that the batch times for stages 3 and 5 are 21 and 42 respectively. Stage 5 is thus rate limiting and in periods of continuous 24 hour production it can be seen from the stage 5 timechart that specifically vessel 7A08 is rate limiting. Allowing a 8 hour dead time for vessel 7A08 for cleaning and to provide a buffer between batches gives us a cycle time of approx 48 hours.

Using a batch size of 290 kg of dry product

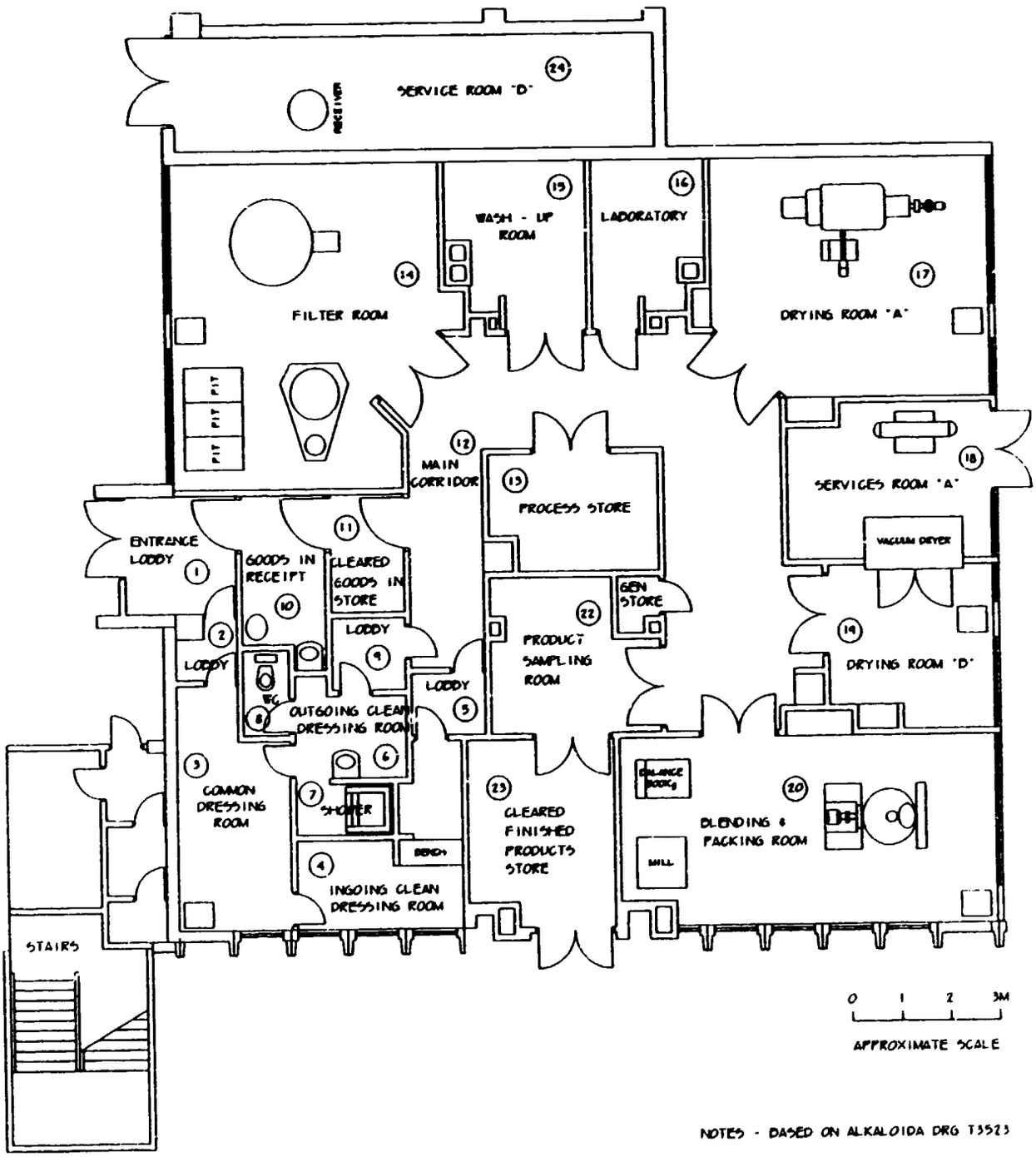
$$\text{Estimated Maximum Production Rate} = \frac{290 \times 7 \times 24}{48} = 1015 \text{ kg/working week}$$

In summary, in periods of 24 hours continuous production, of the order of a maximum 1 tonne dry product per working week is produced. It must be emphasized that these figures are provisional based on GRC estimates and serve as a guide only. They are subject to modifications in the light of Alkaloida's present operating experience.

It is understood that in the short term the plant will be operated on a one shift basis which will be sufficient to meet the limited demand. It is understood that at a later date three shift working will be introduced.

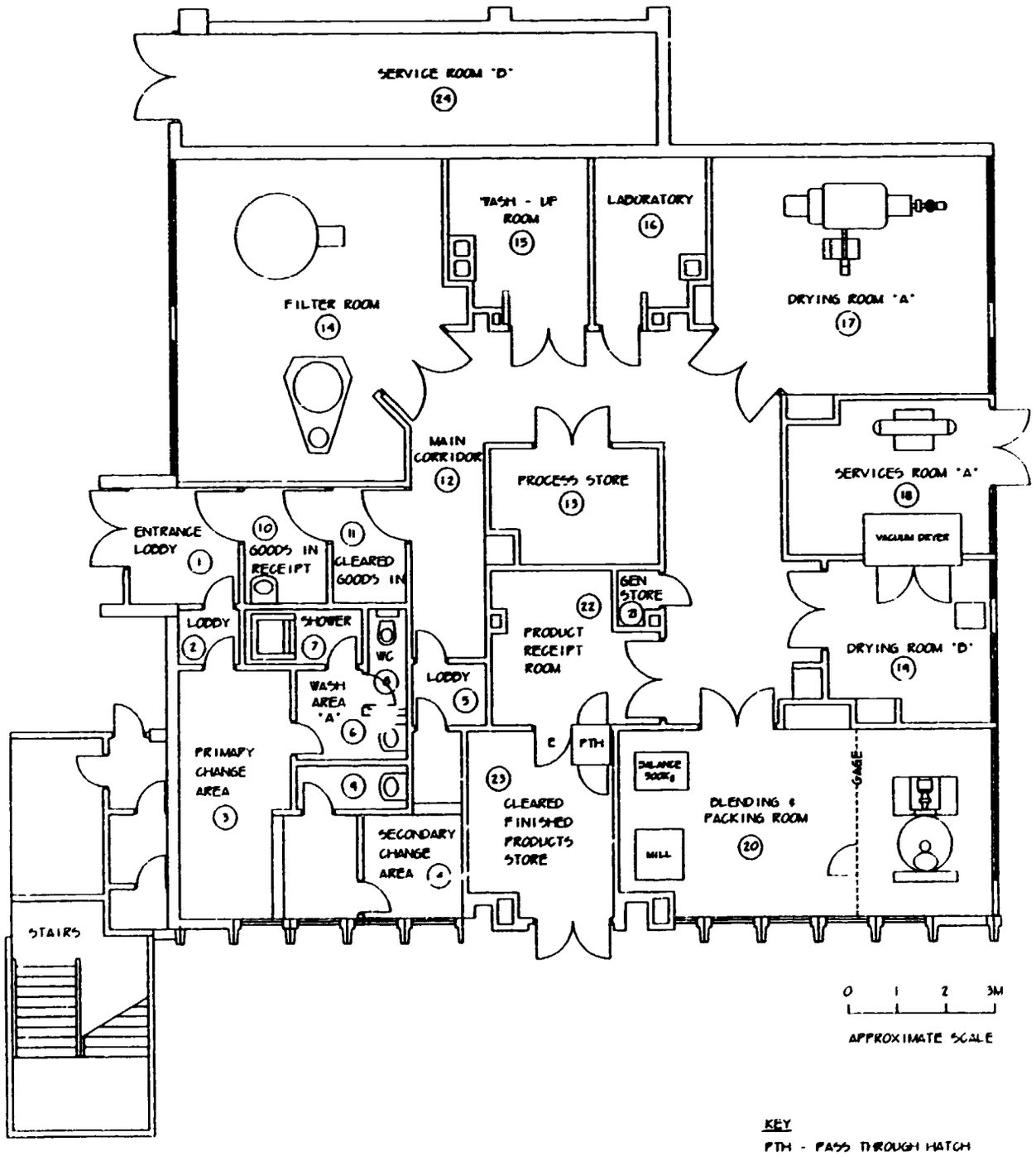
3.5.2 Downstream Processing (DSP)

The operations in DSP are performed in a simple batchwise linear fashion on isolated equipment. It is therefore not considered essential to perform a full analysis at this stage.



NOTES - BASED ON ALKALOIDA DRG T3523

GRC CONSULTANTS	CLIENT: UNIDO, P O BOX 300, A-1400 VIENNA AUSTRIA FAX 232156	PROJECT: ALKALOIDA I TF/HUN/90/907	TITLE: GROUND FLOOR ALKALOIDA LAYOUT
	DATE: MAY 1992 SCALE: N/A DIMENSIONS IN: METRES		DRAWING NUMBER: 92/005/A01 REVISION: A

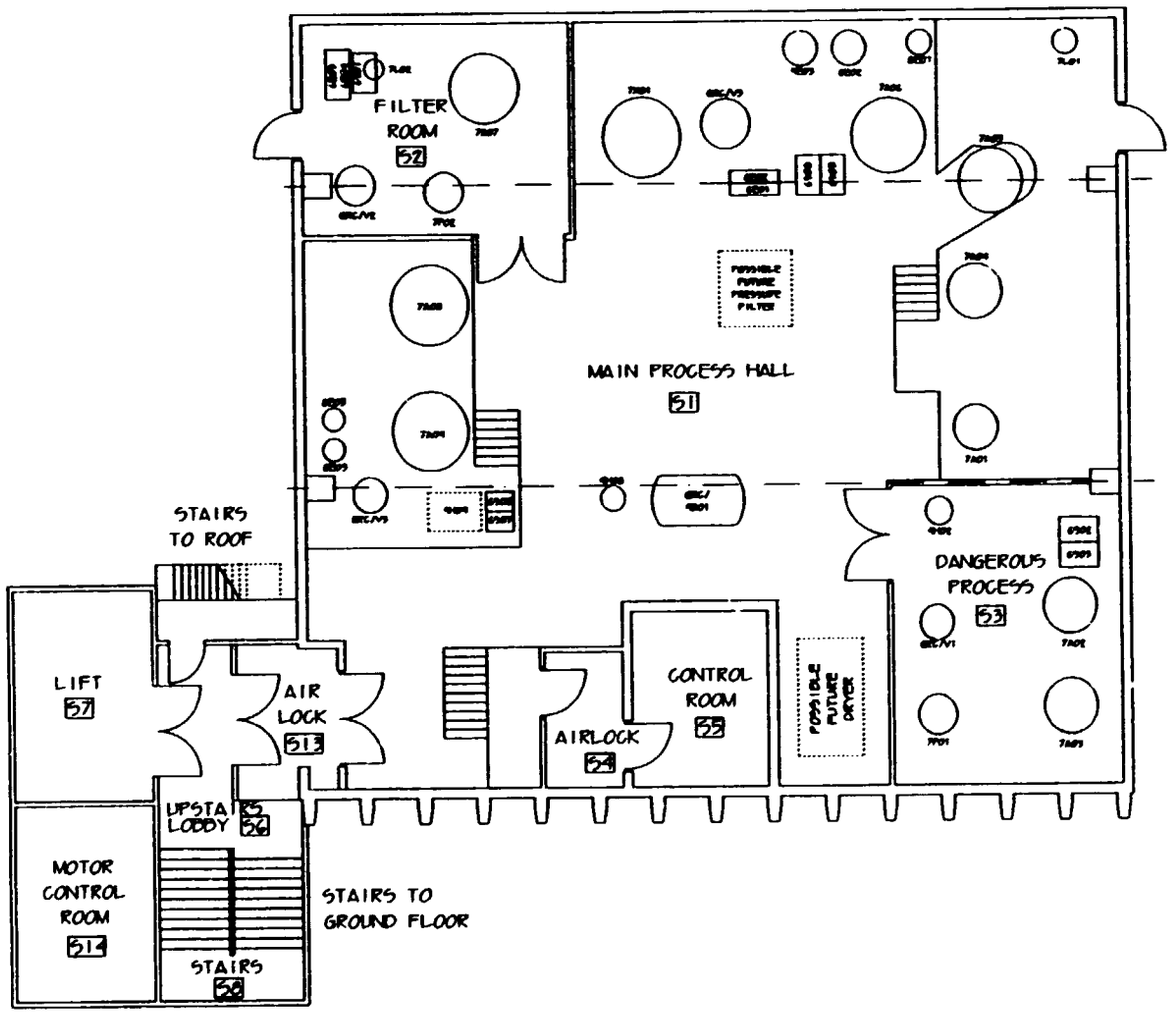


KEY

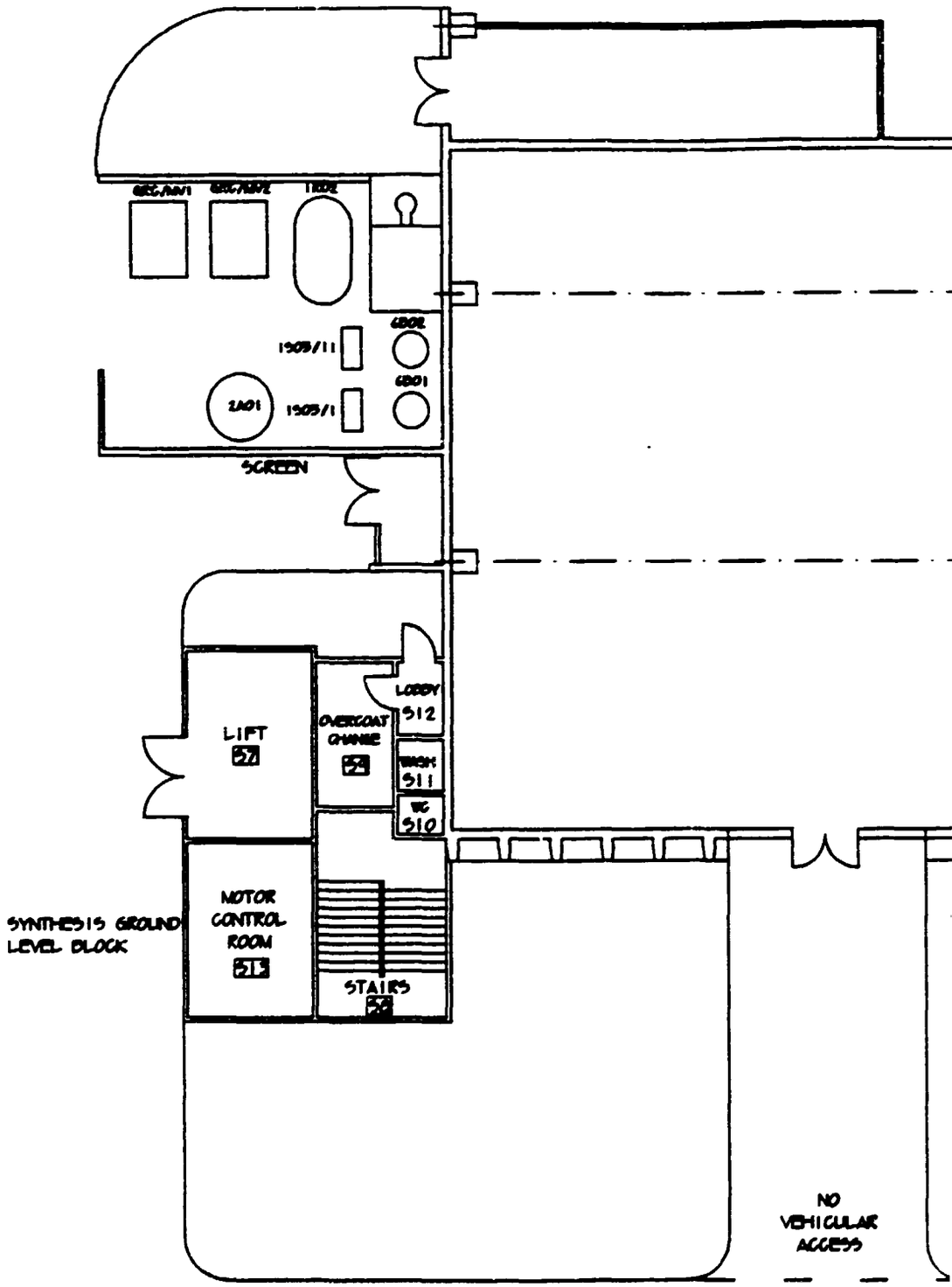
PTH - PASS THROUGH HATCH

E - EMERGENCY DOOR

GRC CONSULTANTS	CLIENT: UNIDO, P O BOX 300, A-1400 VIENNA, AUSTRIA FAX 232156	PROJECT: ALKALOIDA I TF/HUN/90/907	TITLE: GROUND FLOOR ROOM LAYOUT	
	DATE: MAY 1992		DRAWING NUMBER: 92/005/A02	REVISION: D
	SCALE: N/A			
	DIMENSIONS IN: METRES			



GRC CONSULTANTS WATERGATE HOUSE 1 THE WINDMILLS ST MARY'S CLOSE ALTON HANTS TEL - 0420 84847 FAX - 0420 84917	CLIENT UNIDO, P.O.BOX 300, A-1400 VIENNA, AUSTRIA. FAX: 232156	PROJECT ALKALOIDA 2 TF/HUN/90/910	TITLE FIRST FLOOR EQUIPMENT LAYOUT
	DATE: DEC '92 SCALE: N/A DIMENSIONS IN MM		DRAWING NUMBER 92/013/102
			REVISION A



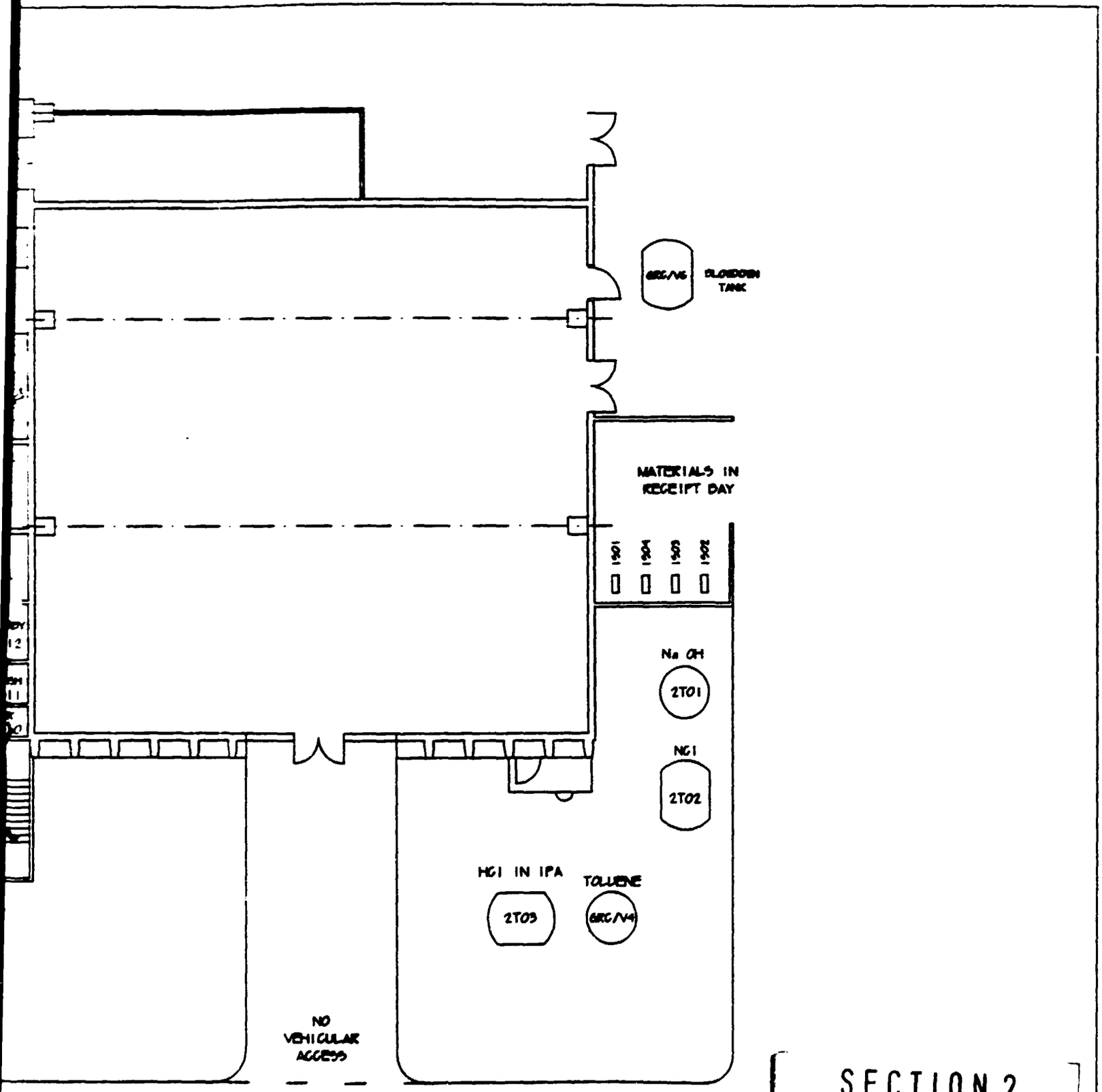
SECTION 1

REV	DATE	DESCRIPTION	BY
A	17/12/92	ISSUED WITH REPORT	HS

GRC CONSULTANTS
WATERCRESS HOUSE 1, THE WINDMILLS
ST MARYS CLOSE, ALTON, HANTS, GU34 1EF
TEL: 0420 89847 FAX: 0420 89427

CLIENT
UNIDO
A-1400 VI
AUSTRIA,

ALL DIMS



SECTION 2

GRC CONSULTANTS WATERCRESS HOUSE 1, THE WINDMILLS ST MARYS CLOSE, ALTON, HANTS, GU34 1EF TEL: 0420 89847 FAX: 0420 89427	CLIENT UNIDO P.O. BOX 300, A-1400 VIENNA, AUSTRIA, FAX 232156	PROJECT ALKALOIDA 2 TF/HUN/90/910	DRAWING TITLE EXTERNAL EQUIPMENT LAYOUT
	ALL DIMS IN MILLIMETRES		DRAWING NUMBER: 92/013/103 — REV: A

SECTION 4

EQUIPMENT

4 EQUIPMENT

This section details the main process equipment and identifies any special features.

An equipment list is given which details equipment numbers, operating conditions and sizes.

The equipment specification section is a written description of each major item of equipment and any special features are noted.

Equipment data sheets are given as a summary of the equipment specification.

4.1 EQUIPMENT LIST

The equipment list included in this section contains details of all the main pieces of process equipment and provides basic information such as equipment number, operating temperature, etc.

The list includes the major process equipment items identified by Alkaloida and retains the Alkaloida numbering system for these items. Where equipment has been added by GRC Consultants, the numbers assigned begin with the letters GRC.

Where specific operating temperatures and pressures were not available typical figures have been used. Specifications based on firm Alkaloida information are identified in the table (confidential data in the technical annex).

The table also ncludes some additional pieces of equipment which are required for plant operation and the following notes should be read in conjunction with the equipment list.

GRC Consultants

EQUIPMENT LIST

PLANT DESCRIPTION: SSMPU

PROJECT NO.: TF/HUN/90/907

AREA NO.: –

AREA: DSP

LOCATION: TISZAVASVARI

CLIENT: UNIDO

SHEET NO.: 1 OF 2

ITEM NO.	DESCRIPTION	NO. OFF	MATERIALS	CAPACITY OR RATE EACH	TEMPERATURE °C		PRESSURE Bar a		MOTOR POWER (EACH)		REMARKS	PROVISIONAL DIMENSIONS MM HEIGHT FIRST
					WORKING	DESIGN	WORKING	DESIGN	ABSORBED	INSTALLED		
4F01	PRESSURE FILTER	1	STAINLESS STEEL	2m² FILTER AREA *	50	75	5/FV	5.5/FV	–	–	–	3400 X 3500 X 1800 *
4F02	BASKET CENTRIFUGAL FILTER	1	STAINLESS STEEL	0.7m² * FILTER AREA	50	75	2.0	2.2	–	–	–	980 X 1206 X 1555 *
4T01	HORIZONTAL VACUUM DRYER	1	STAINLESS STEEL	200kg CHARGE *	100	125	2.0/FV	2.2/FV	–	–	–	3000 X 3600 X 1000 *
4T02	VACUUM TRAY DRYER	1	STAINLESS STEEL	200kg CHARGE *	100	125	2.0/FV	2.2/FV	–	–	–	3000 X 1800 X 2400 *
4H01	DOUBLE CONE BLENDER	1	STAINLESS STEEL	200kg CHARGE *	30	50	1.1	1.2	–	–	–	2275 X 2400 X 1200 *
4H02	HAMMER MILL	1	STAINLESS STEEL	50kg/hr	30	50	2	2.2	–	–	–	1500 X 1000 X 1000
3S01	FILTER ROOM PUMPS	2	STAINLESS STEEL	100L/min *	50	75	–	–	–	–	–	400 X 300 X 300
6M02	SCALE	1	STAINLESS	200kg *	30	50	–	–	–	–	–	1500 X 1000 X 1000

ISSUE LETTER	A	B	C	D	E	F	G
	3/7/92						

* SPECIFIED BY ALKALOIDA

GRC Consultants

EQUIPMENT LIST

PLANT DESCRIPTION	PROJECT NO.	AREA NO.	AREA
SSMPU	TF/HUN/90/907	–	DSP
	LOCATION TISZAVASVARI	CLIENT UNIDO	SHEET NO. 2 OF 2

ITEM NO.	DESCRIPTION	NO. OFF	MATERIALS	CAPACITY OR RATE EACH	TEMPERATURE °C		PRESSURE Bar a		MOTOR POWER (EACH)		REMARKS	PROVISIONAL DIMENSIONS MM HEIGHT FIRST
					WORKING	DESIGN	WORKING	DESIGN	ABSORBED	INSTALLED		
GRC01	FILTER ROOM TANKS	3	STAINLESS STEEL	1M³	50	75	1.0	1.1	–	–	PROPOSED NEW TANKS WITH BOTTOM DRAIN	1600 X 800 X 800
GRC02	FILTER DISHARGE PUMP	1	STAINLESS STEEL	150L/MIN	50	75	–	–	–	–	SELF PRIMING PUMP TO SERVE BOTH FILTERS	400 X 300 X 300
GRC03	WHEELED 100L CLOSED VESSEL	10	INERT	100L	–	–	–	–	–	–	–	900 X 460 X 450
GRC04	WHEELED 250L CLOSED VESSEL	10	INERT	250L	–	–	–	–	–	–	–	1200 X 600 X 600
GRC05	TROLLEY FOR CARRYING BINS ETC	1	INERT	0.5TONNE	–	–	–	–	–	–	–	1400 X 1200 X 1000
GRC06	SIEVE MECHANISM	1	STAINLESS STEEL	50kg/hr	30	50	–	–	–	–	–	800 X 700 X 700
GRC07	VACUUM SETS FOR DRYERS	2	–	–	–	–	–	–	–	–	–	–

ISSUE LETTER	A	B	C	D	E	F	G
	3/7/92						

GRC Consultants

EQUIPMENT LIST

PLANT DESCRIPTION: SSMPU | PROJECT NO.: TF/HUN/90/910 | AREA NO.: — | AREA: SYNTHESIS

LOCATION: TISZAVASVARI | CLIENT: UNIDO | SHEET NO.: 1 OF 8

ITEM NO.	DESCRIPTION	NO. OFF	MATERIALS	CAPACITY OR RATE EACH	TEMPERATURE °C WORKING	TEMPERATURE °C DESIGN	PRESSURE Bar A WORKING	PRESSURE Bar A DESIGN	MOTOR POWER (EACH) KW ABSORBED	MOTOR POWER (EACH) KW INSTALLED	REMARKS	PROVISIONAL DIMENSIONS MM
2T01	REACTOR	1	ENAMELLED	2m³	120	150	3	6	—	5.5	50rpm Impeller	ϕ=1500 H=4000
2A01	REACTOR	1	ENAMELLED	2m³	120	150	3	6	—	5.5	50rpm Impeller	ϕ=1500 H=4000
7A01	REACTOR	1	ENAMELLED	0.4m³	120	150	3	6	—	2.2	25rpm horseshoe Impeller	ϕ=900 H=2970
7A02	REACTOR	1	ENAMELLED	0.63m³	120	150	3	6	-	2.2	50rpm Impeller	ϕ=1100 H=3300
7A03	REACTOR	1	ENAMELLED	0.63m³	120	150	3	6	—	2.2	50rpm Impeller	ϕ=1100 H=3300
7A04	REACTOR	1	ENAMELLED	0.63m³	120	150	3	6	—	2.2	50rpm Impeller	ϕ=1100 H=3130
7A05	REACTOR	1	ENAMELLED	1m³	120	150	3	6	—	2.2	50rpm Impeller	ϕ=1300 H=3390
7A06	REACTOR	1	ENAMELLED	1.6m³	120	150	3	6	—	5.5	100rpm 3 bladed Impeller	ϕ=1500 H=4200
7A07	REACTOR	1	ENAMELLED	1.6m³	120	150	3	6	—	5.5	50rpm, 2 bladed Impeller	ϕ=1500 H=4200
7A08	REACTOR	1	ENAMELLED	1.6m³	120	150	3	6	—	5.5	Variable speed drive	ϕ=1700 H=4400

ISSUE LETTER	A	B	C	D	E	F	G
	1/12/92						

GRC Consultants

EQUIPMENT LIST

PLANT DESCRIPTION: SSMPU

PROJECT NO.: TF/HUN/90/910

AREA NO.: —

AREA: SYNTHESIS

LOCATION: TISZAVASVARI

CLIENT: UNIDO

SHEET NO.: 2 OF 8

ITEM NO.	DESCRIPTION	NO. OFF	MATERIALS	CAPACITY OR RATE EACH	TEMPERATURE °C		PRESSURE Bar A		MOTOR POWER (EACH) KW		REMARKS	PROVISIONAL DIMENSIONS MM
					WORKING	DESIGN	WORKING	DESIGN	ABSORBED	INSTALLED		
7A09	REACTOR	1	ENAMELLED	$1.6m^3$	120	150	3	6	—	5.5	50rpm Impeller	Ø=1500 H=4200
7X01	EXTRACTION VESSEL	1	STAINLESS STEEL	$1.2m^3$	120	150	3	6	—	5.5	Variable Speed Impeller, Conical vessel bottom	Ø=1500 H=4200
9H02	HEAT EXCHANGER	1	GRAPHITE	$0.6m^2$	120	200	3	6	—	—		Ø=400 H=900
9H07	HEAT EXCHANGER	1	GRAPHITE	$12m^2$	120	160	3	6	—	—		1600× 400× 1500
9H08	HEAT EXCHANGER	1	GRAPHITE	$1.7m^2$	120	200	3	6	—	—		Ø=500 H=1000
9H09	HEAT EXCHANGER	1	GRAPHITE	$12m^2$	120	150	3	6	—	—		1600× 400× 1500
9E03	TANK	1	STAINLESS STEEL	$.25m^3$	30	150	ATMOSPHERIC	2	—	—	Vertical cylindrical vessel	Ø650× 1400
8E02	TANK	1	STAINLESS STEEL	$.25m^3$	30	150	ATMOSPHERIC	2	—	—	Vertical cylindrical vessel	Ø650× 1400
1R01	TANK	1	POLYTHENE	$1m^2$	30	50	ATMOSPHERIC	ATMOSPHERIC	—	—	Mobile, Rectangular tank	2000× 1000× 1800
1R02	TANK	1	STAINLESS STEEL	$2m^3$	30	150	ATMOSPHERIC	1	—	—	Horizontal cylindrical Vessel	2450× 1300× 2200

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GRC Consultants

EQUIPMENT LIST

PLANT DESCRIPTION: SSMPU | PROJECT NO.: TF/NUN/90/910 | AREA NO.: — | AREA: SYNTHESIS

LOCATION: TISZAVASVARI | CLIENT: UNIDO | SHEET NO.: 3 OF 8

ITEM NO.	DESCRIPTION	NO. OFF	MATERIALS	CAPACITY OR RATE EACH	TEMPERATURE °C		PRESSURE Bar A		MOTOR POWER (EACH) kW		REMARKS	PROVISIONAL DIMENSIONS mm
					WORKING	DESIGN	WORKING	DESIGN	ABSORBED	INSTALLED		
2T02	TANK	1	POLYTHENE	3 m^3	30	80	ATMOS-PHERIC	1	—	—	horizontal cylindrical vessel	Ø1250 × 2650 × 2000
2T03	TANK	1	ENAMELLED	2 m^3	30	150	ATMOS-PHERIC	6	—	—	horizontal cylindrical vessel	Ø=1400 × 2000 × 2055
6K01	MOBILE TANK	1	STAINLESS STEEL	.5 m^3	30	150	ATMOS-PHERIC	1	—	—	horizontal cylindrical vessel	1730 × 900 × 1630
6K04	MOBILE TANK	1	STAINLESS STEEL	.5 m^3	50	150	ATMOS-PHERIC	1	—	—	horizontal cylindrical vessel	1730 × 900 × 1600
7L01	GAS SCRUBBER	1	GLASS	Ø400	50	80	ATMOS-PHERIC	ATMOS-PHERIC	—	—		Ø 400 N=3000
7L02	GAS SCRUBBER	1	GLASS	Ø 300	50	80	ATMOS-PHERIC	ATMOS-PHERIC	—	—		Ø 300 N=3000
6E01	TANK	1	POLY-PROPYLENE	.1 m^3	50	80	ATMOS-PHERIC	ATMOS-PHERIC	—	—	Scrubber liquor tank for 7L01	1000 × 500 × 900
6E02	TANK	1	POLY-PROPYLENE	.1 m^3	50	80	ATMOS-PHERIC	ATMOS-PHERIC	—	—	Scrubber liquor tank for 7L01	1000 × 500 × 900
6E03	TANK	1	POLY-PROPYLENE	.1 m^3	50	80	ATMOS-PHERIC	ATMOS-PHERIC	—	—	Scrubber liquor tank for 7L02	1000 × 500 × 900
6E04	TANK	1	POLY-PROPYLENE	.1 m^3	50	80	ATMOS-PHERIC	ATMOS-PHERIC	—	—	Scrubber liquor tank for 7L02	1000 × 500 × 900

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GRC Consultants

EQUIPMENT LIST

PLANT DESCRIPTION	PROJECT NO.	AREA NO.	AREA
SSMPU	TF/HUN/90/910	—	SYNTHESIS
	LOCATION TISZAVASVARI	CLIENT UNIDO	SHEET NO. 4 OF 8

ITEM NO.	DESCRIPTION	NO. OFF	MATERIALS	CAPACITY OR RATE EACH	TEMPERATURE °C		PRESSURE Bar A		MOTOR POWER (EACH) KW		REMARKS	PROVISIONAL DIMENSIONS
					WORKING	DESIGN	WORKING	DESIGN	ABSORBED	INSTALLED		
8601	TANK	1	GLASS	.25M³	30	80	ATMOS-PHERIC	ATMOS-PHERIC	—	—		Ø500 x 1600
8E03	TANK	1	GLASS	.25M³	30	80	ATMOS-PHERIC	ATMOS-PHERIC	—	—		Ø500x 1600
8E05	TANK	1	GLASS	.25M³	30	80	ATMOS-PHERIC	ATMOS-PHERIC	—	—		Ø500x 1600
9E01	TANK	1	GLASS	.1M³	30	80	ATMOS-PHERIC	ATMOS-PHERIC	—	—		Ø450 x 1000
7F01	PRESSURE FILTER	1	ENAMELLED	.3M³	120	150	3	6	—	—	Heated	Ø900x 2200
7F02	PRESSURE FILTER	1	ENAMELLED	.3M³	120	150	3	6	—	—		9900x 2200
9V01	FAN	1	POLY PROPYLENE	1000M³/hr	50	80	—	—	—	—	Fan for Scrubber 7L01	700x 700
9V02	FAN	1	POLY PROPYLENE	1000M³/hr	50	80	—	—	—	—	Fan for Scrubber 7L02	700x 700
1S01	CENTRIFUGAL PUMP	1	STAINLESS STEEL	~100L/Min	30	80	2.5	3	—	4kW		500 x 1500
1S02	CENTRIFUGAL PUMP	1	CARBON STEEL	~100L/Min	30	80	2.5	3	—	5kW		500 x 1500

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GRC Consultants

EQUIPMENT LIST

PLANT DESCRIPTION: SSMPU

PROJECT NO.: TF/HUN/90/910

AREA NO.: –

AREA: SYNTHESIS

LOCATION: TISZAVASVARI

CLIENT: UNIDO

SHEET NO.: 5 OF 8

ITEM NO.	DESCRIPTION	NO. OFF	MATERIALS	CAPACITY OR RATE EACH	TEMPERATURE °C		PRESSURE Bar A		MOTOR POWER (EACH) KW		REMARKS	PROVISIONAL DIMENSIONS
					WORKING	DESIGN	WORKING	DESIGN	ABSORBED	INSTALLED		
1503	CENTRIFUGAL PUMP	1	GLASS	~80l/min	30	80	2.5	3	–	4		500x 900
1504	CENTRIFUGAL PUMP	1	GLASS	~80l/min	30	80	2	3	–	4		500x 900
6501	CENTRIFUGAL PUMP	1	GLASS	~80l/min	30	80	1.5	2	–	3		500x 700
6502	CENTRIFUGAL PUMP	1	GLASS	~40l/min	30	80	1.5	2	–	2		500x 500
6503	CENTRIFUGAL PUMP	1	GLASS	~40l/min	30	80	1.5	2	–	2		500x 500
6505	CENTRIFUGAL PUMP	1	GLASS	~100l/min	30	80	1.5	2	–	4		500x 1500
6507	CENTRIFUGAL PUMP	1	GLASS	~80l/min	30	80	2.5	3	–	4		500x 900
6508	CENTRIFUGAL PUMP	1	GLASS + PTFE	0-1.5m³/hr	30	80	2.5	3	–	2	Variable Speed drive	500x 500
6509	CENTRIFUGAL PUMP	1	STAINLESS STEEL	~100l/min	30	80	2.5	3	–	4		500x 1500
6M01	BALANCE	1	STAINLESS STEEL	1500kg	–	–	–	–	–	–	Accuracy ± 3 kg	1500x 1000

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GRC Consultants EQUIPMENT LIST	PLANT DESCRIPTION SSMPU	PROJECT NO. TF/HUN/90/910	AREA NO. —	AREA SYNTHESIS
		LOCATION TISZAVASVARI	CLIENT UNIDO	SHEET NO. 6 OF 8

ITEM NO.	DESCRIPTION	NO. OFF	MATERIALS	CAPACITY OR RATE EACH	TEMPERATURE °C		PRESSURE Bar A		MOTOR POWER (EACH) KW		REMARKS	PROVISIONAL DIMENSIONS
					WORKING	DESIGN	WORKING	DESIGN	ABSORBED	INSTALLED		
6M02	BALANCE	1	STAINLESS STEEL	200Kg	—	—	—	—	—	—	Accuracy ±0.5kg	1400 x 900

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GRC Consultants EQUIPMENT LIST	PLANT DESCRIPTION SSMPU	PROJECT NO. TF/HUN/90/910	AREA NO. —	AREA SYNTHESIS
		LOCATION TISZAVASVARI	CLIENT UNIDO	SHEET NO. 7 OF 8

ITEM NO.	DESCRIPTION	NO. OFF	MATERIALS	CAPACITY OR RATE EACH	TEMPERATURE °C		PRESSURE B — A		MOTOR POWER (EACH) KW		REMARKS	PROVISIONAL DIMENSIONS
					WORKING	DESIGN	WORKING	DESIGN	ABSORBED	INSTALLED		
GRC/ 9301	TANK	1	STAINLESS STEEL	$1\,m^3$	30	150	ATMOS-PHERIC	2	—	—	HORIZONTAL CYLINDRICAL VESSEL	Ø1000 x 1900
GRC/ V1	TANK	1	STAINLESS STEEL	$0.5\,m^3$	30	80	ATMOS-PHERIC	ATMOS-PHERIC	—	—	VERTICAL CYLINDRICAL VESSEL	Ø700 x 1300
GRC/ V2	TANK	1	STAINLESS STEEL	$0.5\,m^3$	30	80	ATMOS-PHERIC	ATMOS-PHERIC	—	—	VERTICAL CYLINDRICAL VESSEL	Ø700 x 1300
GRC/ V3	TANK	1	STAINLESS STEEL	$0.5\,m^3$	30	150	ATMOS-PHERIC	1	—	—	VERTICAL CYLINDRICAL VESSEL	Ø700 x 1300
GRC/ V4	TANK	1	STAINLESS STEEL	$2\,m^3$	30	150	ATMOS-PHERIC	2	—	—	HORIZONTAL CYLINDRICAL VESSEL	Ø1500 x 4000
GRC/ V5	TANK	1	STAINLESS STEEL	$0.5\,m^3$	30	80	ATMOS-PHERIC	ATMOS-PHERIC	—	—	VERTICAL CYLINDRICAL VESSEL	Ø700 x 1300
GRC/ TR1	CAKE BIN TROLLEY	1	STAINLESS STEEL	500kg	—	—	—	—	—	—	MANUAL WHEELED TROLLEY	1000 x 1000
GRC/ P1	PUMP	1	GLASS	~80l/min	30	80	2	3	—	—		500 x 900
GRC/ P2	PUMP	1	GLASS	~80l/min	30	80	1.5	2	—	—		500 x 900
GRC/ P3	PUMP	1	GLASS	~80l/min	30	80	1.5	2	—	—		500 x 900

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GRC Consultants

EQUIPMENT LIST

PLANT DESCRIPTION: SSMPU

PROJECT NO.: TF/HUN/90/910

AREA NO.: —

AREA: SYNTNESIS

LOCATION: TISZAUJVAROS

CLIENT: UNIDO

SHEET NO.: 8 OF 8

ITEM NO.	DESCRIPTION	NO. OFF	MATERIALS	CAPACITY OR RATE EACH	TEMPERATURE °C		PRESSURE Bar A		MOTOR POWER (EACH) kW		REMARKS	PROVISIONAL DIMENSIONS
					WORKING	DESIGN	WORKING	DESIGN	ABSORBED	INSTALLED		
GRC/PA.	PUMP	1	STAINLESS STEEL	N40l/min	30	80	1.5	2	—	—		500 x 500
GRC/MV1	MOBILE VESSEL	1	STAINLESS STEEL	..5m³	30	150	ATMOS-PHERIC	1	—	—		1730 x 900 x 1600
GRC/MV2	MOBILE VESSEL	1	STAINLESS STEEL	.5m³	30	150	ATMOS-PHERIC	1	—	—		1730 x 900 x 1600
GRC/V6	BLOWDOWN TANIC	1	ENAMELLED	2.1m³	30	150	3	6	—	—		1600 x 2000

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4.1.1 Synthesis

A number of modifications of the original Alkaloida design have been made which affect the equipment list.

It is not considered good Western practice to have a toluene head tank so this will be replaced with a new storage tank GRCN4, located outside in the raw materials tanks area.

In order to provide a convenient and reliable means of quality control raw material sample that plant is provided with its own dedicated bulk liquid raw material tanks. A new water head tank GRC/9B01 is added ensuring that the plant operates independently of any site ring mains, thus ensuring quality fluctuations may be more easily detected.

It is not considered good practice to have a large amount of wheeled vessels operating on the plant floor when these wheeled vessels also travel across the site and may bring considerable contamination into the plant area. The entry of externally operating wheeled vessels into the plant area has been made unnecessary by the inclusion of ground floor pumping and materials receipt stations.

Mobile tanks 6K02, 6K03 and 6K05 have been replaced with fixed tanks GRC/V1, GRC/V2 and GRC/V5 respectively.

The balances have been included in this equipment list but will be located in a nearby storage area which Alkaloida have allocated for storage and dispensing purposes.

4.1.2 DSP

The preliminary Alkaloida design for the filter room shows submerged tanks as liquid containers which are drained by means of a down leg and suction pump. The cleanability of

this system is doubtful and an alternative arrangement is proposed which uses three upright tanks which are bottom draining. The centrifuge and pressure Nutsche drains are pumped to these tanks via a self priming filter discharge pump mounted at a level below the drain discharges. The tanks and the filter discharge pump are included in the equipment list.

Process material transfer from room to room on the ground floor is in the form of slurry or powder contained in wheeled bins. Nominally ten 100l and ten 250l bins have been specified. The number and type of these bins may be clearly defined at a later stage with reference to process operating conditions.

One hand operated pallet type trolley is included for the transfer of finished product bins and general transfer duties throughout the plant.

It is noted that Alkaloida do not include a sieve in their equipment list. However, if the final product is intended for further processing, other than redissolving, then a size classification step is required in the process. The hammer mill arrangement may provide a crude size classification but a sieve is required for improved classification, hence it is included in the list.

The two driers on the plant require a vacuum set each and these have been included in the list. The vacuum sets include a pre vacuum pump condenser.

The detailed requirements for the fitting out of the laboratory with items such as scales, glassware and particularly any specialist analytical equipment have to be developed by Alkaloida.

Provision should also be made for the supply of cleaning hoses, a vacuum cleaner and other miscellaneous cleaning supplies and equipment.

4.2 EQUIPMENT KEY FEATURES

The following notes are intended to illustrate the more important features and aspects of the key equipment items. The 'general' notes are self explanatory and may be read in conjunction with section 11 on detailed engineering standards as appropriate.

4.2.1 General

All equipment supplied is to be of a quality consistent with use in the pharmaceutical industry. Equipment suppliers must have the necessary quality control procedures in place to ensure consistent quality of their products.

All equipment in this multi-product plant is capable of being easily cleaned in a reproducible manner. Welds will be neat and polished and there will be a minimum of voids or pockets in the equipment design, thus minimising the retention of contaminating material.

The equipment will have sufficient instruments and sample points to confirm correct and reliable operation.

Equipment spares for the purchased model will be readily available.

Equipment in contact with process material will be constructed from inert material which poses no contamination or reaction hazard.

Equipment lubrication or coolant will be separated from process material in order to minimise contamination.

Electrical equipment shall be provided in an appropriate form suitable for use in areas containing flammable vapours. The areas are classified into electrical zones in Section 8.

Where valves are in contact with process material, diaphragm valves or valves with a minimised dead zone should be used.

4.2.2 Key Equipment Items

Features of key items are noted below and possible suppliers are listed in Appendix I.

4P01 PRESSURE FILTER

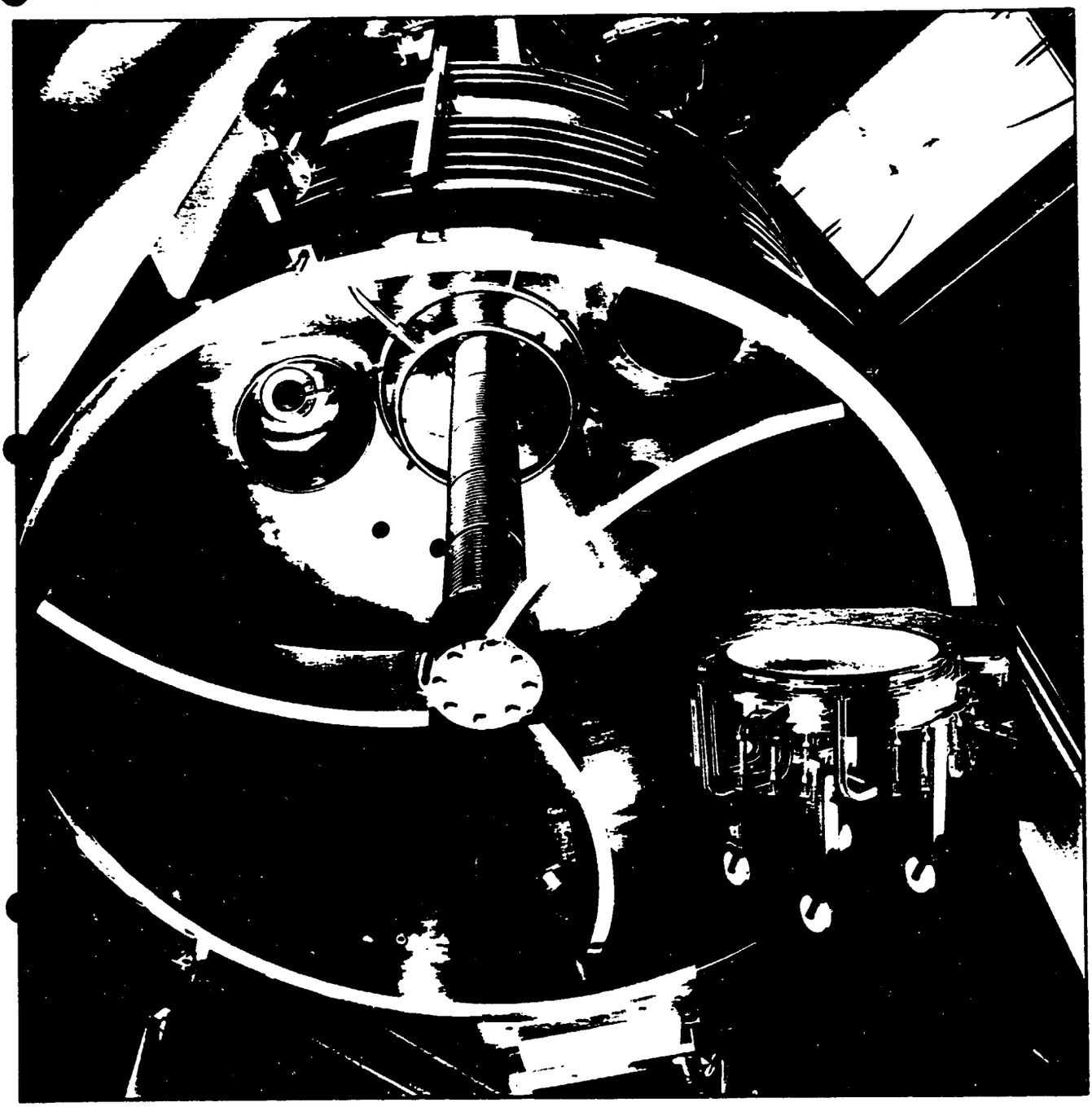
The pressure filter separates a slurry into its component parts producing a liquor (the filtrate) and a solid cake. The separation is achieved by means of filtration. The driving force for filtration is a top pressure and/or a vacuum below the filter surface. An internal rotating arm which may be raised or lowered is usually provided for cake smoothing, reslurrying and product discharge.

Pressure filters of this type are manufactured by Rosenmund among others.

Fig. 4.2.1 shows a pressure filter with the upper and base sections split for cleaning. The rotating arm in the upper section and the filter surface on the top of the base section can be clearly seen.

A pressure filter may be supplied of the 'Rosenmund' type with a $2m^2$ filtration surface. An internal arm is required together with a liquid distribution system of nozzles for cake washing.

Fig 4.2.1 Pressure Filter



The pressurising gas used is nitrogen.

The equipment and associated ancillary vessels are fully inerted with a nitrogen blanket system which is integral with the equipment operation. An engineering flow diagram, Drg. 92/005/207, shows a suitable system and is included in Volume 2.

A local data logger and printer are provided to confirm correct batch operation.

4P02 BASKET CENTRIFUGE

The basket centrifuge separates a slurry into its component parts producing a liquor (the filtrate) and a solid cake. The separation is achieved by means of filtration, with the filtration surface around the outside of a basket travelling at high speed.

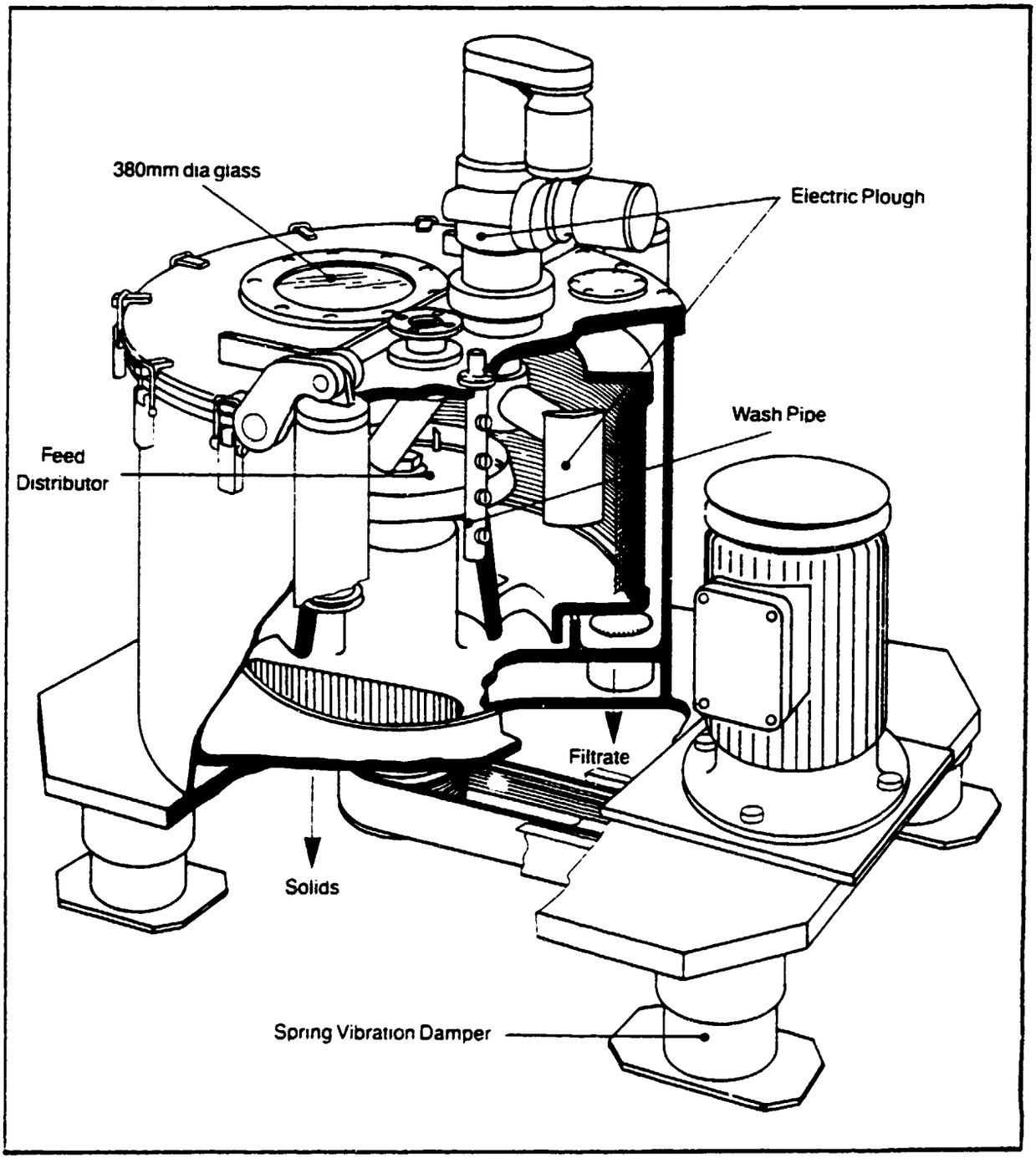
A typical centrifuge of this type is manufactured by Broadbent.

Fig. 4.2.2 illustrates a drawing of a basket centrifuge. (An electric plough solids discharge arrangement is shown which is not in fact required for the SSMPU).

The basket centrifuge of the 'Broadbent' type is supplied with a filtration surface area of 0.7 m^2. Cake washing facilities are included. The product is removed manually at the end of a batch.

The equipment and associated ancillary vessels will be fully inerted with a nitrogen blanket with oxygen analysis under normal operation. This system will automate some parts of the centrifuge operation. Further details of the methods of inerting are included in Section 9.

Fig 4.2.2 **Basket Centrifuge**



An engineering flow diagram of a suitable centrifuge is included in Volume 2.

A motion sensor and lid safety interlock will be fitted. There should be a large opening area on the top of the centrifuge for easy cleaning access. For flexibility and use in scale up work the basket motor drive should be a variable speed type.

The filter media and maximum 'G' factor required (related to basket speed) should be assessed using specially constructed trials and/or analysis of data already collected.

4T01 HORIZONTAL VACUUM DRIER

A horizontal vacuum drier dries the wet filter cake and produce a dry powder. The equipment consists of a heated hollow cylinder mounted horizontally. A ribbon blender or other mechanism distributes the process material over the heated metal surface.

A drier of this type is manufactured by Buss AG.

Fig. 4.2.3 shows a photograph of a horizontal vacuum drier. There is a vacuum take-off point incorporating a filter section to retain process material.

An engineering flow diagram for this piece of equipment is given in Volume 2.

A horizontal vacuum drier is supplied to process a wet batch size of 200 kg.

The equipment is steam heated and the powder is agitated using a ribbon blender inside the drying cylinder.

Fig 4.2.3 Horizontal Vacuum Drier

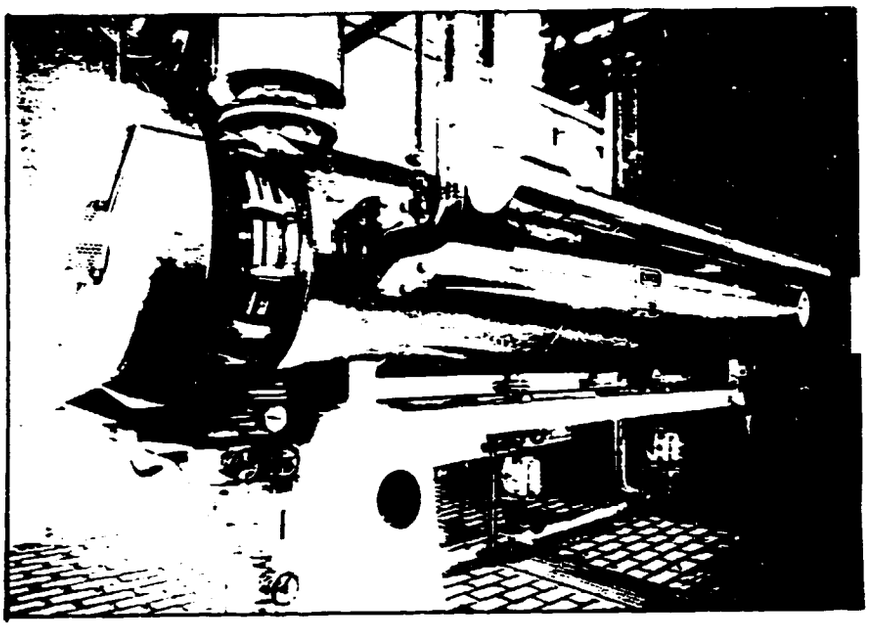
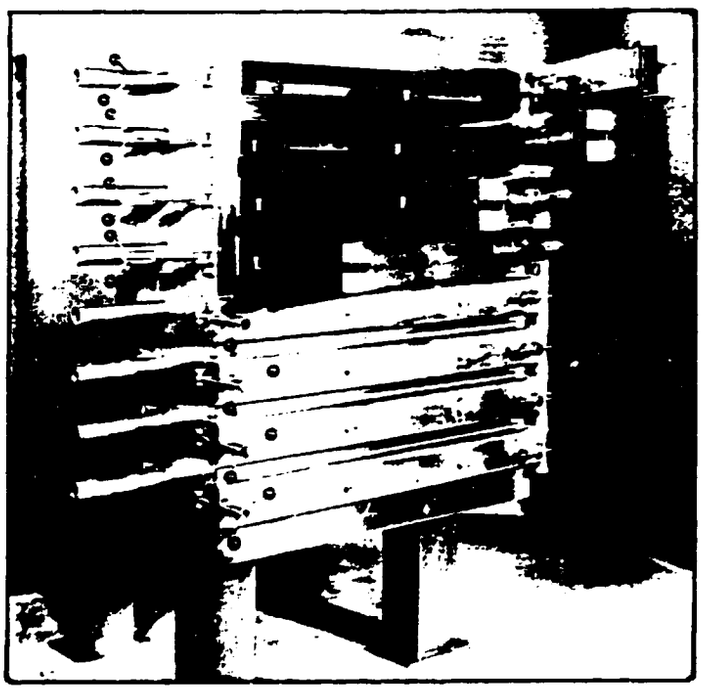


Fig 4.2.4 Vacuum Tray Drier



The drier has a dedicated vacuum and condenser unit located in a nearby service room. The type of condenser required must be assessed with reference to process details.

A bag filtration unit is used to retain the product powder in the body of the drier.

An explosion vent is placed on an appropriate part of the equipment.

A local data logging unit with printer is used to confirm correct batch operation.

4T02 VACUUM TRAY DRIER

A vacuum tray drier dries the wet filter cake and produces a dry powder. The equipment consists of one or more heated evacuated chambers on which trays of process material are placed.

Driers of this type are manufactured by Calmic Eurovent Ltd.

Fig. 4.2.4 shows a drier which has tray compartments which may be used separately.

An engineering flow diagram for this piece of equipment is given in Volume 2.

The vacuum tray drier is supplied to process a wet batch size of 200 kg.

The drier is designed to be mounted flush with a clean room wall and serviced via a service room which the main body of the drier is housed in.

The drier has a dedicated vacuum and condenser unit located in the service room. The type of condenser must be finalised by reference to process details.

The drier shall be designed to an explosion resistant shock pressure of 9 bar g (Kirkby and Suvek, ref. 5).

A local data logging unit with printer is used to confirm correct batch operation.

4H01 DOUBLE CONE BLENDER

Double cone blenders mix powders by means of a tumbling vessel often incorporating internal baffles. They comprise a short vertical cylinder with truncated cones at each end which rotates about a horizontal axis.

Blenders of this type are manufactured by Gardners.

Fig. 4.2.5 illustrates a double cone blender in use in the pharmaceutical industry.

An engineering flow diagram for this piece of equipment is given in Volume 2.

A double cone blender is supplied to blend a batch size of 400 kg.

The blender is fitted with a suitable device to explosion relieve or inert the equipment. Alternatively the blender could be built to withstand the maximum pressure of an explosion.

Fig 4.2.5 Double Cone Blender

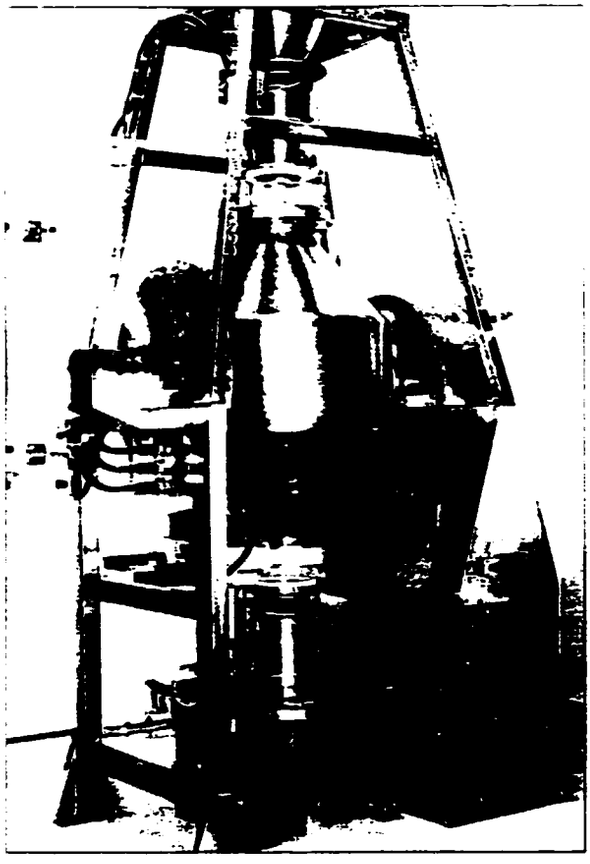
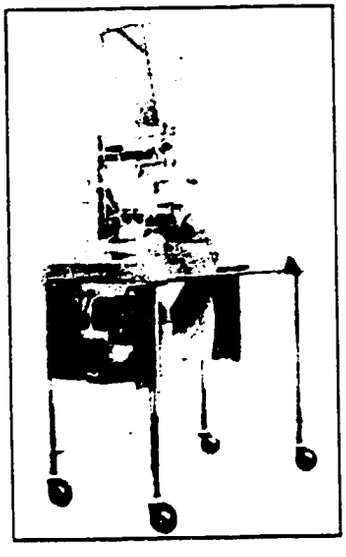


Fig 4.2.6 Hammer Mill



4H02 HAMMER MILL

A hammer mill causes vertical size reduction by means of the impact action of hammers rotating at high speed.

Hammer mills of this type are supplied by Apex.

Fig. 4.2.6 illustrates this type of equipment.

An engineering flow diagram of this piece of equipment is included in Volume 2.

A hammer mill is supplied of an appropriate size, provisionally specified as 50 kg/hr.

The mill discharges to a transfer bin, with local extraction to minimise airborne dust.

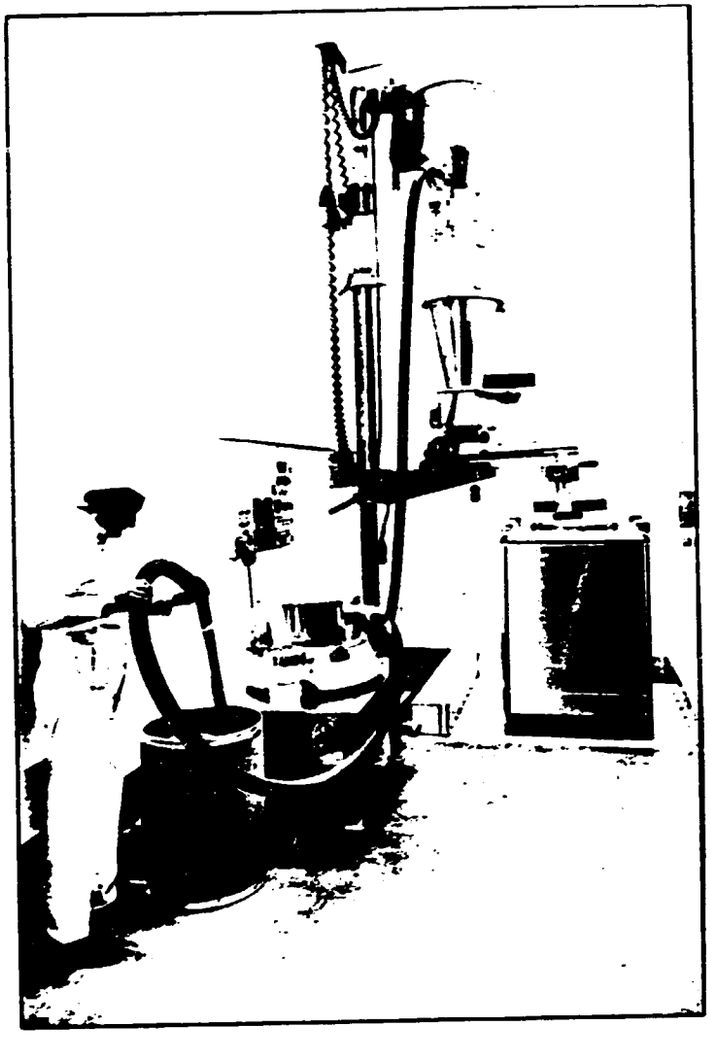
The mill is supplied with appropriate explosion venting or containment.

GRC06 SIEVE

A sieve classifies materials in terms of size by means of one or more agitated screens. Screen areas, screen mesh element sizes and number of meshes required will be decided at the detailed design stage when product specifications are finalised.

The sieve is provisionally sized at a throughput of 50 kg/hour. It should be able to accept a variety of mesh elements with various aperture sizes. The equipment should be mounted on antivibration mounts and have a variable vibration frequency for flexibility.

Fig 4.2.7 Sieve



Consideration should be given to the use of an air swept sieve system, utilising pneumatic conveying. A drawing of a suitable system utilising Vac-U-Max pneumatic conveying technology is given in Volume 2 and is shown in Fig. 4.2.7. The sieve in the bottom left of the picture is mounted on a stainless steel table with castors. The operator can be seen loading the sieve by means of a vacuum pipe.

GM02 SCALE

A scale is used to measure final product weight during packing.

The scale weighs a maximum of 200 kg and be connected to a time, date and weight ticket printer. The weight should be displayed locally but the ticket printer may have to be located out of the process room for electrical safety reasons.

The printed tickets are included in the process batch documentation.

REACTOR (VARIOUS)

A number of reactors are present in the synthesis suite used for various parts of the process.

These reactors are steel vessels which have a chemically resistant glass lining and are supplied with top mounted agitator to facilitate mixing. They are in general a two piece unit with a main cover clamped to a base unit. The vessels are often designed to withstand elevated pressure and can be protected against overpressure by a bursting disk arrangement.

It is often necessary with stirred reactors containing materials capable of producing a flammable atmosphere to inert the reactor headspace using nitrogen.

7L01/2 SCRUBBER

A scrubbing tower operates by bringing a dirty exit gas into close contact with a scrubbing liquor. The scrubbing liquor may then either dissolve and/or chemically react with the gas.

A typical scrubber consists of three main sections. A base unit which contains the scrubbing liquor which is pumped up and sprayed across the packed section. The packed section contains packing such as polypropylene 'pall' rings. The scrubbing liquor flows down and over these rings contact the dirty gas which is flowing upwards. A top section, the mist eliminator, prevents entrained droplets of liquid leaving the tower.

The tower shown in Fig. 4.2.8 shows the scrubber liquor tank to be an integral part of the scrubber. The Alkaloida plant contains two scrubber towers each with two scrubber liquor tanks sited separately from the tower.

Fig 4.2.8 Glass Lined Steel Reactor

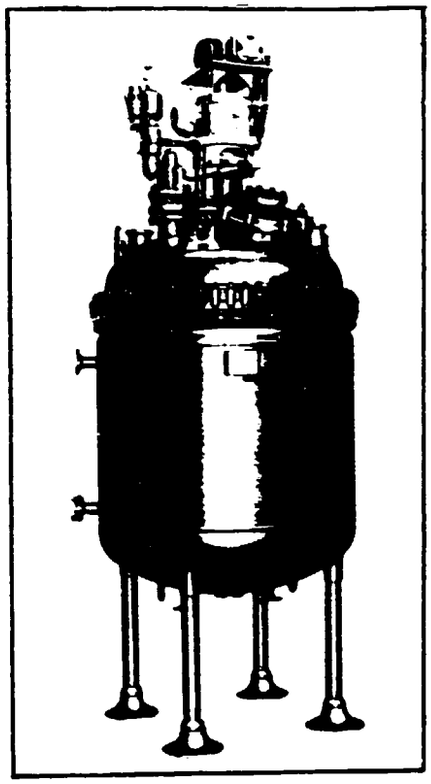
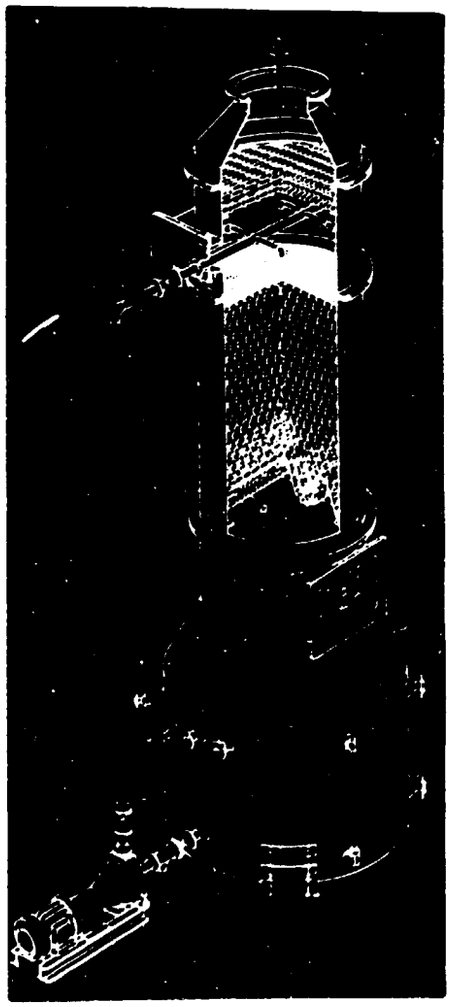


Fig 4.2.9 Scrubber



4.3 EQUIPMENT DATA SHEETS

Equipment data sheets are provided for all key items of process equipment.

As appropriate, typical operating temperatures and pressures are noted.

4.3.1 Synthesis

GR

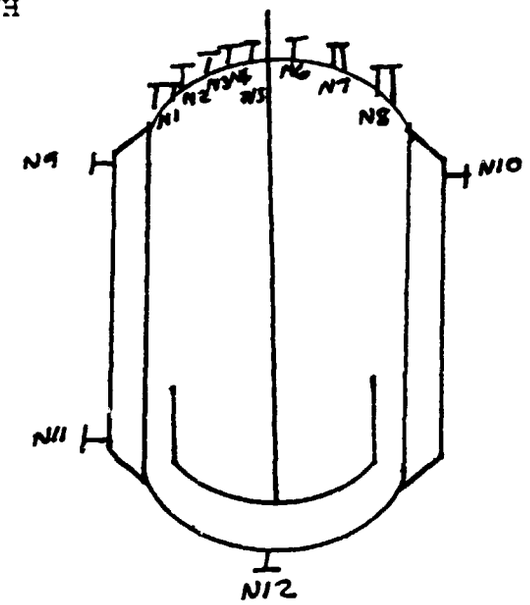
CLIENT UNIDO PROJECT TF/HUN No. 90/910

VESSEL DATA SHEET

NAME BRINE MAKE-UP TANK ITEM No. 7A01 No. OFF 1

FUNCTION THE DISSOLUTION OF SALT IN WATER

SKETCH



NOZZLE REQUIREMENTS

AS INDICATED OR NEAREST MANUFACTURERS STANDARD

N1 - SIGHT GLASS
N2 - TEMP PROBE
N3/N4 - FUTURE USE
N5 - MATERIALS INLET
N6 - VENT
N7 - LIGHT
N8 - SOLIDS PORT
N9/N10/N11 JACKET SERVICES
N12 DRAIN

	VESSEL	JACKET
WORKING VOLUME	$0.4 m^3$	AS STANDARD
GROSS VOLUME	$0.5 m^3$ NOTE A	AS STANDARD
DIMENSIONS	AS STANDARD	—
OPERATING TEMPERATURE	120°C	120°C
DESIGN TEMPERATURE	150°C	150°C
OPERATING PRESSURE	3 Bar A	2.5 Bar A
DESIGN PRESSURE	6 Bar A	4.5 Bar A
CONTENTS	BRINE	STEAM, WATER
DENSITY	—	—
PH	—	—
STERILE	NO	NO
MATERIAL OF CONSTRUCTION	ENAMELLED M.S.	
AGITATOR REQUIRED	25 rpm FIXED 2.2 KW	—

NOTES A. AS MANUFACTURERS STANDARD VESSEL SIZE

REV: A DATE: 20/11/92 BY: JO APPROVED:

A01.303

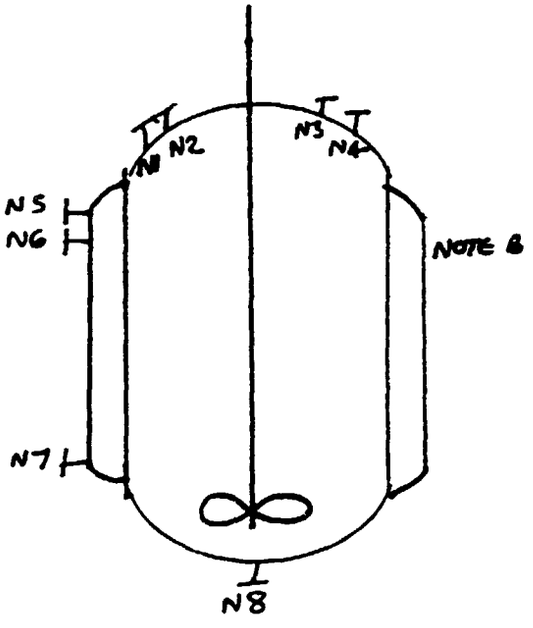
CLIENT UNIDO PROJECT TF/HUN No. 90/910

VESSEL DATA SHEET

NAME SODIUM HYDROXIDE TANK ITEM No. 2T01 No. OFF 1

FUNCTION SODIUM HYDROXIDE STORAGE

SKETCH



NOZZLE REQUIREMENTS

AS INDICATED OR CLOSEST MANUFACTURERS STANDARD
N1 - LEVEL PROBE
N2 - TEMP PROBE
N3 - LIQUID INLET
N4 - LIQUID INLET
N5/N6/N7 - SERVICE CONNECTION
N8 - VESSEL DRAIN

	VESSEL	JACKET
WORKING VOLUME	2 m³	—
GROSS VOLUME	~2.7 m³ NOTE A	AS STANDARD
DIMENSIONS	AS STANDARD	—
OPERATING TEMPERATURE	120°C	120°C
DESIGN TEMPERATURE	150°C	150°C
OPERATING PRESSURE	3 Bar A	2.5 Bar A
DESIGN PRESSURE	6 Bar A	4.5 Bar A
CONTENTS	CONC NaOH	STEAM / WATER
DENSITY	—	—
pH	—	—
STERILE	NO	NO
MATERIAL OF CONSTRUCTION	ENAMELLED M.S.	—
AGITATOR REQUIRED	50 rpm FIXED 5.5 kW	—

NOTES A. AS MANUFACTURERS STANDARD VESSEL SIZE
B. JACKET OR HEATING COILS ACCEPTABLE

REV: A DATE: 20/11/92 BY: JO APPROVED:

5.

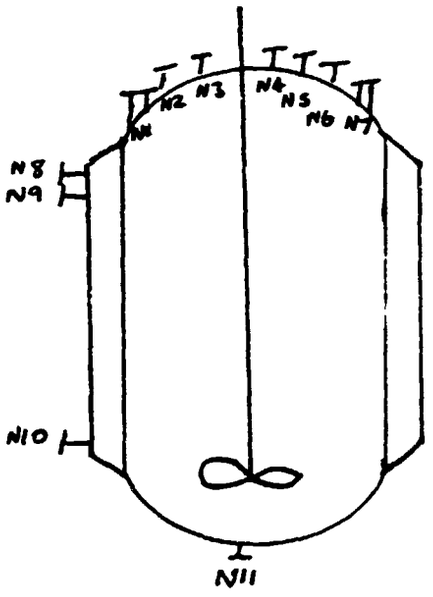
CLIENT UNIDO PROJECT TF/HUN No. 90/910

VESSEL DATA SHEET

NAME WASTE WATER TANK ITEM No. 2A01 No. OFF 1

FUNCTION TREATMENT OF WASTE WATER

SKETCH



NOZZLE REQUIREMENTS

AS INDICATED OR NEAREST MANUFACTURERS STANDARD

N1 - SIGHT GLASS
N2 - TEMP PROBE
N3 - LEVEL PROBE
N4 - VENT/BURSTING DISC
N5 - LIGHT
N6 - VENT
N7 - SOLIDS INLET
N8/9/10 - JACKET SERVICES
N11 - VESSEL DRAIN

	VESSEL	JACKET
WORKING VOLUME	2 m³	—
GROSS VOLUME	~2.7m³ NOTE A	AS STANDARD
DIMENSIONS	AS STANDARD	—
OPERATING TEMPERATURE	120°C	120°C
DESIGN TEMPERATURE	150°C	150°C
OPERATING PRESSURE	3 Bar A	2.5 Bar A
DESIGN PRESSURE	6 Bar A	4.5 Bar A
CONTENTS	—	STEAM/WATER
DENSITY	—	—
pH	—	—
STERILE	NO	NO
MATERIAL OF CONSTRUCTION	ENAMELLED M.S.	—
AGITATOR REQUIRED	50 rpm FIXED 5.5 KW	—

NOTES A. AS MANUFACTURERS STANDARD VESSEL SIZE

REV: A DATE: 20/11/92 BY: APPROVED:

W01/308

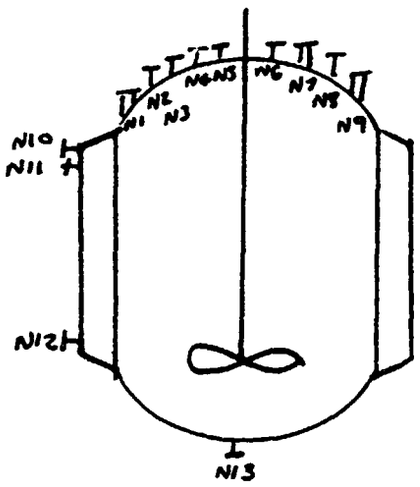
CLIENT UNIDO PROJECT TF/HUN No. 90/910

VESSEL DATA SHEET

NAME AZIDATION REACTOR ITEM No. 7A02 No. OFF 1

FUNCTION REACTION VESSEL FOR EPC AZIDATION

SKETCH



NOZZLE REQUIREMENTS

AS INDICATED OR NEAREST MANUFACTURERS STANDARD
N1 - SIGHT GLASS
N2 - LEVEL PROBE
N3/N4 - FUTURE USE
N5 - LIQUID INLET
N6 - VENT
N7 - LIGHT
N8 - VAPOUR OUT
N9 - SOLIDS INLET
N10/11/12 JACKET SERVICES
N13 - VESSEL DRAIN

	VESSEL	JACKET
WORKING VOLUME	0.63 m^3	—
GROSS VOLUME	~0.82 m^3 NOTE A	AS STANDARD
DIMENSIONS	AS STANDARD	—
OPERATING TEMPERATURE	120°C	120°C
DESIGN TEMPERATURE	150°C	150°C
OPERATING PRESSURE	3 Bar A	2.5 Bar A
DESIGN PRESSURE	6 Bar A	4.5 Bar A
CONTENTS	—	STEAM/WATER
DENSITY	—	—
pH	—	—
STERILE	NO	NO
MATERIAL OF CONSTRUCTION	ENAMELLED M.S.	—
AGITATOR REQUIRED	50 rpm FIXED 2.2kW	—

NOTES A. AS MANUFACTURERS STANDARD VESSEL SIZE

REV: A DATE: 20/11/92 BY: JO APPROVED:

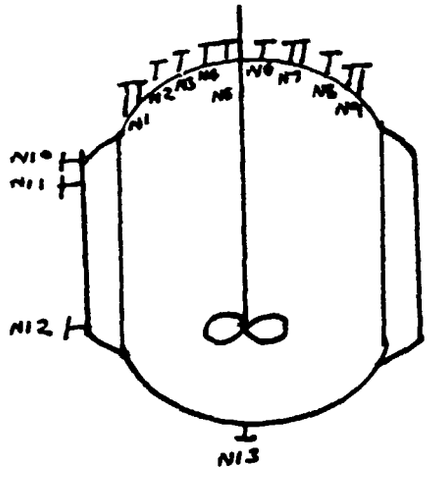
CLIENT UNIDO PROJECT TF/HUN No. 90/910

VESSEL DATA SHEET

NAME FILTER 1 FEED VESSEL ITEM No. 7A03 No. OFF 1

FUNCTION FEED VESSEL FOR FILTER SET 1 (7F01)

SKETCH



NOZZLE REQUIREMENTS

AS INDICATED OR NEAREST MANUFACTURERS STANDARD
N1 - SIGHT GLASS
N2 - TEMP PROBE
N3/N4 - FUTURE USE
N5 - UNIDO INLET
N6 - VENT
N7 - LIGHT
N8 - FILTRATE RETURN
N9 - SOLIDS INLET
N10/11/12 JACKET SERVICES
N13 - VESSEL DRAIN

	VESSEL	JACKET
WORKING VOLUME	0.63m³	—
GROSS VOLUME	NO.82m³ NOTE A	AS STANDARD
DIMENSIONS	AS STANDARD	—
OPERATING TEMPERATURE	120°C	120°C
DESIGN TEMPERATURE	150°C	150°C
OPERATING PRESSURE	3 Bar A	2.5 Bar A
DESIGN PRESSURE	6 Bar A	4.5 Bar A
CONTENTS	—	STEAM/WATER
DENSITY	—	—
pH	—	—
STERILE	NO	NO
MATERIAL OF CONSTRUCTION	ENAMELLED MILD STEEL	—
AGITATOR REQUIRED	50rpm FIXED 2.2kW	—

NOTES A. AS MANUFACTURERS STANDARD VESSEL SIZE

REV: A DATE: 20/11/92 BY: JO APPROVED:

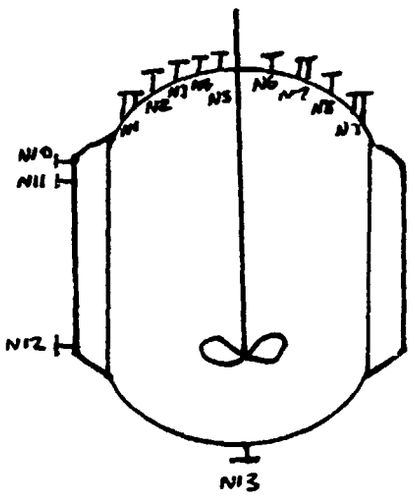
CLIENT UNIDO PROJECT TF/HUN No. 90/910

VESSEL DATA SHEET

NAME DEAZIDATION REACTOR 1 ITEM No. 7A04 No. OFF 1

FUNCTION REACTOR FOR FIRST STAGE OF WATER DEAZIDATION

SKETCH



NOZZLE REQUIREMENTS

AS INDICATED OR NEAREST MANUFACTURERS STANDARD
N1 - SIGHT GLASS
N2 - TEMP PROBE
N3/N4 - FUTURE USE
N5 - LIQUID INLET
N6 - VENT
N7 - LIGHT
N8 - SCRUBBER OUTLET
N9 - SOLIDS INLET
N10/11/12 JACKET SERVICES

	VESSEL	JACKET
WORKING VOLUME	0.63m³	—
GROSS VOLUME	~0.82m³ NOTE A	AS STANDARD
DIMENSIONS	AS STANDARD	—
OPERATING TEMPERATURE	120°C	120°C
DESIGN TEMPERATURE	150°C	150°C
OPERATING PRESSURE	3 Bar A	2.5 Bar A
DESIGN PRESSURE	6 Bar A	4.5 Bar A
CONTENTS	—	STEAM/WATER
DENSITY	—	—
pH	—	—
STERILE	NO	NO
MATERIAL OF CONSTRUCTION	ENAMELLED MILD STEEL	—
AGITATOR REQUIRED	30 rpm FIXED 2.2 kW	—

NOTES A. AS MANUFACTURERS STANDARD VESSEL SIZE

REV: A DATE: 20/11 92 BY: JD APPROVED:

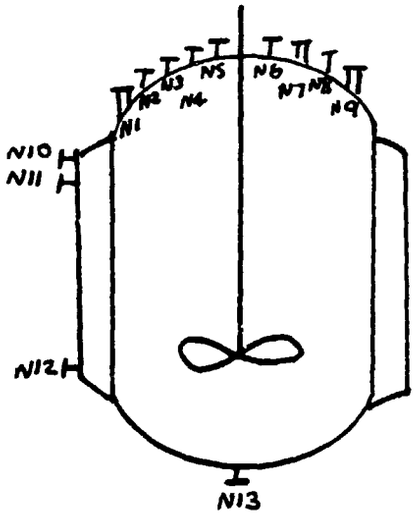
CLIENT UNIDO PROJECT TF/HUN No. 90/910

VESSEL DATA SHEET

NAME DEAERATION REACTOR 2 ITEM No. 7A05 No. OFF 1

FUNCTION REACTOR FOR SECOND STAGE OF WATER DEAERATION

SKETCH



NOZZLE REQUIREMENTS

AS INDICATED OR NEAREST MANUFACTURERS STANDARD
N1 - SIGHT GLASS
N2 - TEMP PROBE
N3&4 FUTURE USE
N5 - LIQUID INLET
N6 - VENT
N7 - LIGHT
N8 - SCRUBBER OUTLET
N9 - SOLIDS INLET
N10/11/12 - JACKET SERVICES
N13 - VESSEL DRAIN

	VESSEL	JACKET
WORKING VOLUME	1.0 m³	—
GROSS VOLUME	~1.3 m³ NOTE A	AS STANDARD
DIMENSIONS	AS STANDARD	—
OPERATING TEMPERATURE	120°C	120°C
DESIGN TEMPERATURE	150°C	150°C
OPERATING PRESSURE	3 Barg	2.5 Barg
DESIGN PRESSURE	6 Barg	4.5 Barg
CONTENTS	—	STEAM/WATER
DENSITY	—	—
pH	—	—
STERILE	NO	NO
MATERIAL OF CONSTRUCTION	ENAMELLED MILD STEEL	—
AGITATOR REQUIRED	50 rpm AXED 2.2 kW	—

NOTES A. AS MANUFACTURERS STANDARD VESSEL SIZE

REV: A DATE: 20/11/92 BY: JO APPROVED:

6.3 EQUIPMENT DATA LOGGING AND INSTRUMENTATION REQUIREMENT

Tables 6.3.1 and 6.3.2 give the equipment data monitoring requirements and the means by which they are achieved.

The simpler pieces of equipment with less reliance on external services such as vacuum are manually logged. Process equipment that comes into this category includes the basket centrifugal filter (4F02), double cone blender (4H01), hammer mill (4H02), and the vacuum sets for the driers.

The more complex pieces of equipment, with several operating parameters and relying on the performance of services, are locally automatically datalogged. This data is also printed at a local station.

Table 6.3.1

ITEM	DESCRIPTION	NO OFF	DATA LOGGED	METHOD
2T01	Reactor	1	None	
2A01	Reactor	1	None	
7A01	Reactor	1	None	
7A02	Reactor	1	Vessel temperature, vessel pressure, vapour exit temperature	Central computer
7A03	Reactor	1	None	
7A04	Reactor	1	None	
7A05	Reactor	1	None	
7A06	Reactor	1	Versel temperature,vessel pressure	Central computer
7A07	Reactor	1	Vessel temperature, vessel pressure, impeller speed, vessel weight	Central computer

7A08	Reactor	1	Vessel temperature, vessel pressure, impeller speed, vapour exit temperature	Central computer
7A09	Reactor	1	Vessel temperature, vessel pressure, vapour exit temperature	Central computer
7X01	Extraction Vessel	1	Vessel temperature, vessel pressure, impeller speed	Central computer
9H02	Heat Exchanger	1	Liquor exit temperature	Central computer
9H07	Heat Exchanger	1	None	
9H08	Heat Exchanger	1	Liquor exit temperature	Central computer
9H09	Heat Exchanger	1	Liquor exit temperature	Central control
9E03	Tank	1	None	
8E02	Tank	1	None	

1R01	Tank	1	None
1R02	Tank	1	None
2T02	Tank	1	None
2T03	Tank	1	None
6K01	Mobile Tank	1	None
6K04	Mobile Tank	1	None
7L01	Gas Scrubber	1	None
7L02	Gas Scrubber	1	None
6E01	Tank	1	None
6E02	Tank	1	None
6E03	Tank	1	None

6E04	Tank	1	None	
8E01	Tank	1	None	
8E03	Tank	1	None	
8E05	Tank	1	None	
9E01	Tank	1	None	
7F01	Pressure Filter	1	None	
7F02	Pressure Filter	1	Pressure, rotating arm speed	Central computer
9V01	Fan	1	None	
9V02	Fan	1	None	
1S01	Centrifugal Pump	1	None	

1S02	Centrifugal Pump	1	None
1S03	Centrifugal Pump	1	None
1S04	Centrifugal Pump	1	None
6S01	Centrifugal Pump	1	None
6S02	Centrifugal Pump	1	None
6S03	Centrifugal Pump	1	None
6S05	Centrifugal Pump	1	None
6S07	Centrifugal Pump	1	None
6S08	Centrifugal Pump	1	None

6S09	Centrifugal Pump	1	None	
6M01	Balance	1	Weight, time and date	Local printer
6M02	Balance	1	Weight, time and date	Local printer
GRC/ 9B01	Tank	1	None	
GRC/ V1	Tank	1	None	
GRC/ V2	Tank	1	None	
GRC/ V3	Tank	1	None	
GRC/ V4	Tank	1	None	
GRC/ V5	Tank	1	None	
GRC/ TR1	Tank	1	None	

GRC/ P1	Tank	1	None
GRC/ P2	Tank	1	None
GRC/ P3	Tank	1	None
GRC/ P4	Pump	1	None
GRC/ MV1	Mobile Vessel	1	None
GRC/ MV2	Mobile Vessel	1	None

Table 6.3.2

ITEM	DESCRIPTION	NO OFF	DATA LOGGED	METHOD
4F01	Pressure	1	Impeller speed, operating time, differential pressure	Local Automatic datalogging with printout
4F02	Basket Centrifugal Filter	1	Rotational speed, operating time	Manual
4T01	Horizontal Vacuum paddle Dryer	1	Impeller speed, operating time, pressure, temperature	Local automatic datalogging with printout
4T02	Vacuum Tray Dryer	1	Operating time, temperature, pressure	Local automatic datalogging with printout
4H01	Double Cone Blender	1	Rotational speed, operating time	Manual
4H02	Hammer Mill	1	Rotational speed, operating time, Screen size	Manual
3S01	Centrifuge Room Pumps	2	Operating time	Manual (if required)
6M02	Scale	1	Weight with time reference	Automatic printout with date and time

GRC01	Filter Room Tanks	3	Volume and for weight	Manual
GRC02	Filter Discharge Pump	1	Operating time	Manual
GRC03	Sieve Mechanism	1	Operating time, Screen sizes Oscillation rate	Manual
GRC07	Vacuum sets for dryers	2	Operating time, operating temperature	Manual
	Services		Steam Pressure, nitrogen pressure Process vacuum, cooling water temp, chilled brine temp, various service flows	Log services automatically/manually when ou of specification, use totalising meters to log various service flows

Sufficient local instrumentation is installed on both the process equipment and the utilities and services to enable the plant to be operated under the full control of the plant operators. Where equipment is normally operated as part of a process system, instrument readouts for all the instruments in the system are grouped at the normal operator control position.

All the instrumentation scales are based on the same acceptable system of units, e.g. SI Units.

6.4 EQUIPMENT ALARMS

The centralisation of alarm monitoring is readily achieved by the use of a central monitoring PC and a distributed control system. Alarm actuation and sounding should be carried out at a local level with the central PC ideally detecting the presence of an alarm flag in the local controller. A central alarm system may also be developed in a more conventional hardware type system utilising relays.

The mode of operation in the SSMPU may mean equipment is always supervised locally. In this case a central alarm system is not necessary.

6.5 SERVICE AND UTILITY ALARMS

Alarms are to be installed for service failures which could compromise batch quality or cause a risk to personnel. Alarms are therefore recommended on the following services.

1. Process Steam, required for the operation of the drier.

2. Nitrogen, for the operation of the pressure filter and also must be present for safety reasons on the pressure filter and centrifuge.

3. Process Vacuum, for some operations of the pressure filter.

4. HVAC, for the maintenance of a suitable process environment and also for safety reasons.

5. Breathing Air, maintained for safety reasons.

6. Chilled Brine and Cooling Water, used in the condenser which protect the vacuum pumps. Failure of this supply could lead to premature failure of the vacuum pumps.

7. Demineralised water quality, used for cleaning process equipment and may come into contact with the product.

The alarm service should be central as one service may be used in several parts of the plant. The physical location of the control panel will be specified as part of the detailed design.

The services can be logged in one of 4 main ways.

(a) Automatic monitoring of service conditions, with constant datalogging and alarm facility.

(b) Automatic monitoring of service conditions with alarm facility and datalogging when in alarm condition.

(c) Automatic monitoring of service conditions with alarm facility and frequent manual logging of services under alarm condition.

(d) Manual monitoring of service conditions with frequent manual logging of services under alarm conditions.

Note that even with automatic monitoring of service conditions, manual recordings will still have to be made, but at less frequent intervals.

For this facility 'Automatic monitoring of service conditions with alarm facility and frequent manual logging of services under alarm conditions' is considered suitable.

HVAC Alarms

The pressures of individual rooms are fed to a central area where they are recorded manually on a regular basis. Alarms are fitted to this system to ensure correct pressure differentials between rooms.

Each room has a flush fitting wall mounted temperature gauge.

Process rooms handling powder have a flush fitting wall mounted humidity gauge.

The alarming of the HVAC equipment will be dealt with at the detailed design stage and will be influenced by the exact type of equipment used.

Fire Alarms

A central alarm system providing adequate alarm to all parts of this system is to be installed. This system is to be interfaced with other nearby alarm systems from areas which may prejudice the safety of workers in this area. The fire

detection signals located in individual rooms are fed back to a suitable overall site monitoring area and also displayed locally in this facility.

6.6 ON-SITE COMMUNICATION

The form of plant communication must be assessed by Alkaloid. It is expected that a centralised Tannoy system would be suitable. Access to this Tannoy system could be achieved via a telephone operator elsewhere on the site. The system could be mounted in the corridor or ceiling space. An inter-room intercom is not expected to be required for this facility. This will be finalised as part of the detailed design.

6.7 PLANT AND EMERGENCY LIGHTING

Lighting on the plant is arranged so that all areas are well illuminated. Where necessary as indicated by the hazardous zone classification drawings in section 9.2, flameproof lighting is used.

An emergency lighting system is to be provided to enable safe evacuation from the plant.

Alkaloida must advise on the requirement for back-up power from an emergency generator for process and economic reasons. This emergency lighting can be provided from this circuit if available or can be of rechargeable type.

6.8 ELECTRICAL SPECIFICATION

The plant is provided with single and three phase electricity rated at

Single phase	220 V 50 Hz
Three phase	380 V 50 Hz

SECTION 7

LAYOUT

7 LAYOUT

The plant layout is described with respect to site location and personnel and materials flow.

7.1 BUILDING LAYOUT

The SSMPU is located on two floors in the empty section of an existing building adjacent to a plant producing the intermediate, Iminodibenzyl. The new plant does not, however, share any HVAC equipment and has separate entrances.

The synthesis plant is located on the first floor and has a separate entrance to the DSP plant

7.1.1 Synthesis

The first floor synthesis suite is accessed by means of a small changing area and staircase which is located on the ground floor but is isolated from the DSP facility. The ground floor entrance block also contains washing and WC facilities, as can be seen as part of the external equipment layout drawing 92/013/103, included in Section 3.

Also contained in Section 3, the first floor layout, drg. 92/013/102, shows that there is a central main Process Hall surrounded by several smaller rooms.

Two process rooms are segregated from the main area, the dangerous process room and the filter room. The whole area is overlooked by a raised control room which is isolated from the main process hall by an air lock.

7.1.2 DSP

The ground floor DSP process rooms are arranged to give a reasonably linear flow of 'in process material' from reception on the ground floor via a pipeline to the filter room to despatch from the 'cleared finished products' store. Hungarian convention on the glass venting of rooms containing potentially explosive mixture requires that all the process rooms are adjoining an outside wall.

The lack of availability of space has required that some pieces of equipment share rooms. This is not expected to cause problems with regulatory authority approval as the plant will be dedicated to one product at a time.

The ingoing and outgoing change facilities share the same rooms. This is acceptable for a medicinal chemicals plant producing one product at a time. The present scheme is to have one shift per day so little crossing of personnel is likely to occur in these rooms.

Alkaloida have proposed a layout as defined by Alkaloida drawing no. T3523. This is reproduced in this report as GRC drawing no. 92/005/101. The work on the construction of the internal walls of this plant, as defined by this drawing, is substantially complete.

GRC Consultants proposes a new layout, drg. no. 92/005/102 which retains as much of the internal, already constructed walls as practical. These layouts are contained in Section 3.

The new layout retains most of the original internal walls, the changes occur in the changing area. There is also a small change with the inclusion of an emergency escape door and a pass through hatch in the Product Receipt room (room 22) and the Cleared Finished Products Store (room 23).

The changing room now incorporates a two-stage change facility which is shared by personnel coming in and going out. This layout facilitates the limited reuse of clean clothing if required and provides better washing facilities. Movement protocols have been developed as an aid to layout and are included in Section 7.5.

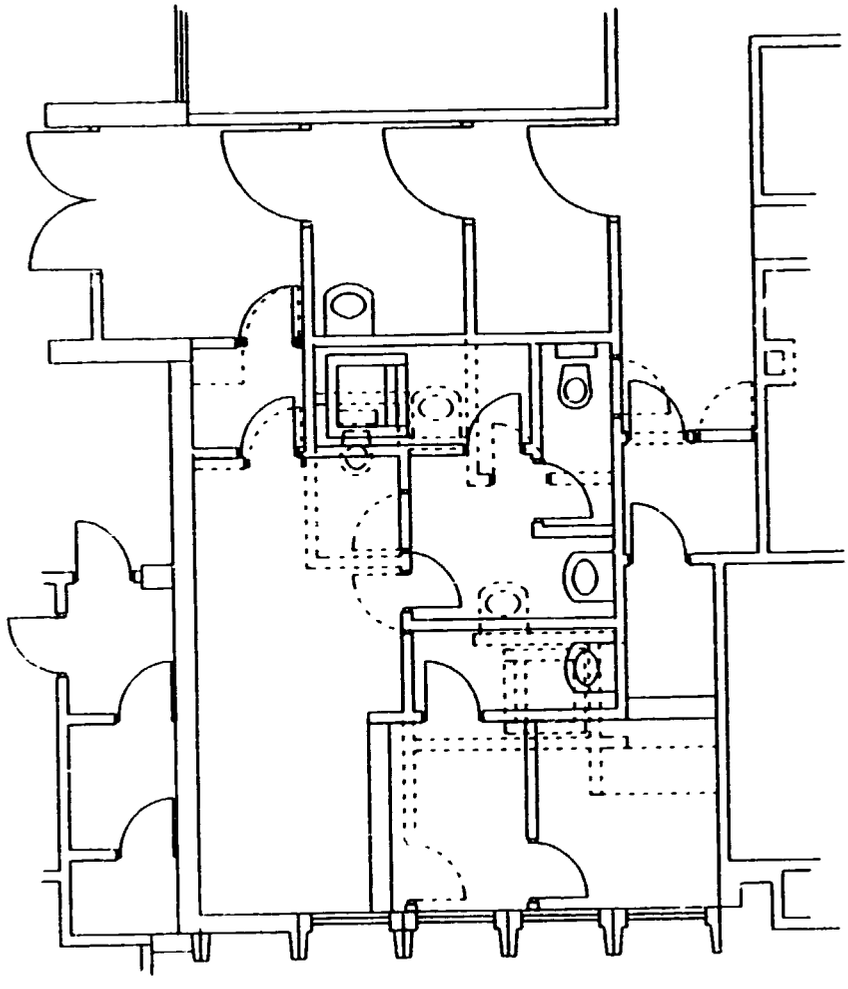
The pass through hatch between the product receipt room (room 22) and the cleared finished products store (room 23) provides a physical barrier between clean and dirty areas. The hatch is constructed in such a way that only one of the two doors can be open at any one time. This mechanism prevents ingress of contaminating material from the dirty cleared finished products store to the clean product receipt room.

The difference between the two layouts is shown in GRC drg. 92/005/111. Substantial changes to the internal walls are not required to upgrade the new layout.

Toilets are not provided in the clean process area. Any requirements for the lavatory must be attended to during breaks as a matter of strict discipline. A toilet is provided in the primary change area for this purpose. Draft changing protocols for the purposes of clarifying room design are detailed later in this section.

The upper level floor is sealed to prevent any leakage between the two levels. A sealed suspended ceiling is installed on the ground floor with HVAC purging of the void area. HVAC ducting and service pipes are also installed in this void area.

Floor drains have already been installed by Alkaloida and are detailed in Alkaloida Drg. EG 2409 (GRC drg. 92/005/112). There is extensive use of floor drains which is not consistent with good practice in a modern pharmaceutical plant. The



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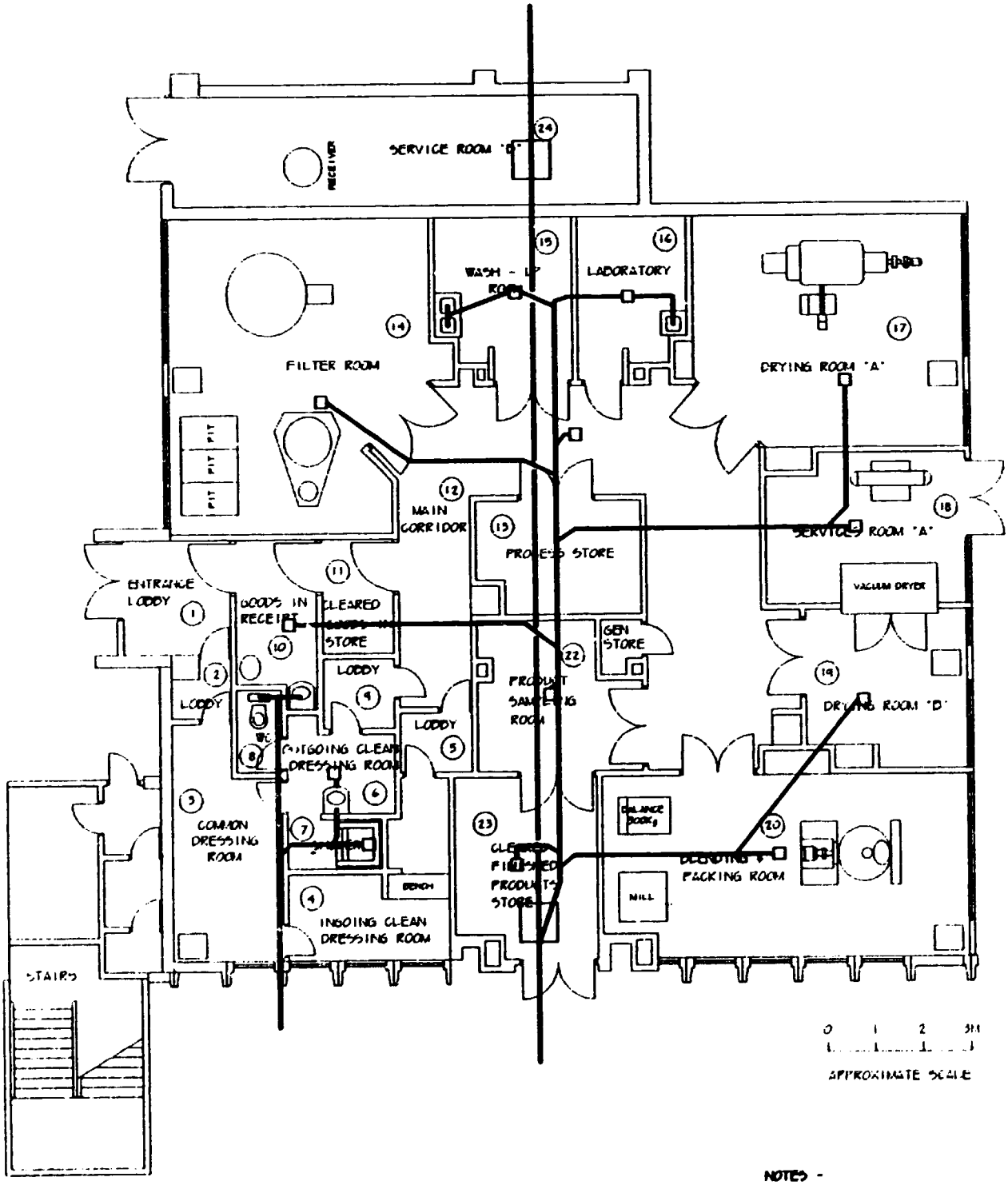
APPROXIMATE SCALE

KEY

- - - - - ORIGINAL ALKALOIDA LAYOUT

——— PROPOSED NEW LAYOUT

GRC CONSULTANTS	CLIENT: UNIDO, P O BOX 300, A-1400 VIENNA, AUSTRIA FAX 232156	PROJECT: ALKALOIDA I TF/HUN/90/907	TITLE: OVERLAY OF ORIGINAL & PROPOSED NEW WALLS
	DATE: MAY 1992		DRAWING NUMBER: 92/005/A11
	SCALE: N/A		REVISION: A
	DIMENSIONS IN METRES		



NOTES -

□ - DRAINS

GRC CONSULTANTS	CLIENT: UNIDO, P O BOX 300, A-1400 VIENNA, AUSTRIA. FAX: 232156	PROJECT: ALKALOIDA I TF/MUN/90/907	TITLE: GROUND FLOOR DRAINAGE LAYOUT	
	DATE: NOV 1992 SCALE: 1:75 DRAWING BY: DETAILED		DRAWING NUMBER: 92/003/112	REVISION: A

layout of floor drains is detailed in Section 5. There should be no floor drains in any process rooms except the filter room, where hoses will be used for cleaning.

Unnecessary drains with infrequent use present a microbiological risk. The loss of the sealing water by evaporation leads to the risk of vapour and aerosol contamination originating from the main drain. The subject of drains and the means by which unnecessary drains should be sealed requires discussion with Alkaloida.

The main process corridors are 2 metres wide which give good access to process material traffic.

7.2 EQUIPMENT LAYOUT

7.2.1 Synthesis

A preliminary equipment layout has been developed by Alkaloida (Alkaloida drg. T3524). A revised layout with the introduction of some new equipment is shown in drg. 92/013/102 first floor equipment layout located at the end of Section 3.

The main process area contains reactors of various sizes and a vessel which will operate as a specialist two phase liquid-liquid extractor. Space has been left for the possible future inclusion of a drier and a pressure filter.

The dangerous process area contains reactors and a pressure filter. A second pressure filter is located in the filter room and will be used with activated carbon in the EPC process.

A control room is provided for location of control equipment and general supervisory duties.

7.2.2 DSP

A preliminary equipment layout in individual rooms has been developed by Alkaloida (Alkaloida Drg. T3523). The revised layout developed by GRC takes into account handling and accessibility to the equipment and is shown in drg. 92/013/102 Ground Floor Room Layout located at the end of Section 3.

The double cone blender is located inside a cage in the blending and packing room (room 20). This is for safety reasons as the blender is classed as rotating machinery.

The service equipment for the dryers is contained within a service area (Service Room A) which is not part of the clean process area and accessed separately. As is normal practice the tray vacuum dryer is sealed into a service wall.

The HVAC equipment for this plant is mounted above service room B on the 1st floor. HVAC ducting is led above the ground floor false ceiling and below the sealed upper level floor.

7.3 PERSONNEL FLOW

7.3.1 Synthesis

Personnel enter the synthesis suite via a dedicated entrance lobby and enter an overcoat change area where a partial change of clothing may occur. A wash and toilet area are located adjacent to the overcoat change area and personnel may use these facilities when in this area.

Process workers then enter the first floor synthesis suite via the stairs and the upstairs lobby. Personnel leave the area in the same manner.

7.3.2 DSP

Personnel enter and leave the building through a common set of changing areas. A worker in the clean area wears essentially two layers of clothing. Good quality relatively clean two piece workwear covered by a one piece clean coverall. Changing from street clothes to workwear occurs in the primary change area and the clean coverall is put on in the secondary change area.

An overview of personnel flow in the plant is presented as drg. 92/005/113. From this drawing it can be seen that the personnel flow is reasonably linear.

In order to confirm the satisfactory layout of the change area a changing protocol has been developed and is presented later in this section.

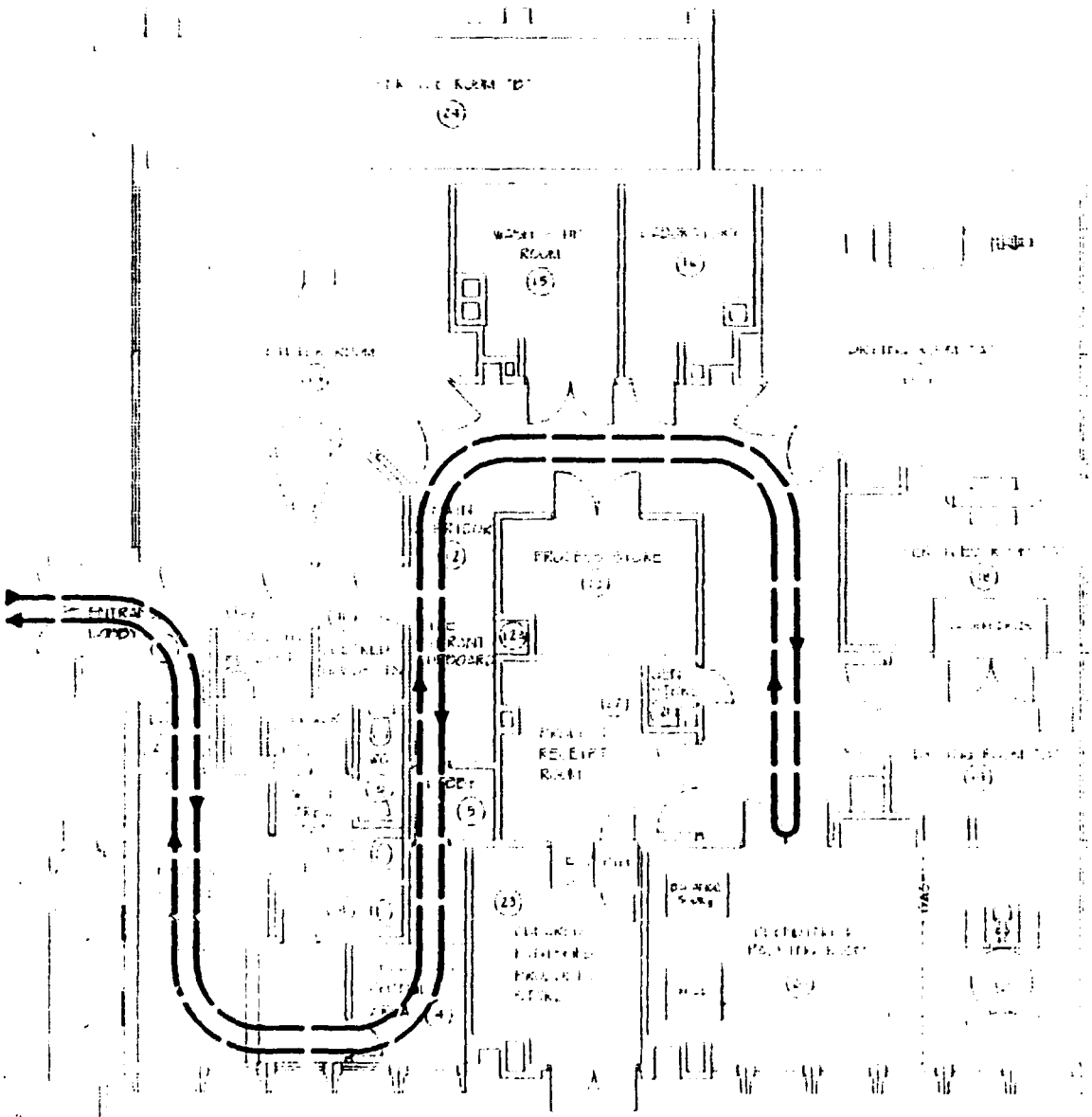
All personnel entering the clean area of this facility must pass through, and change in, the change area as a matter of strict discipline. This includes maintenance and QA personnel.

Breaks by personnel are taken elsewhere on site after changing back into street clothes.

The use of the toilet is strictly limited to arrival, breaktime and work finish. Any emergency use of the toilet requires changing back into street clothes.

A shower is provided for outgoing personnel. A worker enters the shower room with his street clothes. He will then shower, dry himself and emerge from the shower in his street clothes.

All protocols for personnel and material flow once fully developed must be strictly adhered to.



CRC CONSULTANTS	CLIENT: UNIDO, P O BOX 300, A-1400 VIENNA, AUSTRIA. FAX:232156 DATE: MAY 1992 SCALE: N/A DIMENSIONS IN METRES	PROJECT: ALKALOIDA I TF/HUN/90/907	TITLE: OVERVIEW OF PERSONNEL FLOW DRAWING NUMBER: 92/005/A 13 REVISION: A

7.4 MATERIALS FLOW

7.4.1 Synthesis

Solid and small volume liquids are stored and dispensed in a nearby facility. They are transferred in sealed containers and enter the facility via the materials lift.

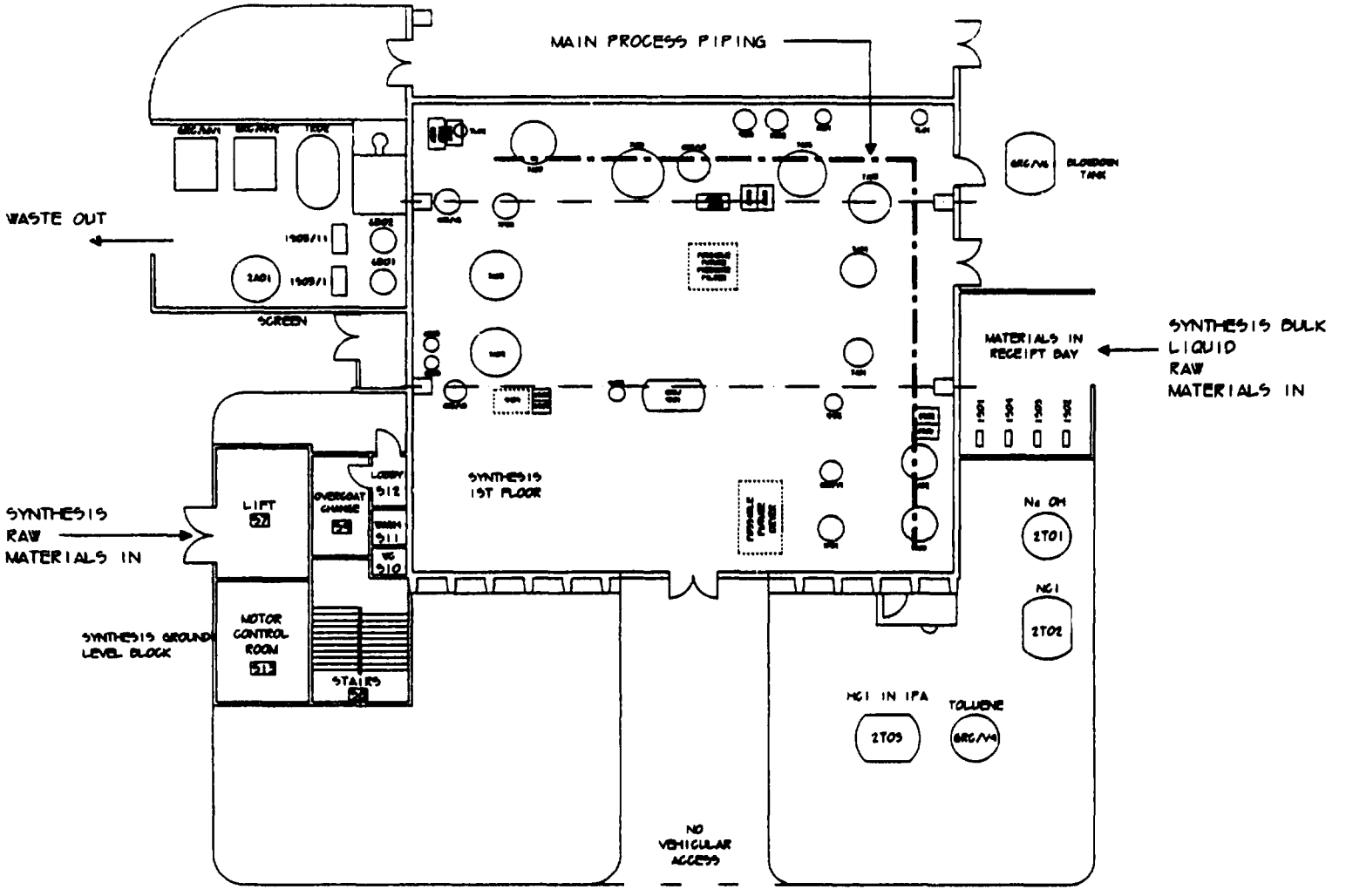
Drg. 92/013/104 gives an overview of materials flow and identifies the bulk storage vessel area and the waste receipt area. Note that the first floor synthesis plant uses ground floor external vessels for both raw material storage and waste collection.

Sodium hydroxide and toluene are delivered to the SSMPU by mobile wheeled vessels and are pumped into bulk storage vessels in the bulk storage vessel area. Hydrochloric acid and HCl in isopropanol are also stored in bulk tanks in this area but these materials are delivered in barrels to the SSMPU.

Wastes are transferred out of the synthesis suite to the waste collection area. Organic wastes are taken away for recycling or incineration.

Aqueous wastes are treated in the external vessel 2A01 in the waste area before running to drain.

The product from the synthesis suite enters the DSP area directly from a pipe connecting first floor vessel 7A08 to the ground floor filter area.



REV	DATE	DESCRIPTION	BY
A	7/12/92	ISSUED WITH REPORT	HG

GRC CONSULTANTS

WATERCRESS HOUSE 1, THE WINDMILLS
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CLIENT
UNIDO P.O. BOX 300,
A-1400 VIENNA,
AUSTRIA, FAX 232156

ALL DIMS IN MILLIMETRES

PROJECT
ALKALOIDA 2
TF/HUN/90/910

DRAWING TITLE
FIRST FLOOR
MATERIALS FLOW

DRAWING NUMBER
92/013/104

REV
A

7.4.2 DSP

Process materials enter the filter room in the form of a slurry piped by gravity from the upper floor. The rooms are arranged along the length of the main corridor in the logical order in which the unit operations are carried out. The flow is basically filtration, drying and then milling, blending and packing and finally despatch.

The packing materials enter the plant via the goods in receipt and cleared goods in. Finished and packed goods leave the plant via the product receipt room and upon receiving QA approval are transferred to the cleared finished products store to await despatch.

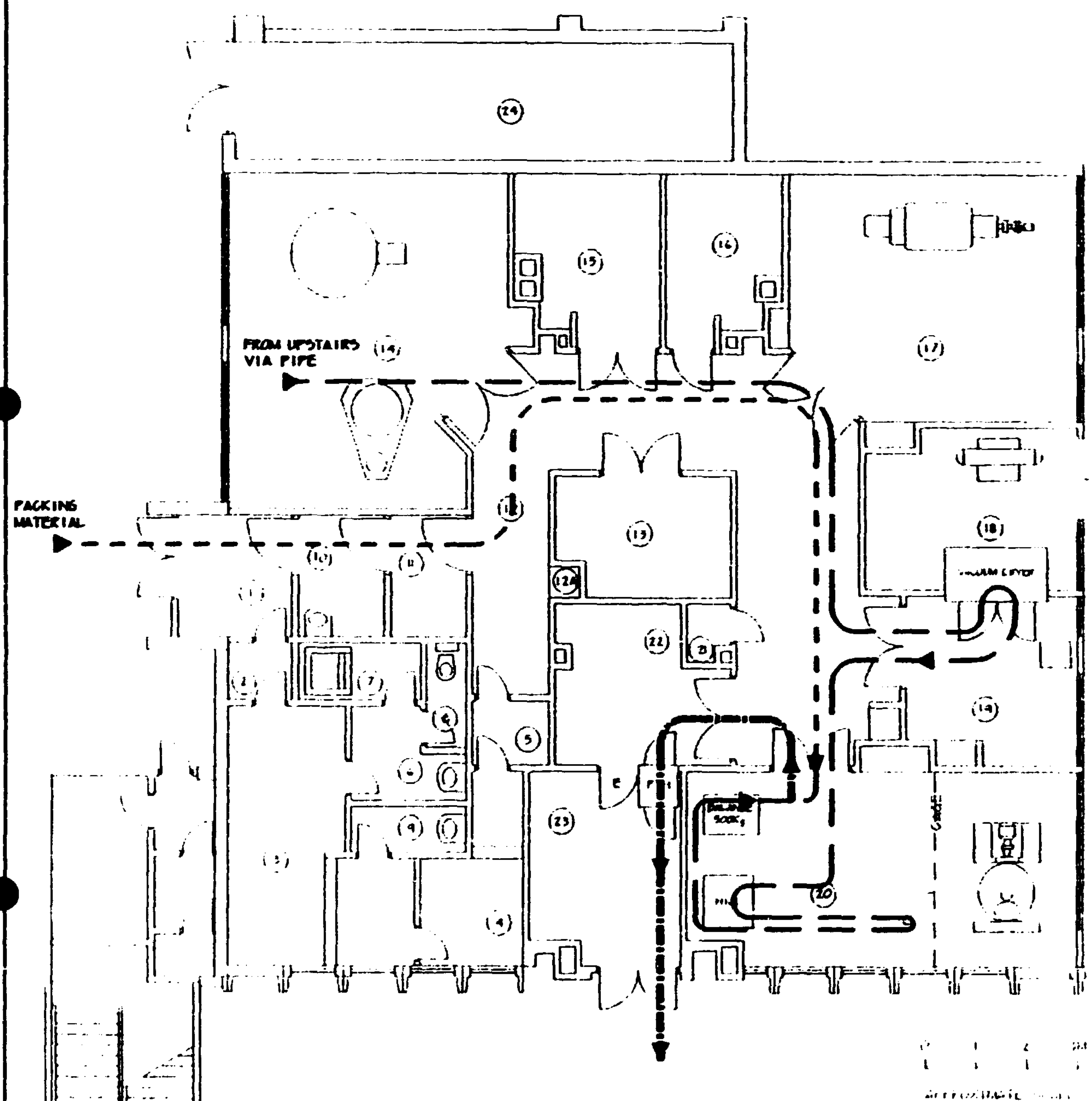
From drg. no. 92/005/114, Overview of Material Flow, it can be seen that this layout gives a reasonably linear flow of materials.

7.5 PERSONNEL MOVEMENT PROTOCOLS

Personnel movement definition in the DSP area is particularly important for Good Manufacturing Practice consideration. For this reason personnel movement protocols have been developed for the ground floor DSP area and are detailed below.

The layout of the changing rooms is dependent on changing protocols and draft changing protocols are presented here for development and integration with the general operating practices of Alkaloida.

The personnel movement protocols include the use of tac mats in the positions shown in drg. 92/005/105.



APPROXIMATE SCALE

NOTES: BASED ON ALKALOIDA [illegible]

KEY:

P.T.H. PASS THROUGH HATCH

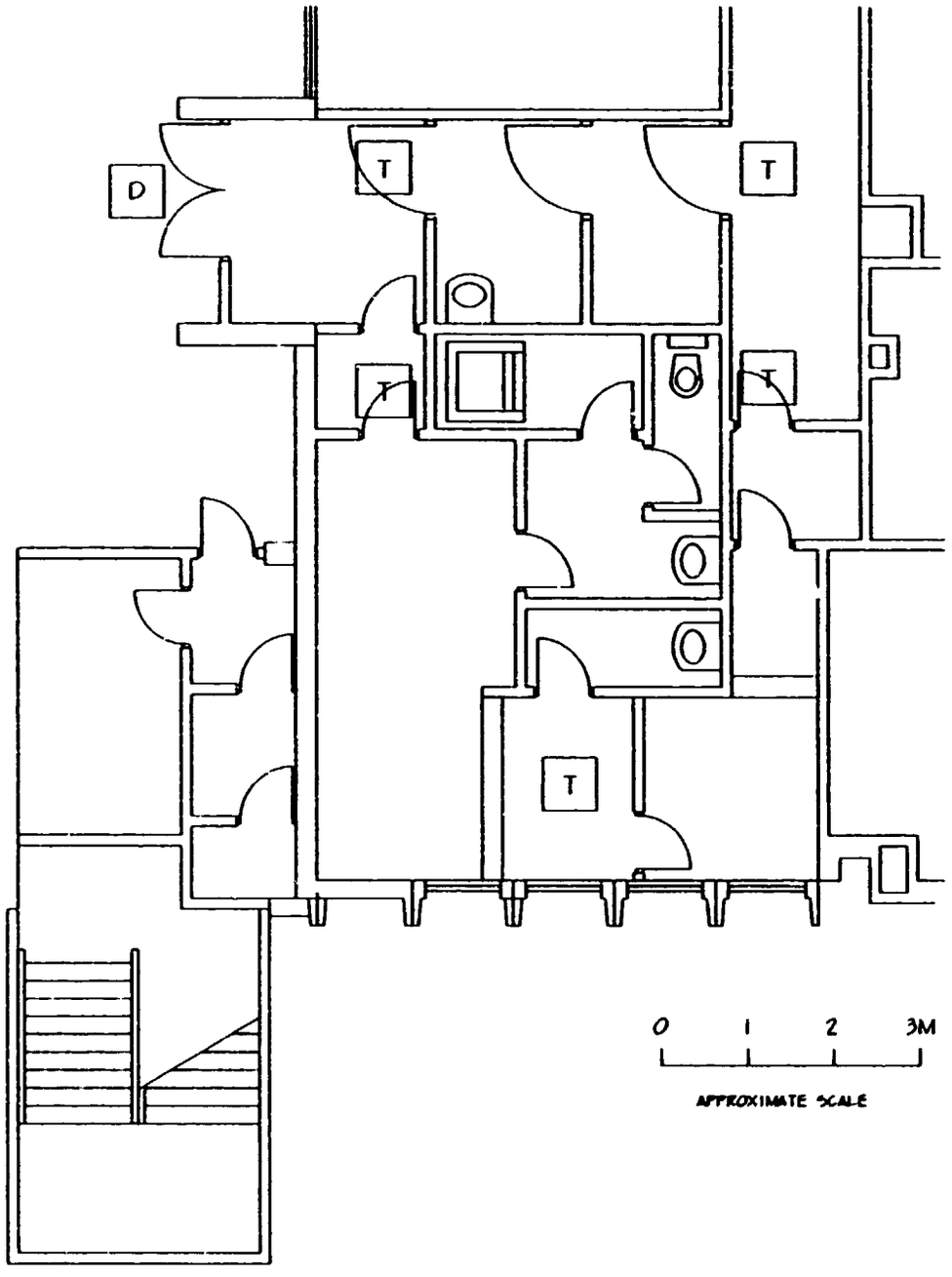
E EMERGENCY DOOR

PROCESS MATERIAL (PROCESS 1)

PACKING MATERIAL

PROCESS & PACKING MATERIAL

GRC CONSULTANTS	CLIENT: UNIDO, P O BOX 300, A-1400 VIENNA, AUSTRIA. FAX 232156	PROJECT: ALKALOIDA I TF/HUN/90/907	TITLE: OVERVIEW OF MATERIAL FLOW
	DATE: MAY 1992		DRAWING NUMBER: 92/005/I 14
	SCALE: N/A		REVISION: A
	DIMENSIONS IN METRES		



APPROXIMATE SCALE

KEY

T - TAC MAT

D - DOOR MAT

GRC CONSULTANTS	CLIENT: UNIDO, P O BOX 300, A-1400 VIENNA AUSTRIA FAX 232156	PROJECT: ALKALOIDA I TF/HUN/90/907	TITLE: GROUND FLOOR TAC MAT POSITIONS
	DATE: MAY 1992		
	SCALE: N/A		DRAWING NUMBER: 92/005/A05
	DIMENSIONS IN: METERS		REVISION: A

Protocol 7.5.1 'Personnel Transfer from Outside to Plant Processing Area' is presented and should be read in conjunction with drg. 92/005/103. The drawing illustrates the route taken during personnel movement and each positional number on the drawing corresponds to an instruction number in the protocol.

It can be seen that a member of staff enters the building via the entrance lobby (room 1) and small lobby (room 2) to the primary change area (room 3). In the primary change area, the person washes and changes in a strict predefined manner and enters the secondary change area (room 4) in relatively clean workclothes. In this area the worker dons a further set of clean clothing including a clean coverall and enters the plant via the lobby (room 5) to go about his duties.

Protocol 7.5.2 'Personnel Transfer from Plant Processing Area to Outside' is the second personnel transfer protocol and should be read in conjunction with drg. 92/005/104. This protocol is essentially the opposite procedure to entering the plant.

Note that the protocols specify that mask, gloves and overshoes are disposable. The clean coverall may undergo limited reuse. These protocols, once finalised and agreed. must be followed in all cases except emergencies by workers entering and leaving the plant. Note that for breaks and lunch workers must completely disrobe and leave the building to take their break elsewhere on site.

The toilet facilities are not accessible to workers in work clothes of any kind. The use of the toilet is strictly limited to arrival, breaktimes and work finish. Any emergency use of the toilet requires changing back into street clothes.

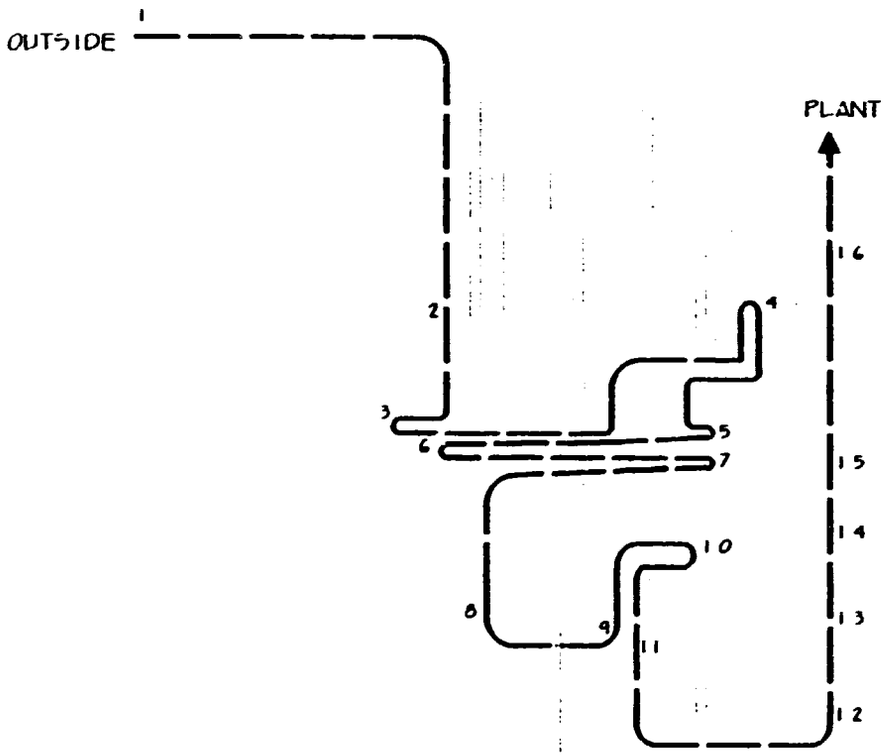
The protocols make use of two step over benches, to physically and psychologically separate areas of differing cleanliness.

Protocol 7.5.1
Personnel Transfer from Outside to Plant Processing Area

LOCATION	OPERATION	INSTRUCTION NUMBER
Outside	Wipe footwear on external mat	1
	Through door to	
Lobby	Through door to	
Lobby	Over tac mat through door to	2
Primary Dressing Room Area A	Remove coat, place in locker	3
	Go to toilet if required	4
	Wash hands	5
	Change into workwear and socks	6
	Wash hands	7
	Step over bench putting on workshoes to	8
Primary Dressing Room Area B	Over tac mat	9
	Wash hands	10
	Over tac mat through door to	11
Secondary Dressing Room Area A	Change into clean coverall	12
	Step over bench putting clean disposable covershoes on to	13
Secondary Dressing Room Area B	Collect and wear disposable mask	14
	Collect and wear disposable gloves	15
	Through door to	
Lobby	Through door to	
Plant	Over tac mat	16
	Proceed to appropriate process area	

Protocol 7.5.2
Personnel Transfer from Plant Processing Area to Outside

LOCATION	OPERATION	INSTRUCTION NUMBER
Plant Processing Area	Over tac mat through door to	1
Lobby	Through door to	
Secondary Dressing Room Area B	Dispose of mask and gloves	2
	Step over bench disposing of overshoes to	3
Secondary Dressing Room Area A	Change out of clean coverall, hang coverall for reuse	4
	Through door to	
Primary Dressing Room Area B	Over tac mat	5
	Wash hands	6
	Over tac mat	7
	Step over bench storing clean shoes for rewearing	8
Primary Dressing Room Area A	Remove workwear place in locker for reuse	9
	Wash hands	10
	Go to toilet and rewash hands if required	11
	Shower if required	12
	Put on coat	13
	Through door to	
Lobby	Over tac mat	14
	Through door to	
Lobby	Through door to	
Outside		



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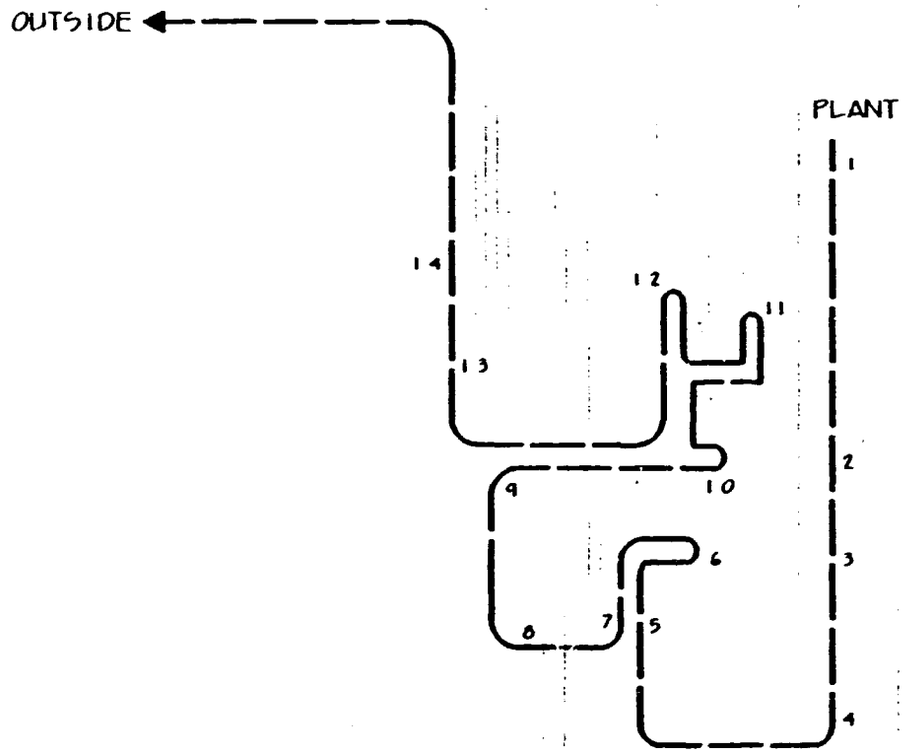
APPROXIMATE SCALE

NOTE
NUMBERS REFER TO OPERATIONS
SEE SECTION 7

GRC CONSULTANTS	CLIENT: UNIDO, P O BOX 500, A-1400 VIENNA AUSTRIA FAX 232156	PROJECT: ALKALOIDA I TF/MEX/90/907	TITLE: PERSONNEL TRANSFER FROM OUTSIDE TO PLANT PROCESSING AREA
	DATE: MAY 1993		
	SCALE: N/A		DRAWING NUMBER: 92/005A03
	DIMENSIONS IN: METRES		REVISION: A



APPROXIMATE SCALE

NOTE
NUMBERS REFER TO OPERATIONS.
SEE SECTION 7

GRC CONSULTANTS	CLIENT: UNIDO, P O BOX 300, A-1400 VIENNA, AUSTRIA FAX 232156	PROJECT: ALKALOIDA I TF/MLN/90/907	TITLE: PERSONNEL TRANSFER FROM PLANT PROCESSING AREA TO OUTSIDE	
	DATE: NOV 1993 SCALE: N/A DIMENSIONS IN: METRES		DRAWING NUMBER: 92/005A04	REVISION: A

7.6 MATERIALS MOVEMENT PROTOCOLS

Materials movement definition in the DSP area is particularly important for Good Manufacturing Practice consideration. For this reason materials movement protocols have been developed for the ground floor DSP area and are detailed below.

The movement of materials in the DSP plant influences the layout of the plant. Draft materials movement protocols are therefore presented here for consideration. The movement of process material, packing material, finished packed goods and process samples is also described in this section.

Process material is transferred via a pipeline from the first floor to the filter room (room 14) on the ground floor. The material is transferred in the form of a slurry and the first unit operation of this part of the process is to separate the slurry into a cake and a liquor. This operation is carried out by one of the two filters in this room.

Drg. 92/005/114 gives an overview of the material flow, showing process and packing material movement. The drawing showing material movement for an example process, process 1 as defined in Section 3.2.

The process material follows a fairly linear path down the main process corridor. Transfer between rooms is by means of closed bins.

The transfer of packing materials from outside to the plant is the subject of protocol 7.6.1. The procedure is based on the procedure of double wrapping, an overwrap to protect a clean underwrap. The material must also await QC approval before being used on the plant and the layout must take this into account.

Protocol 7.6.2 details the transfer of finished products to the outside. This procedure also involves quality control procedures. Finished products may not be transferred to the cleared finished products store (room 23) for despatch until authorisation is given by Quality Control personnel. The transfer involves using a pass through hatch to protect the clean product receipt room (room 22) from contamination originating from the relatively dirty cleared finished goods store (room 23). A pressure differential between these rooms is also used to minimise the risk of contamination. Note that no shedding packing materials may be used in the clean area.

Protocol 7.6.3 details the movement of samples from inside the plant to a laboratory outside of the plant for analysis. The protocol proposes that the sample be taken by a member of Alkaloida production staff and be placed in the pass through hatch between the product receipt room (room 22) and the cleared finished goods store (room 23). The finished bulk pharmaceutical chemical stored in kegs must be sampled before final weighing and sealing in the blending and packing room. A member of quality control staff may then remove the sample for further analysis. This method, together with an appropriate operator sampling accuracy validation procedure, is preferred in Western European plants. GRC Consultants understands that this method is not consistent with existing Alkaloida practices but is consistent with efficient operating practice.

The movement protocols are presented as draft versions for finalisation in the detailed design stages. The protocols must be discussed and integrated into the Alkaloida working practices.

Protocol 7.6.1

Packing Materials Transfer From Outside to Plant

1. Worker wearing outdoor clothing delivers the wrapped packing materials to the 'Goods in Receipt' room.

2. The same worker cleans the outside of the packaging with a damp cloth.

3. QC arrive at a later date and examine packaging.

4. If the packaging passes the QC returns and appropriately labels the goods. The QC remove the external packaging while retaining the internal packaging and passes the goods carefully through to the cleared goods in room without entering this room. Note that materials entering this facility must be double wrapped to ensure proper operation of this protocol.

5. When the packaging is required a clean clothed worker enters the 'Cleared Goods In' room and unpacks the packaging material disposing of the outside wrapping into a bin in this area.

6. The packaging material without its external wrapping is then transferred to the packing area.

Protocol 7.6.2

Transfer of Finished Products to Outside

1. The finished BPC is packed and weighed in the blending and packing room (Room 20).

2. The material is then transferred to the Product Receipt Room (Room 22) and here awaits QC results.

3. If the product passes the QC tests it will be appropriately labelled and passed through to the Cleared Finished Goods Room (Room 23) via the transfer hatch.

4. The Cleared Finished Goods Room (Room 23) is not part of the clean area of the plant and goods are despatched from this area by men in outdoor clothing. The goods should be loaded onto a vehicle under cover.

Protocol 7.6.3
Sample Movement

1. Sample taken by the process operator in clean area and sealed in sample container.

2. Sample taken to the pass through hatch between the product receipt room (room 22) and the cleared finished goods store (room 23).

3. Sample removed by a member of the quality control staff in normal workclothes from the dirty side of the hatchway via the cleared finished goods store (room 23).

4. Sample taken for analysis elsewhere on site.

SECTION 8

BUILDING DESIGN

8 BUILDING DESIGN

This section on building design contains a description of each of the rooms, the required room finishes and environmental conditions. Aspects of the heating, ventilation and air conditioning requirements with particular reference to the GMP considerations are also included.

8.1 ROOM DESCRIPTION

8.1.1 Synthesis

No.	Description
S1	Main Process Hall - contains the main process reactors
S2	Filter Room - contains a filter set for activated carbon filtration
S3	Dangerous Process Room - contains reactors and a filter set
S4	Air Lock - for isolation of the control room
S5	Control Room - raised room for controlling and supervising processes and the work floor
S6	Upstairs Lobby - lobby leading to: stairs going down to ground floor, stairs going to roof, lift, synthesis main process hall
S7	Lift
S8	Stairs - leading from ground to first floor
S9	Overcoat Change - small changing area

S10	WC
S11	Washroom - room leading to WC and containing a wash basin
S12	Downstairs Lobby - lobby between outside and overcoat change
S13	Air Lock - air lock between the process hall and the upstairs lobby
S14	Motor Control Room - contains heavy electrical equipment for the SSMPU

8.1.2 DSP

Room No.	Description
1	Entrance Lobby - People and materials entering the building all enter via this common area.
2	Lobby - An air lock to separate the relatively dirty entrance lobby from the primary change area.
3	Primary Change Area - The area where personnel change from street clothes to workwear.
4	Secondary Change Area - The area where personnel change into coveralls.
5	Lobby - An airlock to separate process area from changing rooms.
6	Wash Area A - Primary change wash area.
7	Shower - Primary change shower.

8	Toilet - Primary change toilet.
9	Wash Area B - Secondary change wash area.
10	Goods in Receipt - Goods awaiting test results prior to release into plant.
11	Cleared Goods In - Goods cleared by QC for use on the plant.
12	Main Corridor - Connecting corridor.
13	Process Store - Store for maintenance, special and other equipment.
14	Filter Room - Containing a basket centrifuge, a pressure filter and associated tanks and pumps.
15	Wash-up Room - For the cleansing of soiled equipment.
16	Laboratory - For in-process testing.
17	Drying Room A - Contains a horizontal vacuum dryer.
18	Service Room B - Contains the service equipment, such as vacuum pumps for the vacuum dryers.
19	Drying Room B - Contains a vacuum tray dryer.
20	Blending and Packing Room - Where milling, sieving, blending, product weighing and packing operations are carried out.
21	General Store - Store for miscellaneous small items.

22 Product Receipt Room - Store for finished BPC awaiting release authorisation from QC.

23 Cleared Finished Products Store - Store for goods which have received release authorisation from QC and are awaiting despatch.

24 Service Room B - Contains service equipment for ground and 1st floors.

8.2 ROOM STANDARDS

8.2.1 General Classification

In this section, five classes of room standards are defined as shown below.

Table 8.2.1

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

N/A Not Applicable
USA Standard is 209D (1988)
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 classes of room.

C5 BASIC INDUSTRIAL STANDARD

This standard applies to all general offices, changing rooms, amenities, corridors, control rooms, and chemical processing areas 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 Alkaloida 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 Alkaloida 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 Alkaloida 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 Alkaloida management

8.2.2 Room Class Specification

The room class specification of the synthesis is given in table 8.2.1. It can be seen that all the rooms are specified as C5 Basic Industrial Standard.

The room class specification for the DSP area is given in table 8.2.2. 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 8.2.1. 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 in the DSP, 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, the goods in and entrance lobby are included in this specification.

Table 8.2.1 shows that a room specified as 'C3 Low Controlled Class' will meet EC Class D under suitable operating conditions. However, for example, the entrance lobby (room 1) 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 the proximity of the room to the external doors or the nature of the materials the rooms may hold. For instance, the changing

room will hold dust laden overcoats. This room does not form part of the clean area and the 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 8.2.1.

The cleared finished product store (room 23) has been specified as 'C4 Hygienic Standard'. This standard has been given since this room does not form part of the plant clean area and is accessed by personnel from outside the plant only.

The service areas (rooms 18 and 24) do not form part of the clean area and are accessed from dedicated doors from the outside. These rooms are therefore specified 'C5 Industrial Standard' since they do not pose any direct risk of contamination to the product.

Tables 8.2.1 and 8.2.2 also detail floor areas for each room, which along with DSP room heights of 2.7m and synthesis plant area room heights of 4.6m form the basis of HVAC design.

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 the tables. 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.

GRC room classification 'C3 Low Controlled Class' specifies by default that there are no floor drains or gulleys in the room. However, certain rooms which have been specified as C3, such as the Wash area 'A' (room 6) have floor drains. For full details of drainage requirements see Section 5 which takes precedence over the room standards.

Table 8.2.1

Synthesis Room Class Specification

No.	Description	Room Area m^2	GRC Room Class	EC Class	Hazardous Zone
S1	Main Process Room	182	C5	NA	1
S2	Filter Room	23	C5	NA	1
S3	Dangerous Process Room	27	C5	NA	1
S4	Air Lock	4	C5	NA	2
S5	Control Room	10	C5	NA	
S6	Upstairs Lobby	9	C5	NA	
S7	Lift	25	C5	NA	
S8	Stairs	19	C5	NA	
S9	Overcoat Change	6	C5	NA	
S10	WC	1	C5	NA	
S11	Washroom	2	C5	NA	
S12	Downstairs Lobby	2	C5	NA	
S13	Air Lock	6	C5	NA	2
S14	Motor Control Room	24	C5	NA	

Table 8.2.2

DSP Room Class Specification

No.	Description	Room Area m^2	GRC Room Class	EC Class	Hazardous Zone
1	Entrance lobby	5.2	C3		
2	Lobby	1.3	C3		
3	Primary change area	14.1	C3		
4	Secondary change area	5.8	C3	D	
5	Lobby	1.8	C3	D	
6	Wash area A	3.2	C3		
7	Shower	2.6	C3		
8	Toilet	1.5	C3		
9	Wash area B	2.0	C3		
10	Goods in receipt	3.9	C3	D	
11	Cleared goods in	3.4	C3	D	
12	Main corridor	838.1	C3	D	2
13	Process store	7.5	C2	C	2
14	Filter room	32.8	C2	C	1
15	Wash-up room	8.9	C2	C	2
16	Laboratory	6.9	C3	D	2
17	Drying room A	25.7	C2	C	1
18	Service room A	12.2	C5		2
19	Drying room B	10.5	C2	C	1
20	Blending and packing room	27.7	C2	C	1
21	General store	0.8	C2	C	2
22	Product receipt room	9.2	C3	D	
23	Cleared finished products store	10.5	C4		
24	Service room B	22.1	C5		2

For full specification see also definitions in Section 8.2.

8.3 ROOM PRESSURES

The pressure 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 changing areas, the goods in area and the goods out area are segregated from the main process corridor by an area of higher pressure.

5. Rooms where water is present are kept at a negative relative to the surroundings to prevent dispersal of aerosols.

The room pressures for the synthesis area are detailed on drg. 92/013/105 and tabulated in table 8.3.1.

The control room S5 has been specified at 95 Pa, the impact of this on the explosion vent panels should be assessed at the detailed design.

The room pressures for the DSP area are detailed on drg. 92/005/106 and tabulated in table 8.3.2.

Note the high pressure of the main corridor in DSP (room 12) and air lock S13 in synthesis with respect to the process 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.

Table 8.3.1

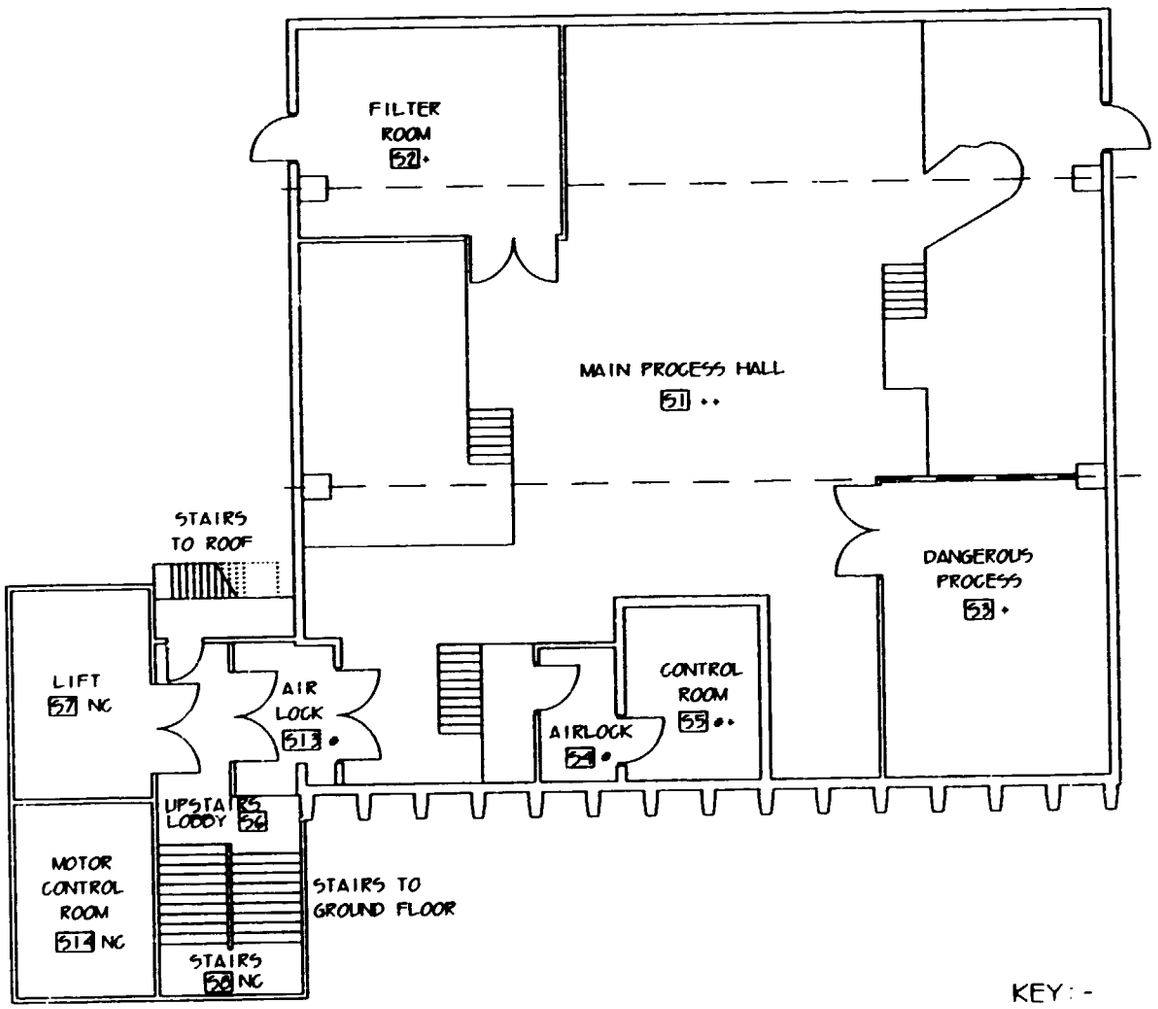
Synthesis Room Pressure Specification

No.	Description	Pressure Symbols	Pressure Pa
S1	Main Process Room	++	30
S2	Filter Room	+	15
S3	Dangerous Process Room	+	15
S4	Air Lock	#	80
S5	Control Room	#+	95
S6	Upstairs Lobby	NC	NC
S7	Lift	NC	NC
S8	Stairs	NC	NC
S9	Overcoat Change	NC	NC
S10	WC	NC	NC
S11	Washroom	NC	NC
S12	Downstairs Lobby	NC	NC
S13	Air Lock	#	80
S14	Motor Control Room	NC	NC

\+ = 15 Pa

\# = 80 Pa

NC = No Control



KEY:-

\+ 15 Pa

\# 80 Pa

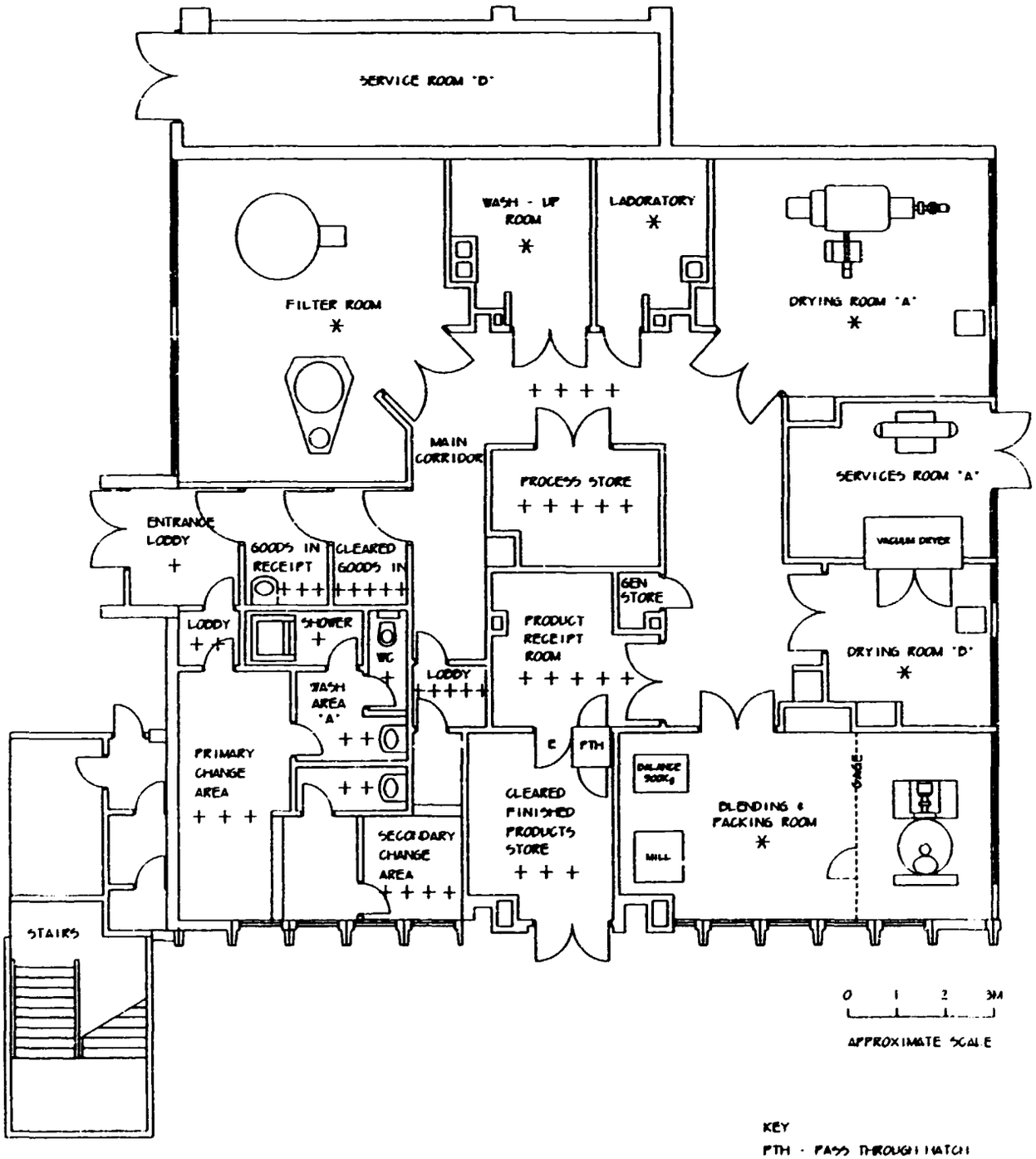
NC NO CONTROL

GRC CONSULTANTS WATERGATE HOUSE 1 DE WINDMILLS ST MARY'S CLOSE ALTON HANTS TEL - 0420 84947 FAX - 0420 84927	CLIENT UNIDO, P.O BOX 300, A-1400 VIENNA, AUSTRIA. FAX: 232156	PROJECT ALKALOIDA 2 TF/HUN/90/910	TITLE FIRST FLOOR ROOM PRESSURES
	DATE: DEC '92 SCALE: N/A DIMENSIONS IN MM		DRAWING NUMBER 92/013/105 REVISION Δ

Table 8.3.2
DSP Room Pressure Specification

No.	Description	Pressure Symbols	Pa
1	Entrance lobby	+	15
2	Lobby	++	30
3	Primary change area	+++	45
4	Secondary change area	++++	60
5	Lobby	+++++	75
6	Wash area A	++	30
7	Shower	+	15
8	Toilet	+	15
9	Wash area B	++	30
10	Goods in receipt	+++	45
11	Cleared goods in	+++++	75
12	Main corridor	++++	60
13	Process store	+++++	75
14	Filter room	*	10
15	Wash-up room	*	10
16	Laboratory	*	10
17	Drying room A	*	10
18	Service room A	NC	NC
19	Drying room B	*	10
20	Blending and packing room	*	10
21	General store	+++++	75
22	Product receipt room	+++++	75
23	Cleared finished products store	+++	45
24	Service room B	NC	NC

+ = 15 Pa
* = 10 Pa
NC = No Control



KEY

PTH - PASS THROUGH HATCH

E - EMERGENCY DOOR

\+ - 15Pa

* - 10Pa

GRC CONSULTANTS	CLIENT: UNIDO, P O BOX 300, A-1400 VIENNA AUSTRIA FAX 232156	PROJECT: ALKALOIDA I TF/HUN/90/907	TITLE: GROUND FLOOR PRESSURE SPECIFICATION	
	DATE: MAY 1992		DRAWING NUMBER: 92/005/A06	REVISION: A
	SCALE: N/A			
	DIMENSIONS IN: METRES			

8.4 HVAC

8.4.1 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. This is particularly relevant in DSP where product will be exposed to the air within the processing rooms. 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.

8.4.2 Detailed Considerations

Individual room specifications are given in Section 8, Building Design.

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.

Alkaloida 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 SSMPU.

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.

8.4.3 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.

The considerations here apply primarily to DSP but are applicable in a much reduced form to the synthesis area.

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.

8.5 BUILDING FINISHES

The building contains rooms with differing levels of cleanliness as given in the room class specification, table 8.2.1 and 8.2.2.

A sealed floor is constructed between the first and ground floor. A sealed suspended ceiling is installed on the ground floor with flush light fittings of an appropriate flameproof type where necessary. Ventilation ducts and pipework run in the void between the suspended ceiling and the sealed floor.

The basic principles of clean room design can be applied to all rooms in varying degrees. However the points relating to hygienic room design apply primarily to DSP.

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. In the SSMPU 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.

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

SECTION 9

SAFETY AND THE ENVIRONMENT

9 SAFETY AND THE ENVIRONMENT

This section contains information on the special requirements for solvent and dust handling together with notes on various aspects of operator safety.

9.1 ENVIRONMENT

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.

Real savings can be achieved by examining the recycling of waste streams and performing energy audits. A draft version of a waste and energy audit checklist is given below and Alkaloida may wish to use this to check their proposed operations in the SSMPU.

- Do any waste streams contain enough product to justify removal?

- Can any solvent or other material used in the process be recycled?

- Can the process be modified to use less raw materials and energy?

- Can the process be modified to produce less waste?

- Have developments of the process been considered to improve yield?

- Can any waste material be sold as a byproduct or used elsewhere on site?

- Are there leaks of steam or other utilities on site.

- Are any furnace burners out of adjustment?

- Is all insulation intact?

- Is equipment running when not required?

- Is the plant shut down for minimum energy waste at night, weekends and holidays?

- Can hot waste streams be used to preheat incoming streams?

- Could a domestic save energy campaigns and posters achieve worthwhile energy savings?

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.

9.2 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.

9.2.1 Synthesis

The classification of the synthesis suite is shown in drg. 92/013/106. Table 8.2.1 also contains this information and is included in section 8.2.

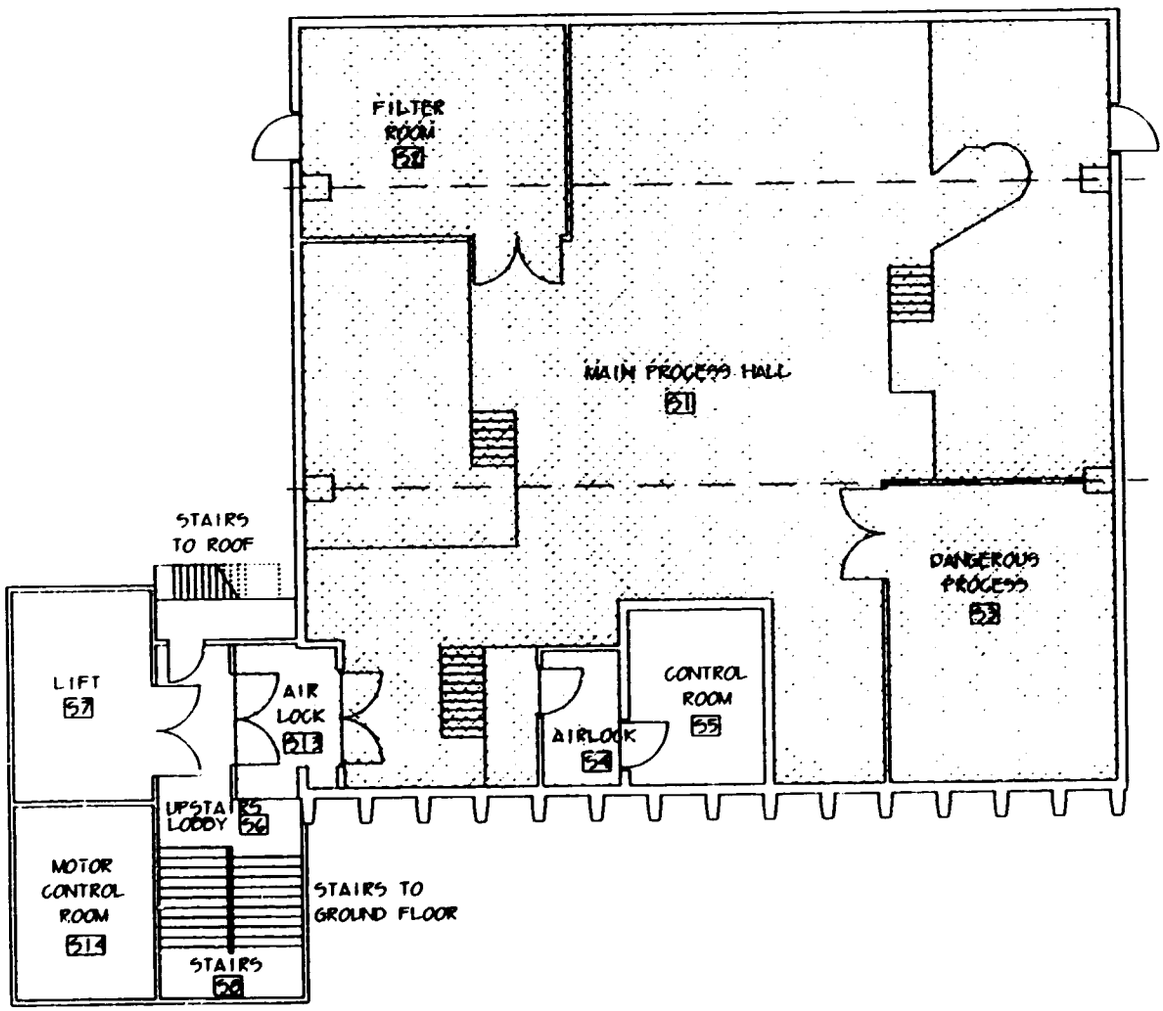
KEY :-

ZONE 1

ZONE 2

CLASSIFIED BY GENERALISED METHOD

NO PERIMETER MARKINGS INDICATES UNCLASSIFIED



GRC CONSULTANTS WATERGATE HOUSE 1 THE WATERMILLS ST MARY'S CLOSE ALTON HANTS TEL - 0420 84847 FAX - 0420 84847	CLIENT UNIDO, P O BOX 300, A-1400 VIENNA, AUSTRIA FAX: 232156 DATE: DEC '92 SCALE: N/A DIMENSIONS IN MM	PROJECT ALKALOIDA 2 TF/HUN/90/910	TITLE FIRST FLOOR ELECTRICAL ZONE DRAWING NUMBER 92/013/106 REVISION A

The entire processing area has been provisionally specified as Zone 1 until the exact nature of the process operations has been established.

The control room is isolated from the processing area by an air lock and so is specified as a safe area.

9.2.2 DSP

Drg. 92/005/110 shows the area classification for each room and other relevant information is given in table 8.2.2 in Section 8.2.

The product receipt room (room 22) is specified as unclassified. There must therefore be no bulk manipulations of powder in this room and all outgoing product must be contained in sealed kegs.

The service rooms contain vacuum pumps and may contain quantities of condensed solvent and are classified Zone 2.

The process rooms which may contain solvents and/or explosive powder are classified Zone 1.

The corridor is classified as Zone 2 and not Zone 1 since process materials transferred between process rooms is achieved using sealed containers.

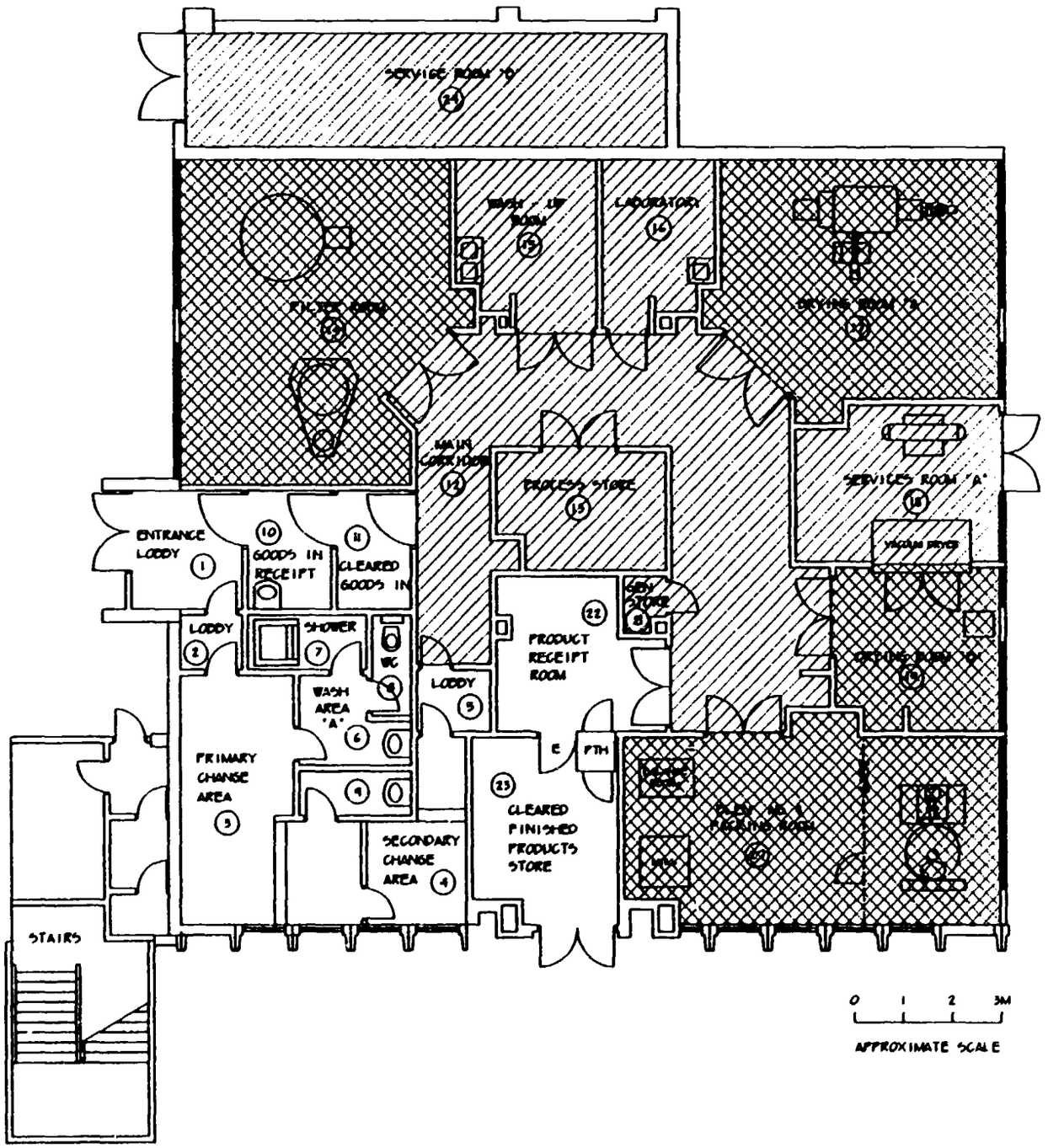
The wash-up room (room 15), laboratory (room 16) and the process store (room 13) are classified Zone 1.

The changing areas are non hazardous and hence are specified as unclassified.

KEY

ZONE 1
ZONE 2
} CLASSIFIED BY GENERALISED METHOD

NO PERIMETER MARKINGS INDICATES UNCLASSIFIED



GRC CONSULTANTS	CLIENT: UNIDO, P O BOX 300, A-1400 VIENNA, AUSTRIA FAX 232156	PROJECT: ALKALOIDA I TF/HUN/90/907	TITLE: GROUND FLOOR ELECTRICAL ZONES
	DATE: MAY 1993		
	SCALE: N/A		
	DIMENSIONS IN: METRES		DRAWING NUMBER: 92/005/A10 REVISION: A

9.2.3 Site

The classification of the area around the SSMPU building is shown in drg. 92/013/107.

It can be seen that the toluene storage tank Zone 2 extends into the access way to the materials out doorway. The use of vehicles is therefore prohibited in this area.

Zones around the materials in receipt bay are given which will apply during the filling of the solvent tanks from barrels. It can be seen that the zones extend into the roadway and hence it is proposed that this road be temporarily cordoned off during solvent tank filling operations. The zones around the bay will be reduced in size during normal operation.

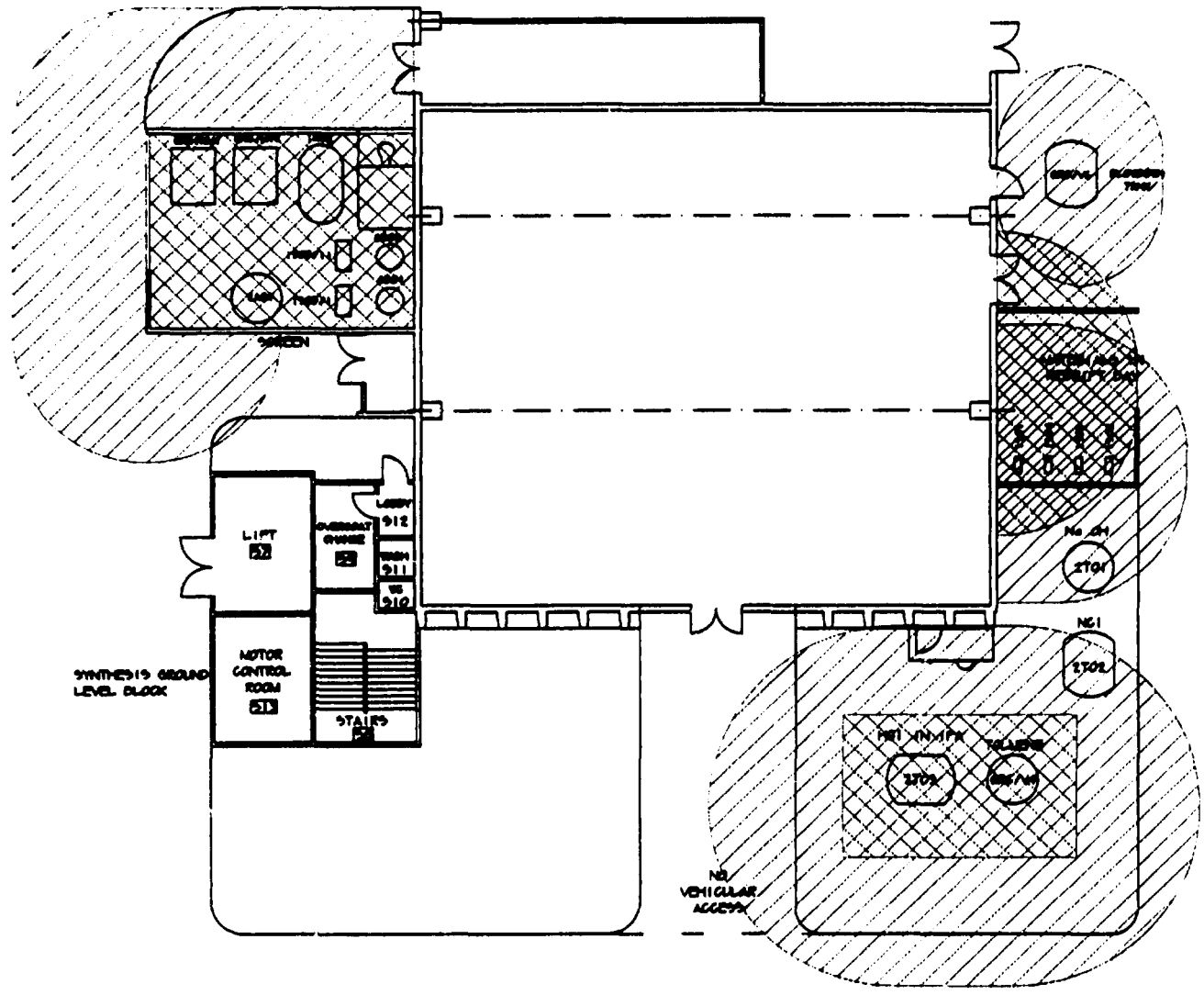
The blowdown tank GRC/V6 will be vented at high level and because of this no Zone 1 is required around the tank.

The waste receipt area hazardous zone extends well into the area which is presently operating as an access road. Alternatives should be investigated for reducing the size of the hazardous zones or relocation of this area.

9.3 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.

A pregnant woman in her own interest should advise her supervisor as she will be particularly susceptible to certain hazards.



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A	17/12/92	ISSUED WITH REPORT	HB

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PROJECT
ALKALOIDA 2
TF/HUN/90/910

DRAWING TITLE
LOCAL SITE ELECTRICAL ZONES

DRAWING NUMBER
92/013/107

REV
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In flammable areas an approved system should be set up for the introduction of new equipment. Each new piece of equipment must satisfy fire regulation and operational requirements.

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 Alkaloida may wish to consider are given in Appendix II.

9.4 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.

9.5 INERTING OF BASKET CENTRIFUGES

9.5.1 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.

9.5.2 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.

9.5.3 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.

Alkaloida have supplied a list of process solvents which they commonly use. Information on the physical properties including flammability is given in Section 9.9.

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 be inert gass blankets to prevent air entering the centrifuge in solution, due to vortex entrainment or running empty. Other potential sources of air ingress should be examined for possible blanketing.

The centrifuge specified for use in the Alkaloida Pilot Plant 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. The recommended method of inert gas blanketing in situations of high risk is monitoring by oxygen concentration and reference may be made to drg. 92/005/201 which shows details of centrifuge fitted with an inert gas purge system.

9.5.4 Definitions

Flammable Liquid	A liquid whose vapour can support combustion in air
Flash Point	The flash point of a liquid is the minimum temperature at which it gives off vapour sufficient to form an ignitable mixture with air

Lower Flammable (or Explosive) Limit, LFL	The least volumetric percentage, under specific conditions, of gas or vapour in air which can just ignite and propagate flame
Upper Flammable (or explosive) Limit, UFL	The richest mixture, as a volumetric percentage, above which ignition and propagation of flame cannot occur.
Flammable or Explosive Range	The concentration of a flammable substance in air between the LFL and UFL
Auto-Ignition Temperature (AIT)	The temperature at which the vapour of a flammable substance will spontaneously ignite in air without the presence of a source of ignition.

9.6 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 Alkaloida SSMPU, 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.

9.6.1 Handling Liquids

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.

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.

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.

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.

Mixing

The design of jet or propellor mixers must be such as to prevent charged liquid from being carried upward through the liquid surface.

9.6.2 Handling Solids

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.

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.

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.

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.

9.6.3 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.

9.6.4 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.

9.6.5 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.

9.7 EFFLUENT AND WASTE

The SSMPU generates a relatively small quantity of effluent and waste which may be treated in accordance with the notes given below.

- Primary and Wash Filtrate from Filter Room - This material is pumped away or collected in drums for reprocessing or disposal.

- General Plant Aqueous Wastes from 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) - Provision is already in place as this plant forms part of the ground floor of an existing building. This waste passes to conventional storm water drains.

- Domestic effluents from laboratories, toilets and other amenity areas pass to the conventional foul sewer.

Where waste material is removed from the plant in kegs or drums, the containers used must be of a high order of cleanliness and enter the building through the normal route and procedures as those used for packing materials (see section 7.4). The sealed containers exit the building through the pass through hatch in the product despatch room.

9.8 SAFEGUARDING OF EQUIPMENT

For reasons of safety, all moving parts on machines both purchased and locally made in the workshop 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.

The double cone blender in the Alkaloida Pilot Plant presents a mechanical hazard and is placed in a cage to protect personnel. The electrical switching to start this equipment is placed outside the cage and is only operational when the cage door is secured.

9.9 PROPERTIES OF MATERIALS

Alkaloida have supplied a list of solvents which are anticipated for use in the SSMPU in the future.

The physical properties of these materials and relevant safety information are given in the properties of materials sheets presented in Appendix III.

SECTION 10

GMP AND VALIDATION

10 GMP AND VALIDATION

This section may be read in conjunction with the QC Audit and GMP Critique report (5).

As mentioned in the Introduction, the SSMPU is designated as a small scale unit for the preparation of medicinal chemicals for sale. Hence the unit must be designed, installed and operated to GMP standards in 'approved' facilities.

Also, as mentioned earlier, the concepts of, and requirements for, documentation and validation are extremely important as they relate to the Alkaloida SSMPU which is to be used to make products for sale. These two topics have significant implications and it is therefore appropriate to review, in this section, key aspects of GMP and validation as they affect the Alkaloida SSMPU.

10.1 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 SSMPU 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 SSMPU 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 Alkaloida 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.

10.1.1 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.

10.1.2 Requirements for GMP

Since the products which are to be made in the SSMPU 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, i.e. the filling and packaging areas, 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.

10.1.3 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, Alkaloida should be encouraged to apply those concepts to the maximum extent as far backward in the processing chain as feasible.

10.1.4 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).

10.2 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.

10.2.1 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 manufacturing 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 SSMPU for Alkaloida at Tiszavasvari, 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 Alkaloida 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.

10.2.2 Validation Planning

Whist 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.

10.2.3 Requirements for Validation

(Note: in the context of this FED study the Purchaser may be Alkaloida and the Supplier normally is the equipment supplier or engineering contractor, but may also be Alkaloida'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 if this is applicable to the Alkaloida SSMPU). 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.

For further information on GMP matters and validation concepts, reference may be made to the report

"GMP and Validation Concepts, and Project Execution Contractors in the Pharmaceutical Industry, Training Material for Alkaloida - September 1992"

which was prepared for the visit of Alkaloida staff to the UK in October 1992.

SECTION 11

ENGINEERING STANDARDS

11 ENGINEERING STANDARDS

As the Alkaloida SSMPU is designed to produce medicinal chemicals which are intended for sale, and the facility is to be 'approvable' and validated, 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 IV) which are intended to give a general appreciation of the type of fabrication and operational standards which apply to the SSMPU. It is neither possible nor appropriate to include in this FED study all possible engineering standards which apply to the SSMPU. It is ultimately the responsibility of the client (Alkaloida) 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 Alkaloida (as part of the validation process).

However, GRC Consultants understands that Alkaloida 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, Alkaloida 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 SSMPU moves to the next stage, this whole subject will have to be addressed by Alkaloida 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 IV:-

GENERAL SPECIFICATIONS AND STANDARDS: NON-STERILE SERVICE

GENERAL SPECIFICATION FOR VESSEL FABRICATION IN AUSTENITIC STAINLESS STEEL

SUPPLEMENTARY REQUIREMENTS FOR VESSEL FABRICATION IN AUSTENITIC STAINLESS STEEL

GENERAL SPECIFICATION FOR ENAMELLED MILD STEEL VESSELS

PIPING SPECIFICATION SUMMARIES

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 12

CAPITAL COST ESTIMATE

12 CAPITAL COST ESTIMATES

Within the Terms of Reference for this study is the requirement for estimates of the main components of the capital investment needed to achieve an approvable SSMPU. The estimate which is provided in this section is based on UK/Western European prices as at 4th quarter 1992 and does not include any allowance for inflation.

The technique used for the estimate is one which is widely used in the UK for feasibility and FED studies of the type produced for this project. The accuracy of the estimate technique is often quoted as ±30% but it is GRC Consultants experience that the final figure is rarely, if ever, lower than estimated by more than 10% but usually greater by 25-30%. Hence GRC Consultants believes that the accuracy of the TOTAL CAPITAL figure should be interpreted as +30, -10%.

12.1 BASIS OF ESTIMATION

For the purposes of this study, the order of magnitude capital cost estimates are prepared following the completion of the equipment flow diagrams, the materials balance and the outline equipment lists from Sections 3 and 4. The order of magnitude estimate is essentially a factored estimate based on itemised costs for all items shown on the equipment lists. The itemised costs are then used to estimate other costs using factors in order to build up the complete estimate for the total plant capital cost.

The following notes give some indication of the key features of the estimates which are presented for the process described in Section 3.

12.1.1 Mechanical:

Items estimated under this heading include:-

Process and packaged equipment costs which are estimated, item by item, from in-house data banks.

Pipework materials costs are related to the prime costs of the process items with allowances made to reflect different materials of construction, differences in piping complexity and different levels of "hygienic/sterile" engineering standards in different areas. Allowances are also included for pipework fittings, valves and supports.

Electrical costs are based on process equipment prime costs with allowances made for high and low power users.

Instrument costs are based on equipment prime costs with allowances made for different levels of control complexity in different areas.

12.1.2 Installation and Construction

All the individual installation and construction sub-contracts are related to the various MECHANICAL costs above but adjusted to allow for differences in areas as above. Items estimated under this heading include:-

Process and packaged equipment installation costs are related to their respective MECHANICAL costs.

Pipework installation costs are based on the MECHANICAL costs and adjusted for materials of construction, complexity and engineering standard.

The civil/structural sub-contract is related to the MECHANICAL sub total and includes allowances for structural steelwork, process plant buildings, control rooms, in-plant storage, footpaths, site excavation, drains, fire mains, landscaping and preliminary site services during construction. No allowances are made for any special foundations, piling or special excavation (blasting).

Electrical and instrument installation costs are related to their respective MECHANICAL costs.

The HVAC costs are related to the process and packaged equipment MECHANICAL costs but adjusted to reflect different ventilation requirements.

Painting and insulation sub-contracts are related to the process equipment MECHANICAL costs and are adjusted, if appropriate, for different area requirements.

12.1.3 Engineering/Design and Site Supervision

These costs are related to the total plant MECHANICAL and INSTALLATION/CONSTRUCTION costs. They include those costs associated with project office design and engineering, procurement, salaries, site supervision, plant hire, vendor costs and insurances.

12.1.4 Exclusions

The following items are excluded from the capital cost:-

Inflation
Land cost
Land purchase costs
Effluent treatment plant

Commissioning expenses
Spares

12.1.5 Contingency

An allowance, or design contingency, is included and is intended to take into account the status of the design and to cover possible omissions and under-design resulting from incomplete process data. The magnitude of the contingency depends on the status of the design and for the purposes of this study a relatively high contingency of 25% is used to reflect the fact that the process design is based on preliminary chemical engineering studies based on the process described in Section 3.

The actual contingency figure is intended to cover the key major cost elements as follows:-

Mechanical Equipment:
Development of engineering during the detailed design stage to allow for equipment items overlooked initially, higher specification of items, R&D results which indicate new or additional process steps or equipment, etc.

Installation and Construction:
The allowances or contingency here provide cover for items/topics such as extra equipment to be installed, higher level of fabrication and construction standards required by tighter specification, unforeseen civil engineering difficulties such as poor soil conditions, etc.

Engineering Design and Site Supervision

The contingency here allows for the normal anticipated development of design caused by the extra activities noted above together with variation orders generated either by the client or contractor and extra site supervision or more stringent inspection during fabrication and construction, etc.

12.2 ESTIMATE RESULT

The results of the estimate for the combined synthesis plus Downstream Processing SSMPU is shown in the tabulation overleaf.

The DSP area used in this capital cost estimate is based on Process 1 in the process flow schematic 92/005/214.

The basic capital investment figure is estimated to be in the range £2.4-3.4m. When an allowance is made for the fact that the main building shell already exists, and a reasonable amount of structural steelwork is already installed, especially on the upper (synthesis) floor, the total capital investment is reduced to be in the range £1.8-2.8m. However, at this stage of the project it would be prudent to regard the range as £2-3m.

The above estimate has been carried out on the basis of UK/Western European prices and labour/management costs as at November 1992. GRC Consultants recognises that savings could possibly be made in the areas noted below:

- Process Equipment: If comparable quality equipment could be sourced in Hungary, then the MECHANICAL costs, as shown in the tabulation, might be reduced by 20-25% but it is doubtful if local glass lined reactors (which make up the greatest portion of the equipment costs) would be of a quality suitable for a modern medicinal chemicals plant.

CAPITAL COST ESTIMATE

	SYNTHESIS £	DSP £
MECHANICAL		
- Process Equipment		
Reactors	249,000	94,000
Tanks (various)	98,000	23,000
Heat Exchangers	37,000	-
Filters	14,000	-
Pumps/Fans	34,000	6,000
Scrubbers	4,000	-
Miscellaneous	1,000	2,000
Sub Total	437,000	125,000
- Pipework	100,000	20,000
- Electrics	45,000	12,000
- Instruments	45,000	12,000
Sub Total (MECH)	627,000	169,000
INSTALLATION & CONSTRUCTION		
- Process Equipment	66,000	18,000
- Pipework	150,000	20,000
- Electrics	40,000	12,000
- Instruments	40,000	12,000
- HVAC	22,000	}
- Civil/Structural	200,000	} 394,000
- Painting/Insulation	13,000	}
	531,000	456,000
Sub Total (MECH) + (INS/CON)	1,158,000	625,000
Total (MECH) + (INS/CON)	1,783,000	
ENGINEERING DESIGN	350,000	
	2,133,000	
DESIGN CONTINGENCY	500,000	
TOTAL	2,633,000	

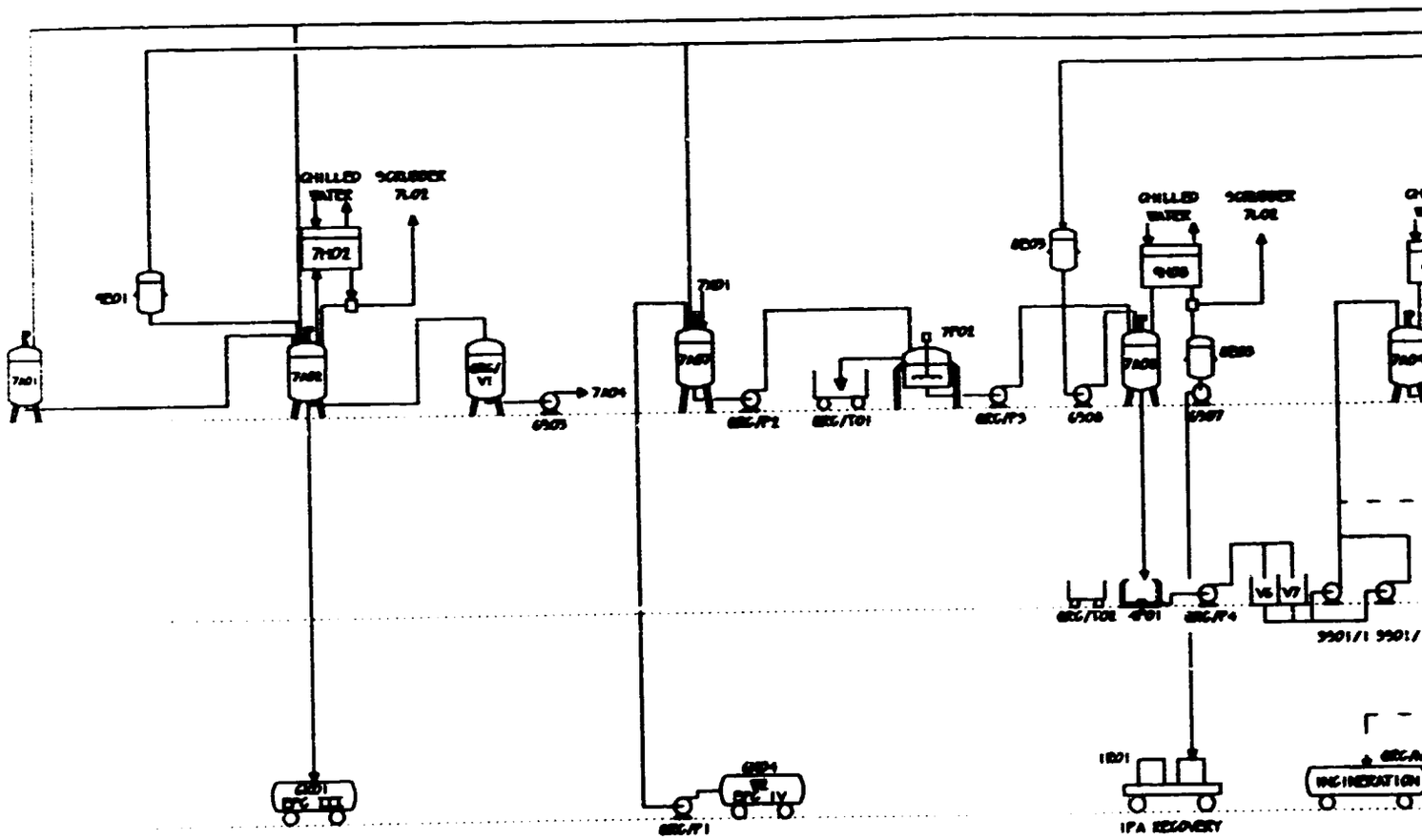
Range +30% -10%
£3.4m - £2.4m

Allowance for existing buildings and steelwork £0.6m

Possible range £2.8m - £1.8m

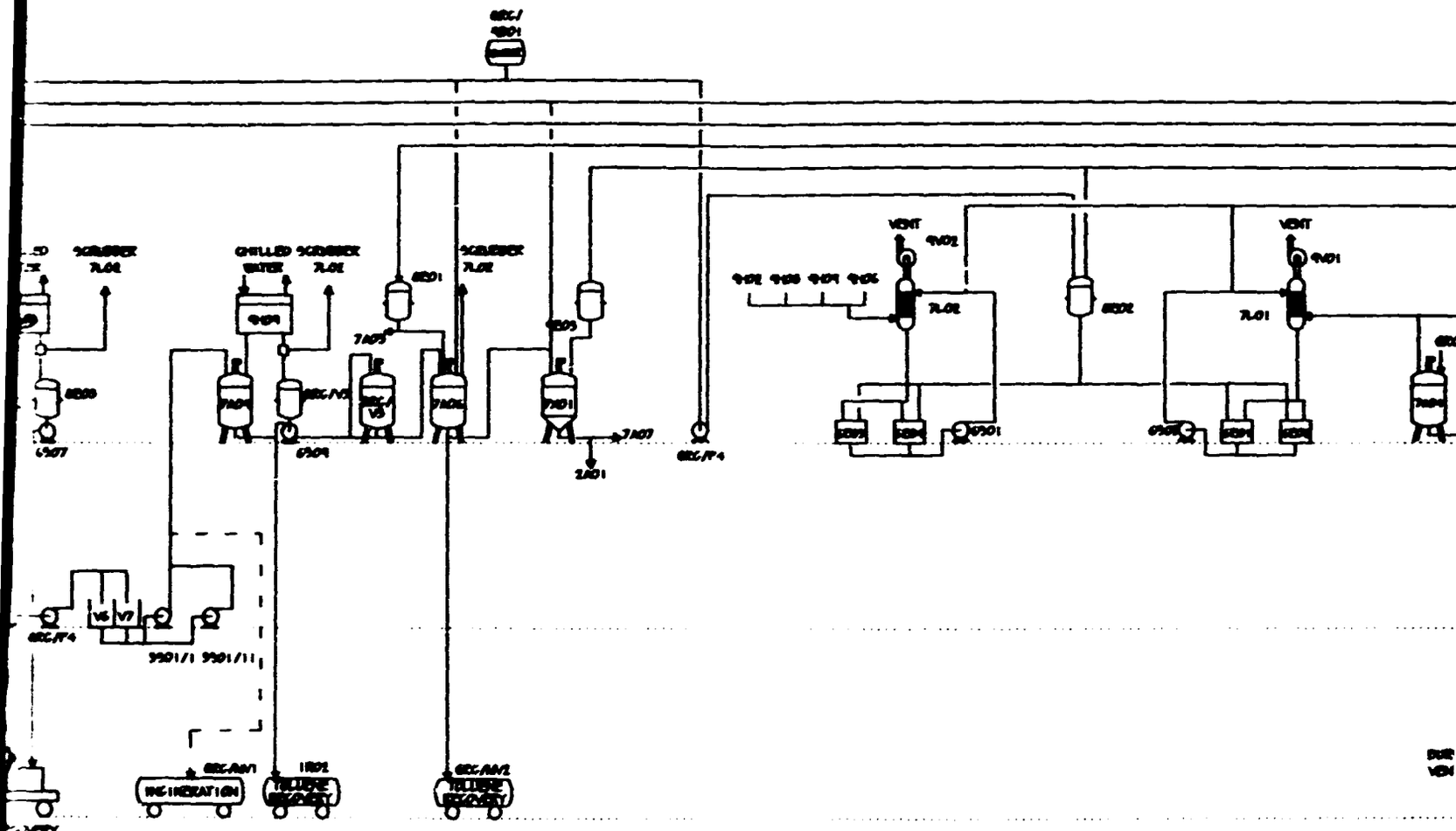
- Installation/Construction Costs: With extensive use of local Hungarian labour, these costs could be reduced, especially in the civil/structural areas. However, it must be recognised that the standards and quality of building finishes, etc, especially in the DSP areas, must be of a quality significantly greater than that for conventional chemical process plants.

- Engineering: Again, by use of local Hungarian process plant contractors, the engineering design and supervision costs could conceivably be reduced. However, GRC Consultants is not totally convinced that such design and management expertise, for FDA approvable medicinal chemical plants, is readily available in Hungary. A compromise may be reached, however, whereby the basic design and engineering is carried out by local Hungarian firms but with the addition and support of UK/Western European expert management and supervision. It must also be recognised that the effort required for validation generally results in an "engineering" cost premium of 15-20% over non-validatable facilities.



PROCESS PLANT

SECTION 1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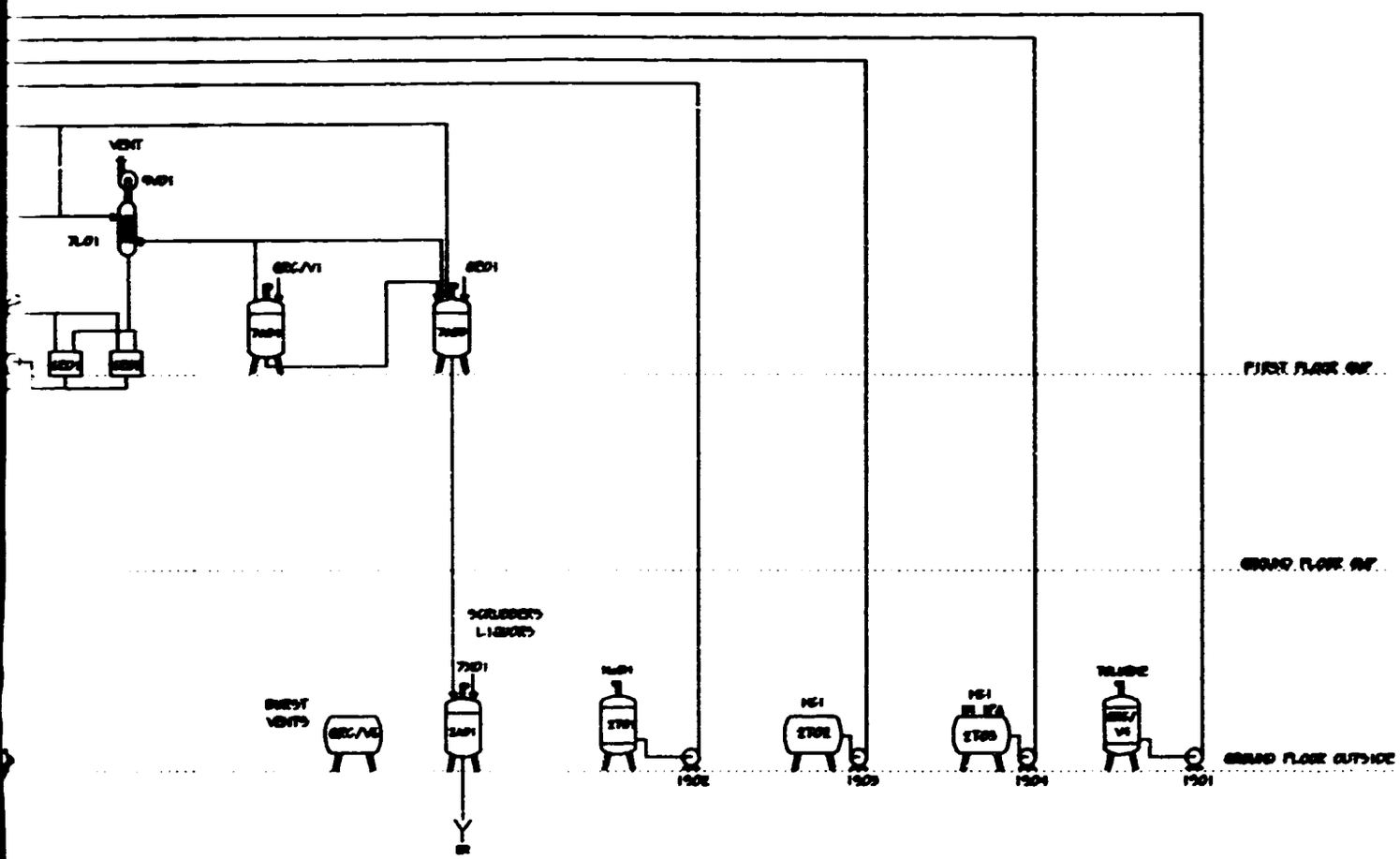
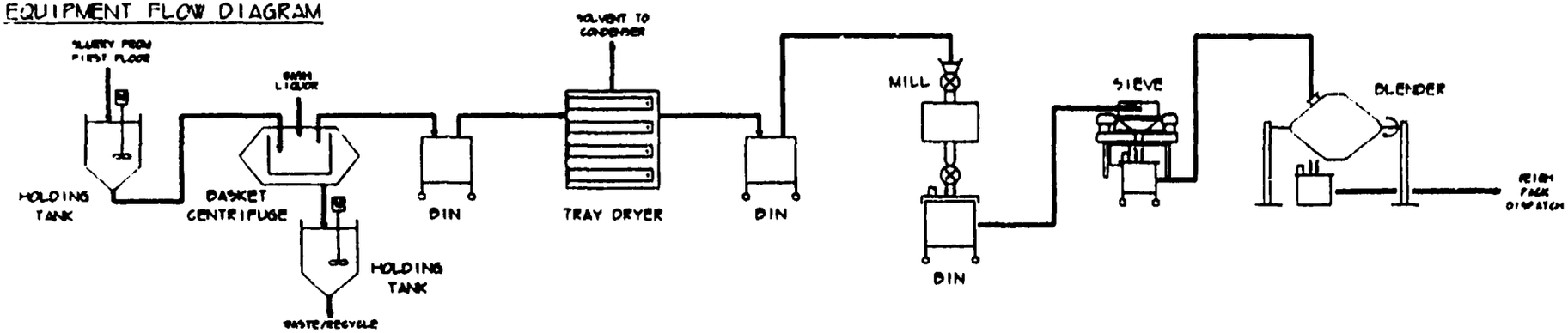
SCRUBBERS



OVERALL EQUIPMENT
FLOW DIAGRAM
92/013/201

SECTION 3

PROCESS 1
EQUIPMENT FLOW DIAGRAM



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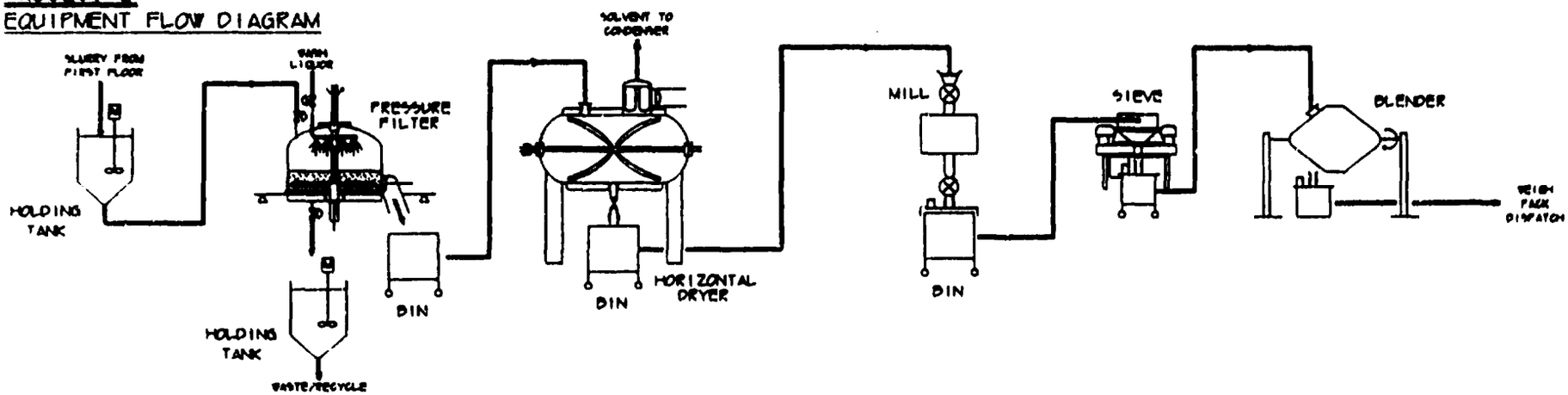

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DATE: JUNE 1992
SCALE: N.T.S.
DIMENSIONS IN: METRES

PROJECT
ALKALOIDA I
TF/HUN/90/907

TITLE
DSP EQUIPMENT FLOW DIAGRAM

DRAWING NUMBER
92/005/214

REV
B

GRC Consultants

20023

(3 of 3)

FRONT END DESIGN STUDY

FOR

SMALL SCALE MULTI PRODUCT UNIT (SSMPU)

FOR

THE ALKALOIDA COMPANY. TISZAVASVARI

VOLUME 2

G E GUIDOBONI

DECEMBER 1992

UNIDO CONTRACT 92/031
92/114

This report has been prepared for the United Nations Industrial Development Organisation (UNIDO) for the projects:-
- TF/HUN/90/907 "Technical Assistance for Upgrading the DSP Section of the Small Scale Multi Product Medicinal Chemical Plant of Alkaloida".
- TF/HUN/90/910 "Upgrading of Quality Assurance and Good Manufacturing Practices in the Multipurpose Medicinal Chemical Pilot Plant of Alkaloida".

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DSP	
Equipment Flow Diagram	1
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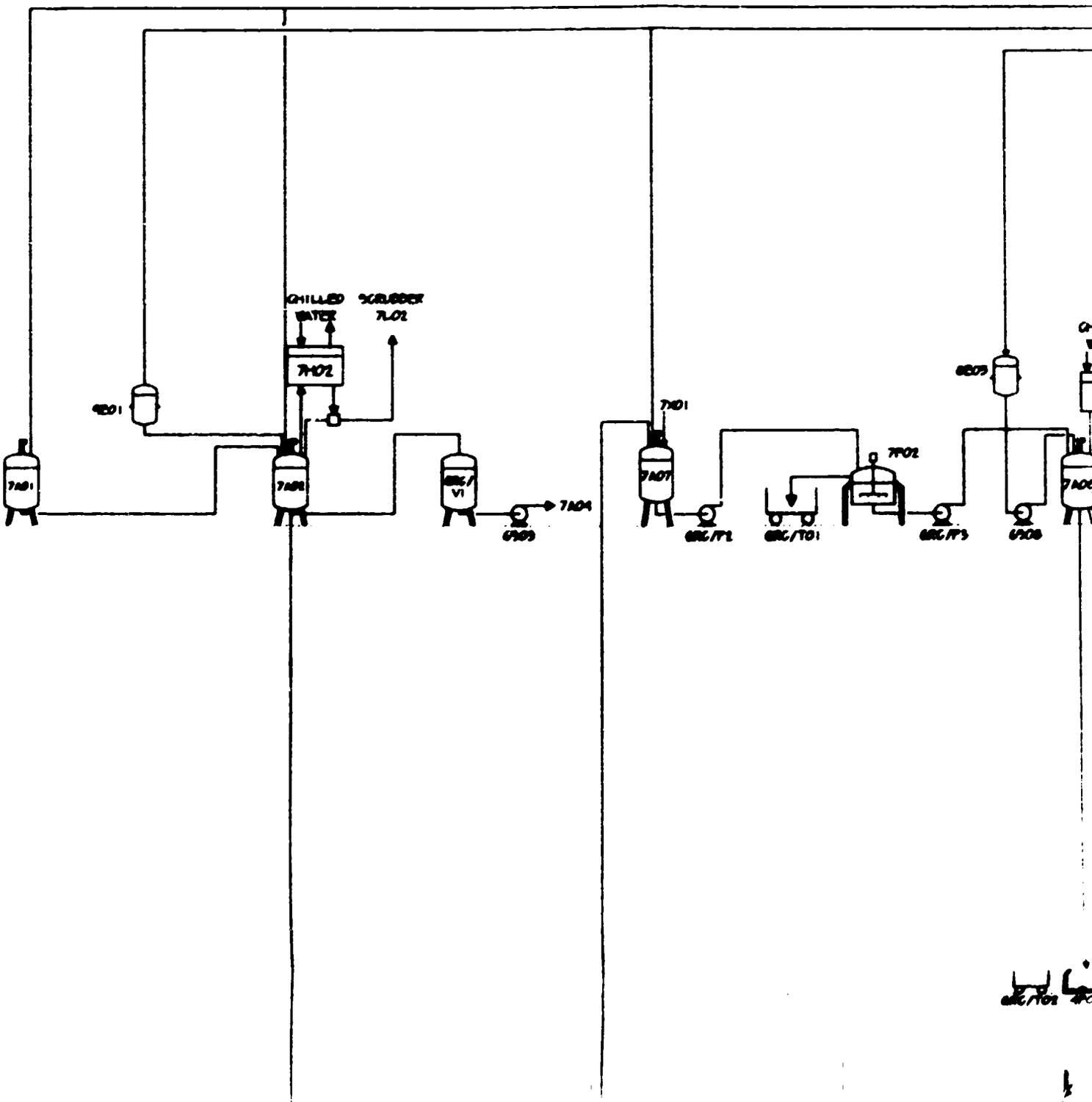
SECTION 1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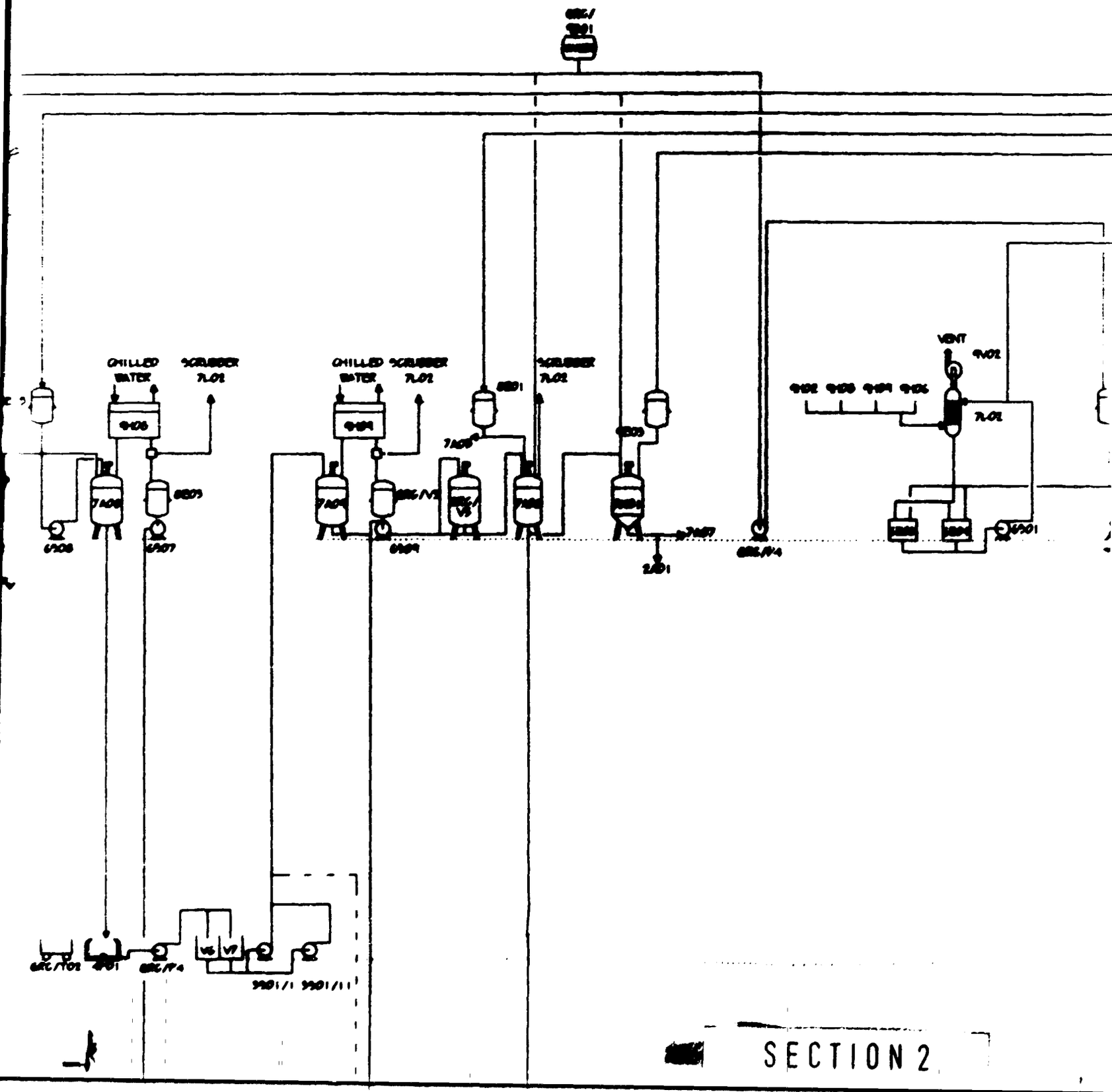
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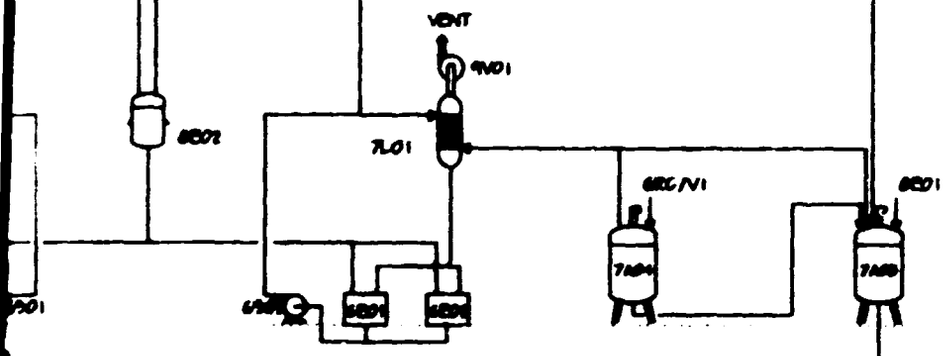

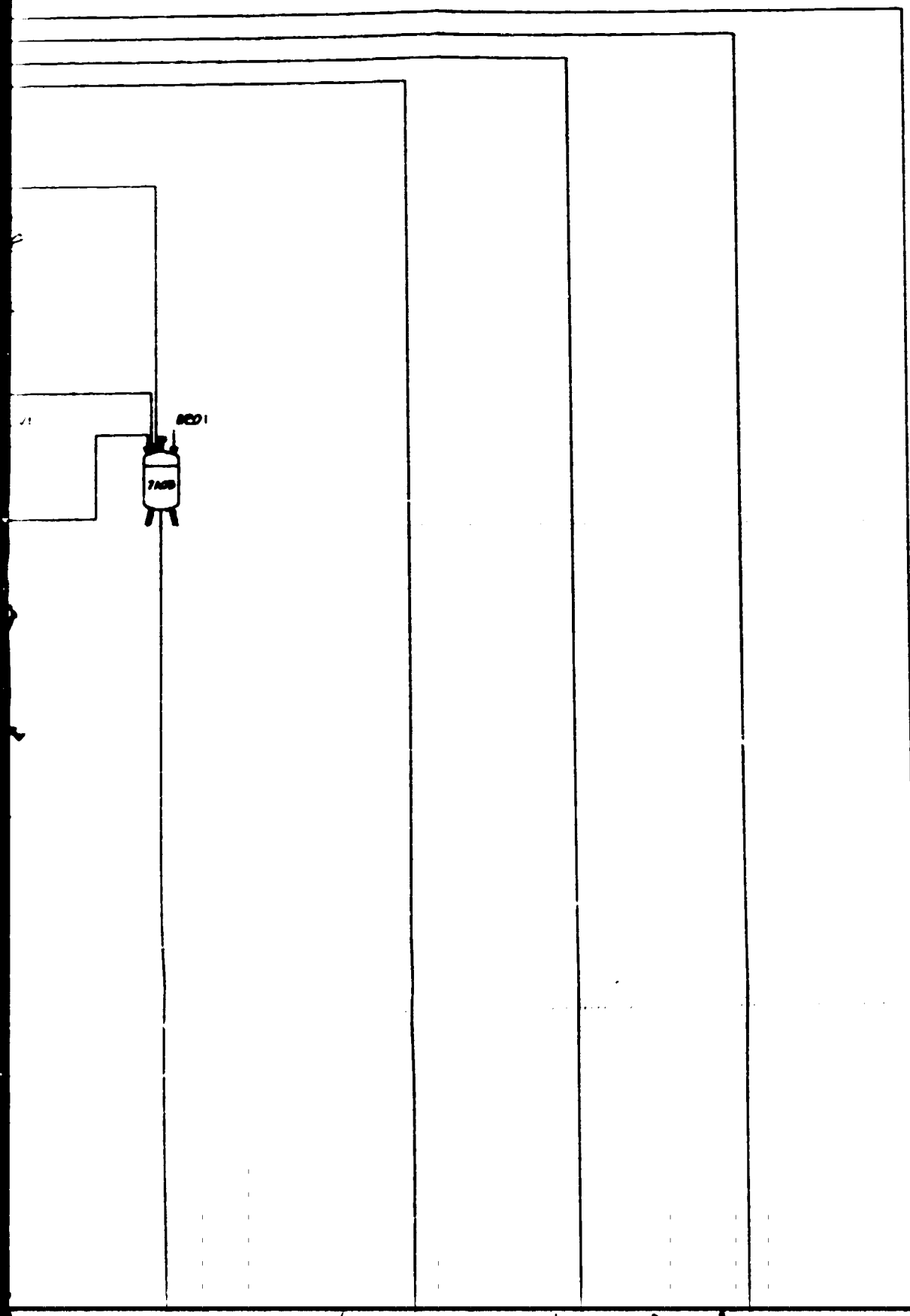
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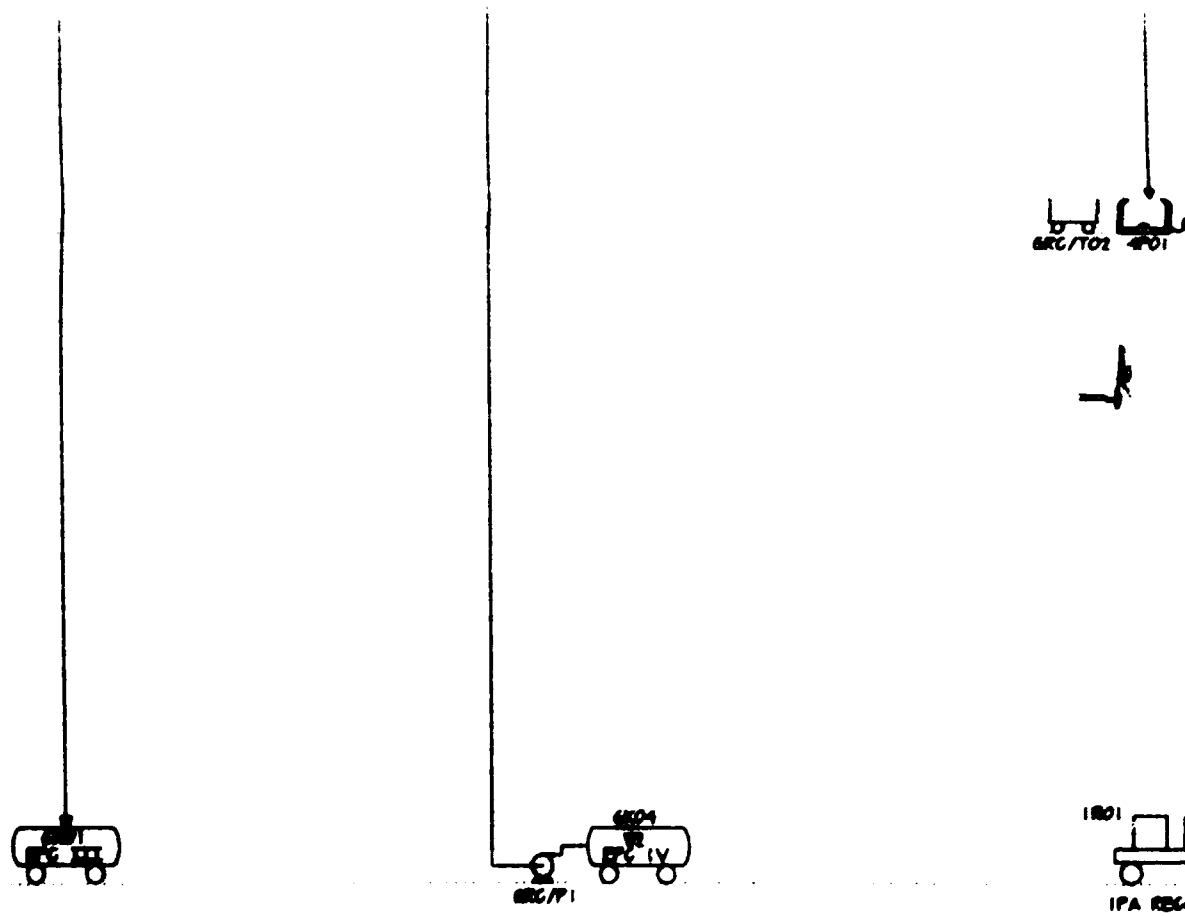

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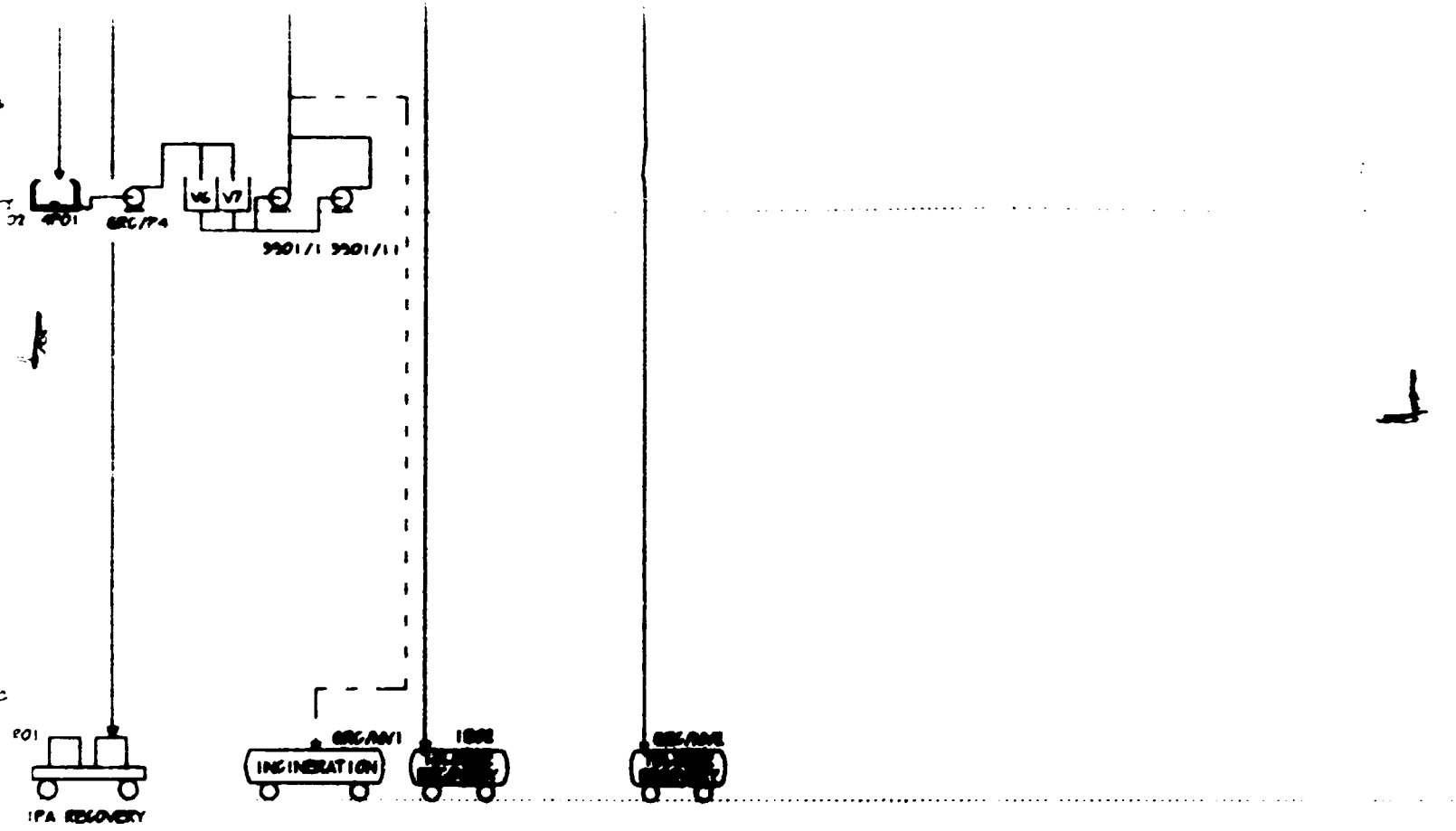

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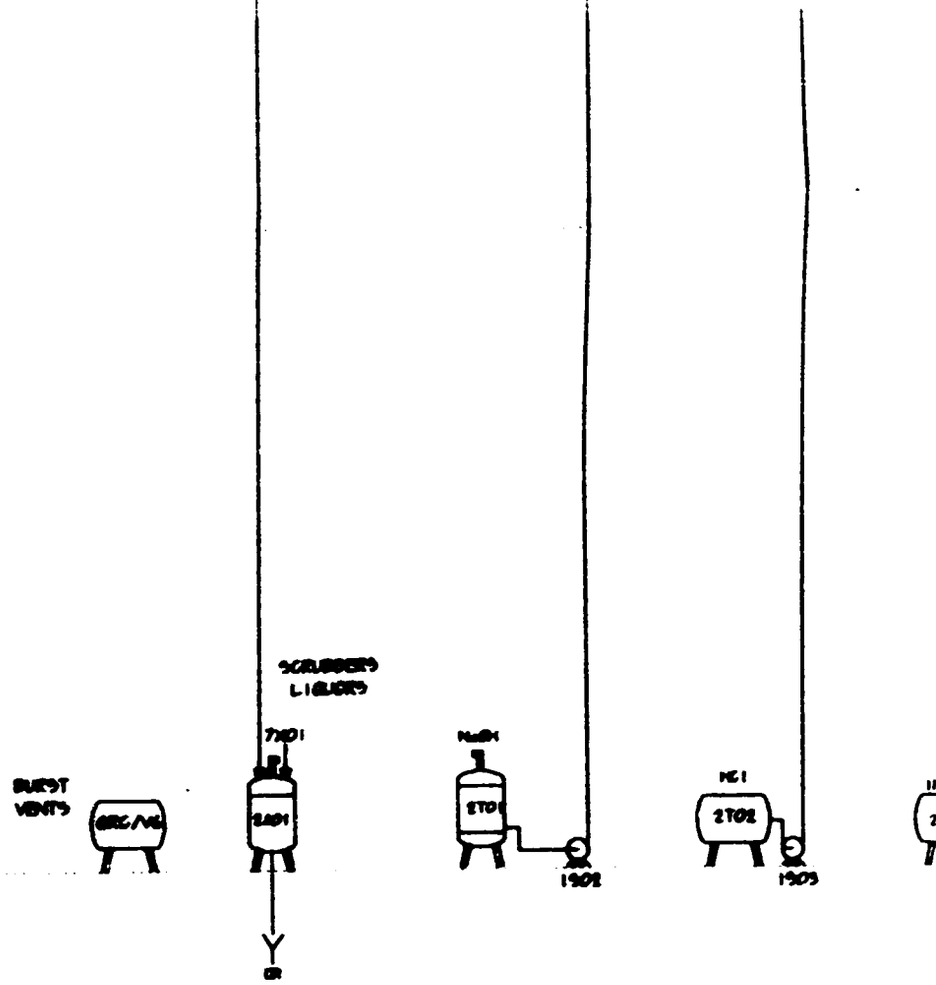
		GRC CONSULTANTS	CLIENT



SCRUBBERS | WASTE TREATMENT | LIQUID RAW MATER

SECTION 7

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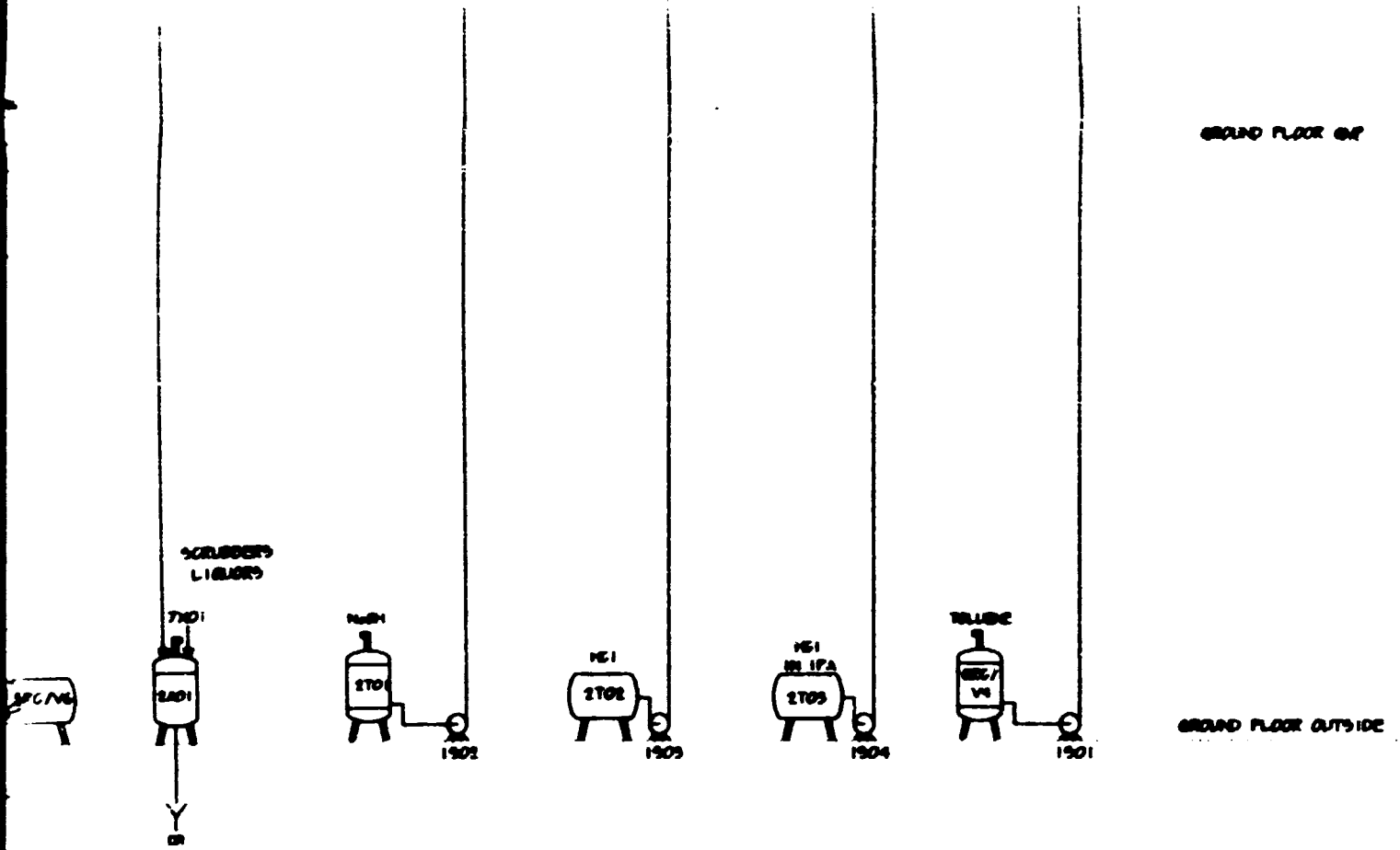

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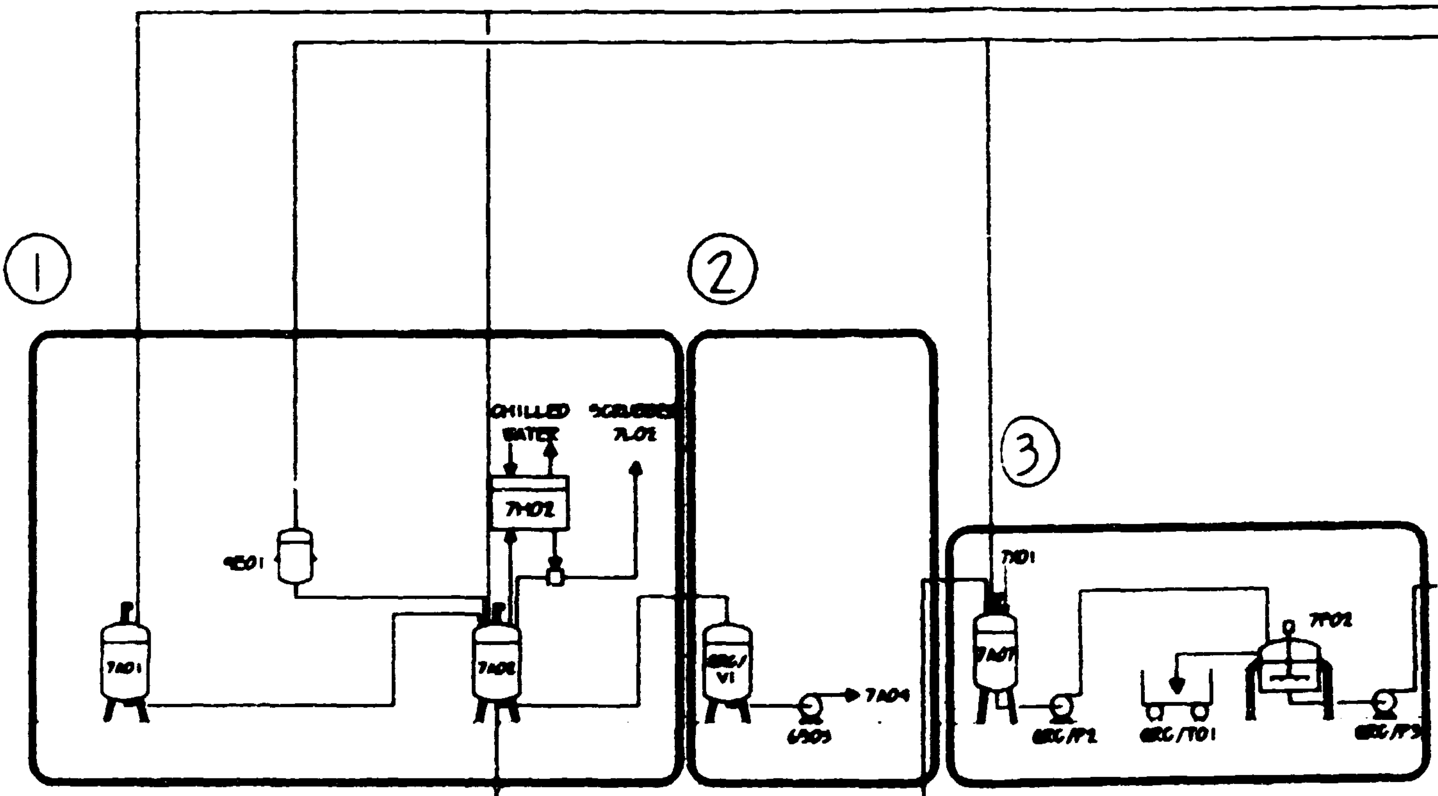

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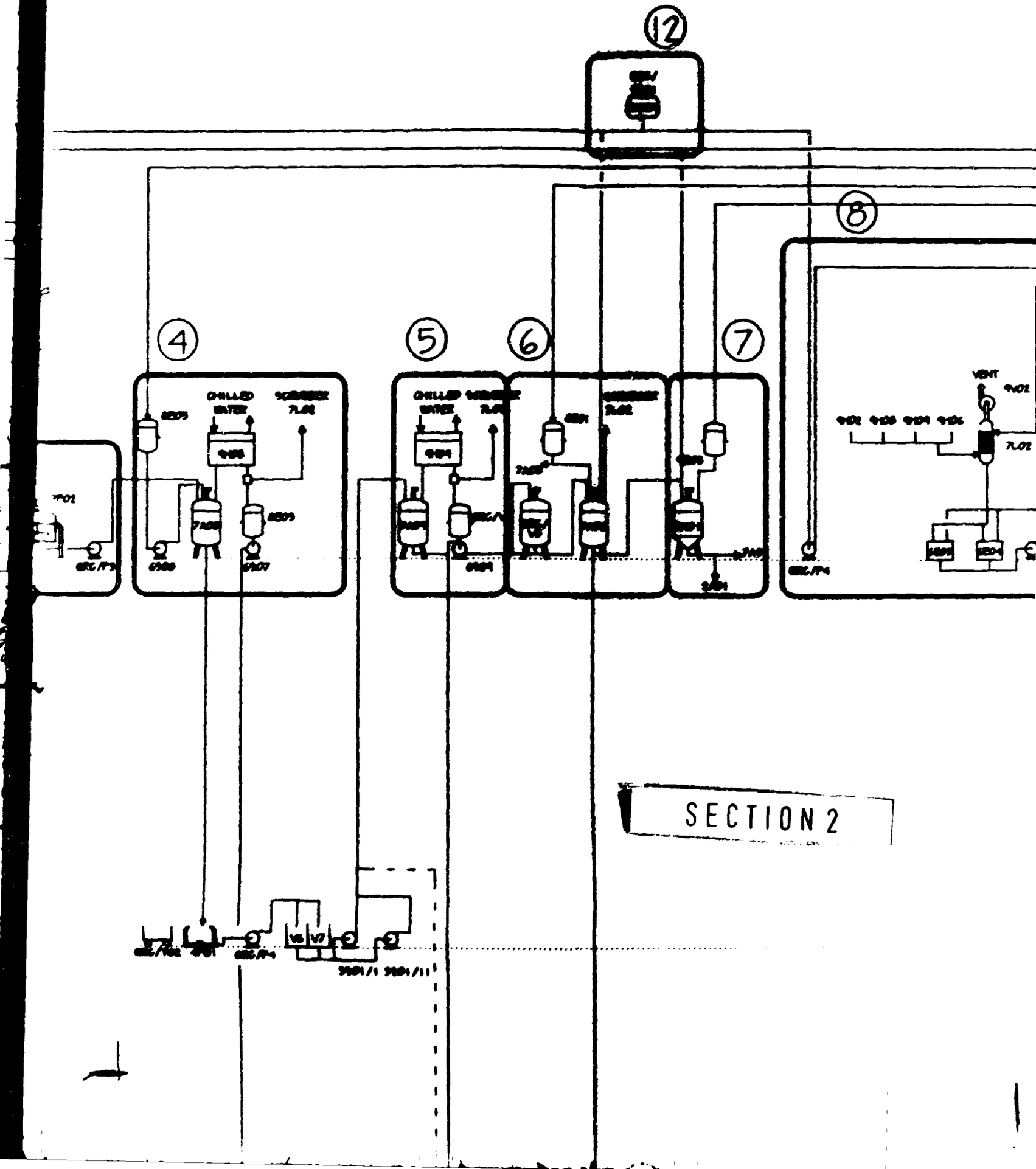
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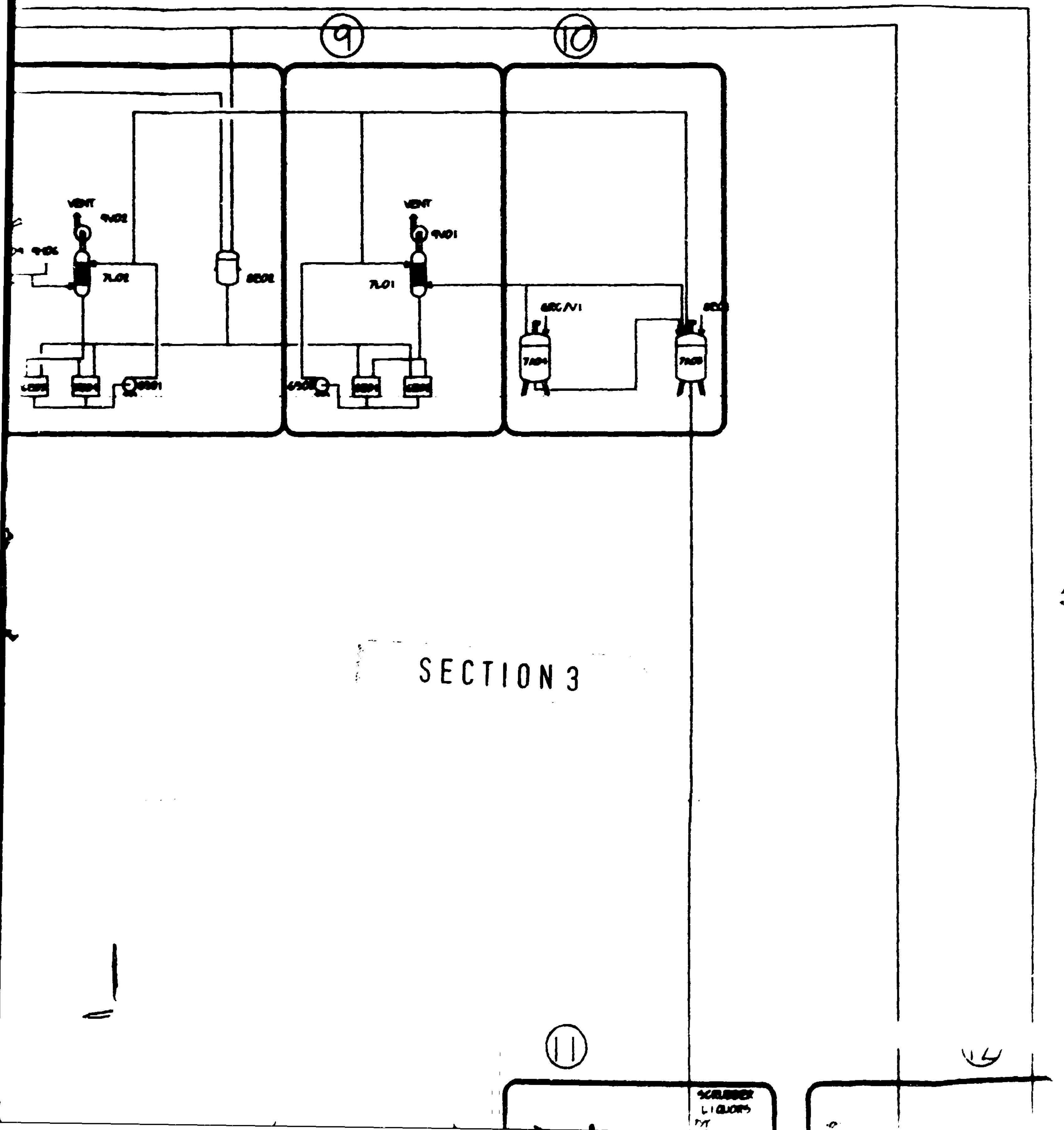
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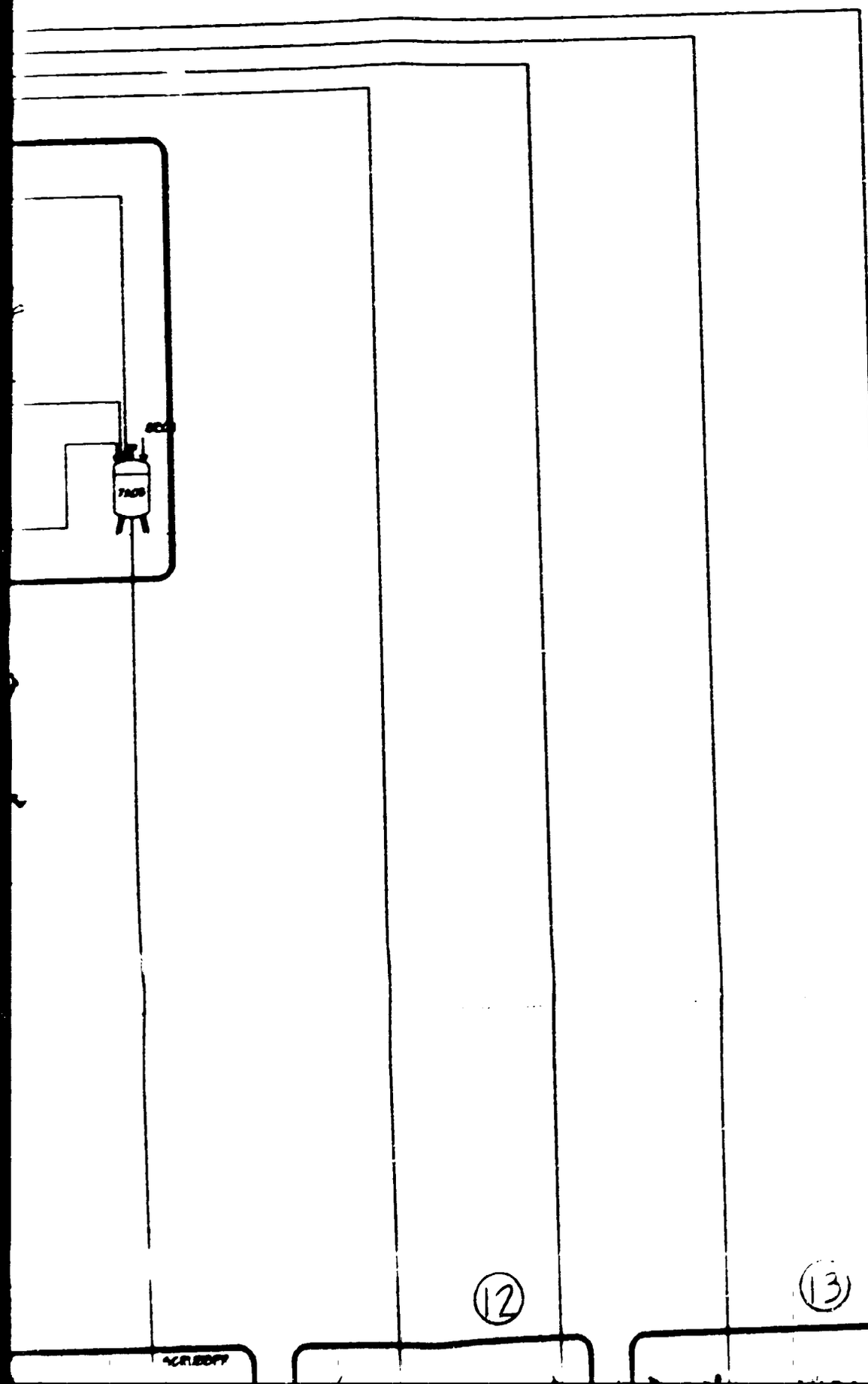
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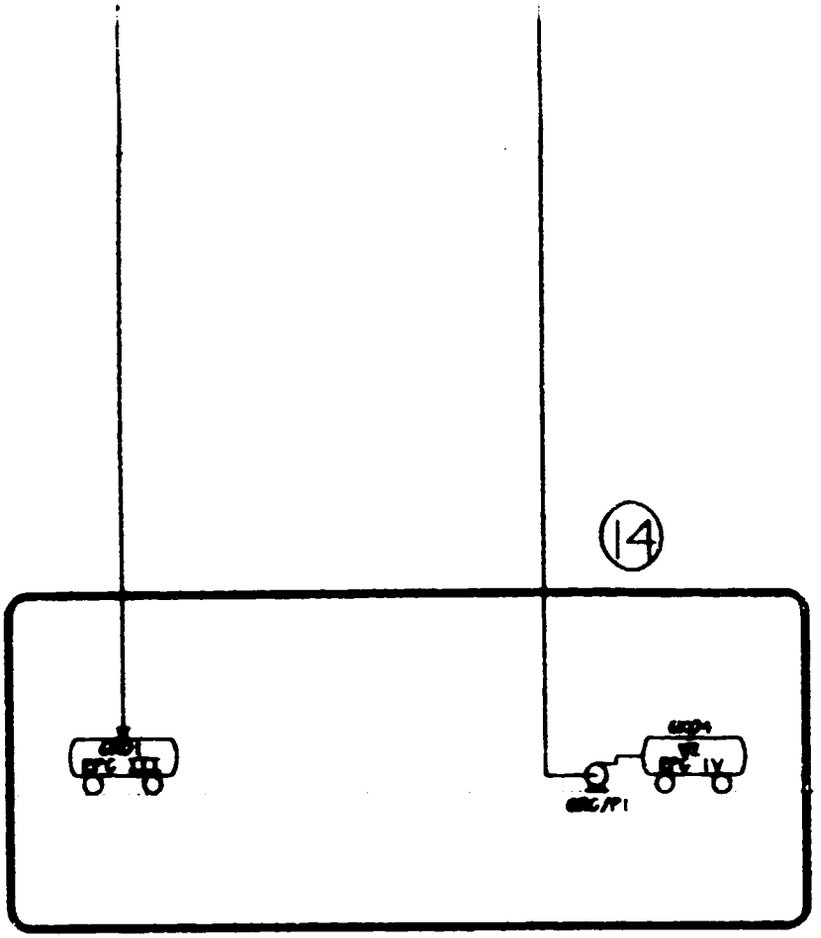

PROCESS PLANT

SECTION 5

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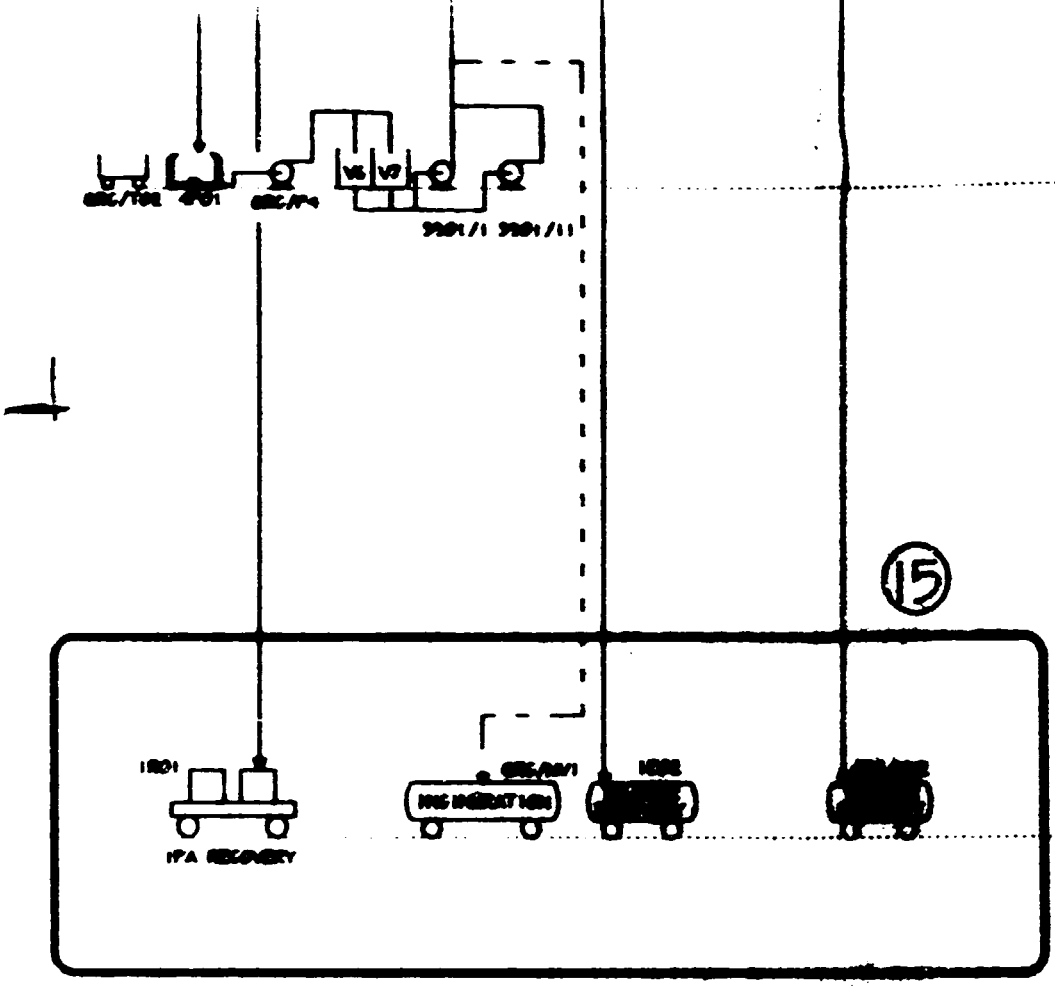

SECTION 6

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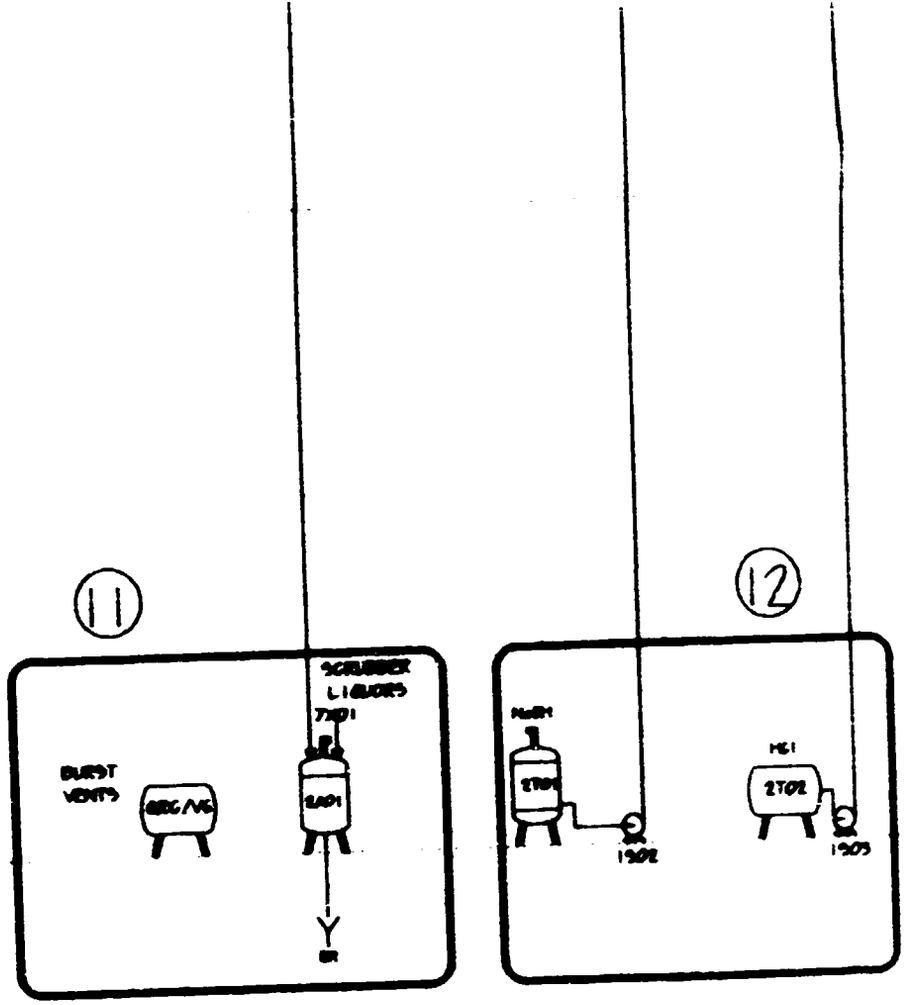
SCALE

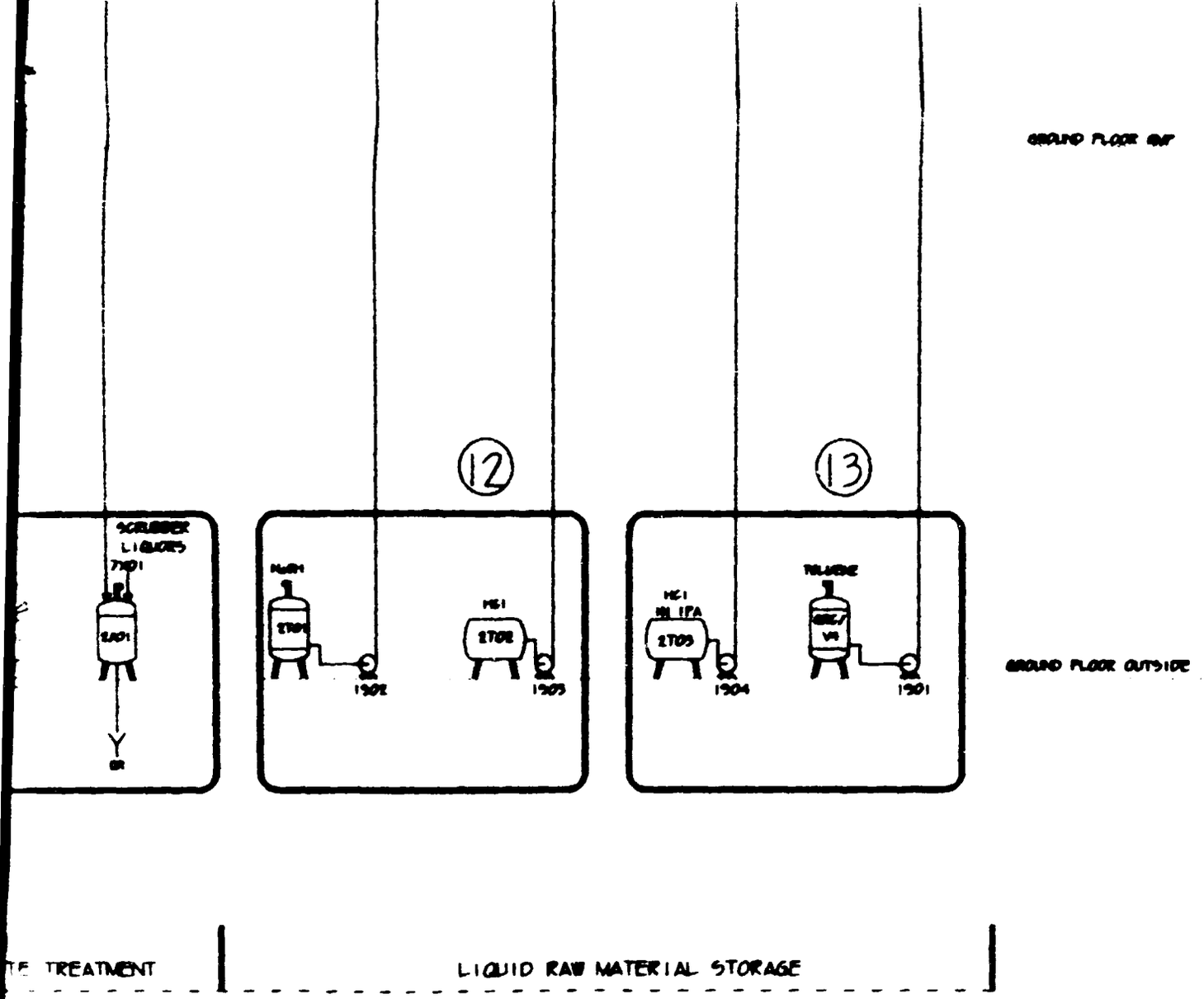
ALL DIMENS



SCRUBBERS | WASTE TREATMENT | LIQUID RAW

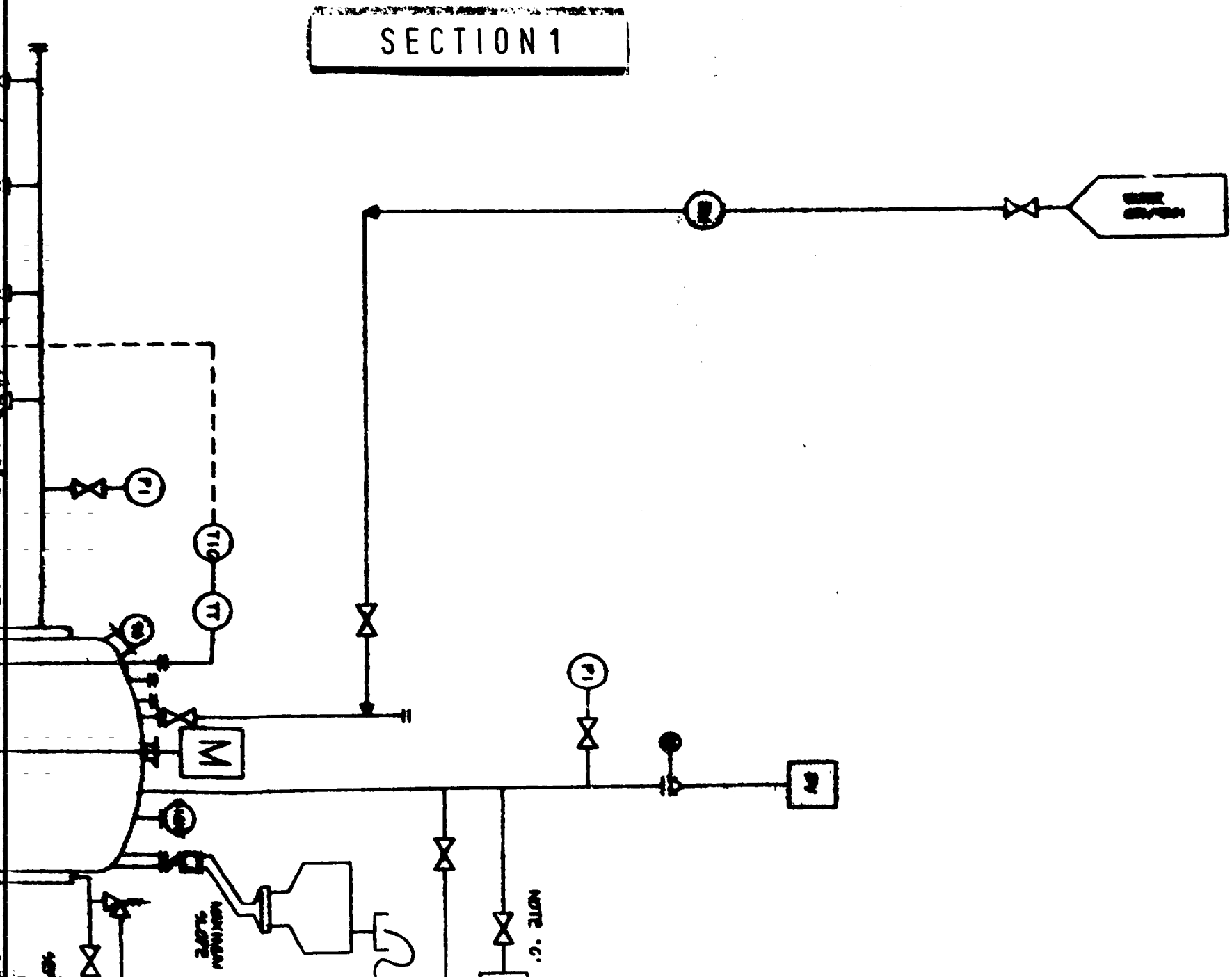
SECTION 7

CLIENT UNIDO P.O BOX 300, A-1400 VIENNA, AUSTRIA FAX: 232156	PROJECT ALKALOIDA 2 TF/HUN/90/910	DRAW EL
SCALE ALL DIMENSIONS IN MILLIMETERS		9

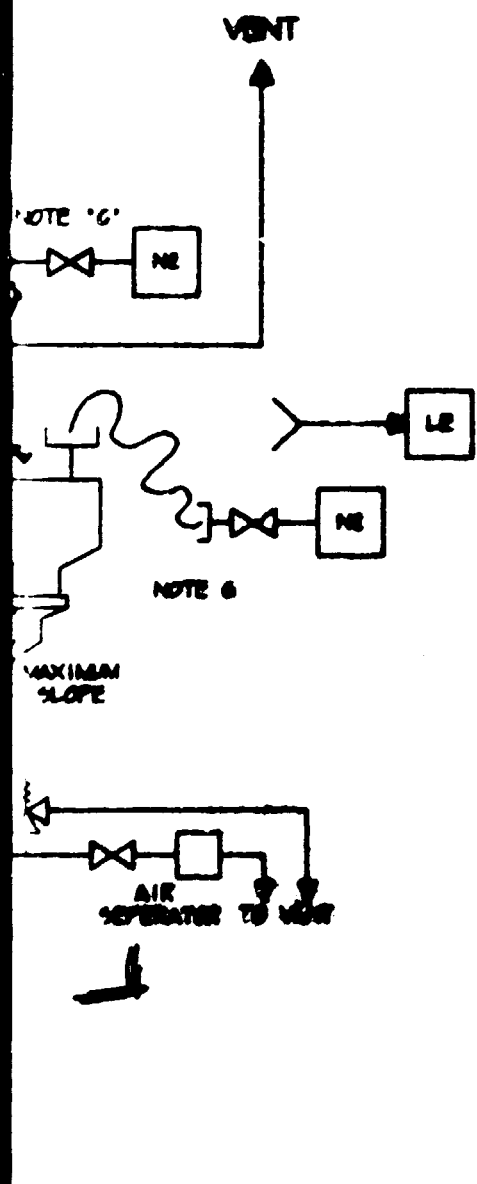


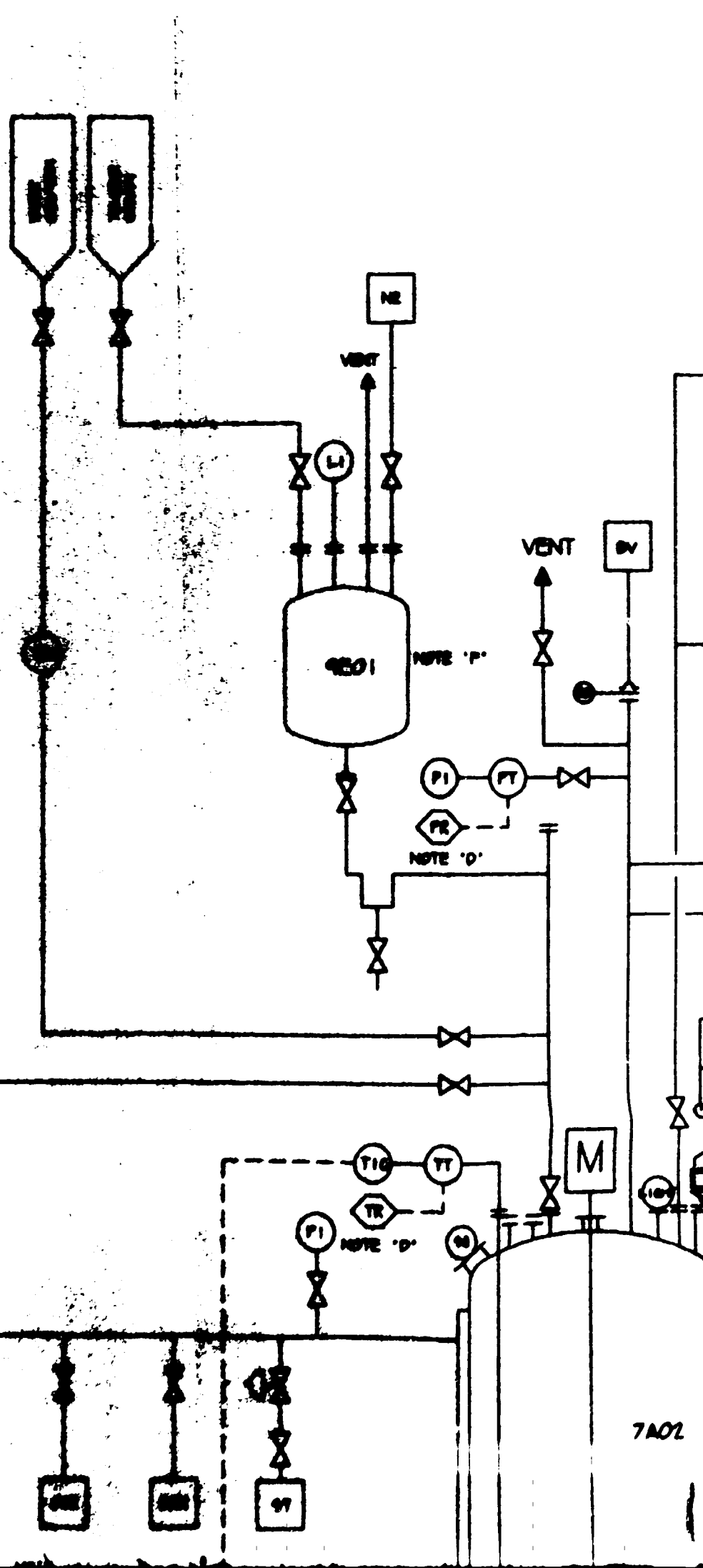
SECTION 8

2 /910	DRAWING TITLE ELD SUBSYSTEM DEFINITION	
	DRAWING NUMBER 92/013/201	REVISION A


SECTION 1

SECTION 2


VENT
NOTE 'C'
NE
LE
NE
NOTE 6
MAXIMUM SLOPE
AIR SEPERATOR TO VENT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NOTE 'P'
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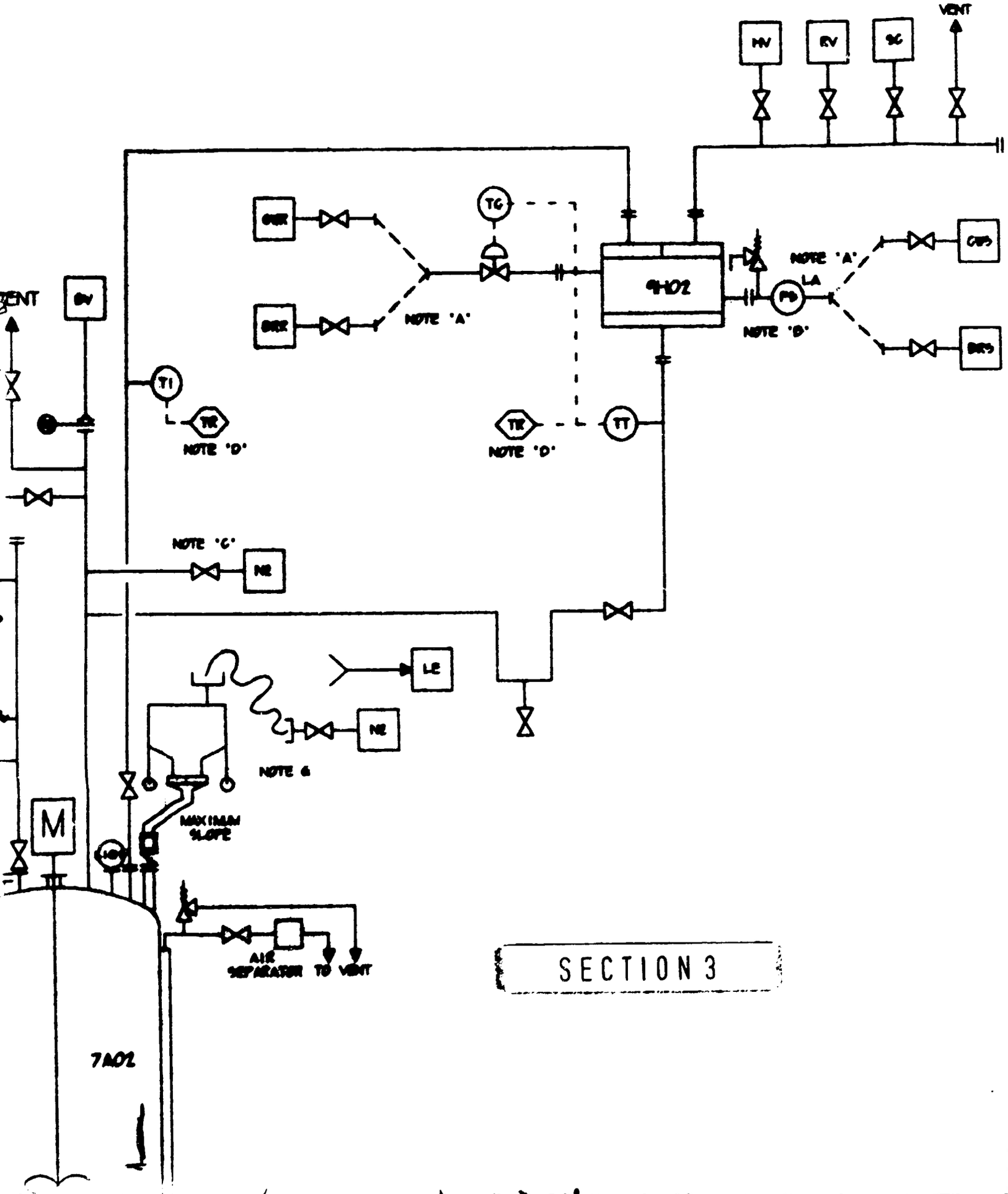
PI
FT
PR
NOTE 'D'
M
TIC
TT
TR
PI
NOTE 'D'
7A02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HV
RV
SG
TG
NOTE 'A'
NOTE 'A'
9-HO2
LA
NOTE 'D'
NOTE 'D'
NOTE 'D'
TI
TR
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NR
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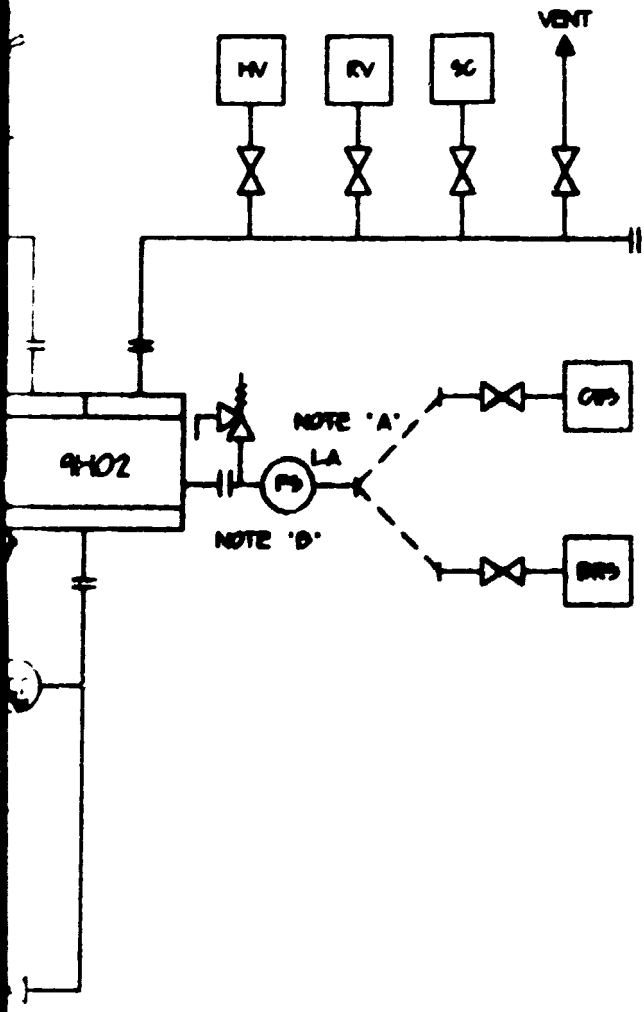
NE
NOTE 6
M
MAXIMUM
SLOPE
AIR
SEPARATOR
TO VENT
7AO2
SECTION 3


VENT
HV
RV
SC
NOTE 'A'
LA
NOTE 'D'

NOTES

A. VALVE SYSTEMS ON VESSEL JACKET AND CONDENSER SERVICES COULD BE PHYSICALLY INTERLOCKED OR CONTROLLED VIA DEDICATED PLC.

B. FLOW SWITCH TO DETECT LOW FLOW, CONNECTED TO SOUNDING ALARM

C. NITROGEN FOR PURGE OR PRESSURISATION.

D. SIGNAL TO DATA LOGGING COMPUTER.

E. ALL SERVICE CONNECTIONS SHOWN IN SQUARE FRAMES OTHER CONNECTIONS SHOWN IN ARROWED FRAMES.

F. SIGHT GLASS OR OTHER LEVEL INDICATION REQUIRED ON 9E01

G. HOPPER DESIGN TO BE FINALISED AT DETAILED DESIGN

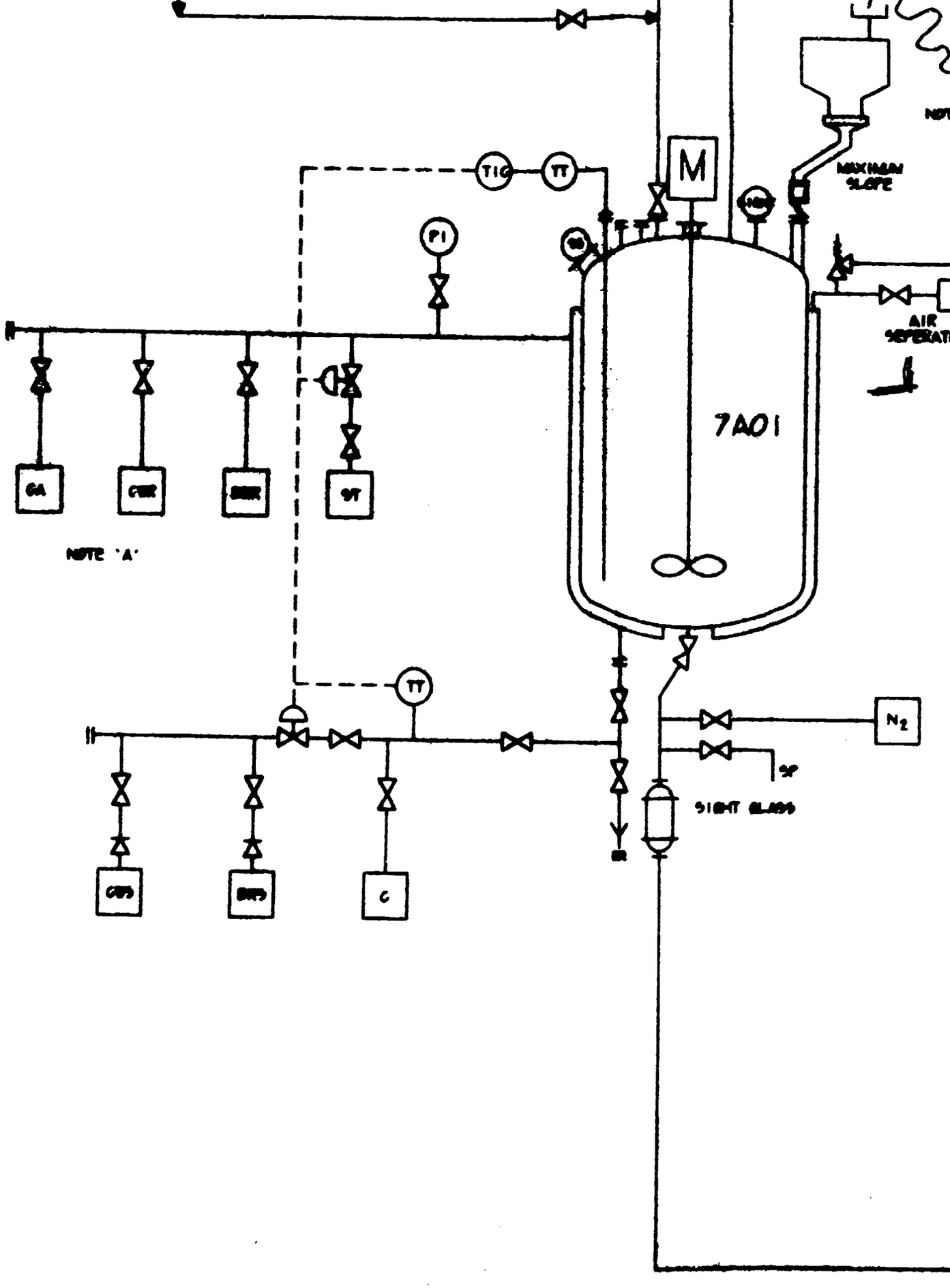
H. VESSEL ACCESS WAYS TO BE PROVIDED AS MANUFACTURERS STANDARD

I. BLANKED NOZZLES INCLUDED FOR POSSIBLE FUTURE USE AS FILL PORTS/CIP SYSTEM

KEY

DM - BATCH METER
SC - SCRUBBER
FS - FLOW SWITCH
CWS - COOLING WATER SUPPLY
CWR - COOLING WATER RETURN
BRS - BRINE SUPPLY
BRR - BRINE RETURN
LE - LOCAL EXTRACTION
ST - STEAM
C - CONDENSATE
SP - SAMPLE POINT
HV - HIGH VACUUM
RV - ROUGH VACUUM
BV - BURSTING VENT

SECTION 4



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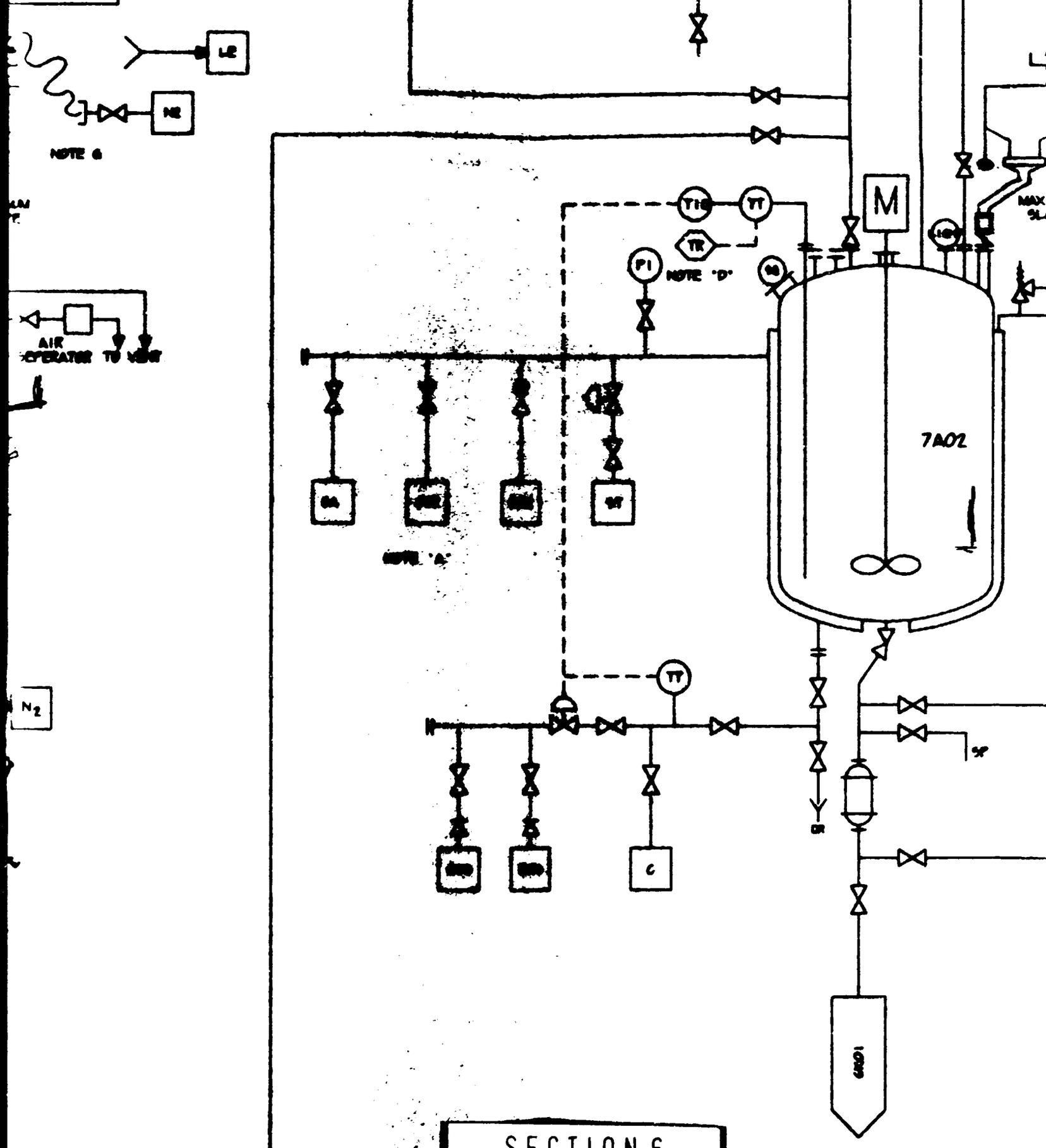
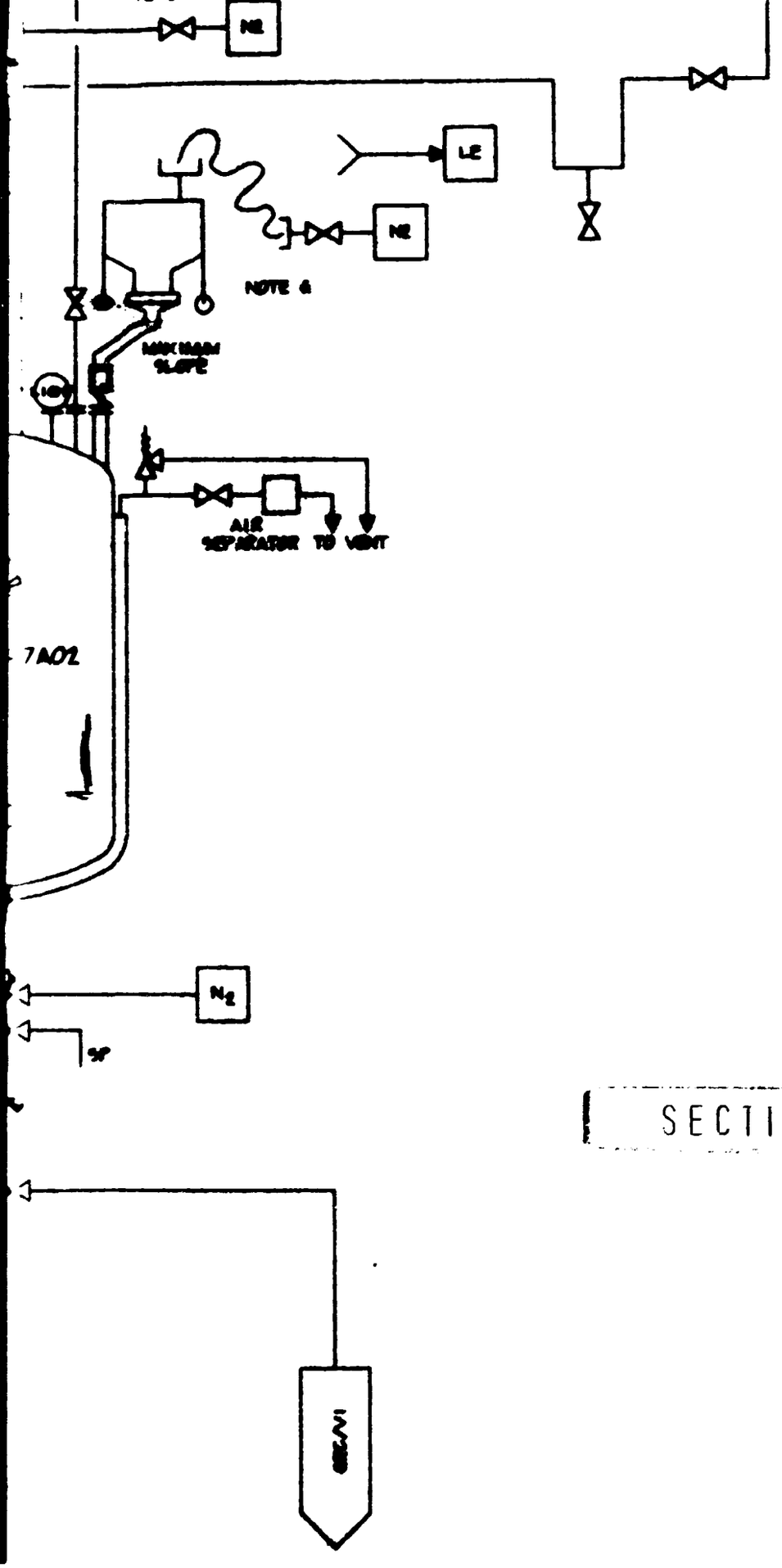

NOTE 6
AIR
OPERATED
TO VENT
N_2
TT
PI
NOTE "D"
M
7A02
NOTE "A"
C
SECTION 6


N2
LE
N2
NOTE 4
AIR
SEPARATOR TO VENT
7A02
N2
SP
SECTION 7

Rev	Date	Description	By
A	14/12/92	ISSUED WITH REPORT	MB

Client

UNIDO
P.O BOX 300, A-1400 VIENNA,
AUSTRIA, FAX:232156

Project

ALKALOIDA 2
TF/HUN/90/910

SECTION 8

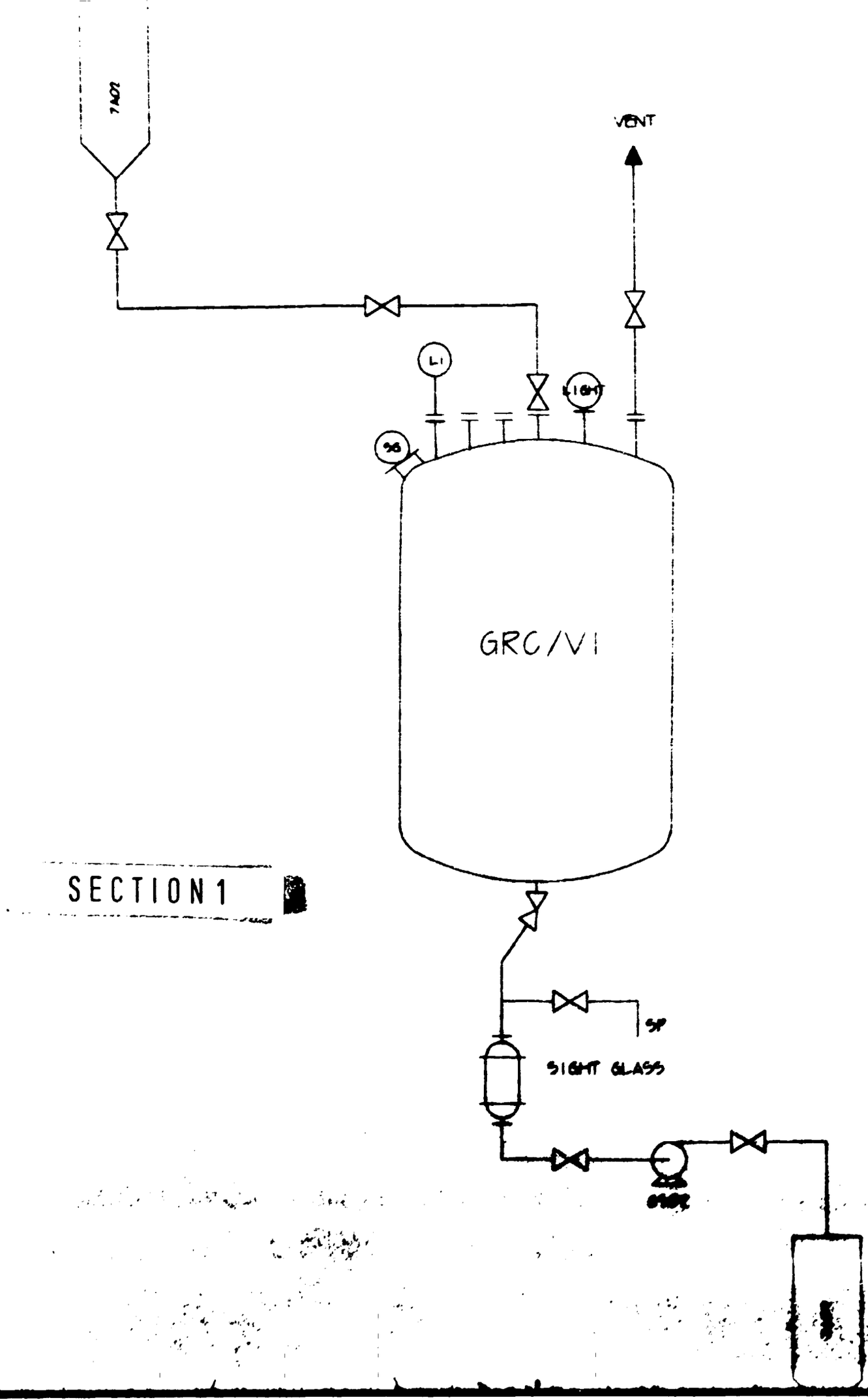
Drawing Title

SUBSYSTEM 1
ENGINEERING LINE
DIAGRAM

GRC CONSULTANTS

WATERCRESS HOUSE
1 THE WINDMILLS ST MARY'S CLOSE,
ALTON HANTS GU34 1EE
TEL 0420

Drawing Number	Scale	Revision
92/013/230	NTS	A



SECTION 1

NOTES

A ALL SERVICE CONNECTIONS SHOWN IN SQUARE FRAMES OTHER CONNECTIONS SHOWN IN ARROWED FRAMES. .

B VESSEL ACCESS WAYS TO BE PROVIDED AS MANUFACTURERS STANDARD

C BLANKED NOZZLES INCLUDED FOR POSSIBLE FUTURE USE AS FILL PORTS/CIP SYSTEM

KEY

DM	- DATCH METER
SC2	- SCRUBBER 7LO2
FS	- FLOW SWITCH
CWS	- COOLING WATER SUPPLY
CWR	- COOLING WATER RETURN
DRS	- DRINE SUPPLY
DRR	- DRINE RETURN
LE	- LOCAL EXTRACTION
ST	- STEAM
C	- CONDENSATE
SP	- SAMPLE POINT
HV	- HIGH VACUUM
RV	- ROUGH VACUUM

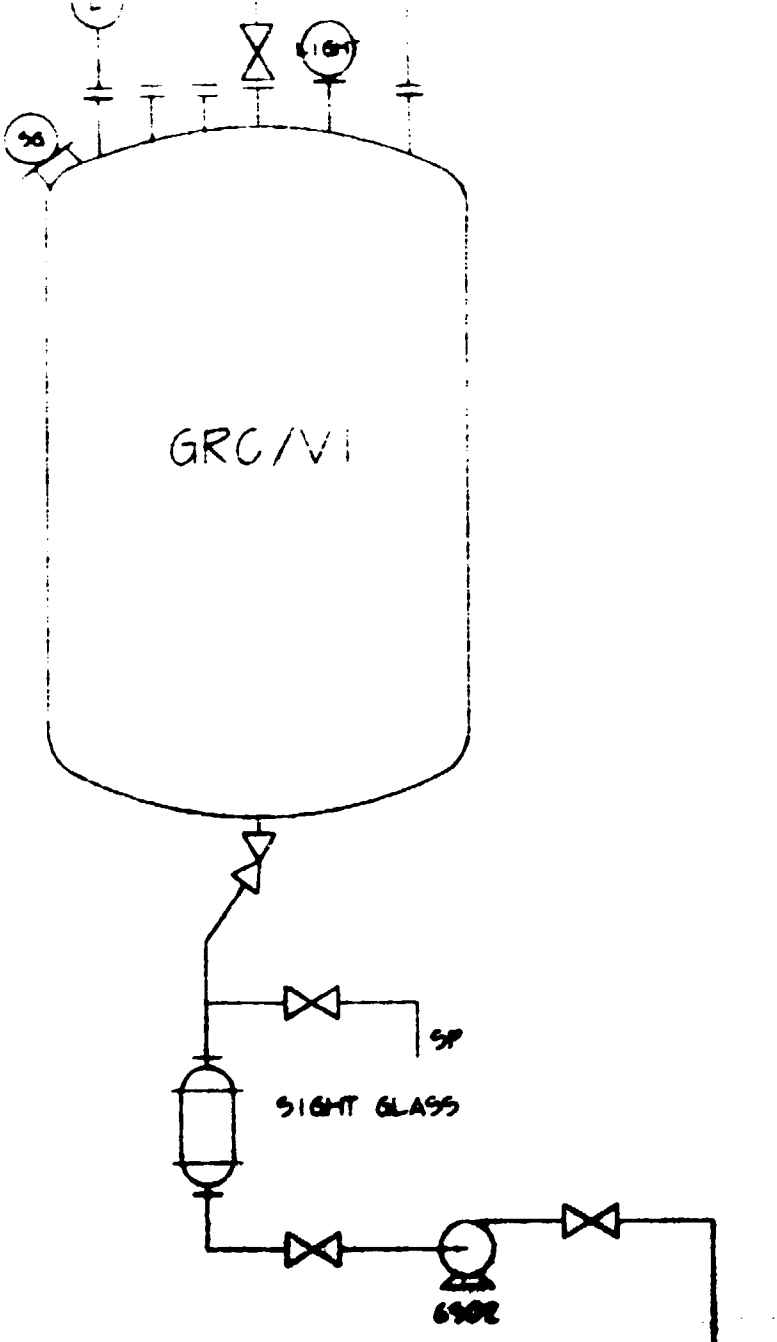
SECTION 2

				ISSUED WITH REPORT	A	14/12/M
				MODIFICATION		

GRC

WATERCRESS
ST MARY'S

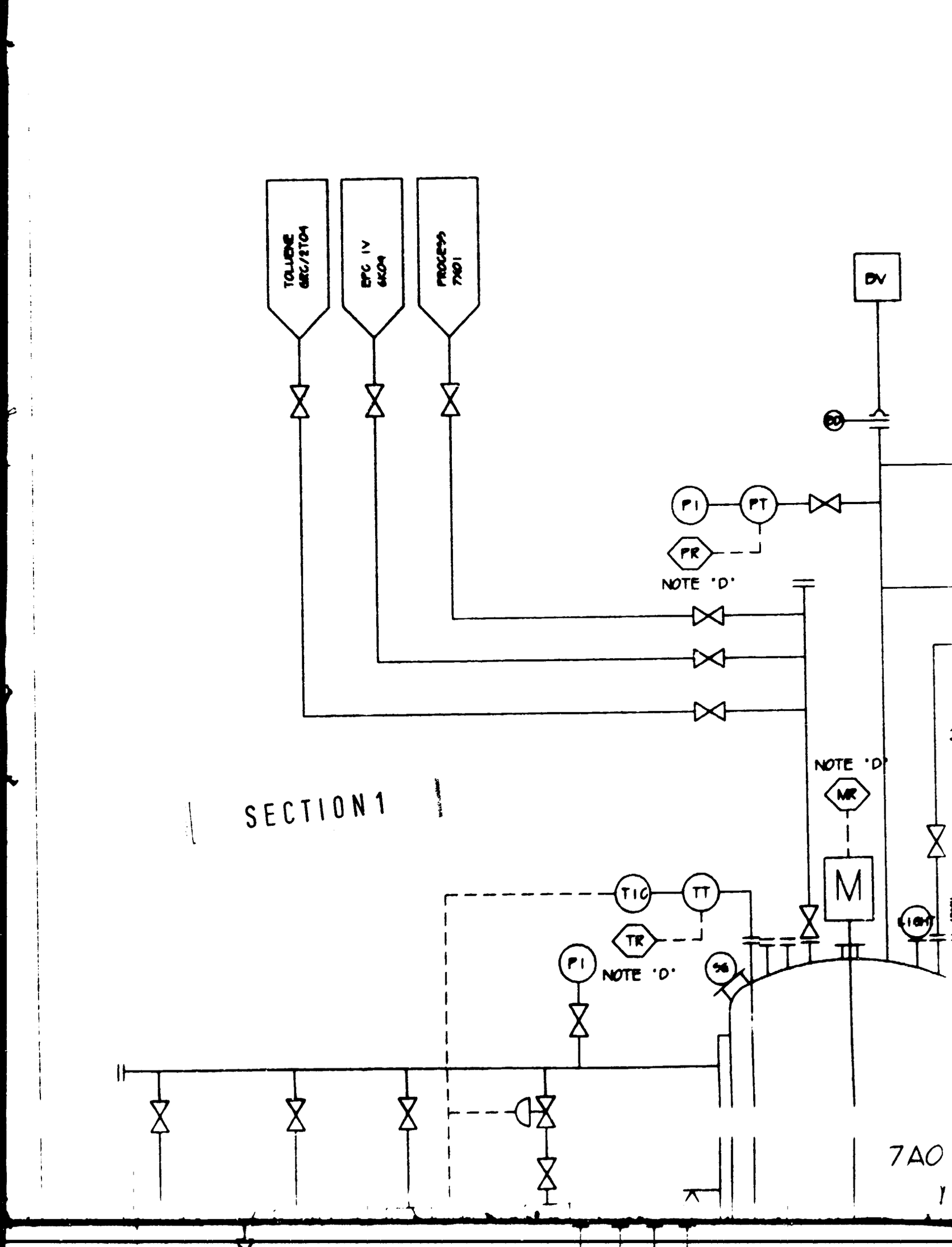
SECTION 3

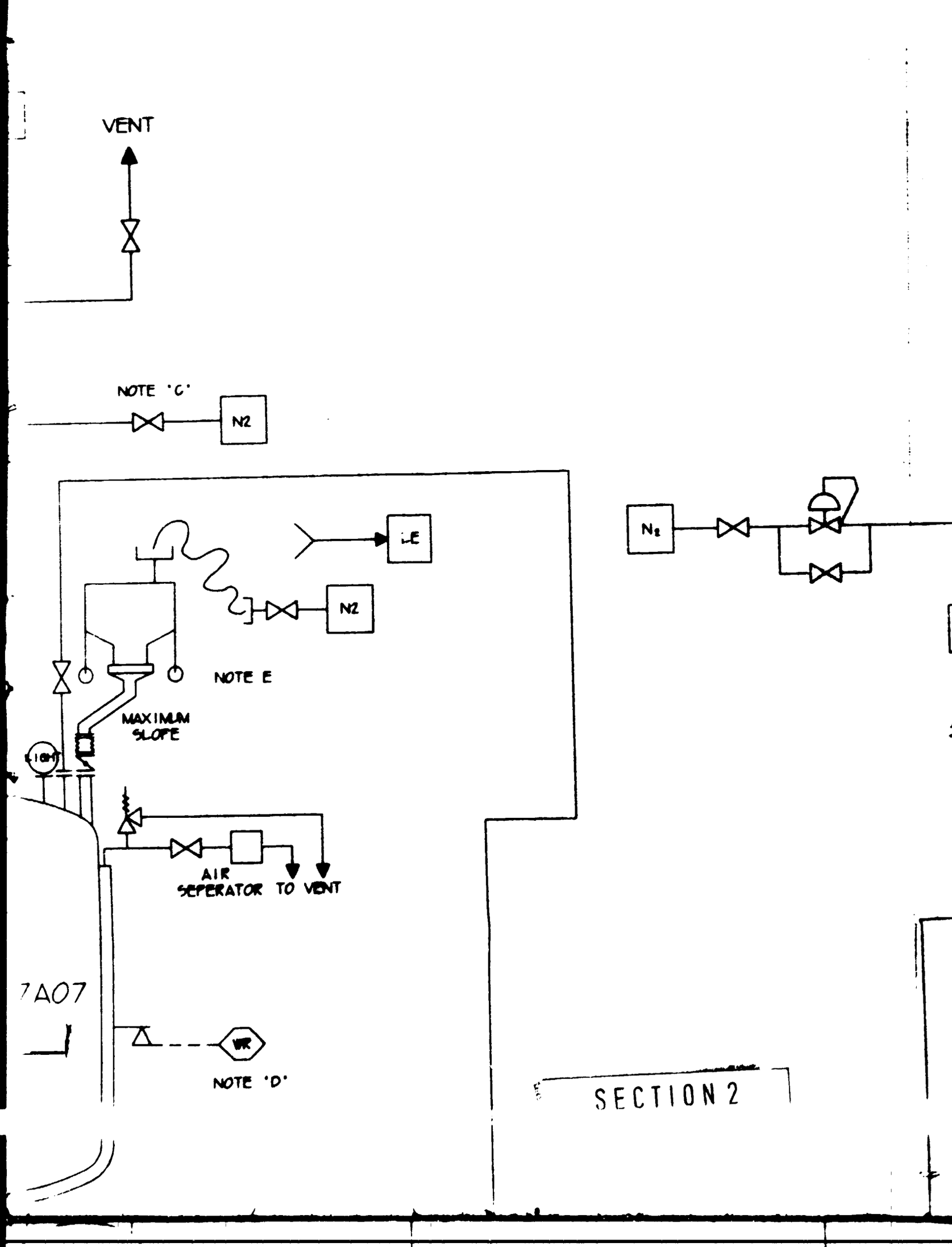

GRC/V1
SP
SIGHT GLASS

SC2 - SCRUBBER 7L02
FS - FLOW SWITCH
CWS - COOLING WATER SUPPLY
CWR - COOLING WATER RETURN
DRS - BRINE SUPPLY
DRR - BRINE RETURN
LE - LOCAL EXTRACTION
ST - STEAM
C - CONDENSATE
SP - SAMPLE POINT
HV - HIGH VACUUM
RV - ROUGH VACUUM

X 300, A-1400 VIENNA , FAX: 232155	PROJECT ALKALOIDA 2 TP/MUN/90/910	TITLE SUBSYSTEM 2 ENGINEERING & PIPE DIAGRAM
SIZE A1 N/A DWG NO		DRAWING NUMBER 92/013/231

SECTION 5


TOLUENE
EPC IV
PROCESS
DV
PI
PT
PR
NOTE 'D'
NOTE 'D'
MR
M
TIC
TT
TR
PI
NOTE 'D'
SECTION 1
7A0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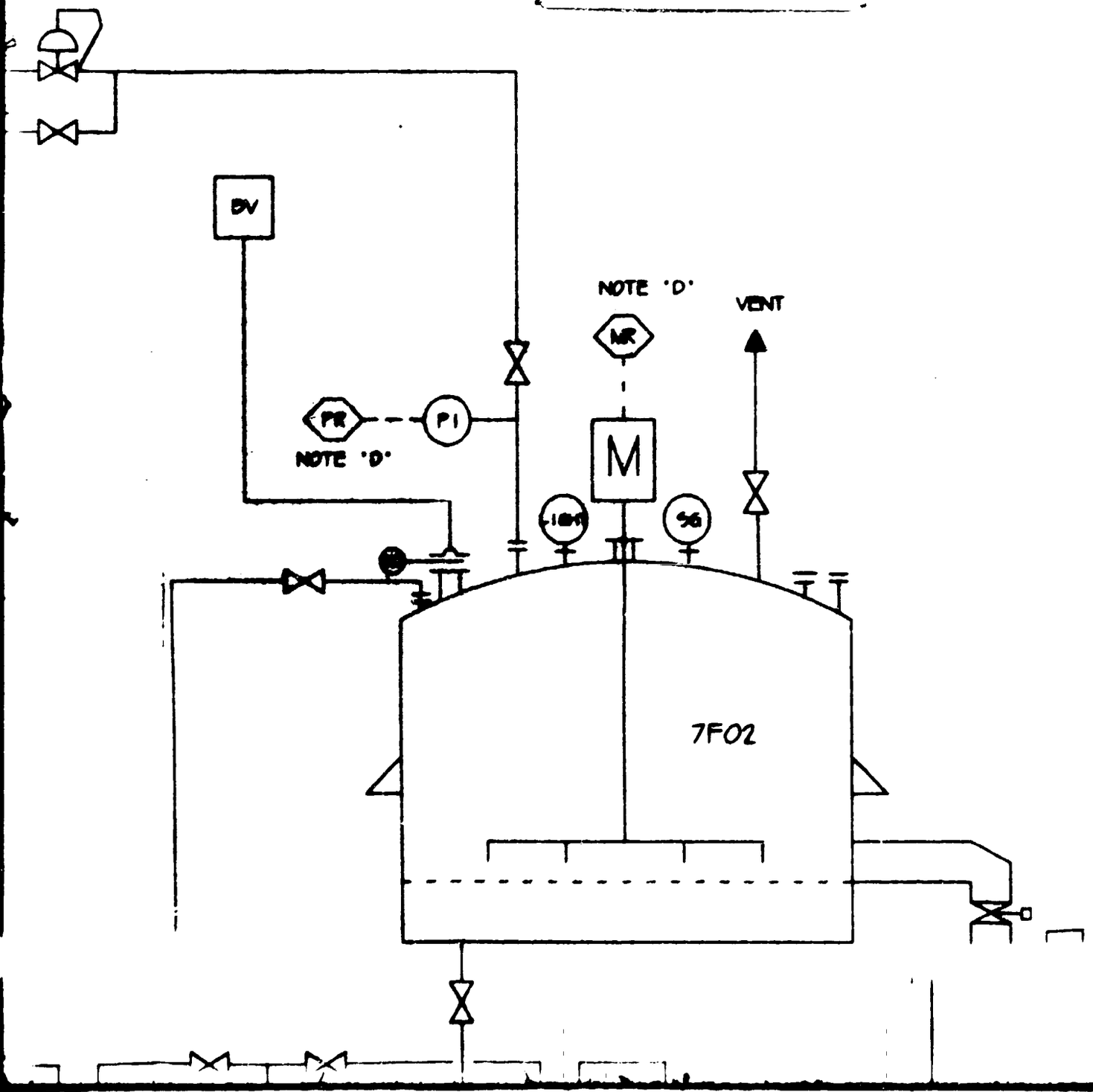
NOTE 'C'
N2
N2
NOTE E
MAXIMUM SLOPE
AIR SEPERATOR
TO VENT
NOTE 'D'
SECTION 2

SECTION 3



NOTES

A. VALVE SYSTEMS ON VESSEL JACKET COULD BE PHYSICALLY INTERLOCKED OR CONTROLLED VIA DEDICATED PLC

D. ALL SERVICE CONNECTIONS SHOWN IN SQUARE FRAMES OTHER CONNECTIONS SHOWN IN ARROWED FRAMES.

C. NITROGEN FOR PURGE OR PRESSURISATION.

D. SIGNAL TO DATA LOGGING COMPUTER.

E. EXACT DETAILS OF SOLIDS FEED ARRANGEMENT TO BE SPECIFIED IN DETAILED DESIGN

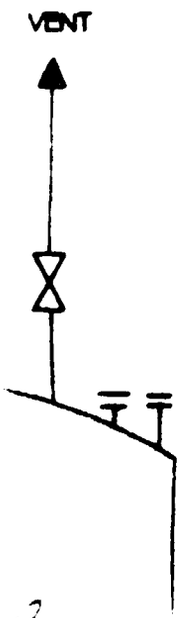
F. PRESSURE TRANSFER MAY BE USED AS AN ALTERNATIVE FILTER FEED ARRANGEMENT TO BE SPECIFIED IN DETAIL DESIGN

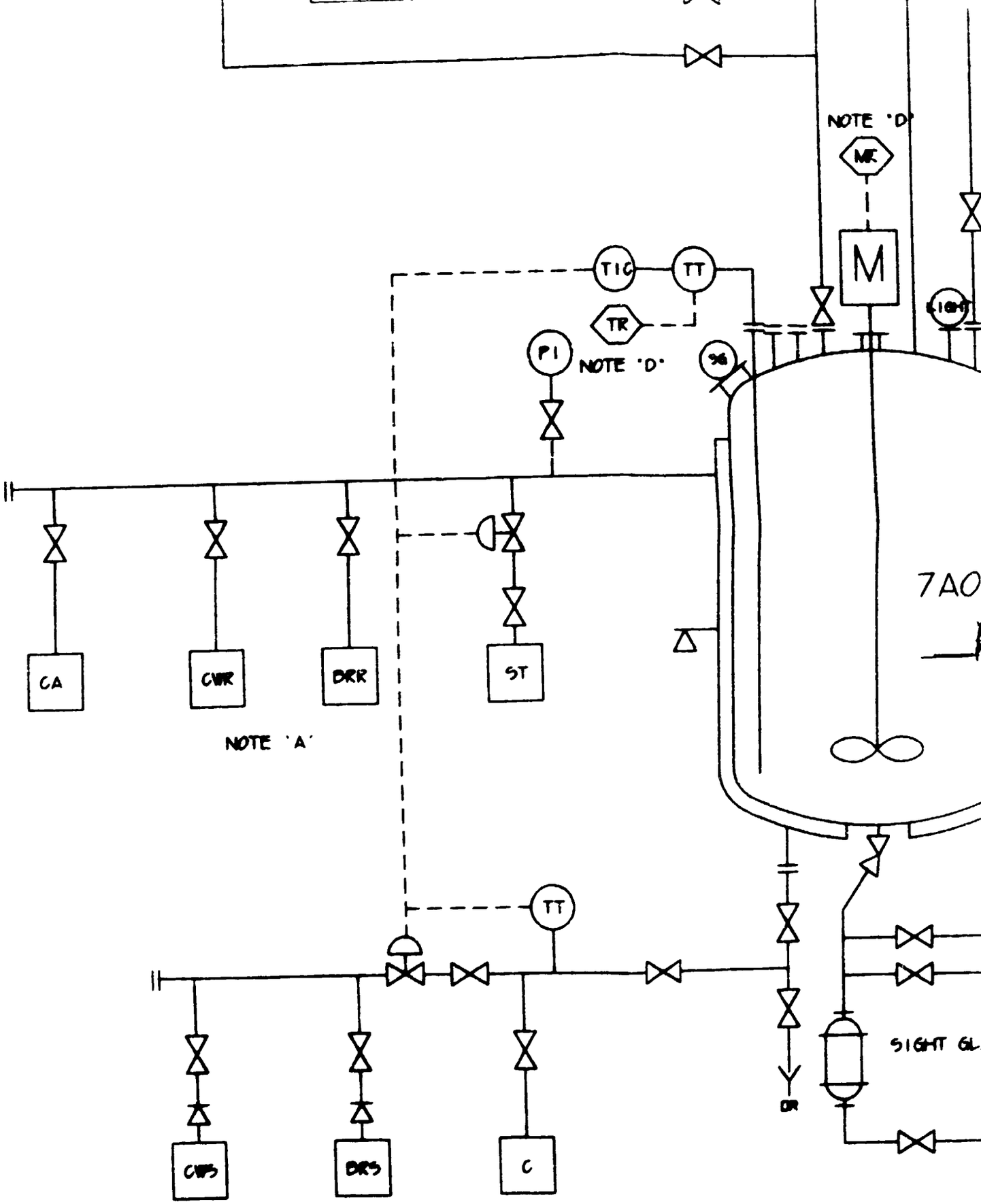
G. VESSEL ACCESS WAYS TO BE PROVIDED AS MANUFACTURERS STANDARD

H. BLANKED NOZZLES INCLUDED FOR POSSIBLE FUTURE USE AS FILL PORTS/CIP SYSTEM

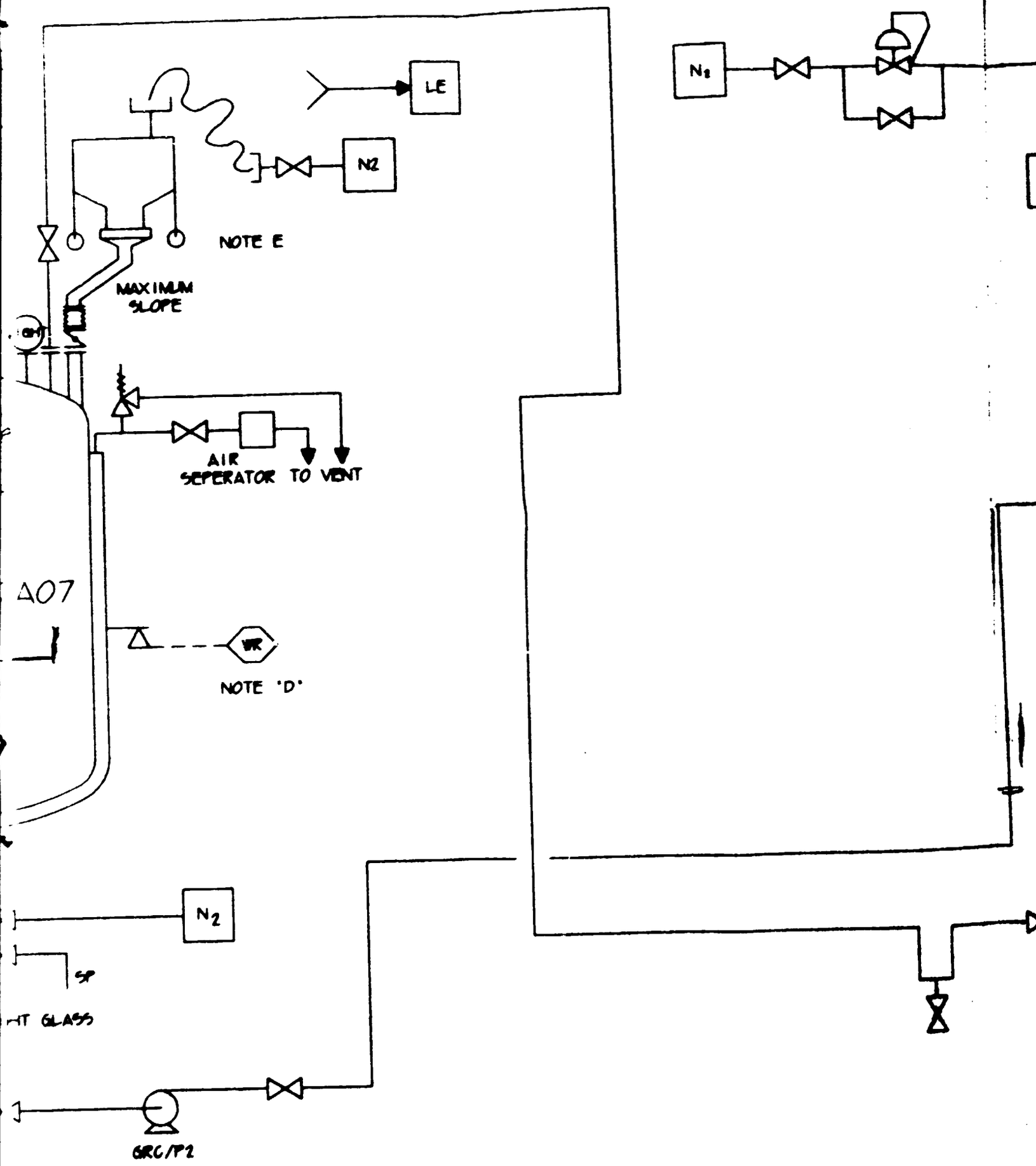
KEY

DM - BATCH METER
SC - SCRUBBER
FS - FLOW SWITCH
CWS - COOLING WATER SUPPLY
CWR - COOLING WATER RETURN
BRS - BRINE SUPPLY
BRR - BRINE RETURN
LE - LOCAL EXTRACTION
ST - STEAM
C - CONDENSATE
SP - SAMPLE POINT
HV - HIGH VACUUM
RV - ROUGH VACUUM

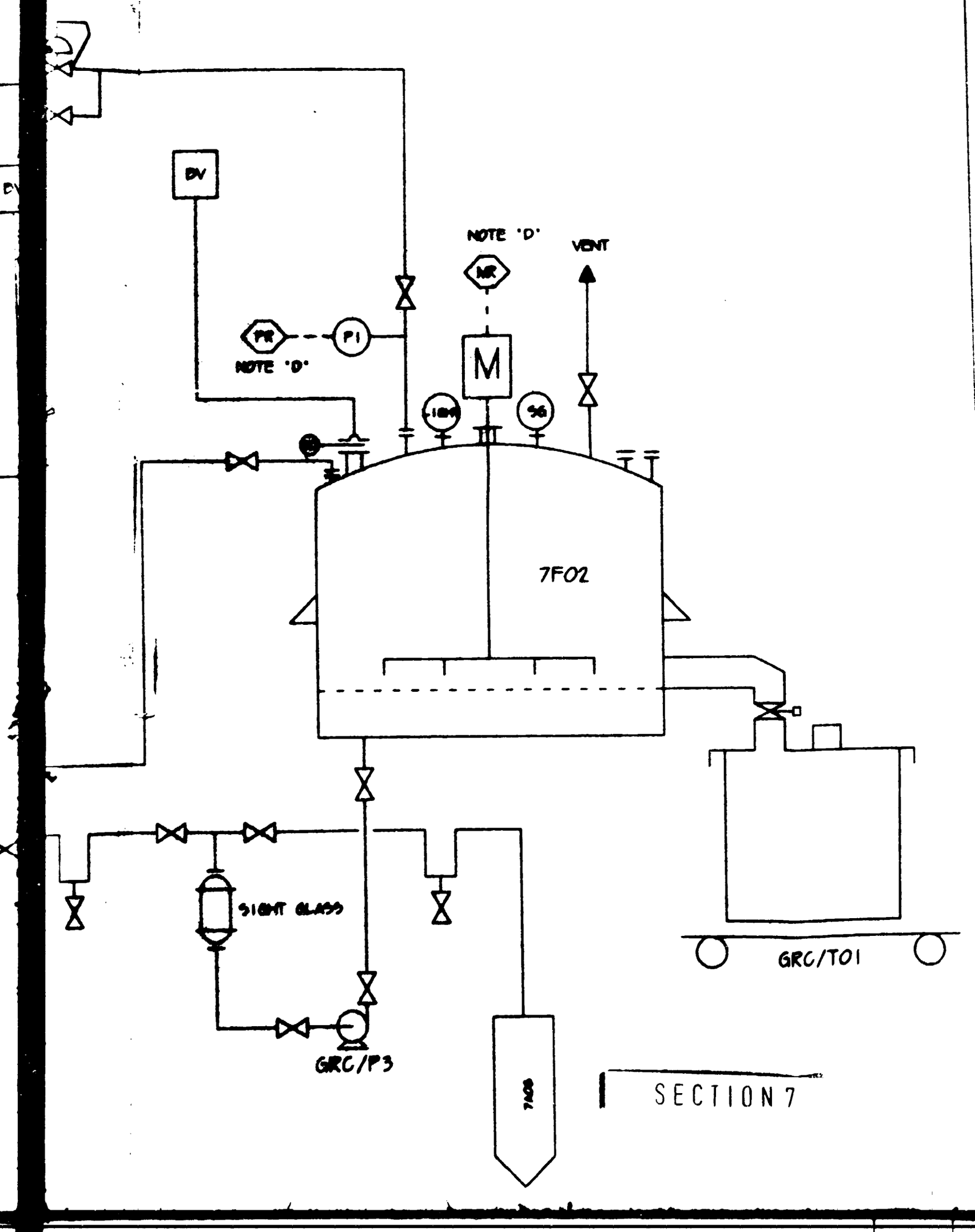



NOTE 'D'
MR
M
TIC
TT
TR
PI
NOTE 'D'
7AO
CA
CWR
DRR
ST
NOTE 'A'
TT
SIGHT GL
DR
CWS
DRS
C

SECTION 5


LE
N2
NOTE E
MAXIMUM SLOPE
AIR SEPERATOR TO VENT
Δ07
VR
NOTE 'D'
N2
SP
HT GLASS
GRC/P2
N2

SECTION 6


DV
NOTE 'D'
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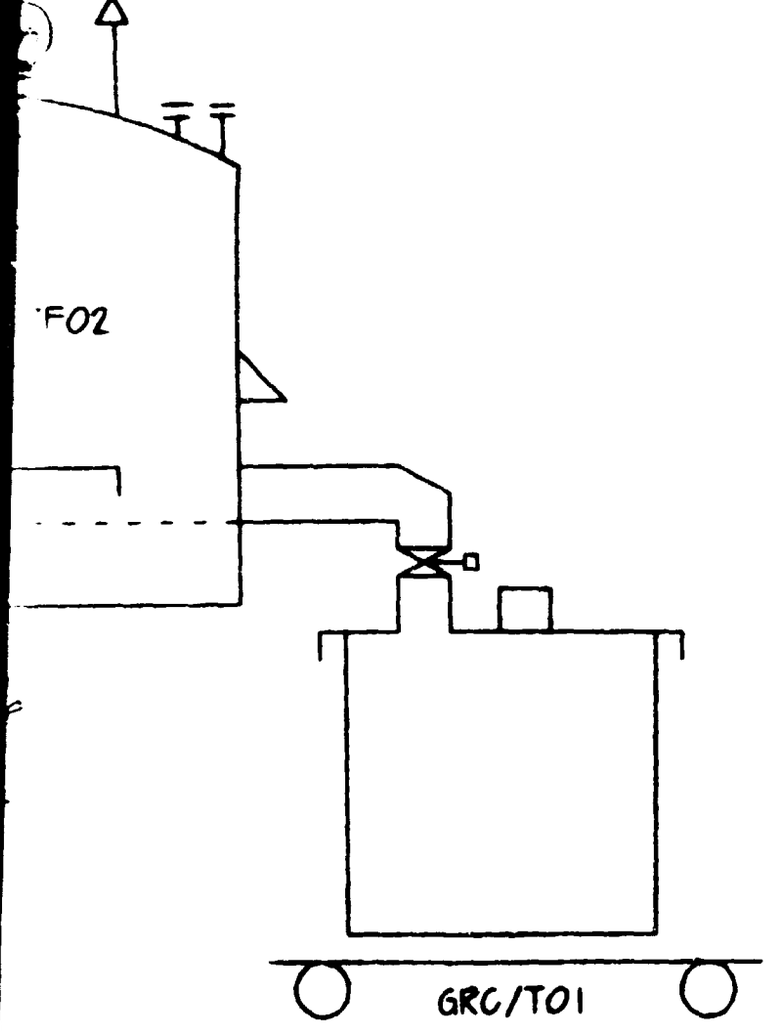
NR
PR
P1
NOTE 'D'
M
7F02
SIGHT GLASS
GRC/T01
GRC/P3
7X08

SECTION 7



SECTION 8

Rev	Date	Description	By
A	14/12/92	ISSUED WITH REPORT	HS

Client

UNIDO
P.O. BOX 300, A-1400 VIENNA,
AUSTRIA, FAX:232156

Project

ALKALOIDA 2
TF/HUN/90/910

Drawing Title

SUBSYSTEM 3
ENGINEERING LINE
DIAGRAM

GRC CONSULTANTS

WATERCRESS HOUSE
1 THE WINDMILLS ST MARY'S CLOSE,
ALTON HANTS GU34 1EF
TEL: 0420 89847 FAX: 0420 89427

Drawing Number	Scale	Rev
92/013/232	NTS	A

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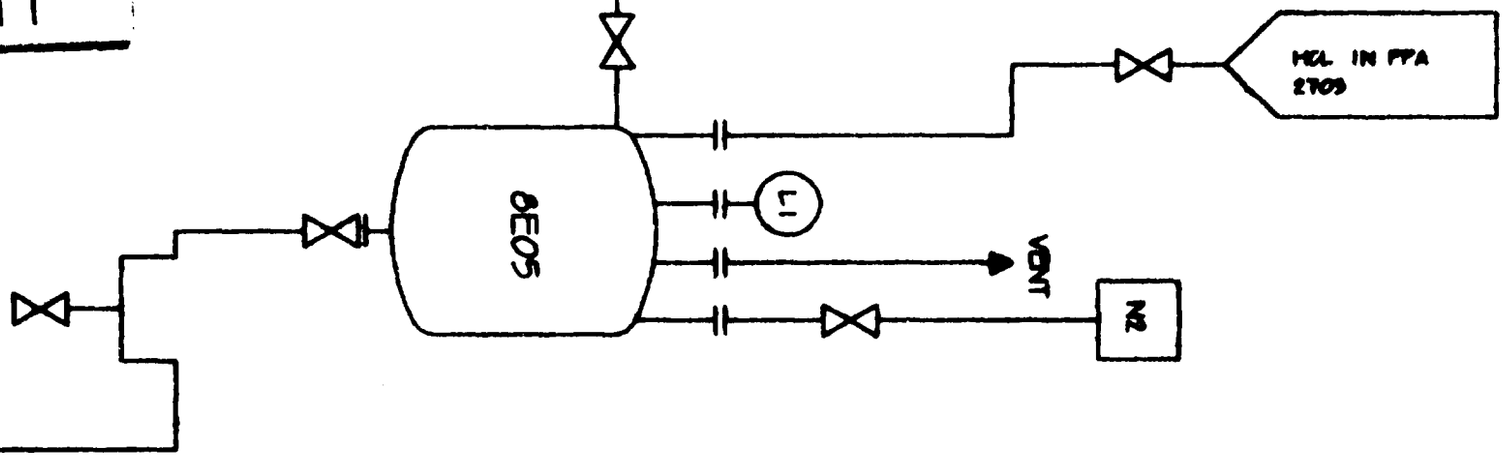

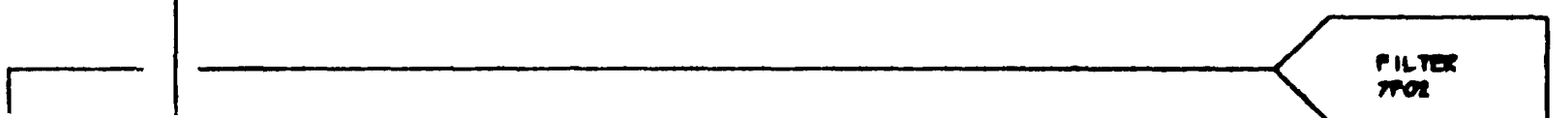

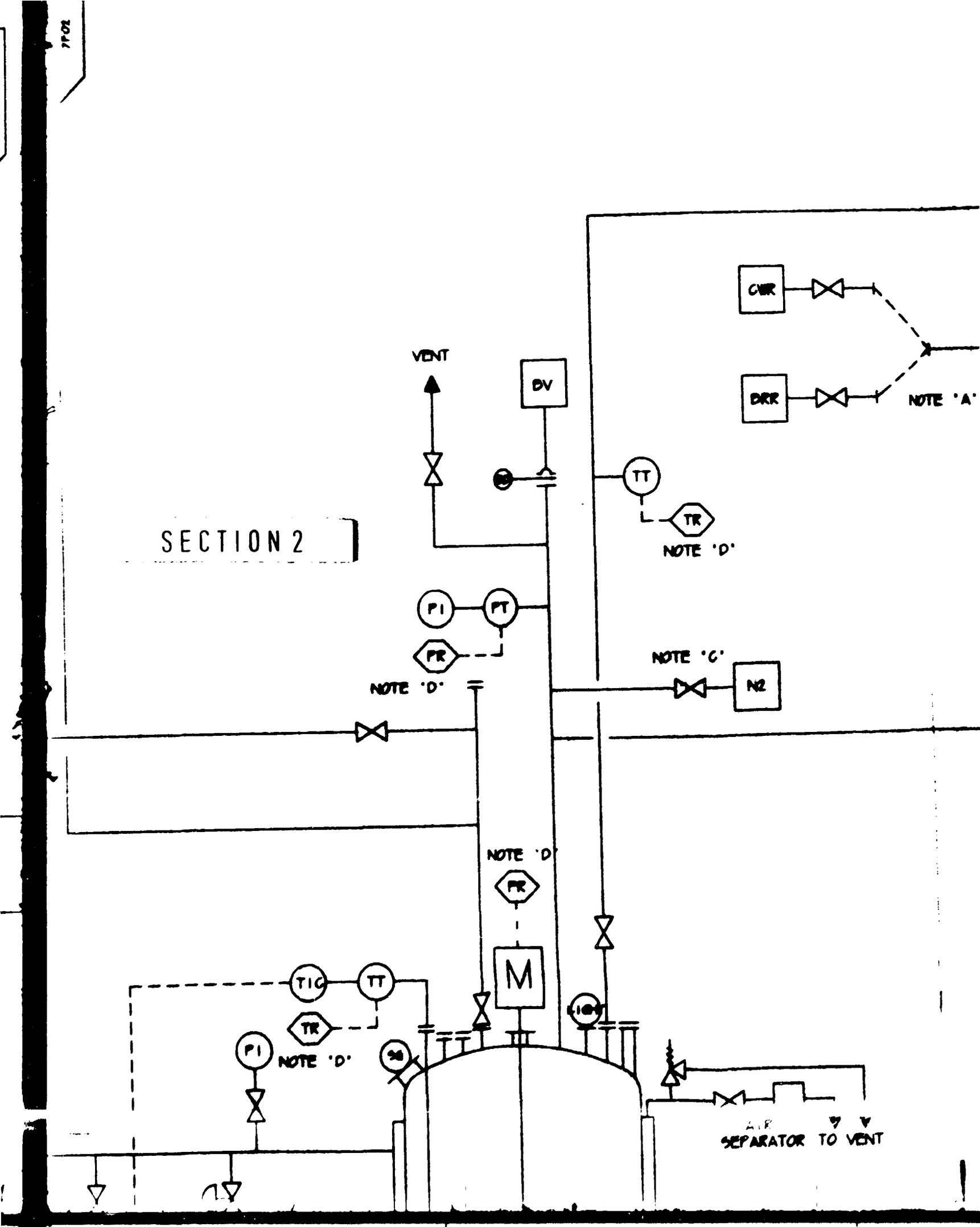
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GVR
DRR
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TT
TR
NOTE 'D'
PI
PT
PR
NOTE 'D'
NOTE 'C'
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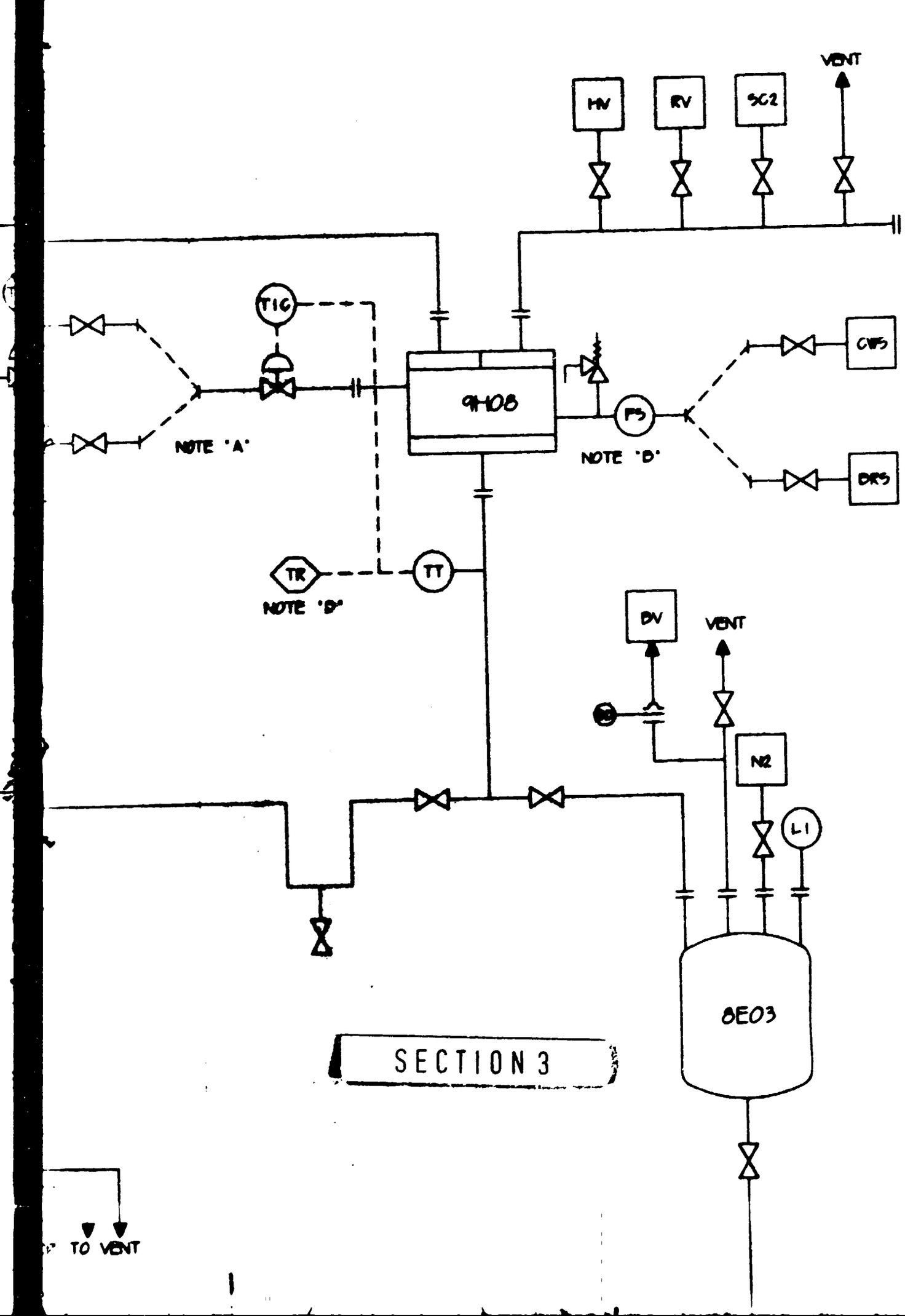
NOTE 'D'
PR
M
TIC
TT
TR
PI
NOTE 'D'
SEPARATOR
TO VENT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HV
RV
SG2
TIC
9H08
CVFS
FS
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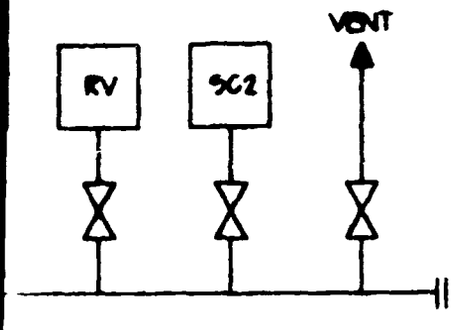
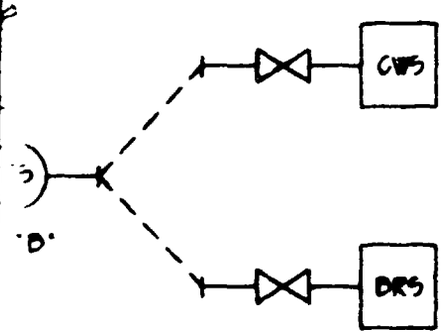
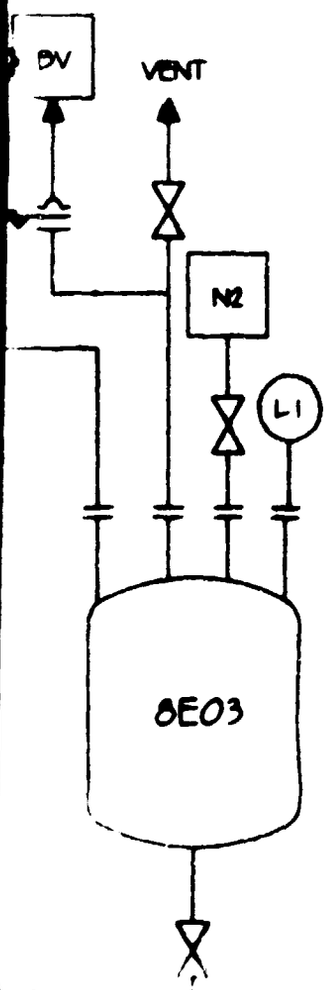
NOTE 'D'
DRFS
TR
NOTE 'D'
TT
DV
VENT
N2
LI
8E03
SECTION 3
TO VENT







NOTES

A. VALVE SYSTEMS ON VESSEL JACKET AND CONDENSER SERVICES COULD BE PHYSICALLY INTERLOCKED OR CONTROLLED VIA DEDICATED PLC

B. FLOW SWITCH TO DETECT LOW FLOW, CONNECTED TO SOUNDING ALARM

C. NITROGEN FOR PURGE OR PRESSURISATION.

D. SIGNAL TO DATA LOGGING COMPUTER.

E. ALL SERVICE CONNECTIONS SHOWN IN SQUARE FRAMES OTHER CONNECTIONS SHOWN IN ARROWED FRAMES.

F. VESSEL ACCESS WAYS TO BE PROVIDED AS MANUFACTURERS STANDARD

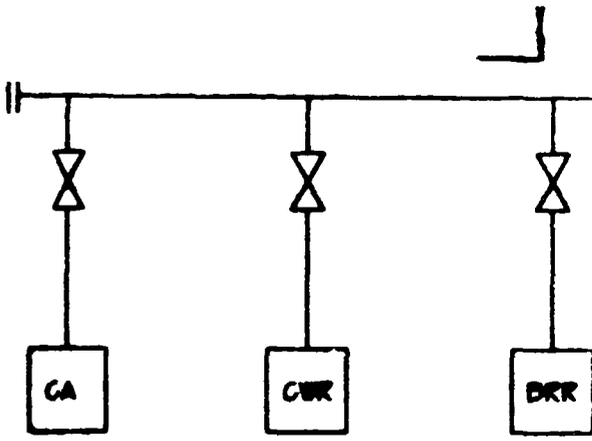
G. BLANKED NOZZLES INCLUDED FOR POSSIBLE FUTURE USE AS FILL PORTS/CIP SYSTEM

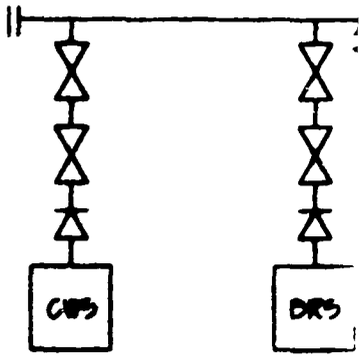
H. SOLIDS FEED MECHANISM TO BE DEFINED AT DETAILED DESIGN

KEY

BM - BATCH METER
SC2 - SCRUBBER 7L02
FS - FLOW SWITCH
CWS - COOLING WATER SUPPLY
CWR - COOLING WATER RETURN
DRS - BRINE SUPPLY
DRR - BRINE RETURN
LE - LOCAL EXTRACTION
ST - STEAM
C - CONDENSATE
SP - SAMPLE POINT
HV - HIGH VACUUM
RV - ROUGH VACUUM
BV - BURST VENT

SECTION 4

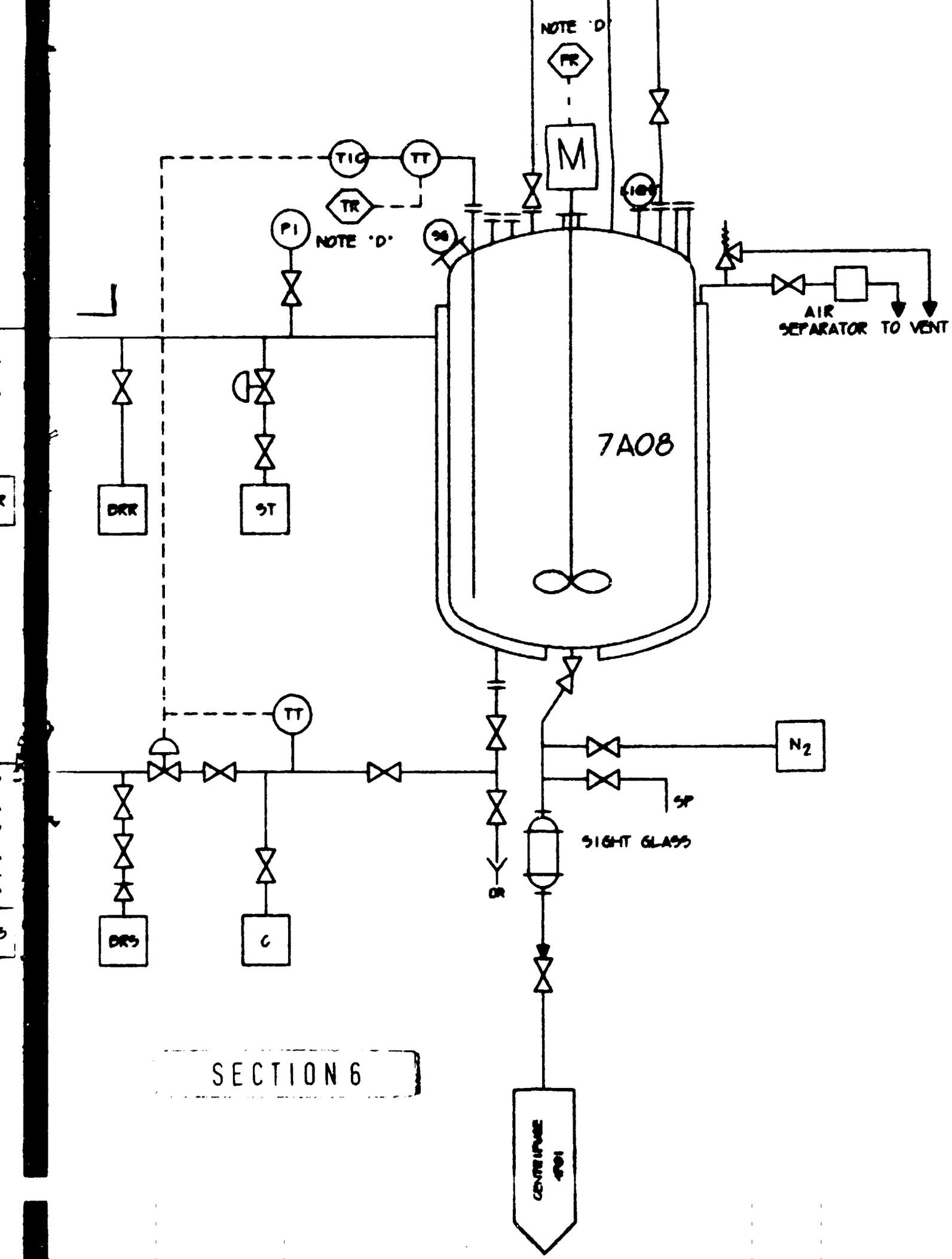




SECTION 5

OVERFLOW 2TO5

6906

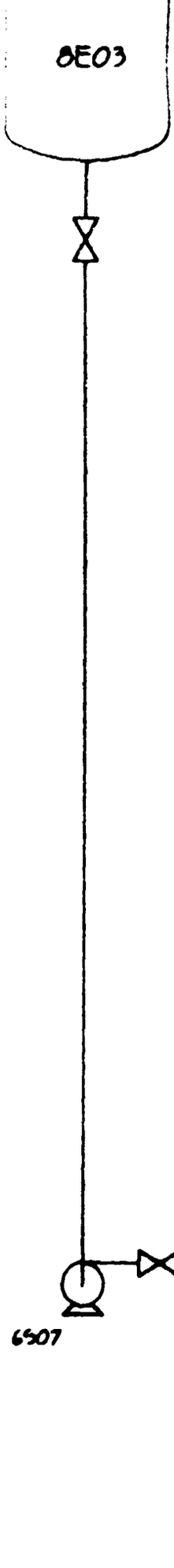

NOTE 'D'
FR
M
TIC
TT
TR
P1
NOTE 'D'
LIC
AIR SEPARATOR TO VENT
7A08
DRR
ST
TT
N2
SP
SIGHT GLASS
DR
DRS
C
SECTION 6
CENTRIFUGE 4701

8E03

TO VENT

SECTION 7

6507



SECTION 8

Rev	Date	Description	By
A	14/12/92	ISSUED WITH REPORT	HG

Client

UNIDO
P.O. BOX 300, A-1400 VIENNA,
AUSTRIA, FAX:232156

Project

ALKALOIDA 2
TF/HUN/90/910

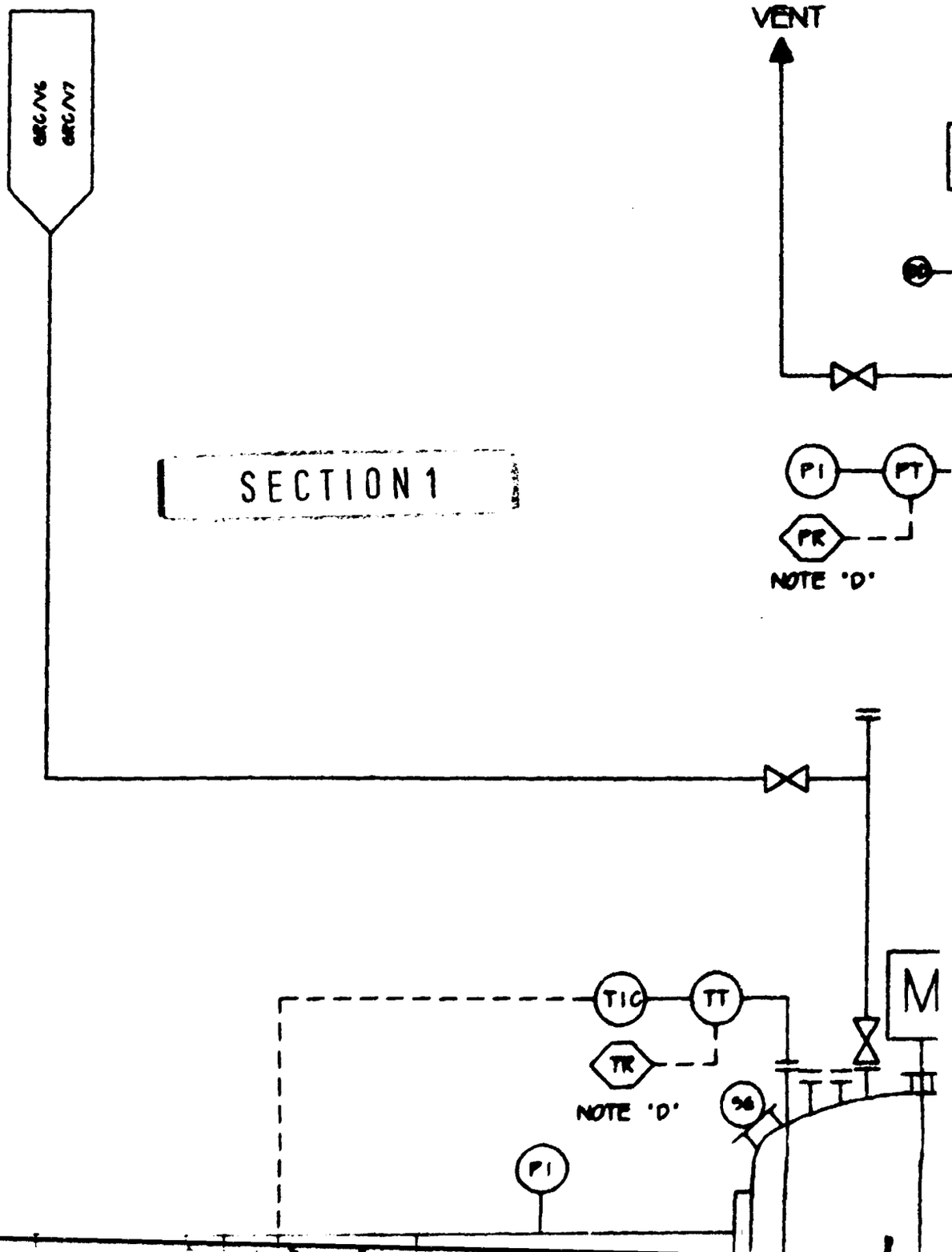
Drawing Title

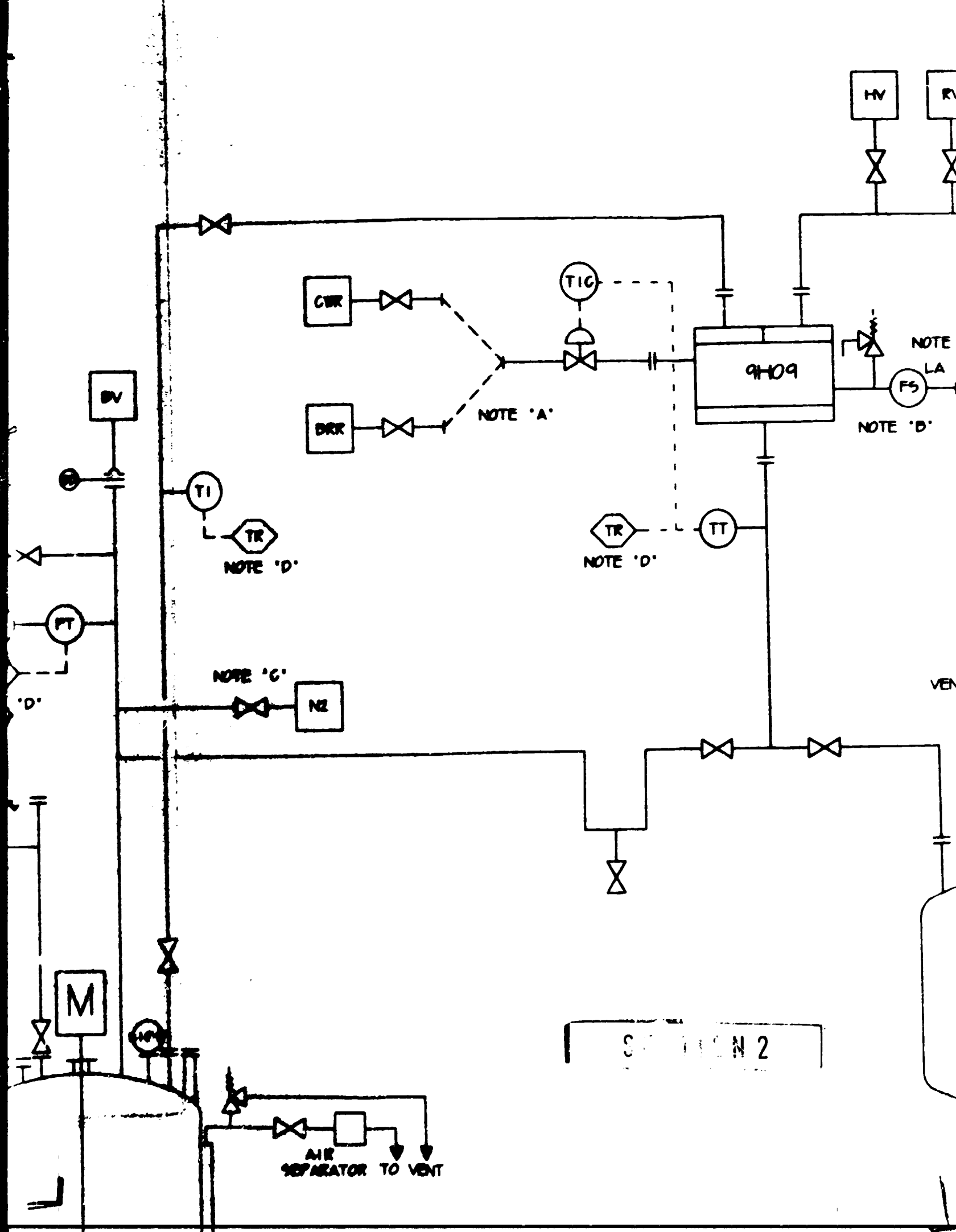
SUBSYSTEM 4 ENGINEERING LINE DIAGRAM

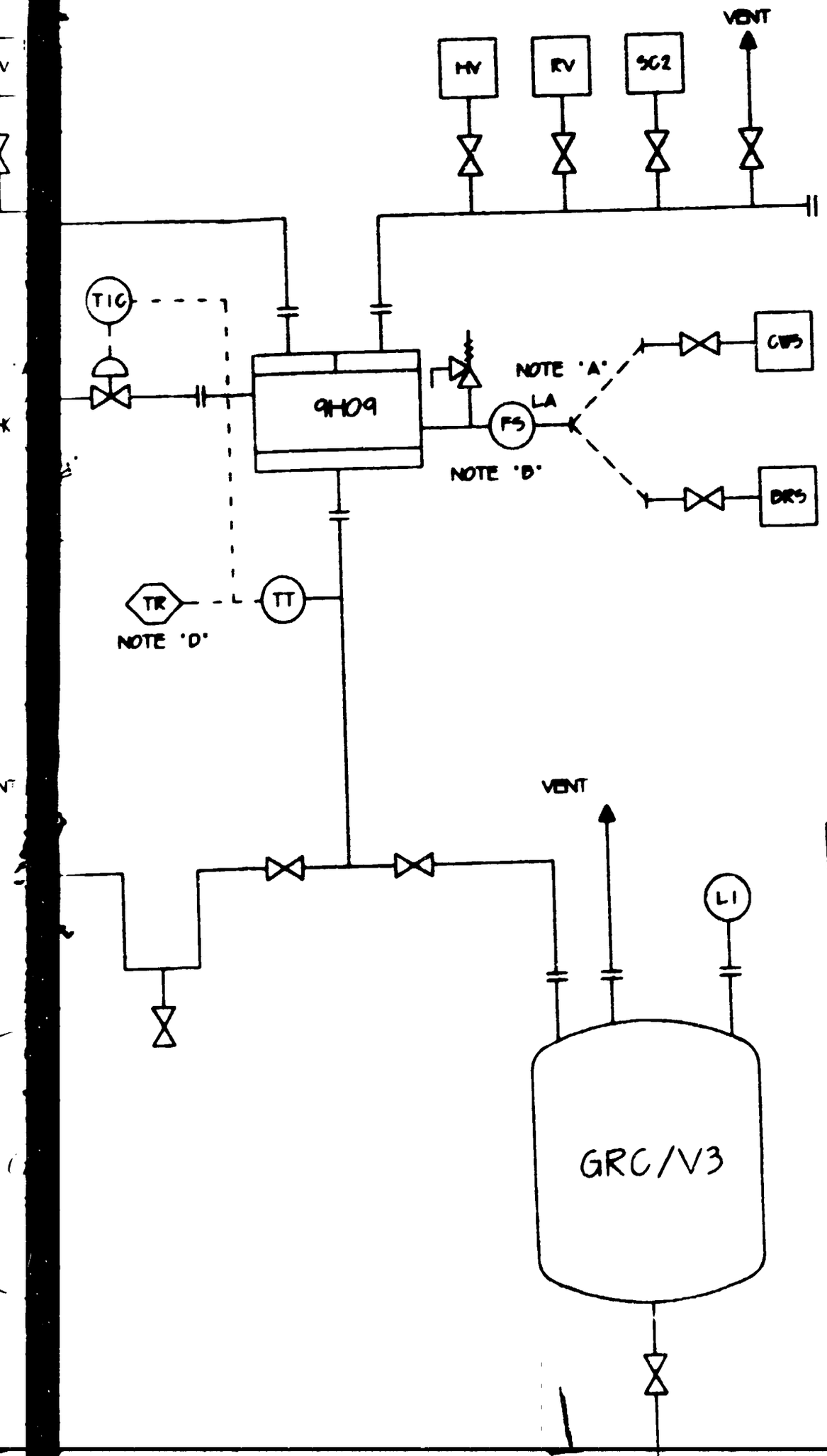
GRC CONSULTANTS

WATERCRESS HOUSE
1 THE WINDMILLS ST MARY'S CLOSE,
ALTON HANTS GU34 1EF
TEL: 0420 89647 FAX: 0420 89427

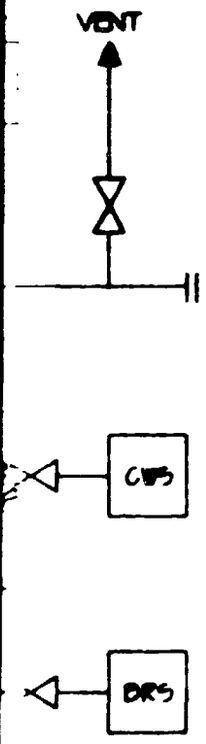
Drawing Number	Scale	Revision
92/013/233	NTS	A


VENT
SECTION 1
PI
PT
PR
NOTE 'D'
TIC
TT
TR
NOTE 'D'
PI


HV
CWR
TIC
DRR
NOTE 'A'
9H09
FS
NOTE 'D'
BV
TI
TR
NOTE 'D'
TR
TT
NOTE 'D'
FT
'D'
NOTE 'C'
N2
M
AIR SEPARATOR TO VENT


VENT
HV
RV
SC2
TIC
9H09
NOTE 'A'
LA
FS
NOTE 'B'
CVFS
DRS
TR
NOTE 'D'
TT
VENT
LI
GRC/V3

SECTION 3



NOTES

A. VALVE SYSTEMS ON VESSEL JACKET AND CONDENSER SERVICES COULD BE PHYSICALLY INTERLOCKED OR CONTROLLED VIA DEDICATED PLC.

B. FLOW SWITCH TO DETECT LOW FLOW, CONNECTED TO SOUNDING ALARM

C. NITROGEN FOR PURGE OR PRESSURISATION.

D. SIGNAL TO DATA LOGGING COMPUTER.

E. ALL SERVICE CONNECTIONS SHOWN IN SQUARE FRAMES OTHER CONNECTIONS SHOWN IN ARROWED FRAMES.

F. VESSEL ACCESS WAYS TO BE PROVIDED AS MANUFACTURERS STANDARD

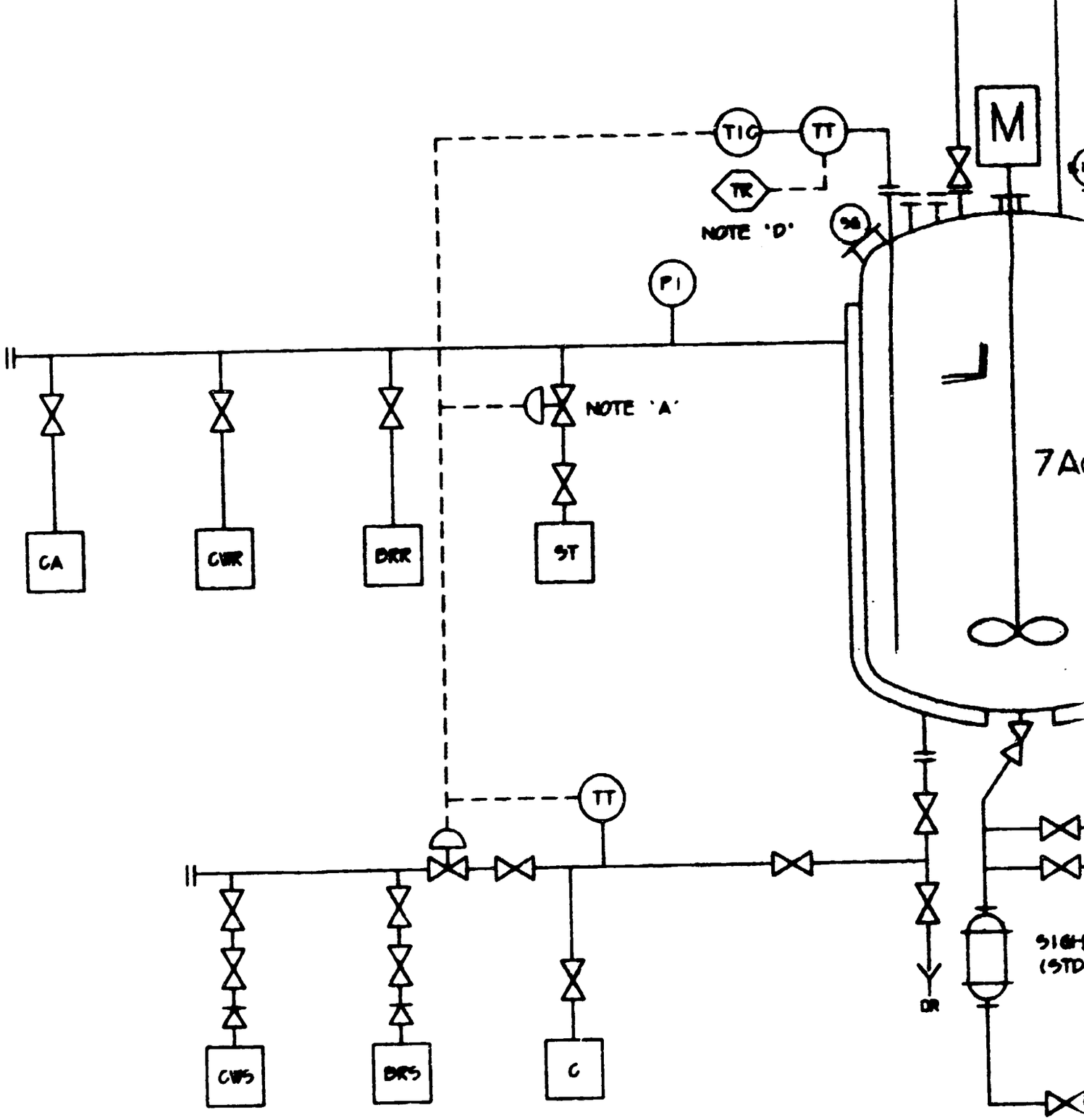
G. BLANKED NOZZLES INCLUDED FOR POSSIBLE FUTURE USE AS FILL PORTS/CIP SYSTEM

H. SOLIDS FEED MECHANISM TO BE DEFINED AT DETAILED DESIGN

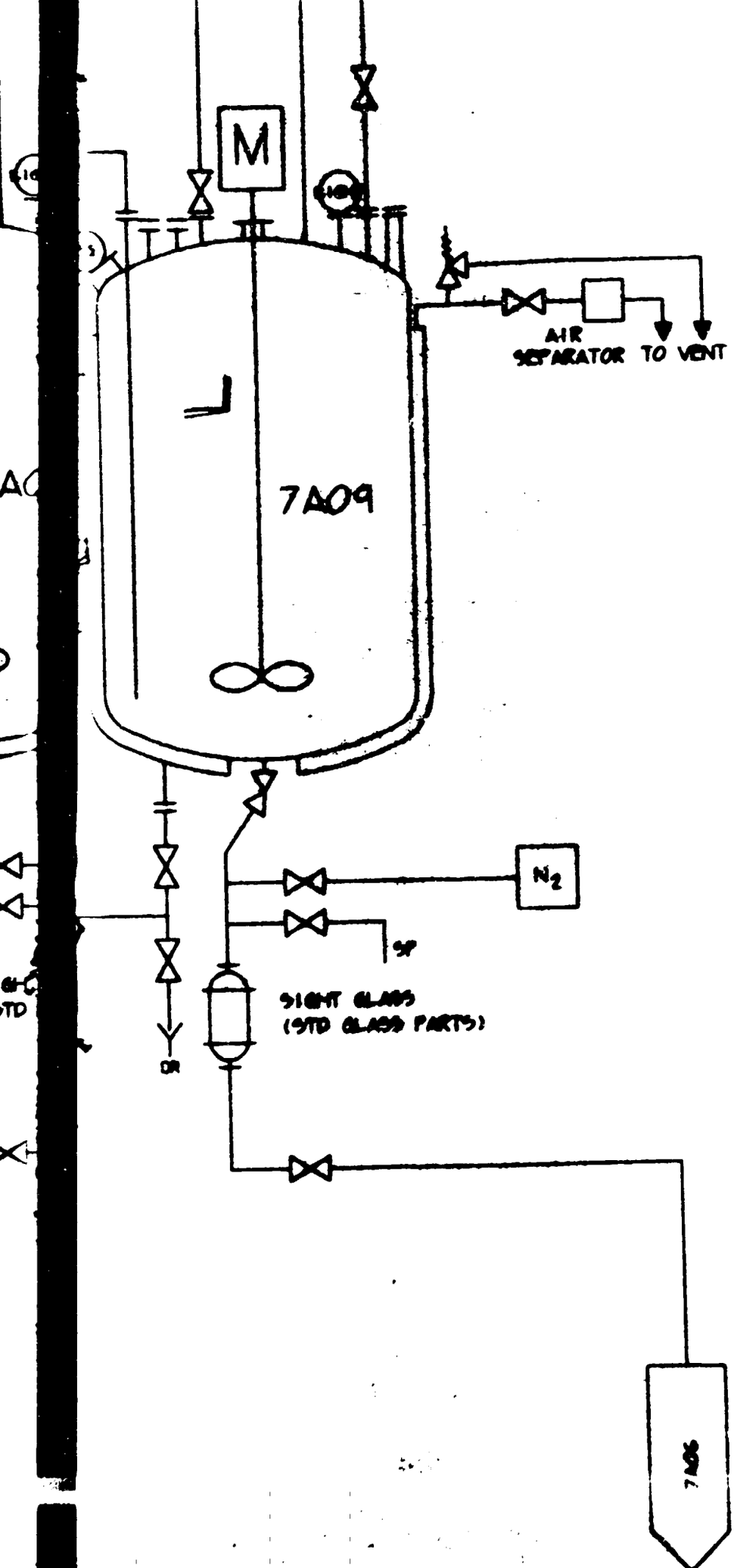
KEY

DM - DATCH METER
SC2 - SCRUBBER 7LO2
FS - FLOW SWITCH
CWS - COOLING WATER SUPPLY
CWR - COOLING WATER RETURN
DRS - DRINE SUPPLY
DRR - BRINE RETURN
LE - LOCAL EXTRACTION
ST - STEAM
C - CONDENSATE
SP - SAMPLE POINT
HV - HIGH VACUUM
RV - ROUGH VACUUM

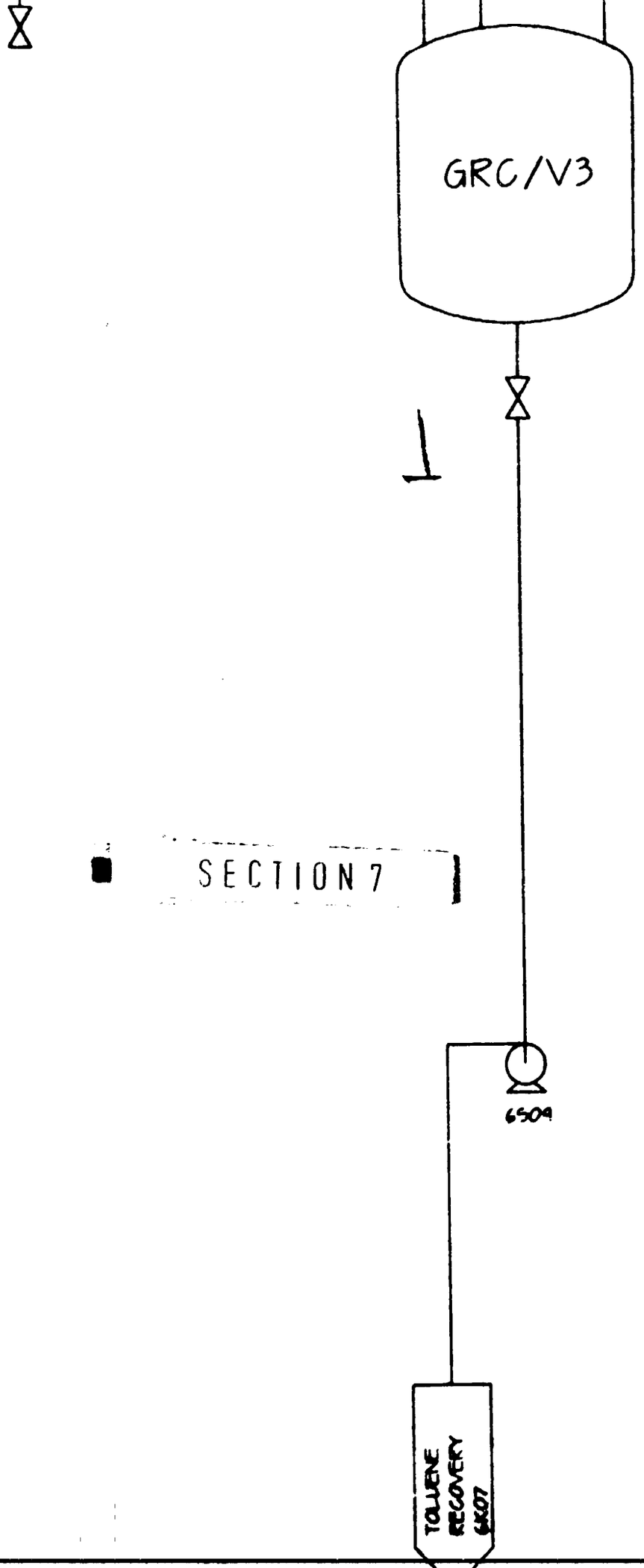
SECTION 4



SECTION 5


M
AIR
SEPARATOR
TO VENT
7A09
N_2
SP
SIGHT GLASS
(STD GLASS PARTS)
DR
7A06

SECTION 6



SECTION 7

Rev	Date	Description	By
A	14/12/92	ISSUED WITH REPORT	HS

Client

UNIDO
P.O. BOX 300, A-1400 VIENNA,
AUSTRIA, FAX:232156

Project

ALKALOIDA 2
TF/HUN/90/910

Drawing Title

SUBSYSTEM 5
ENGINEERING LINE
DIAGRAM

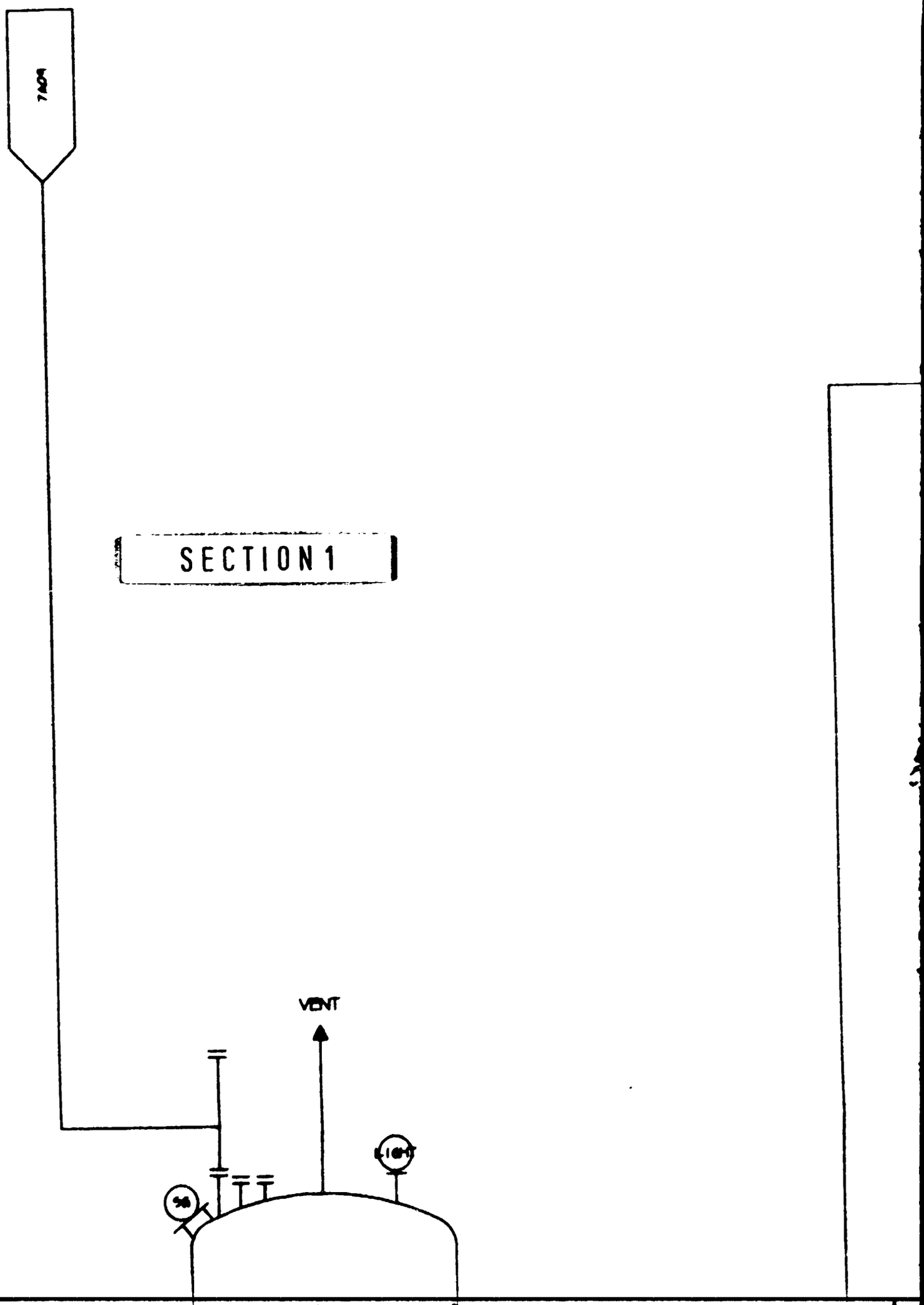
SECTION 8

GRC CONSULTANTS

WATERCRESS HOUSE
1 THE WINDMILLS ST MARY'S CLOSE,
ALTON HANTS GU34 1EF
TEL: 0420 89847 FAX: 0420 89427

Drawing Number

92/013/234 | NTS | A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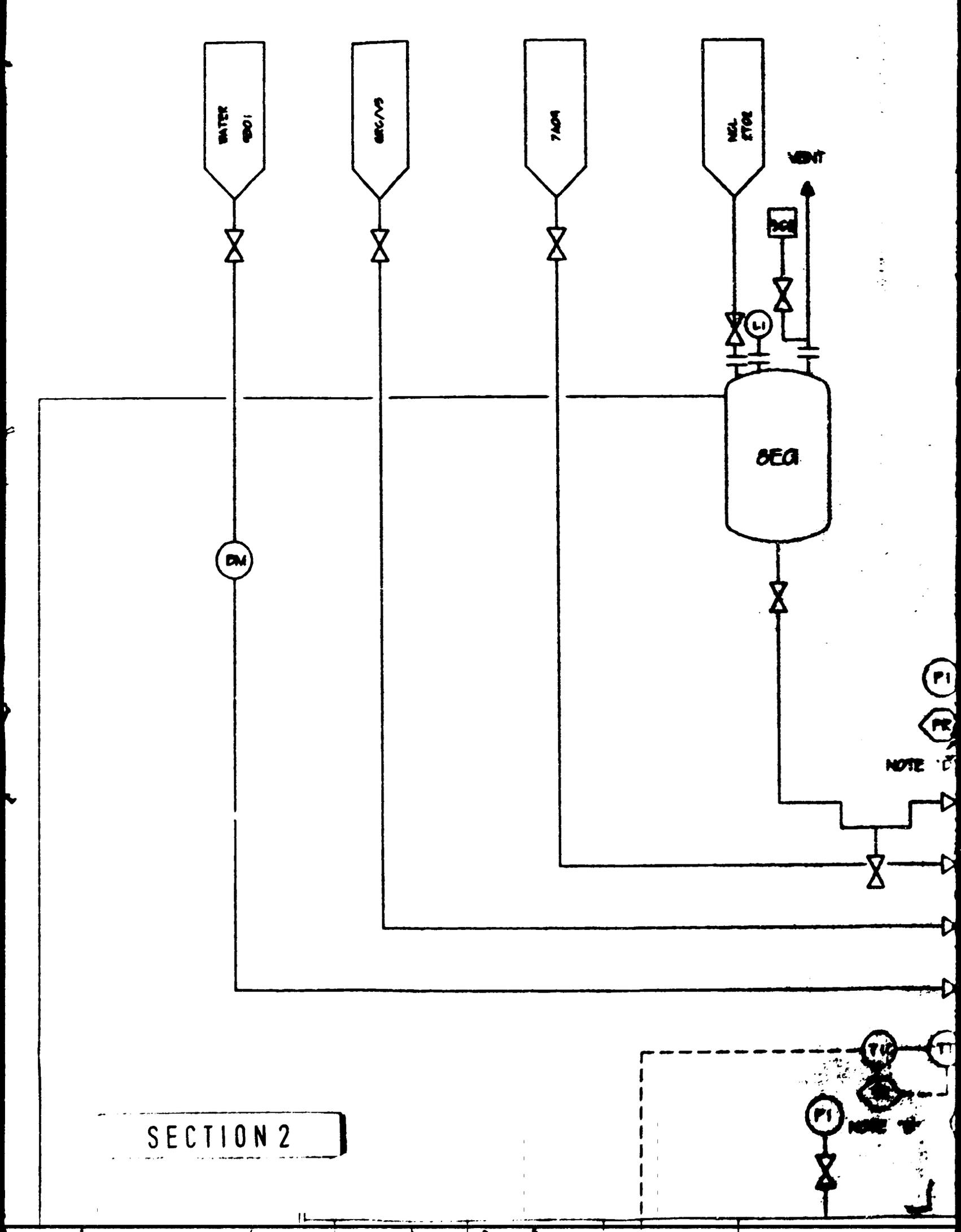
VENT



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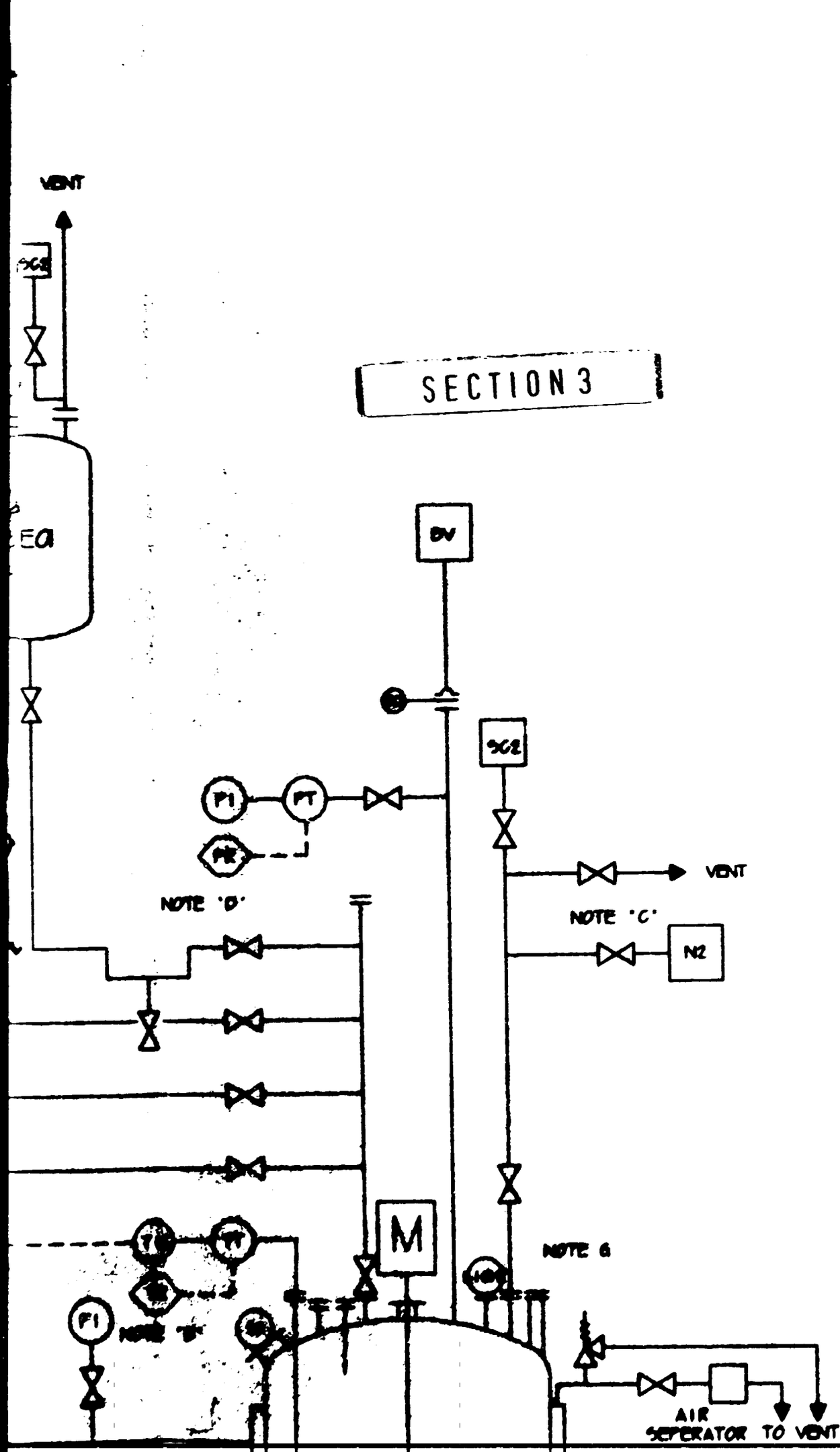

VENT
SECTION 3
EQ
DV
SCE
PI
PT
PE
VENT
NOTE 'D'
NOTE 'C'
N2
M
NOTE 6
TI
TT
TE
FI
AIR
SEPERATOR
TO VENT

NOTES

A. VALVE SYSTEMS ON VESSEL JACKET COULD BE PHYSICALLY INTERLOCKED OR CONTROLLED VIA DEDICATED PLC.

B. ALL SERVICE CONNECTIONS SHOWN IN SQUARE FRAMES OTHER CONNECTIONS SHOWN ARROWED FRAMES.

C. NITROGEN FOR PURGE OR PRESSURISATION.

D. SIGNAL TO DATA LOGGING COMPUTER.

E. VESSEL ACCESS WAYS TO BE PROVIDED AS MANUFACTURERS STANDARD

F. BLANKED NOZZLES INCLUDED FOR POSSIBLE FUTURE USE AS FILL PORTS/CIP SYSTEM

G. SOLIDS FEED MECHANISM TO BE DEFINED AT DETAILED DESIGN

SECTION 4

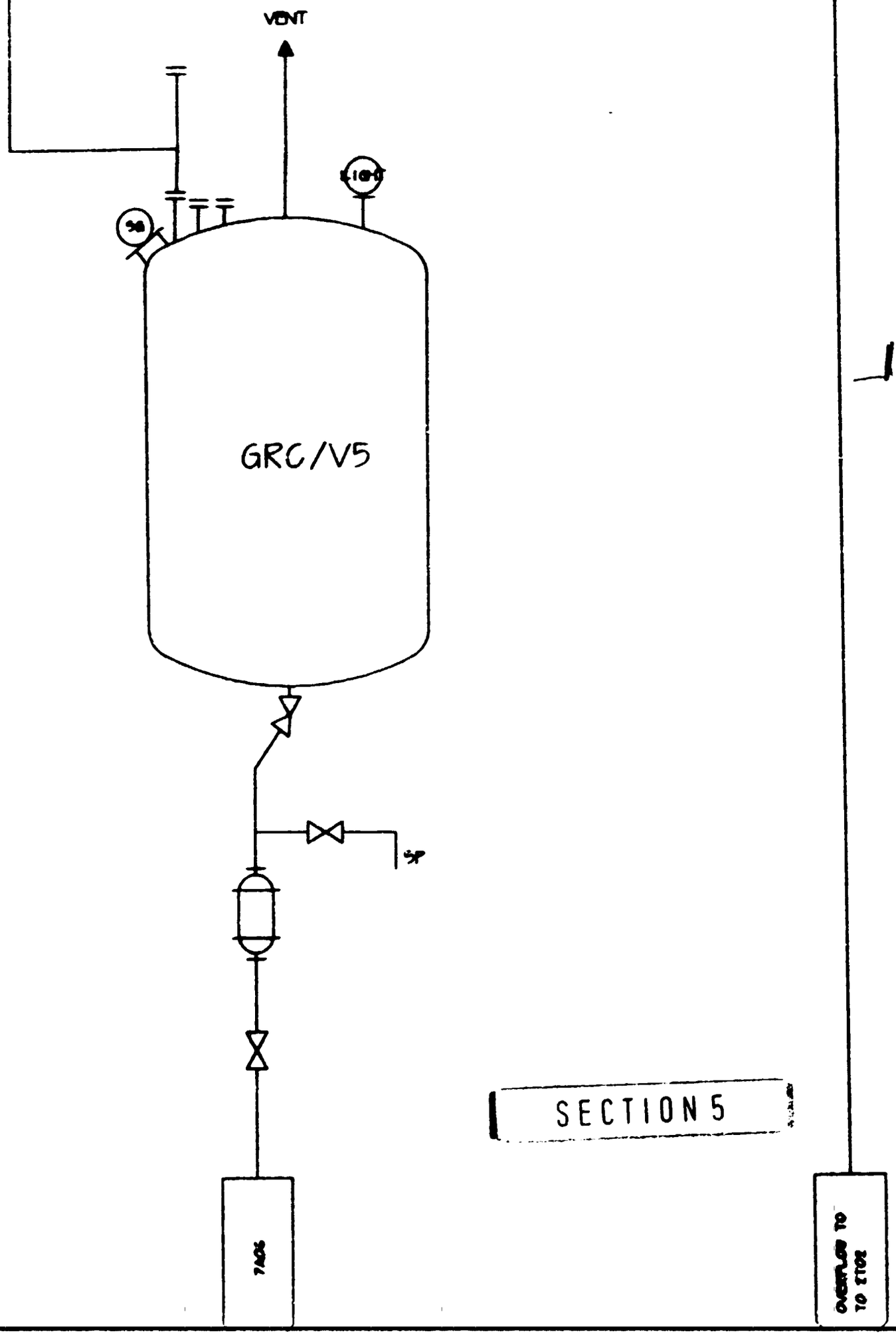
KEY

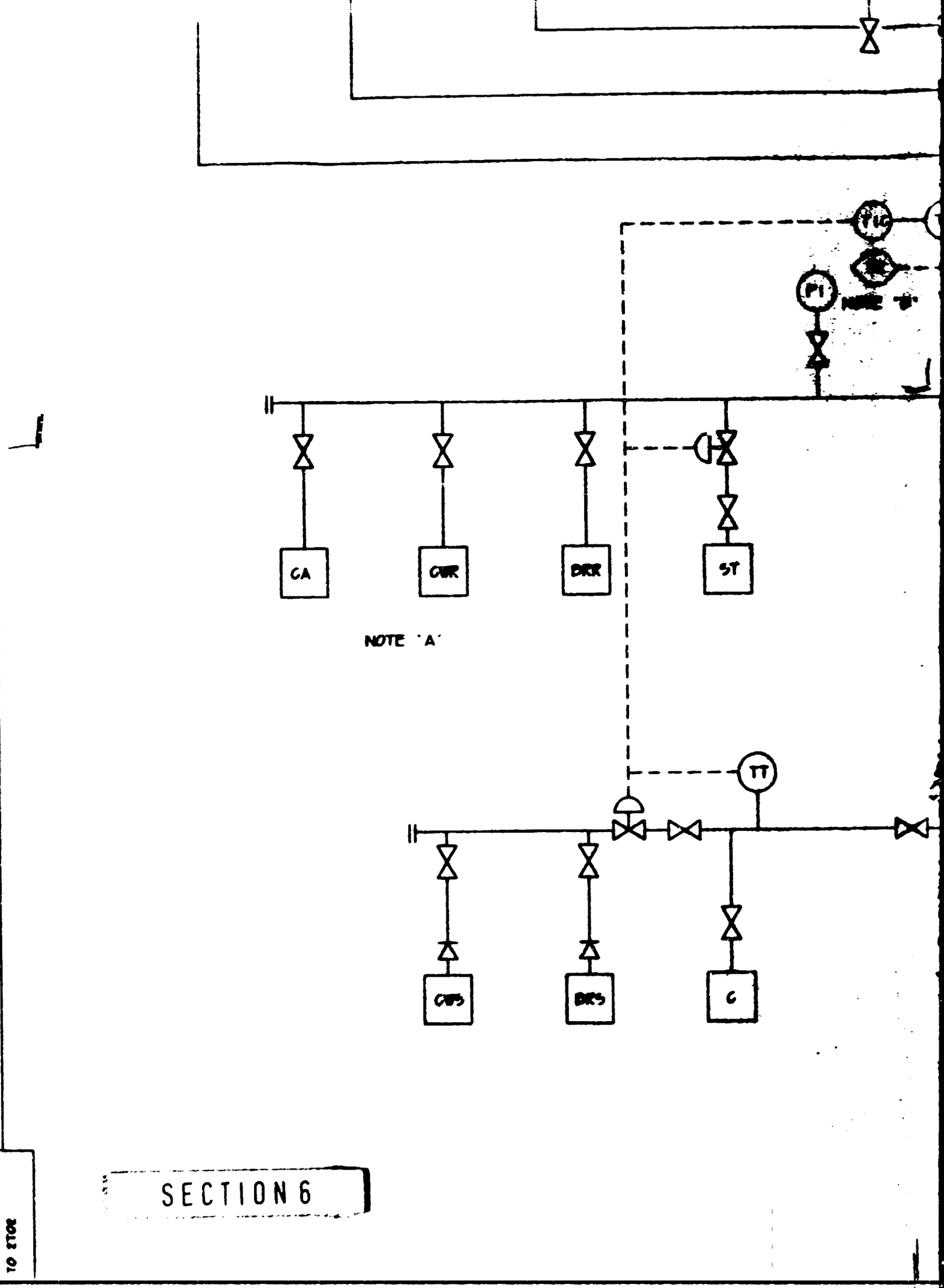
BM - BATCH METER
SG2 - SCRUBBER FLO2
FS - FLOW SWITCH
CWS - COOLING WATER SUPPLY
CWR - COOLING WATER RETURN
BRS - BRINE SUPPLY
BRR - BRINE RETURN
LE - LOCAL EXTRACTION
ST - STEAM
C - CONDENSATE
SP - SAMPLE POINT
HV - HIGH VACUUM
RV - ROUGH VACUUM

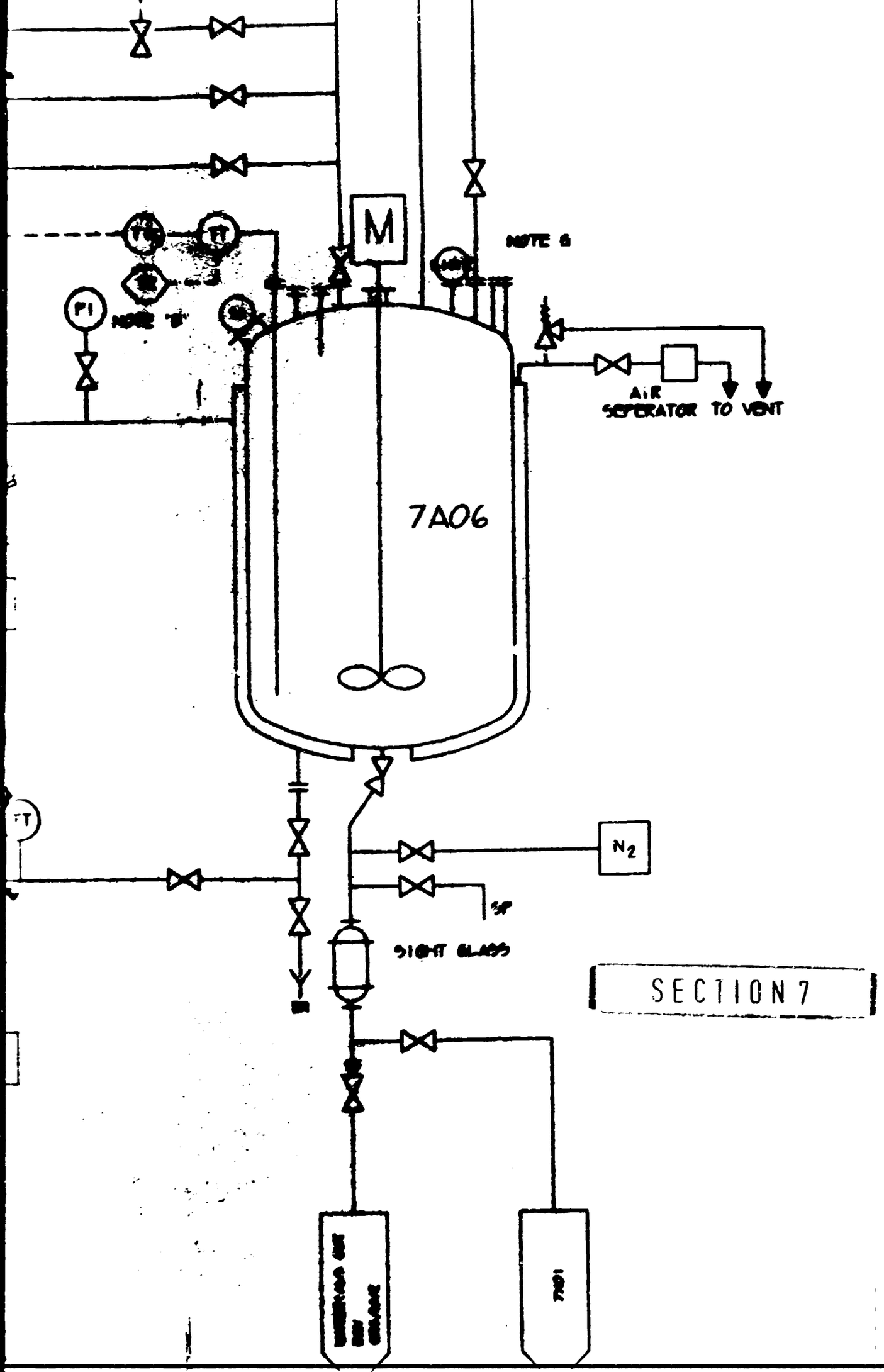
VENT

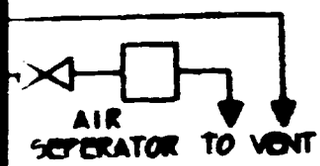
'C'

N2


VENT
GRC/V5
SP
SECTION 5


PIC
PI
CA
CWR
DRR
ST
NOTE 'A'
TT
CWS
DRS
C
OVERFLOW TO
TO ETOX
SECTION 6


M
NOTE 6
FI
NOTE 7
AIR
SEPERATOR TO VENT
7A06
N_2
SIGHT GLASS
SECTION 7



N_2

SECTION 8

Rev	Date	Description	By
A	14/12/92	ISSUED WITH REPORT	HS

Client

UNIDO
P.O. BOX 300, A-1400 VIENNA,
AUSTRIA, FAX:232156

Project

ALKALOIDA 2
TF/HUN/90/910

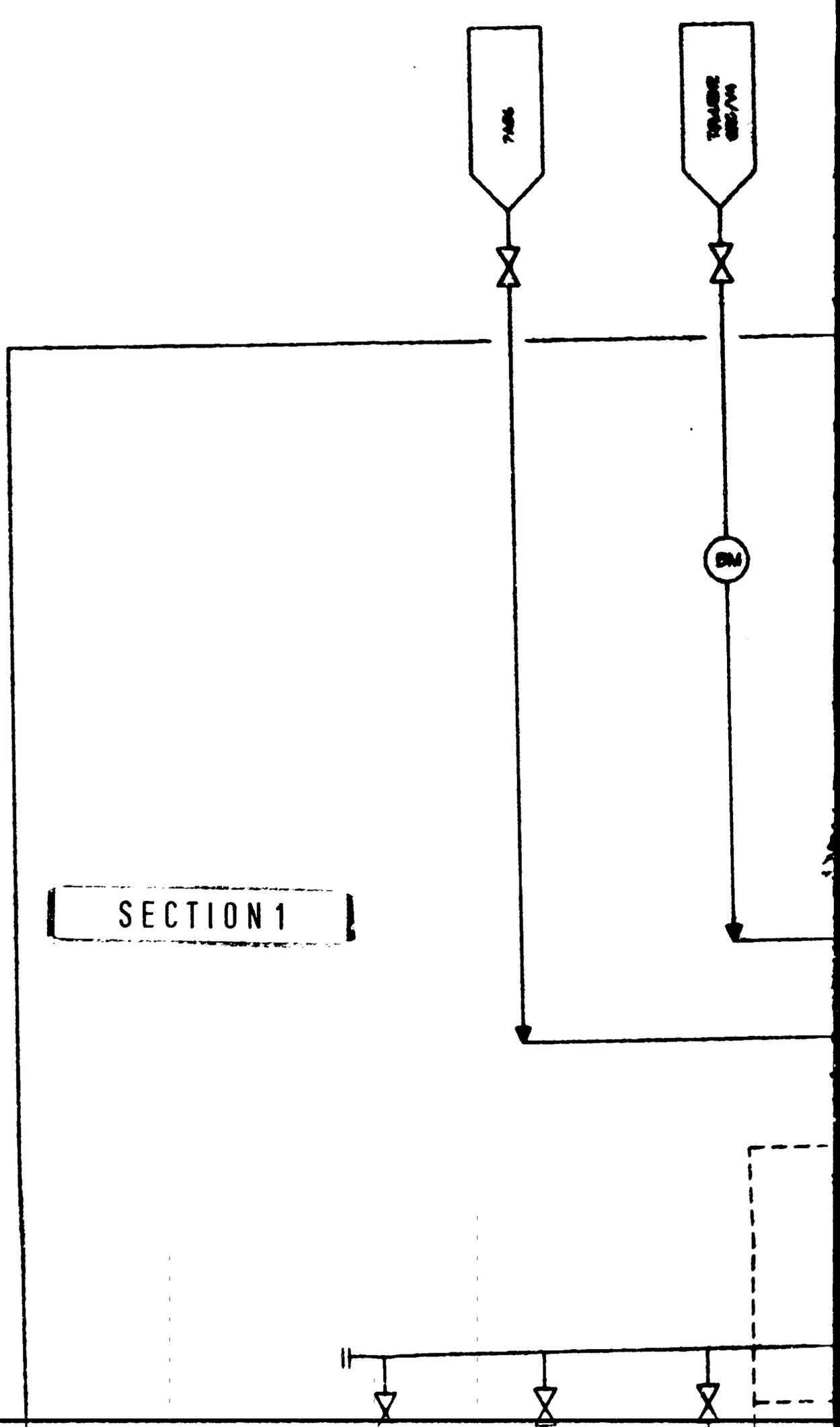
Drawing Title

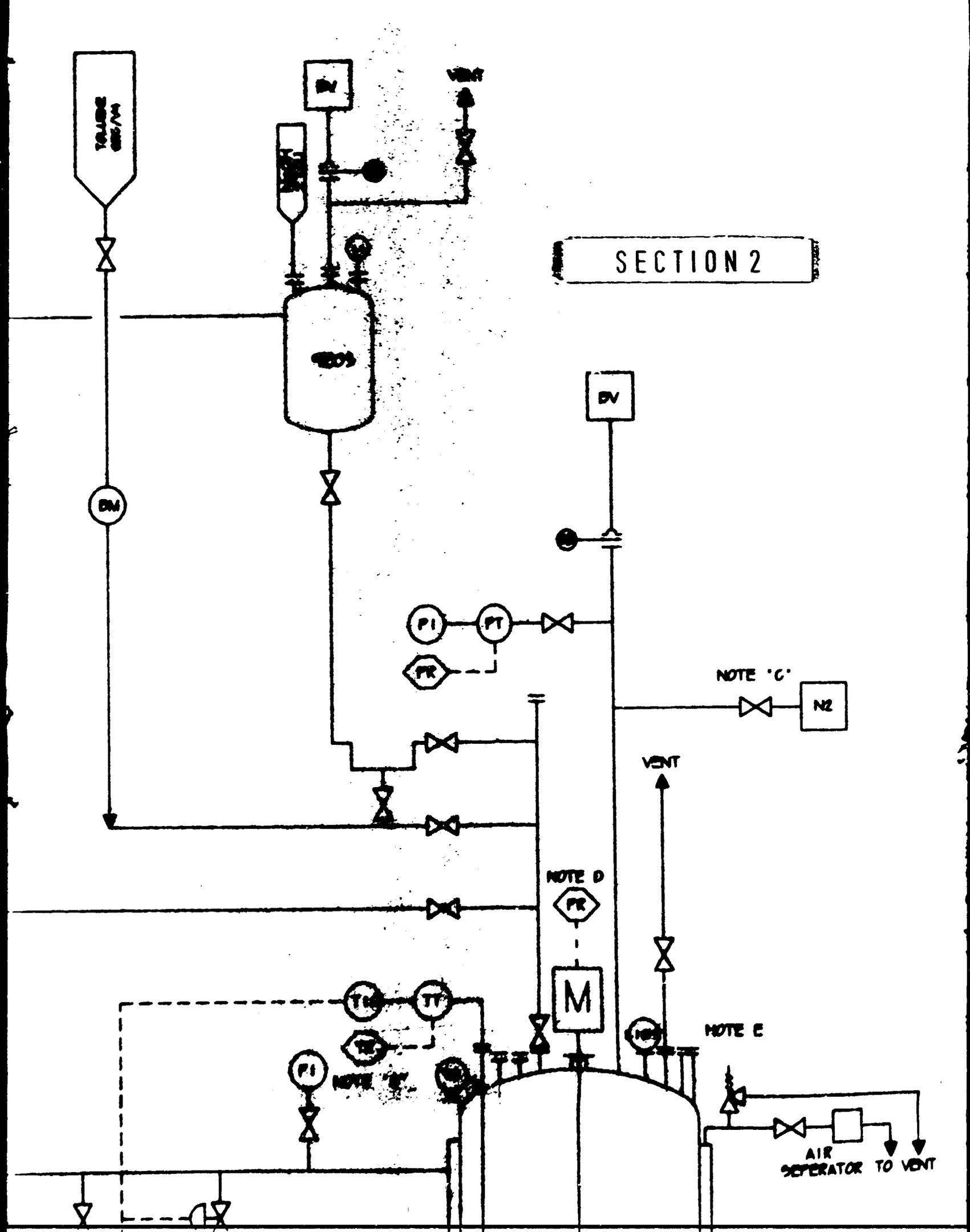
SUBSYSTEM 6
ENGINEERING LINE
DIAGRAM

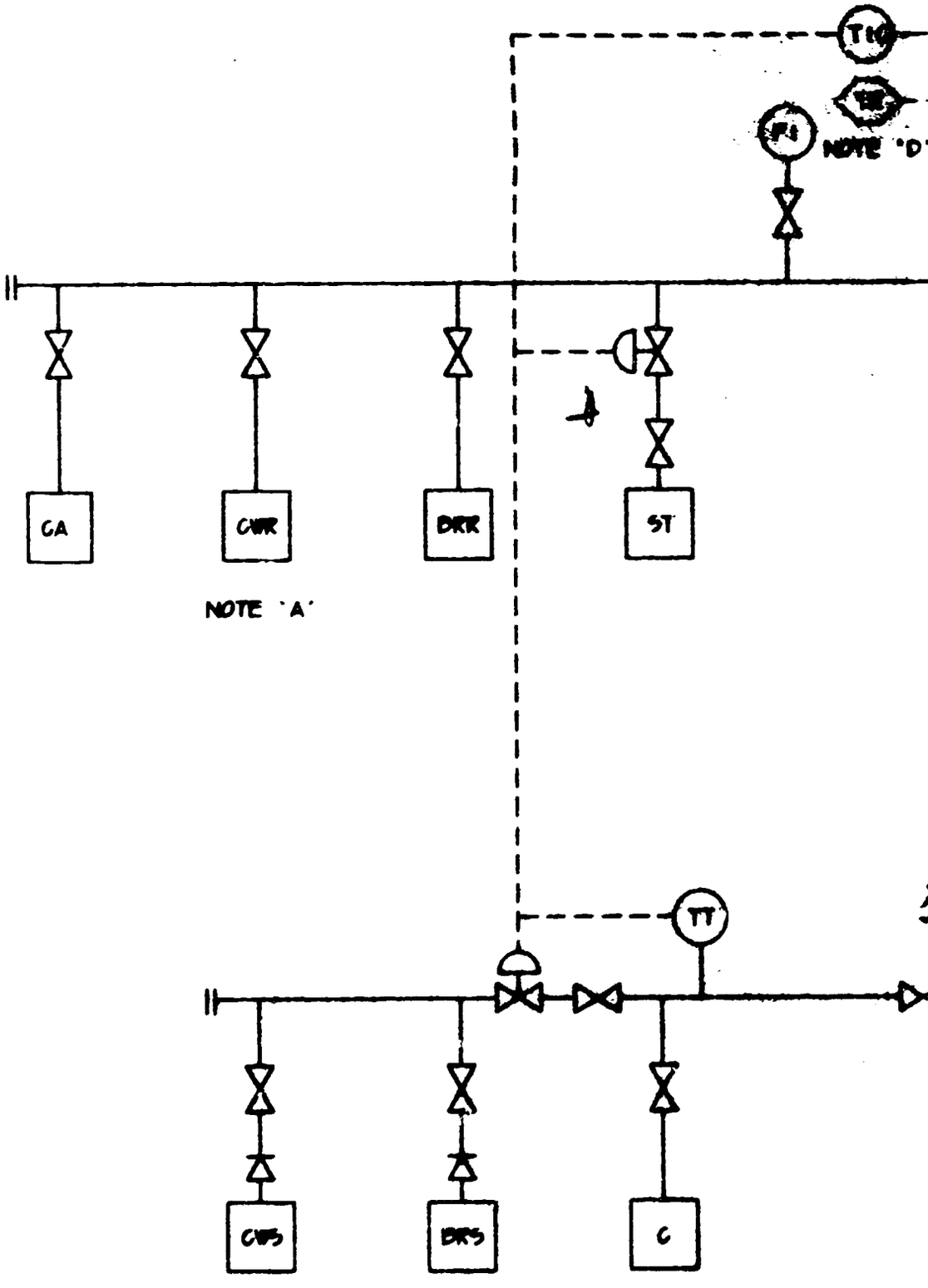
GRC CONSULTANTS

WATERCRESS HOUSE
1 THE WINDMILLS ST MARY'S CLOSE,
ALTON HANTS GU34 1EF
TEL: 0420 89847 FAX: 0420 89427

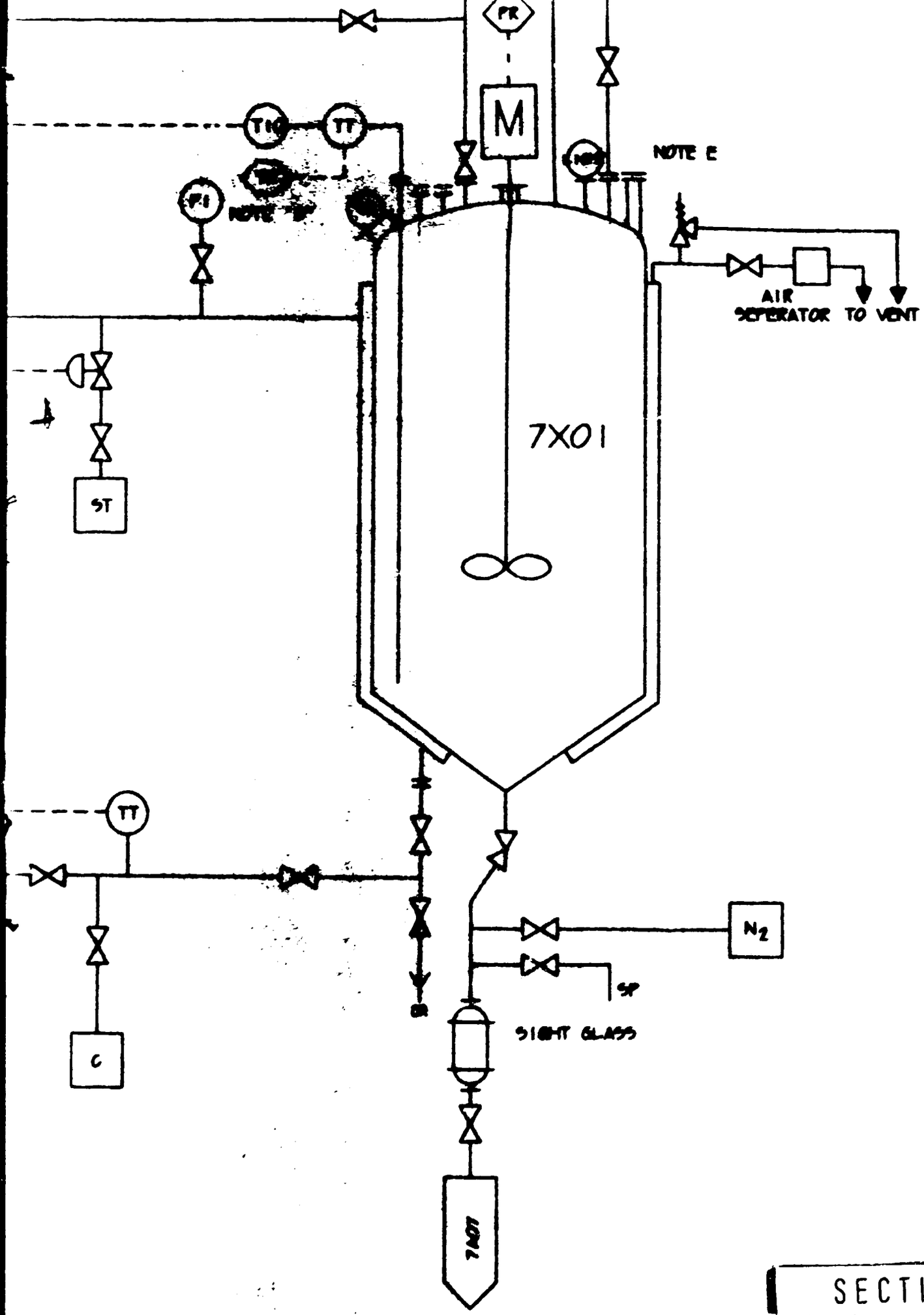
Drawing Number	Scale	Revision
92/013/235	NTS	A


SECTION 1


SECTION 2
DV
DV
PI
PT
PR
NOTE 'C'
N2
VENT
NOTE D
PR
M
TR
TT
TE
PI
NOTE 'B'
NOTE E
AIR
SEPERATOR
TO VENT



OVERFLOW 2TO1


PR
M
TIC
TT
FI
NOTE E
AIR
SEPERATOR TO VENT
7X01
ST
TT
C
N_2
SP
SIGHT GLASS
TO

SECTION 4

NOTES

A. VALVE SYSTEMS ON VESSEL JACKET AND CONDENSER SERVICES COULD BE PHYSICALLY INTERLOCKED OR CONTROLLED VIA DEDICATED PLC.

B. ALL SERVICE CONNECTIONS SHOWN IN SQUARE FRAMES OTHER CONNECTIONS SHOWN IN ARROWED FRAMES.

C. NITROGEN FOR PURGE OR PRESSURISATION.

D. SIGNAL TO DATA LOGGING COMPUTER.

E. SOLIDS FEED ARRANGEMENT TO BE CONFIRMED AT DETAILED DESIGN

F. VESSEL ACCESS WAYS TO BE PROVIDED AS MANUFACTURERS STANDARD

G. BLANKED NOZZLES PROVIDED FOR POSSIBLE FUTURE USE AS FILL PORTS/CIP SYSTEM

KEY

BM - BATCH METER
SG2 - SCRUBBER 7L02
FS - FLOW SWITCH
CWS - COOLING WATER SUPPLY
CWR - COOLING WATER RETURN
BRS - BRINE SUPPLY
BRR - BRINE RETURN
LE - LOCAL EXTRACTION
ST - STEAM
C - CONDENSATE
SP - SAMPLE POINT
HV - HIGH VACUUM
RV - ROUGH VACUUM

SECTION 5

Rev	Date	Description	By
A	14/12/92	ISSUED WITH REPORT	HG

Client

UNIDO
P.O. BOX 300, A-1400 VIENNA,
AUSTRIA, FAX: 232156

Project

ALKALOIDA 2
TF/HUN/90/910

Drawing Title

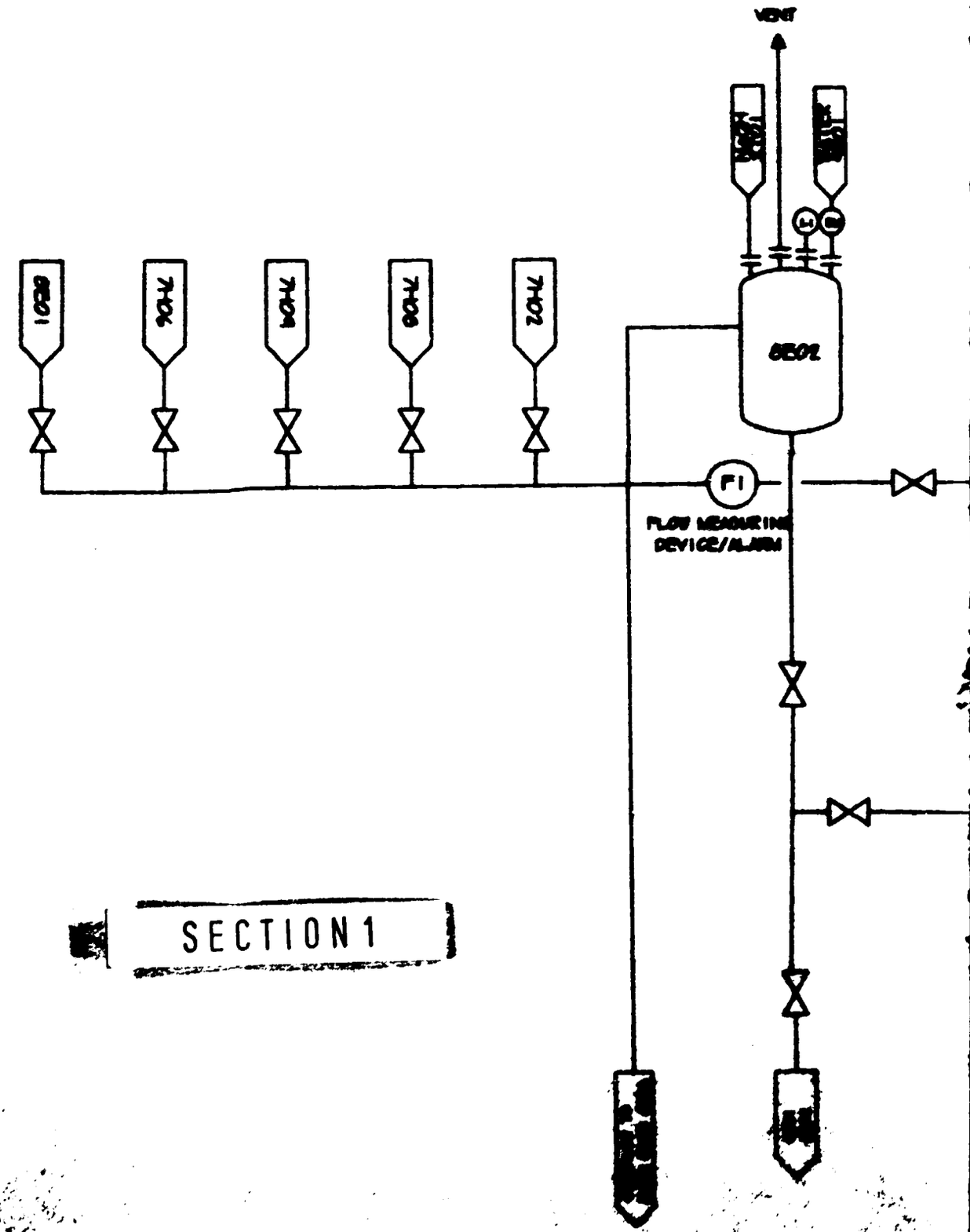
SUBSYSTEM 7
ENGINEERING LINE
DIAGRAM

SECTION 6

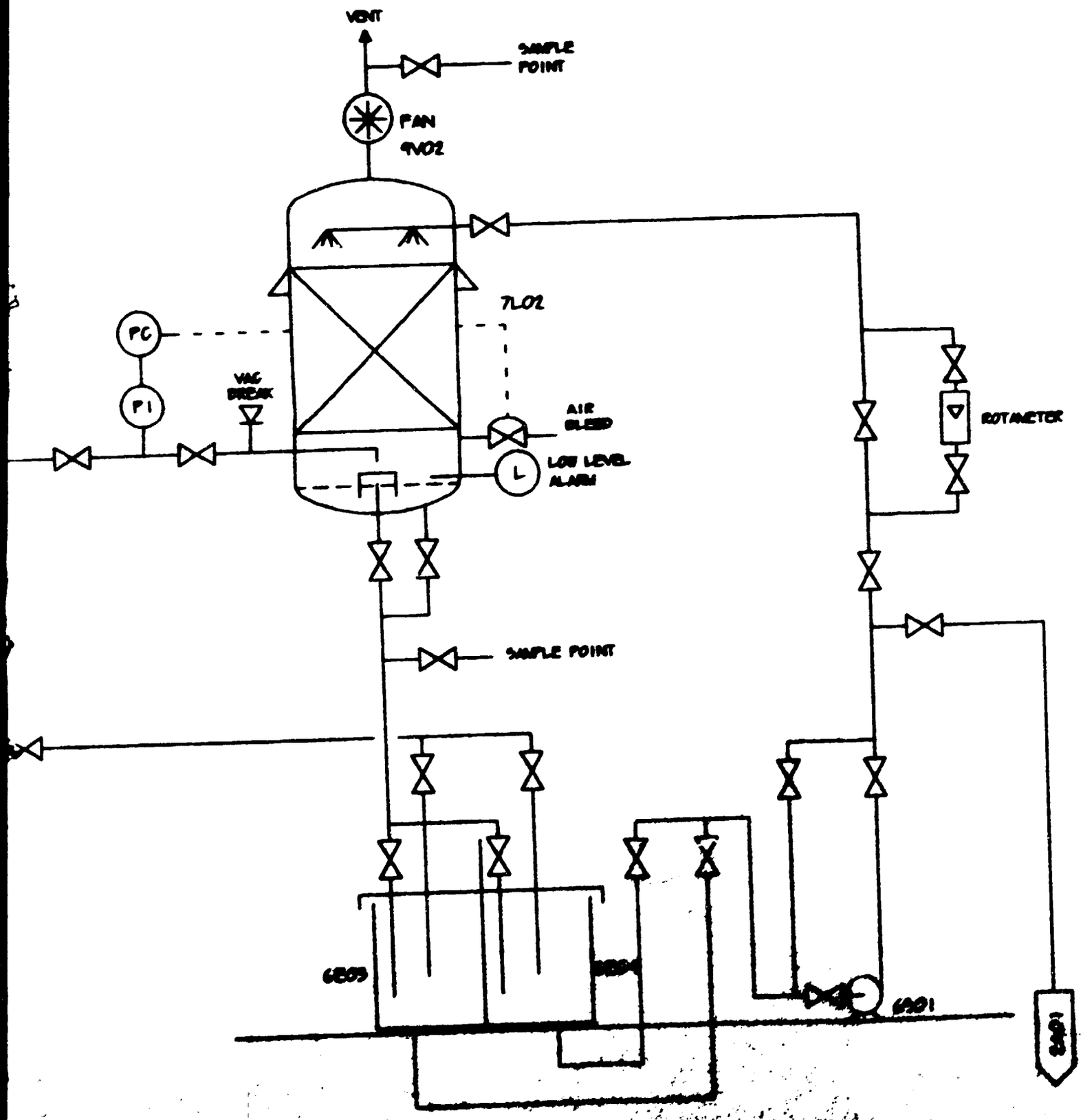
GRC CONSULTANTS

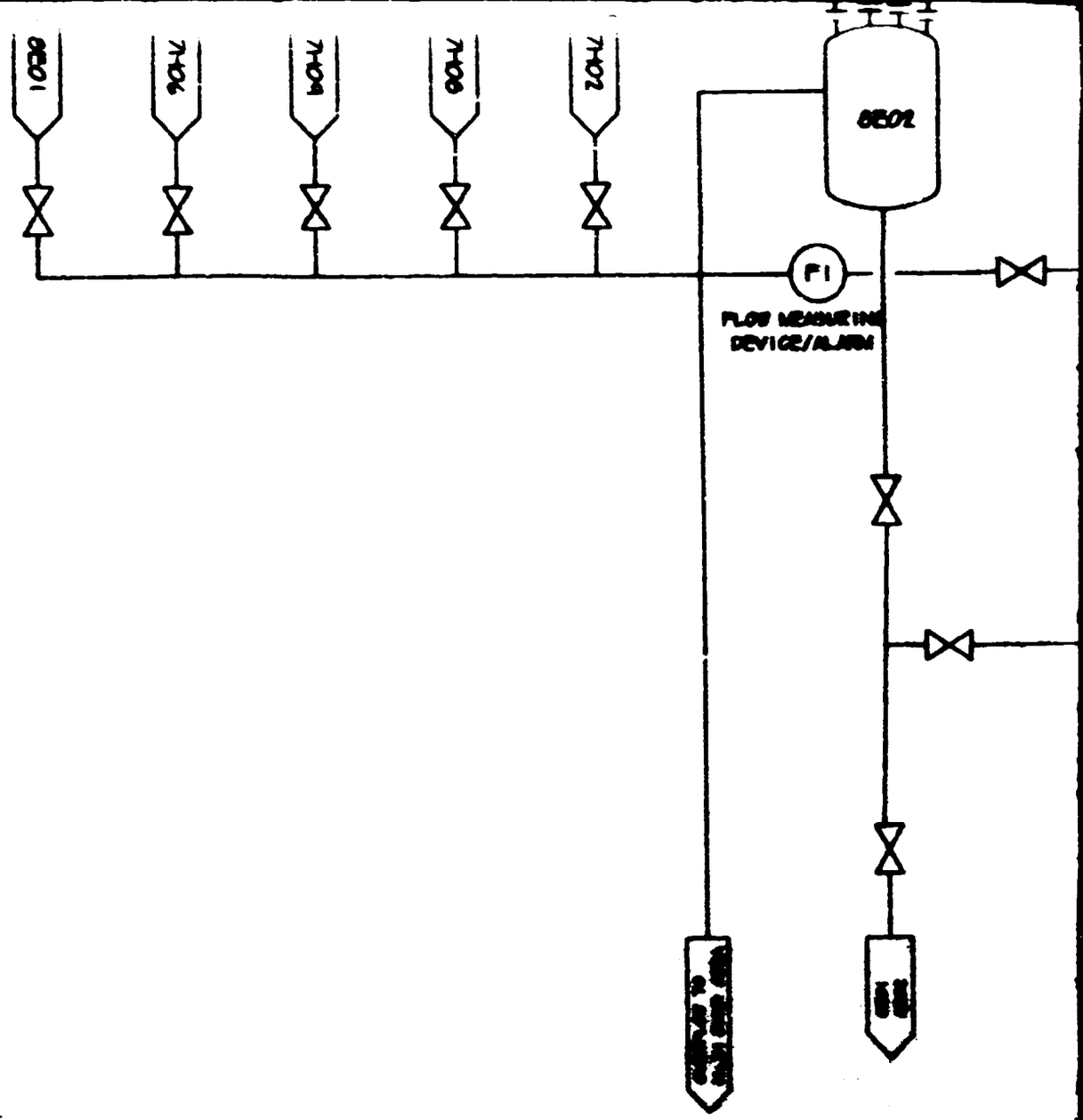
WATERCRESS HOUSE
1 THE WINDMILLS ST MARY'S CLOSE,
ALTON HANTS GU34 1EF
TEL: 0420 89847 FAX: 0420 89427

Drawing Number	Scale	Revision
92/013/236	NTS	A



SECTION 1


VENT
SAMPLE POINT
FAN
4V02
7L02
PC
PI
VAC BREAK
AIR BLEED
LOW LEVEL ALARM
ROTAMETER
SAMPLE POINT
6B05
6V01

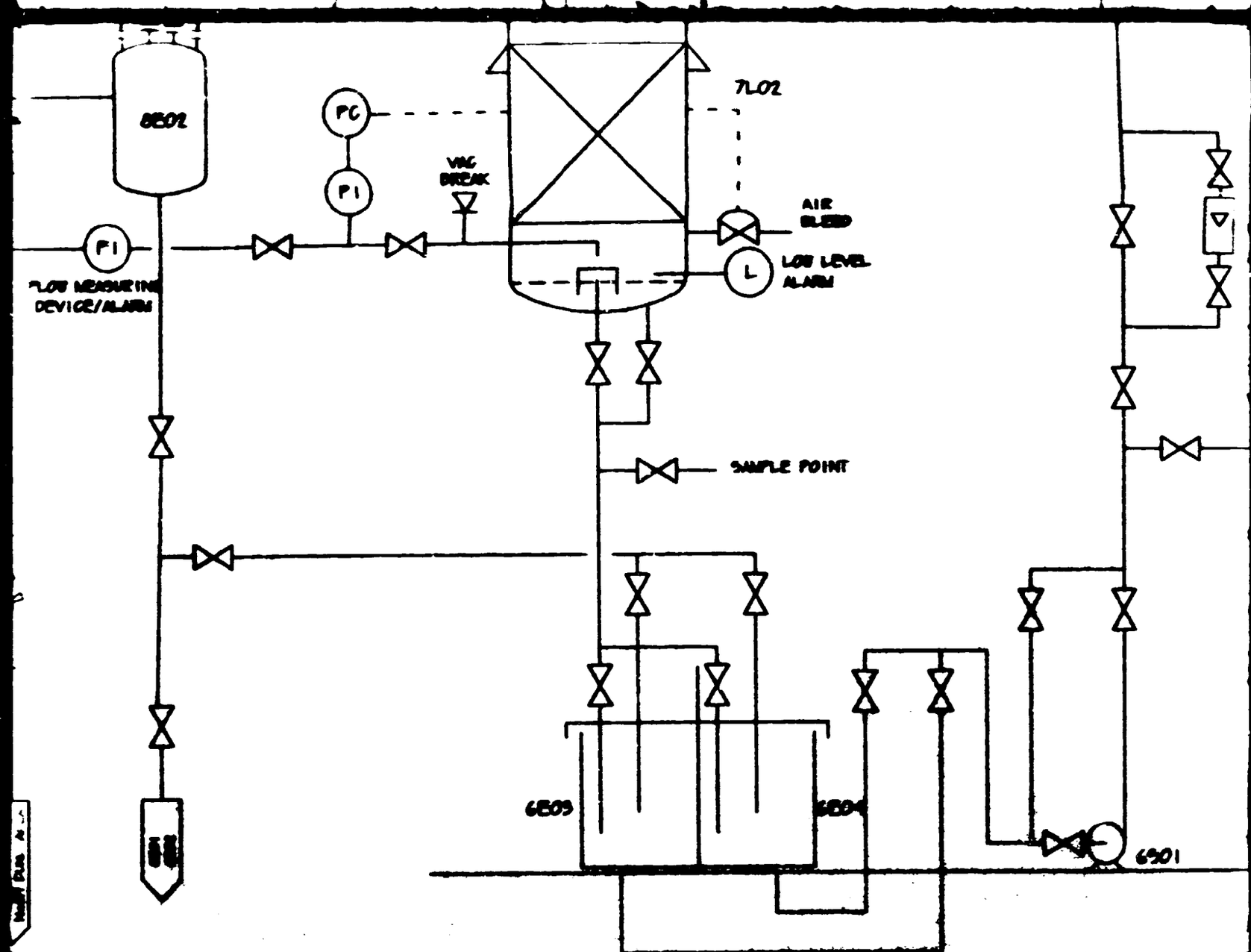


CHECKED						
APPROVED						
DRAWN BY				ISSUED WITH REPORT	A	
				MODIFICATION	ISSUE	DATE

GRC C

WATERWORKS H
ST MARY'S CL
TEL:-0450 69

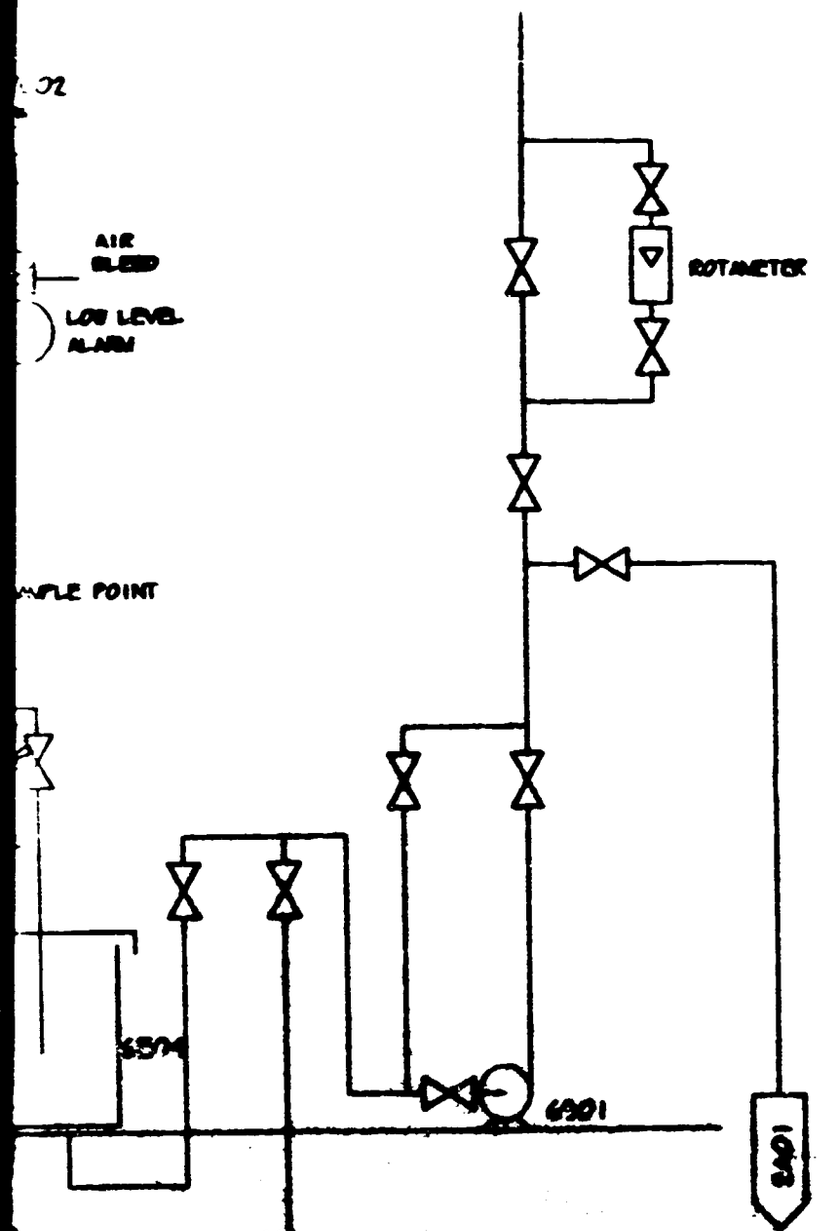
SECTION 3



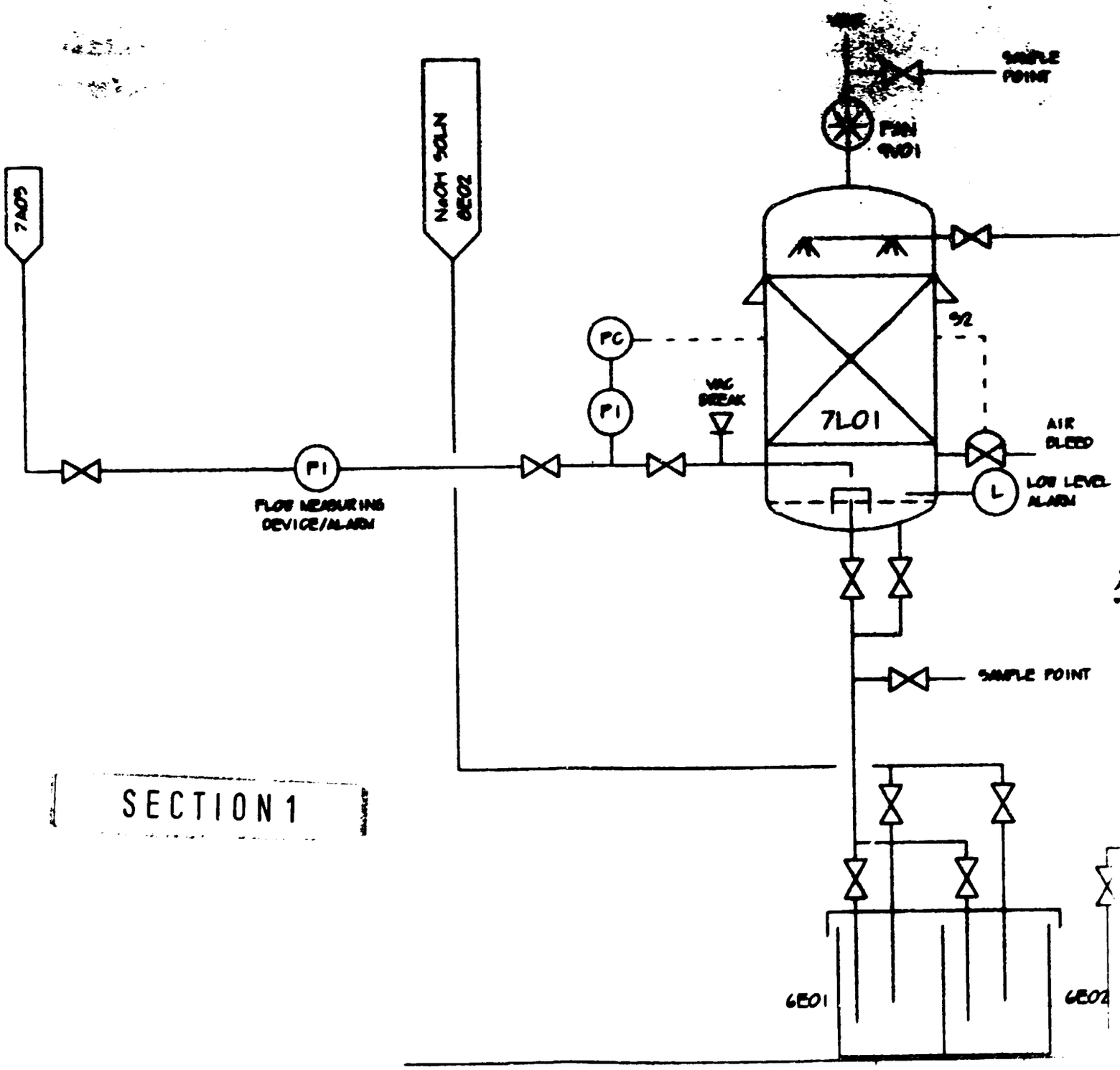
	CRC CONSULTANTS THE WINDMILLS ST MARY'S CLOSE ALTON HANTS TEL: -0420 84847 FAX: -0420 84427	CLIENT UNIDO P.O. BOX 300, A-1400 VIENNA, AUSTRIA FAX: 232156
14/12/95		DATE:
DATE		SCALE:
		DIMENSIONS IN:

PROJECT
ALKALOIDA 2
TF/MLN/90/910

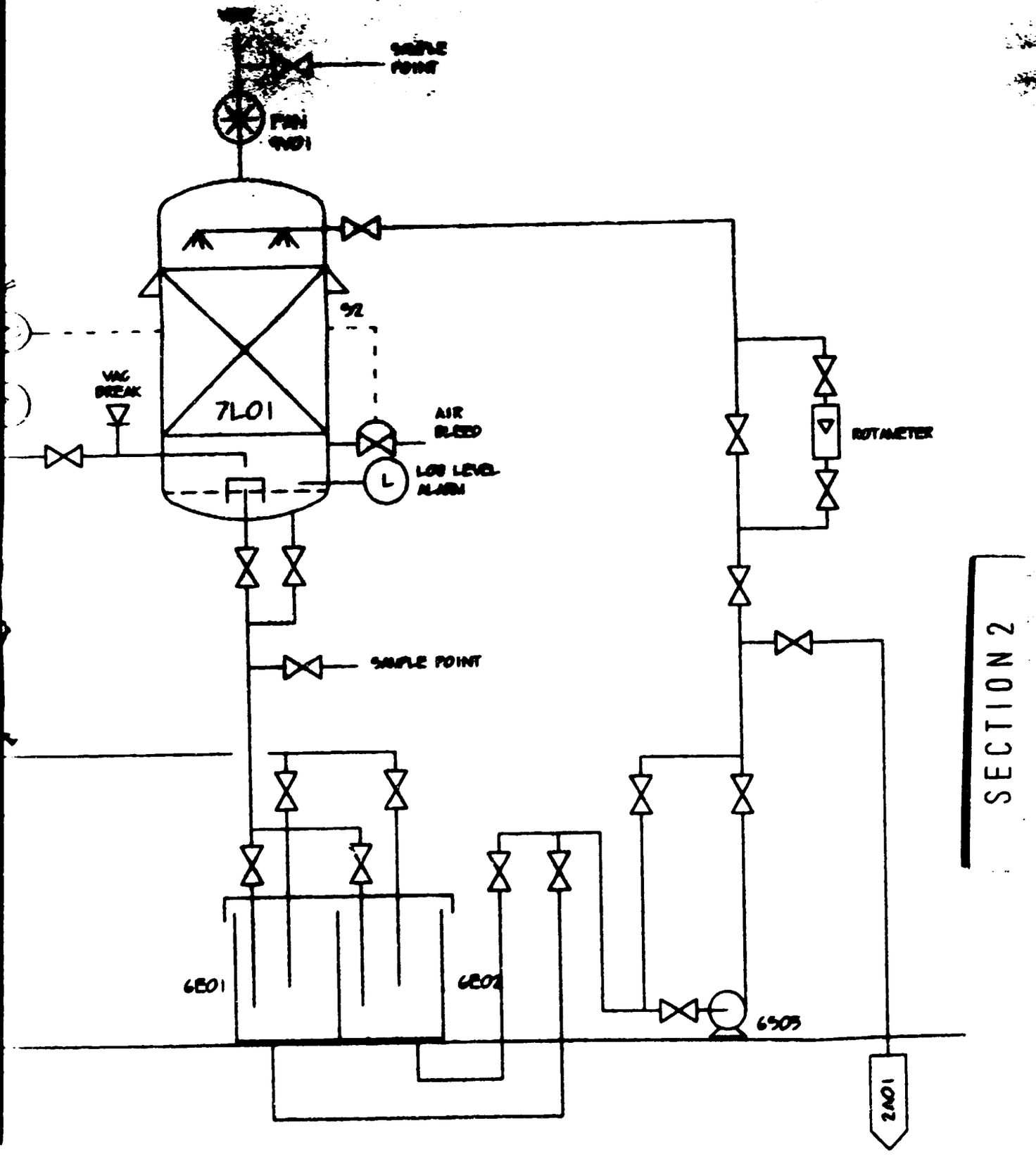
SECTION 4



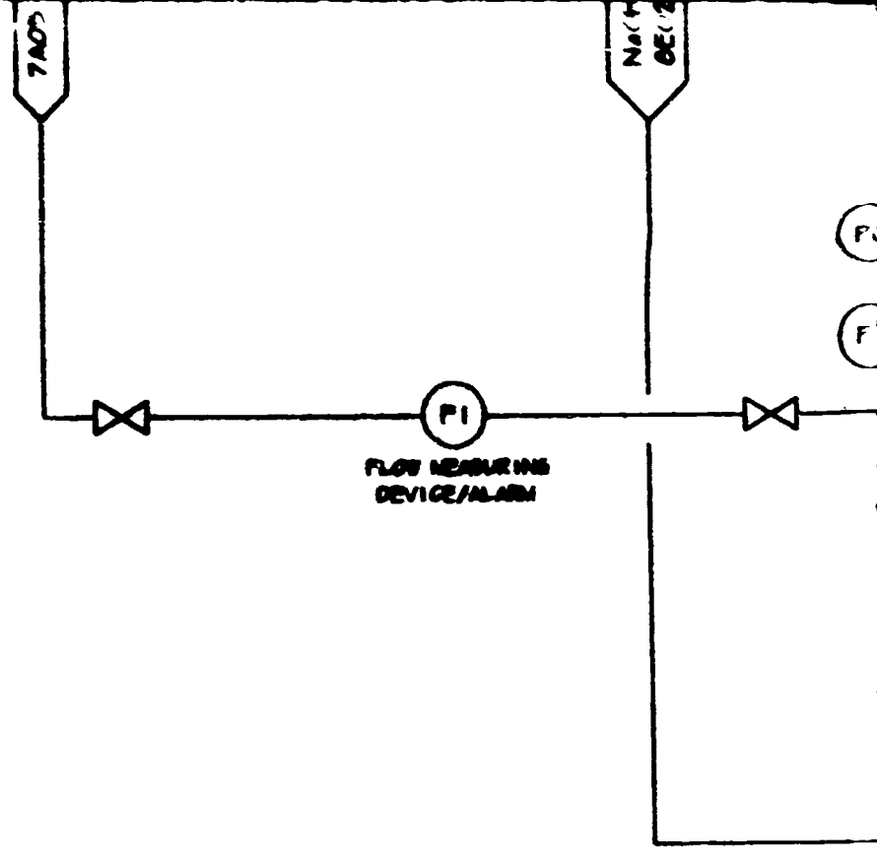
X 300, VIENNA, AUSTRIA 2136	PROJECT ALKALOIDA 2 TF/HUN/90/910	TITLE SUBSYSTEM 6 ENGINEERING LINE DIAGRAM	
		DRAWING NUMBER 92/013/237	REV A
NS IN:			


NaOH SOLN
6E02
FC
FI
VAC BREAK
7L01
AIR BLEED
L
LOW LEVEL ALARM
FI
FLOW MEASURING DEVICE/ALARM
SAMPLE POINT
SAMPLE POINT
6E01
6E02

SECTION 1

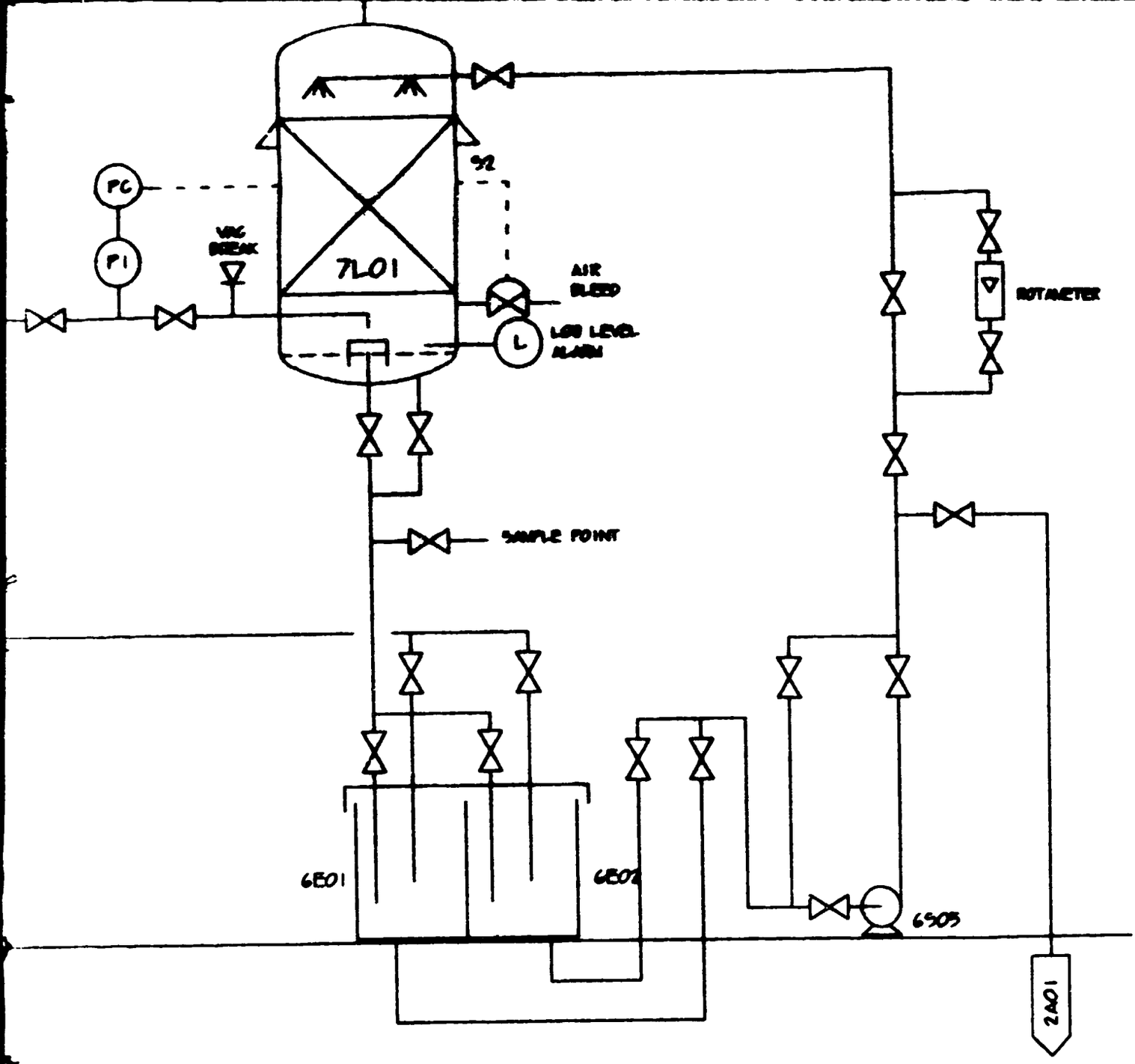

SAMPLE POINT
PSN 9401
VAC BREAK
7L01
92
AIR BLEED
LOW LEVEL ALARM
L
ROTAMETER
SAMPLE POINT
6E01
6E02
6303
2401

SECTION 2



SECTION 3

CHECKED							
APPROVED							
DRAWN BY				ISSUED WITH REPORT	A	14/12/92	WATER ST MA TEL:
				MODIFICATION	ISSUE	DATE	



SECTION 4

GRC CONSULTANTS

WATERCRESS HOUSE 1 THE WINDMILLS
ST MARY'S CLOSE ALTON HANTS
TEL: -0420 89847 FAX: -0420 89427

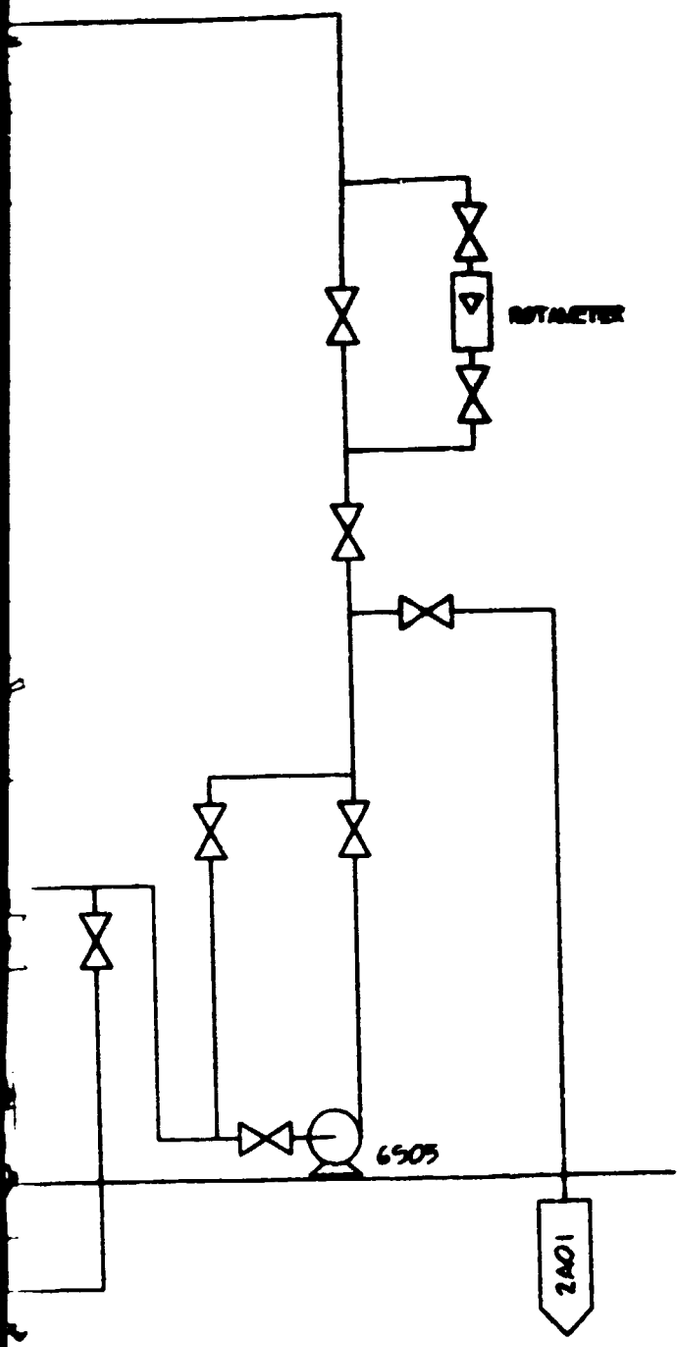
CLIENT
UNIDO
P.O. BOX 300,
A-1400 VIENNA, AUSTRIA
FAX: 232156

PROJECT
ALKALOIDA 2
TF/HUN/90/910

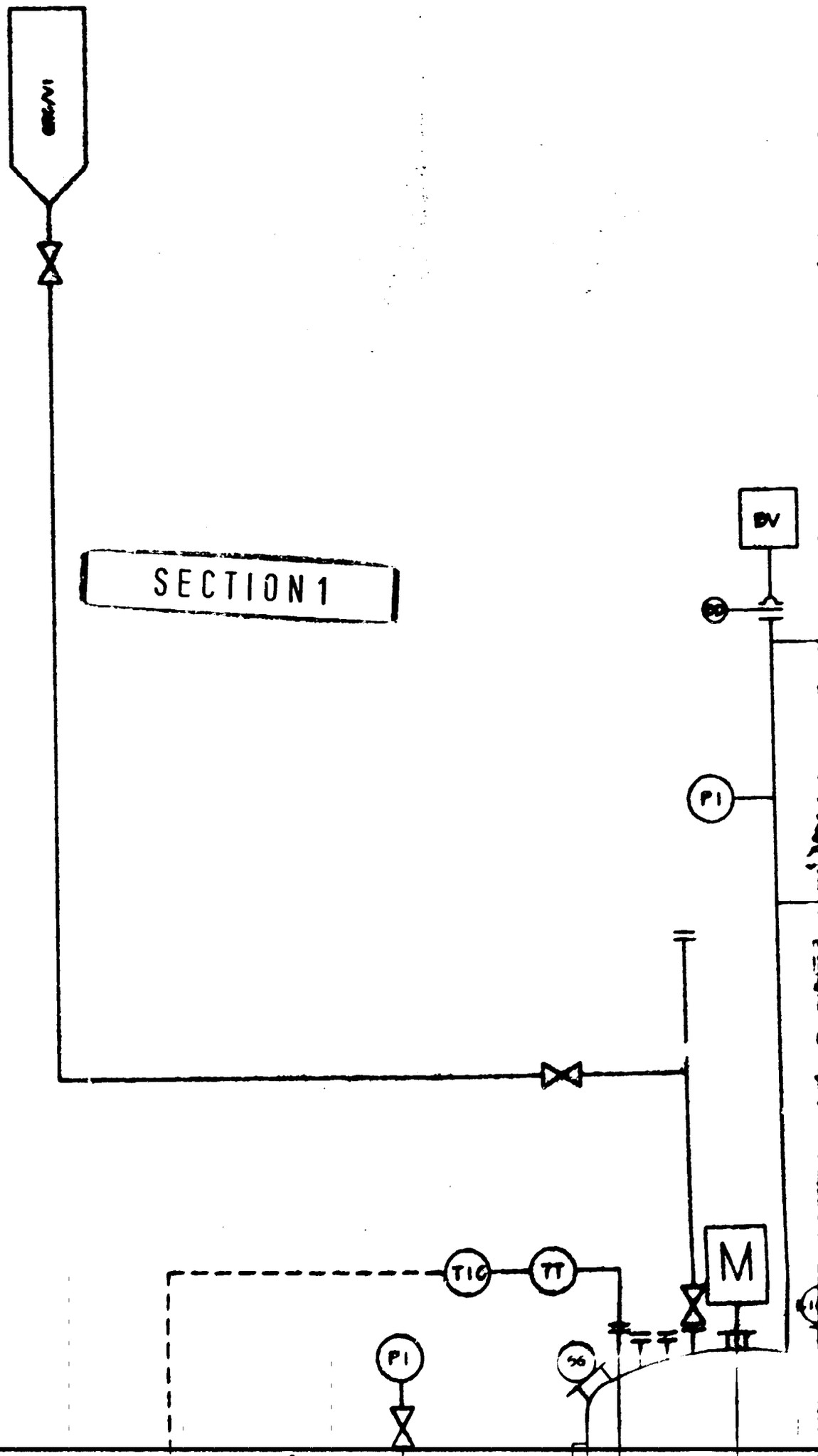
DATE:

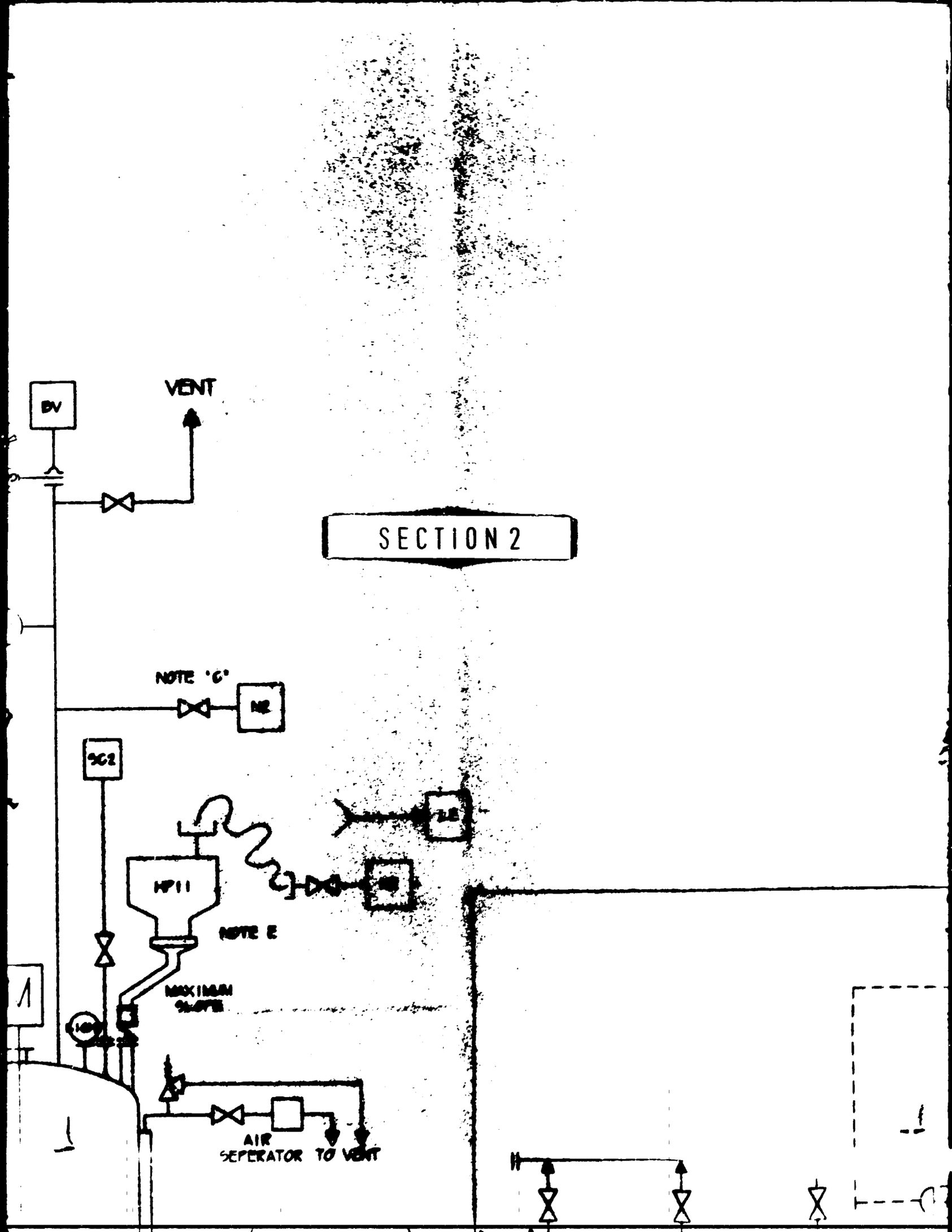
SCALE:

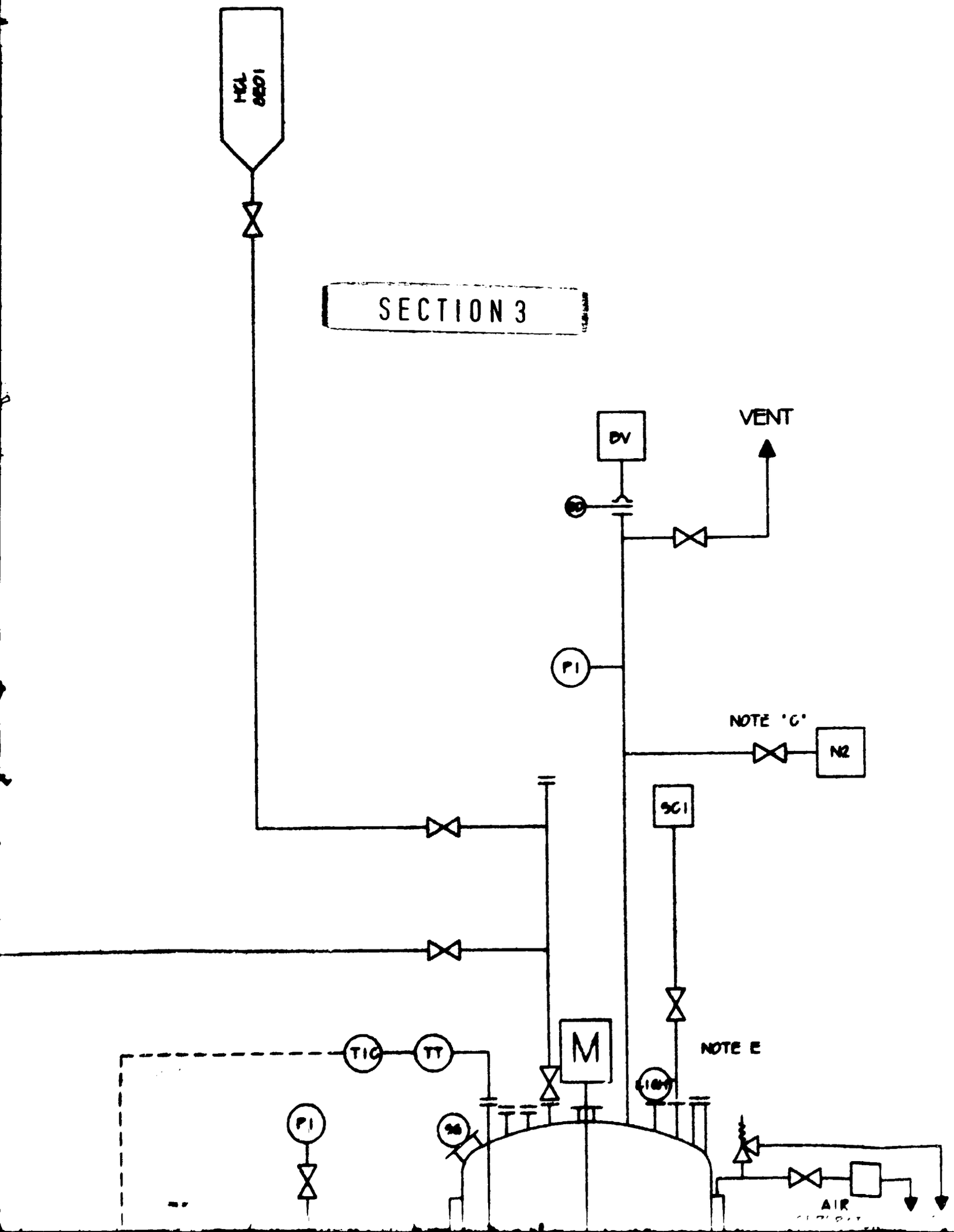
DIMENSIONS IN:

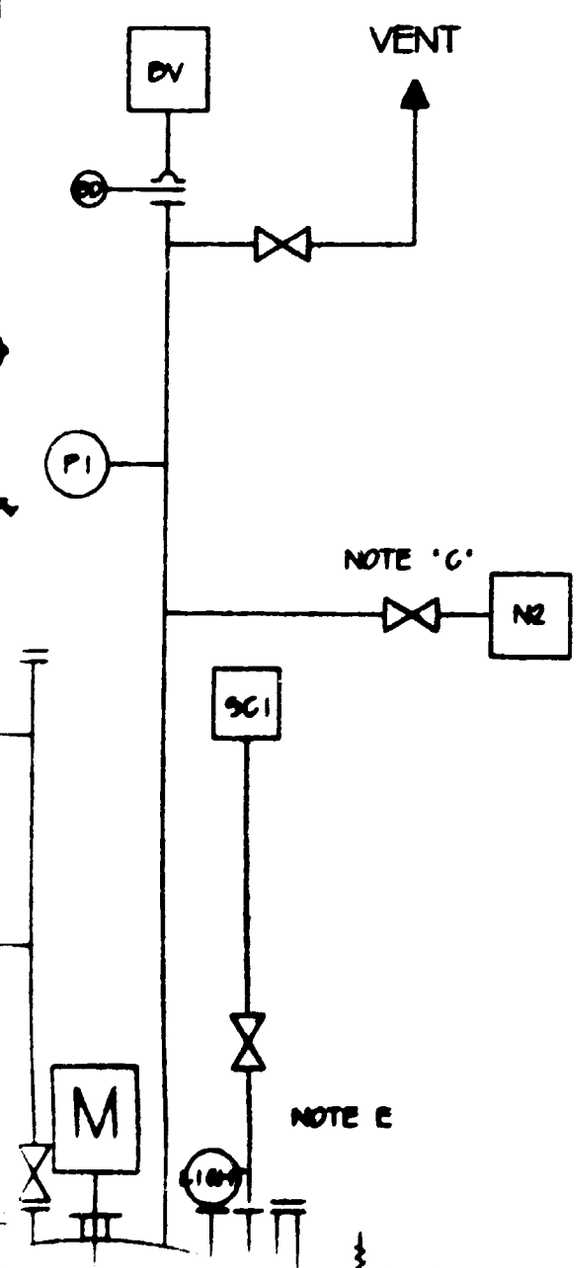


Ux 300, VIENNA, AUSTRIA 2156	PROJECT ALKALOIDA 2 TF/HUN/90/910	TITLE SUBSYSTEM 9 ENGINEERING LINE DIAGRAM	
		DRAWING NUMBER 92/013/238	REV A
INS IN:			


SECTION 1
DV
PI
TIC
TT
M
PI
SG


VENT
BV
SECTION 2
NOTE 'G'
NR
SG2
HP11
NOTE E
MAXIMUM
AIR
SEPERATOR
TO VENT


HCL
SECTION 3
VENT
DV
PI
NOTE 'C'
N2
SCI
M
NOTE E
TIC
TT
PI
AIR



NOTES

A. VALVE SYSTEMS ON VESSEL JACKET SERVICES COULD BE PHYSICALLY INTERLOCKED OR CONTROLLED VIA DEDICATED PLC

B. ALL SERVICE CONNECTIONS SHOWN IN SQUARE FRAMES OTHER CONNECTIONS SHOWN IN ARRONED FRAMES.

C. NITROGEN FOR PURGE OR PRESSURISATION.

D. BLANKED NOZZLES INCLUDED FOR POSSIBLE FUTURE USE AS FILL PORTS/CIP SYSTEM

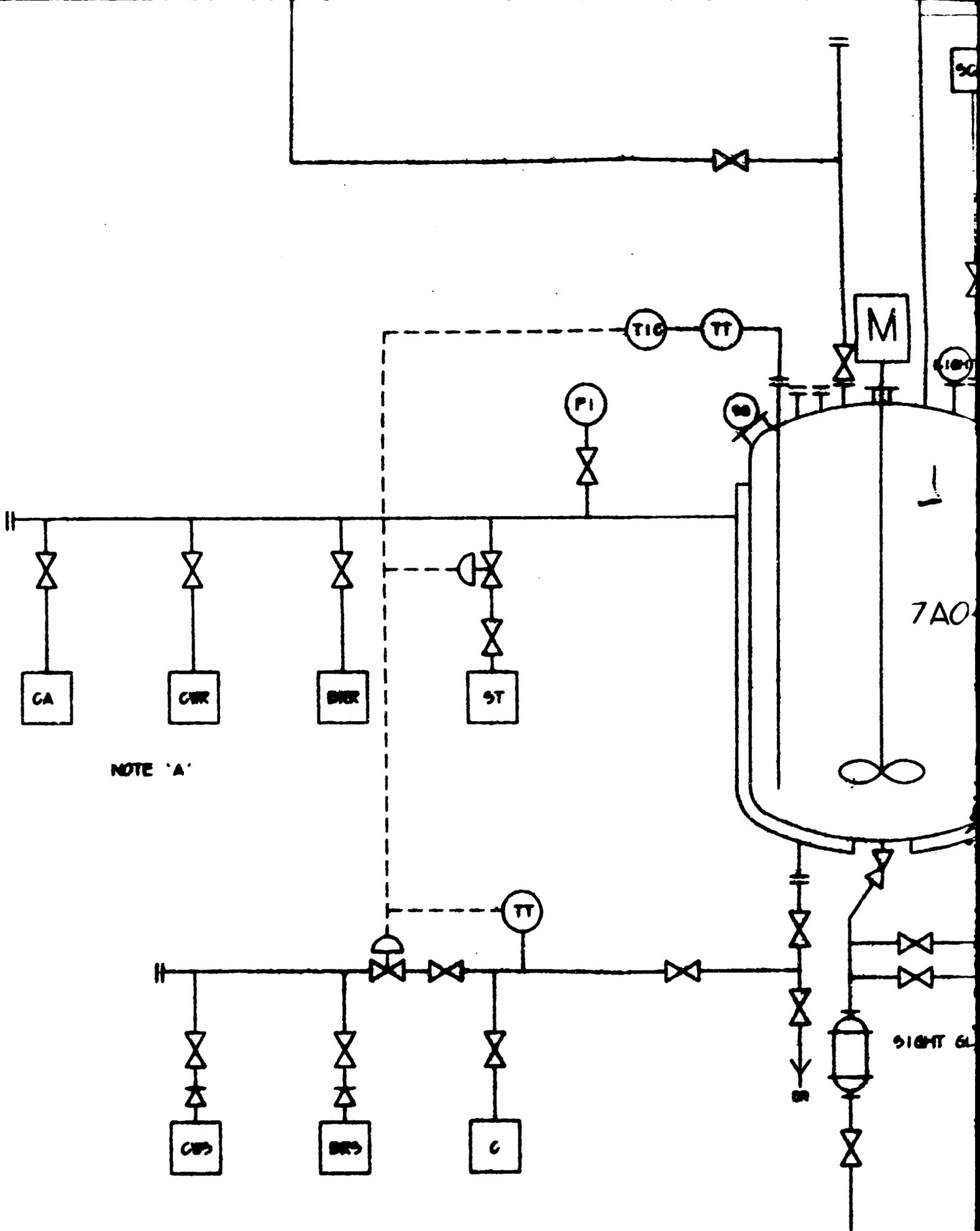
E. SOLIDS ADDITION MECHANISM TO BE DEFINED AT DETAILED DESIGN

F. VESSEL ACCESS WAYS TO BE PROVIDED AS MANUFACTURERS STANDARD

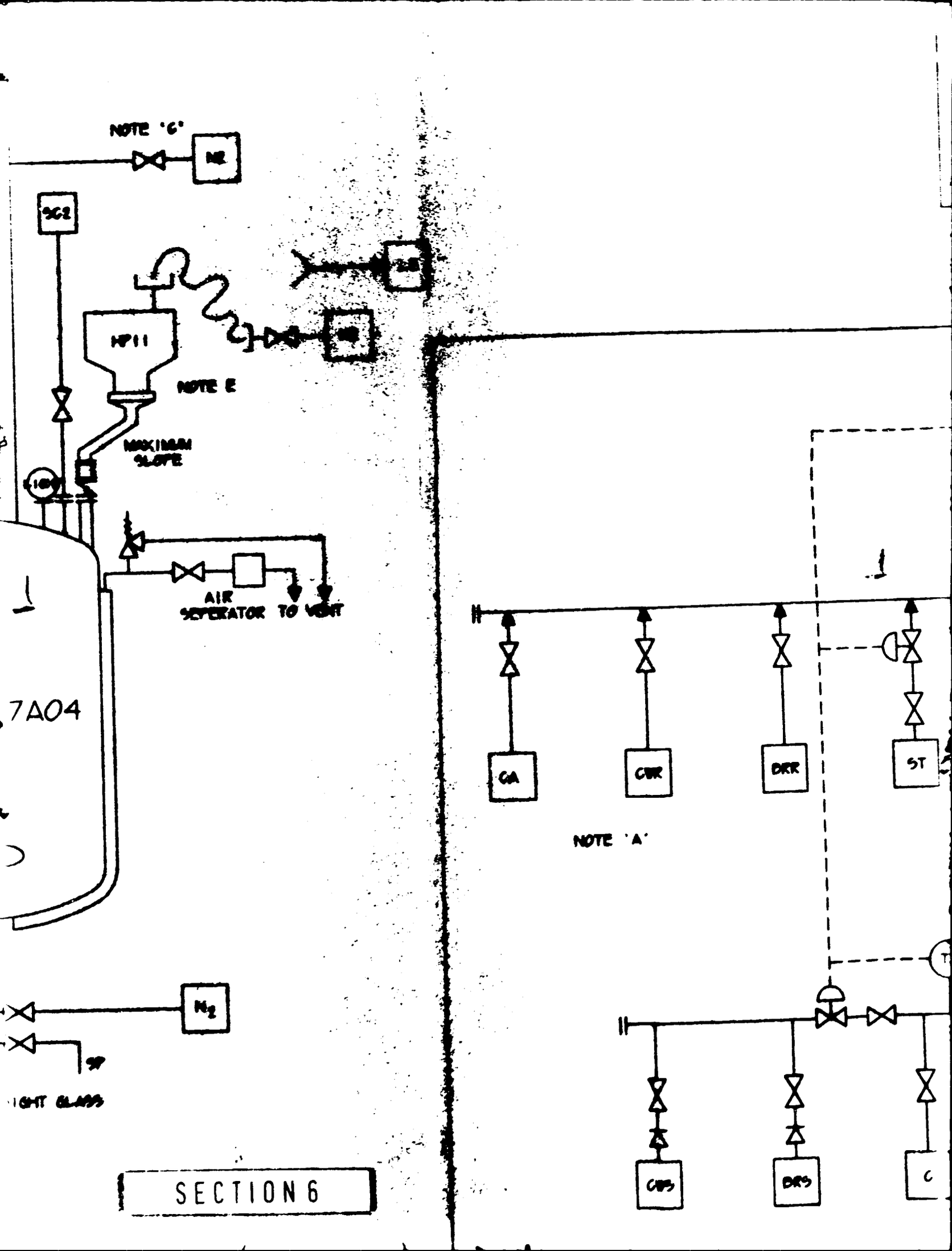
KEY

BM - BATCH METER
SC1 - SCRUBBER 7L01
FS - FLOW SWITCH
CWS - COOLING WATER SUPPLY
CWR - COOLING WATER RETURN
BRS - BRINE SUPPLY
BRR - BRINE RETURN
LE - LOCAL EXTRACTION
ST - STEAM
C - CONDENSATE
SP - SAMPLE POINT
HV - HIGH VACUUM
RV - ROUGH VACUUM

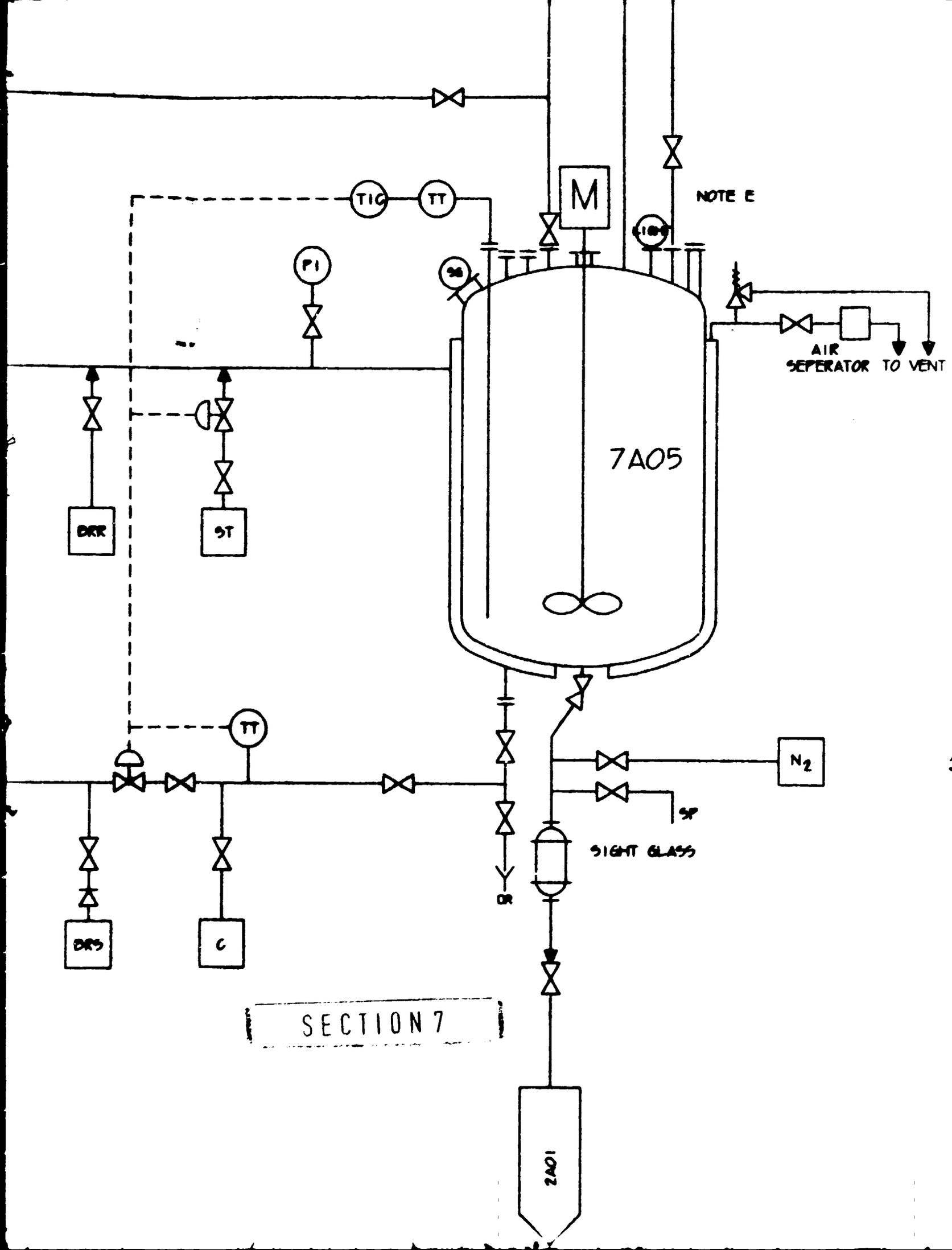
SECTION 4

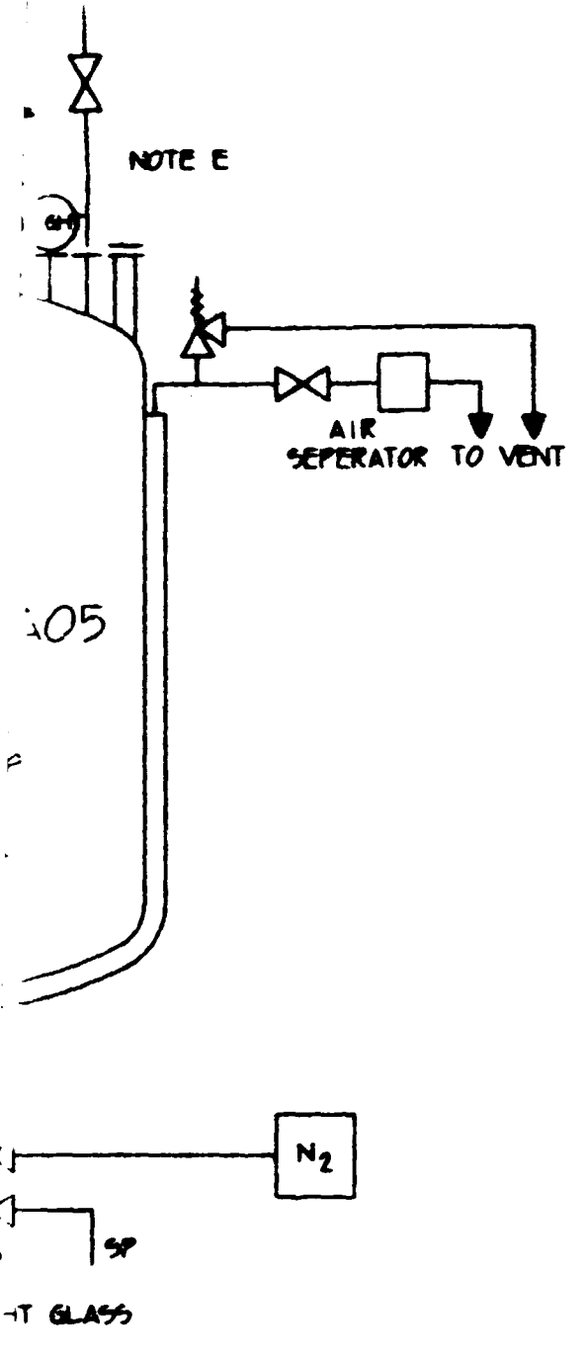


SECTION 5


NOTE 'G'
NE
SC2
HP11
NOTE E
MAXIMUM SLOPE
AIR SEPERATOR TO VENT
7A04
N_2
SP
IGHT GLASS
NOTE 'A'
GA
CBR
DRR
ST
CBS
DRS
C

SECTION 6


M
TIC
TT
PI
NOTE E
AIR
SEPERATOR
TO VENT
7A05
DRR
ST
TT
N2
SP
SIGHT GLASS
DR
DRS
C
SECTION 7
2A01



Rev	Date	Description	Dr
A	14/12/92	ISSUED WITH REPORT	HG

Client

UNIDO
P.O. BOX 300, A-1400 VIENNA,
AUSTRIA, FAX:232156

Project

ALKALOIDA 2
TF/HUN/90/910

Drawing Title

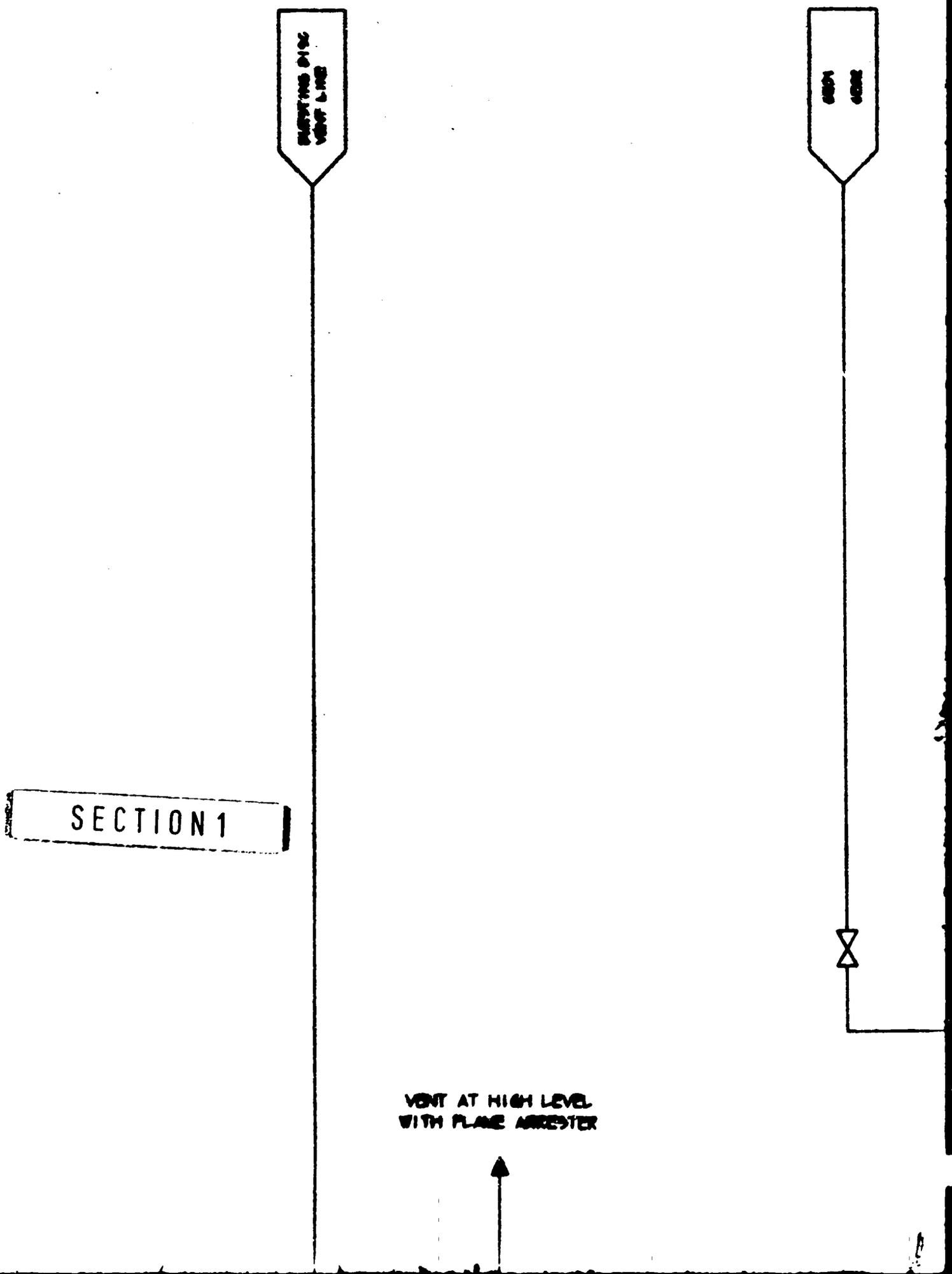
SUBSYSTEM 10
ENGINEERING LINE
DIAGRAM

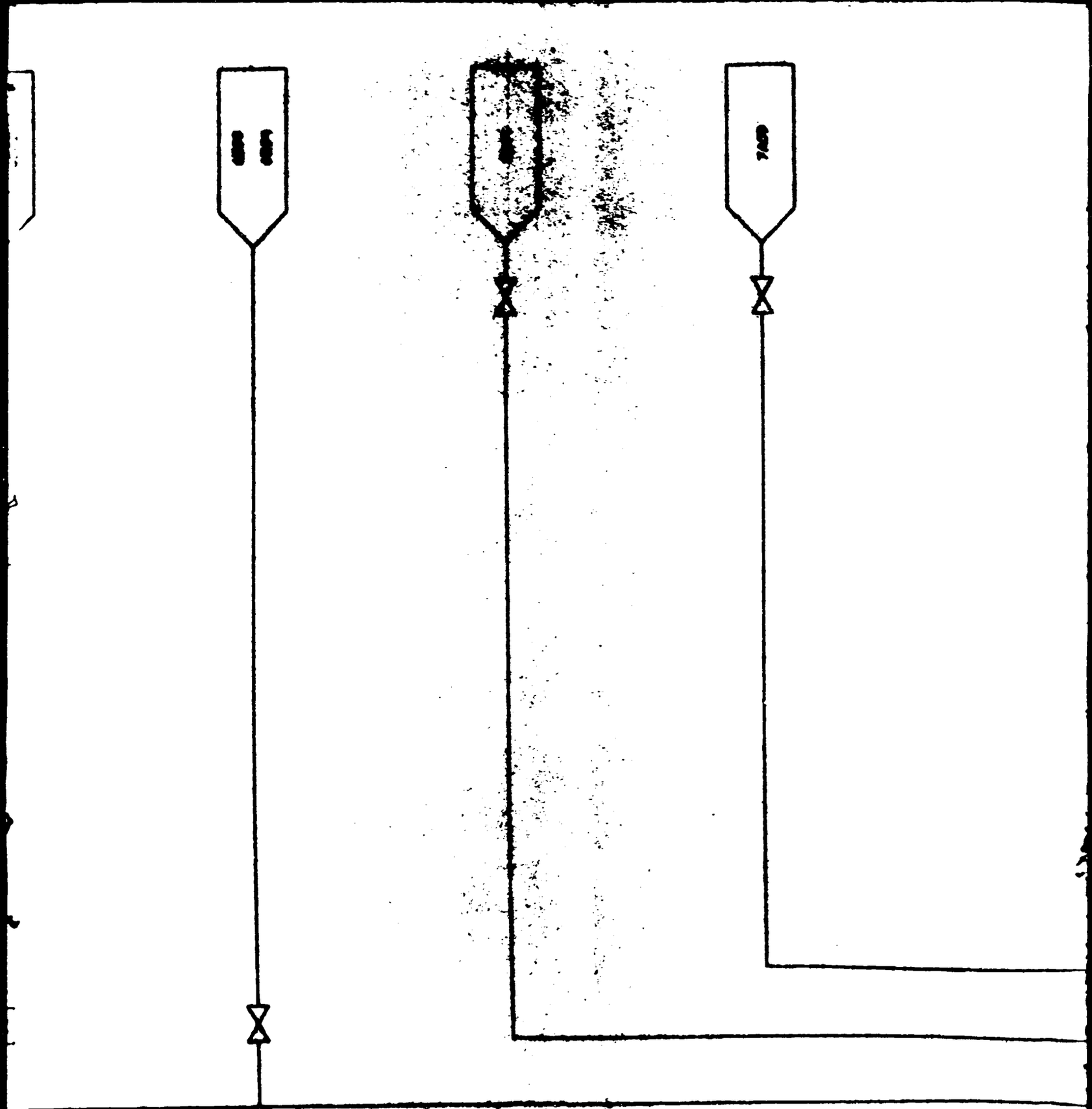
SECTION 8

GRC CONSULTANTS

WATERCRESS HOUSE
1 THE WINDMILLS ST MARY'S CLOSE,
ALTON HANTS GU34 1EF
TEL: 0420 89847 FAX: 0420 89427

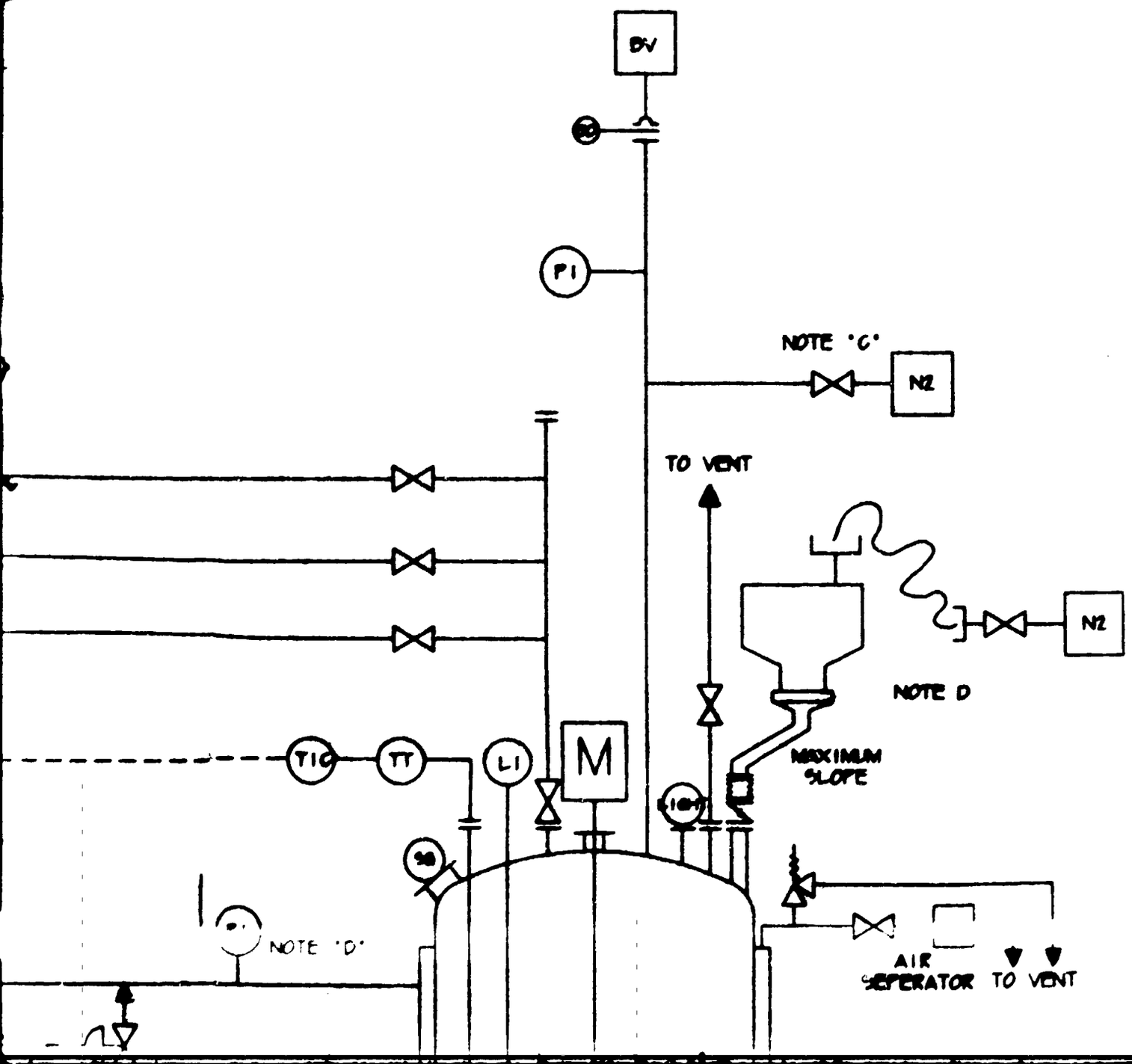
Drawing Number	Scale	Revision
92/013/239	NTS	A


SECTION 1
VENT AT HIGH LEVEL
WITH FLAME ARRESTER



SECTION 2

SECTION 3


DV
PI
NOTE 'C'
N2
TO VENT
N2
NOTE D
MAXIMUM SLOPE
TIC
TT
LI
M
NOTE 'D'
AIR SEPERATOR
TO VENT

NOTES

A. VALVE SYSTEMS ON VESSEL JACKET AND CONDENSER SERVICES COULD BE PHYSICALLY INTERLOCKED OR CONTROLLED VIA DEDICATED PLC.

B. ALL SERVICE CONNECTIONS SHOWN IN SQUARE FRAMES OTHER CONNECTIONS SHOWN IN ARCUED FRAMES.

C. NITROGEN FOR PURGE OR PRESSURISATION.

D. SOLIDS FEED ARRANGEMENT TO BE SPECIFIED AT DETAILED DESIGN

KEY

BM - BATCH METER
SC - SCRUBBER
FS - FLOW SWITCH
CWS - COOLING WATER SUPPLY
CWR - COOLING WATER RETURN
BRS - BRINE SUPPLY
BRR - BRINE RETURN
LE - LOCAL EXTRACTION
ST - STEAM
C - CONDENSATE
SP - SAMPLE POINT

NOTE 'C'

N2

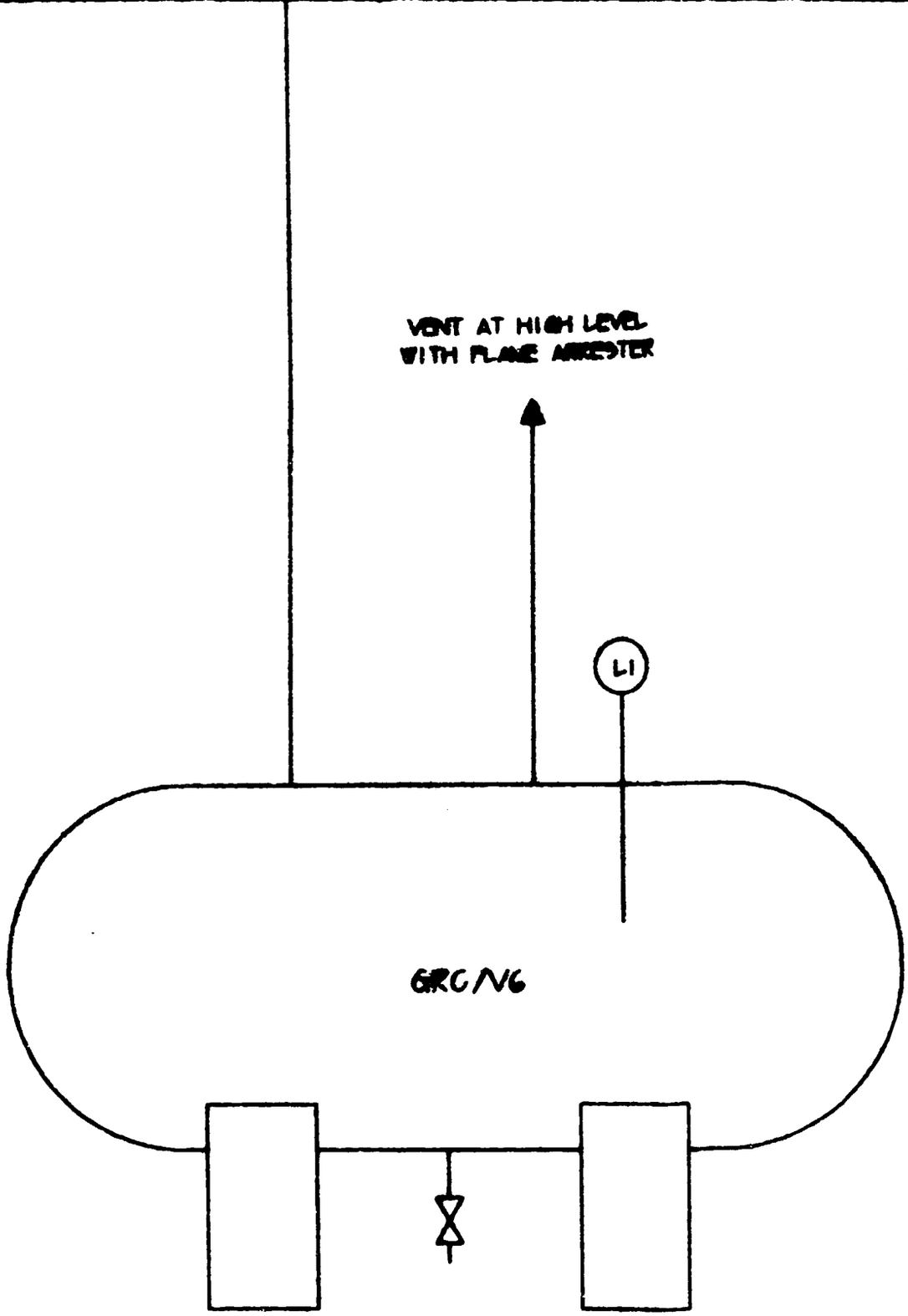
NT

N2

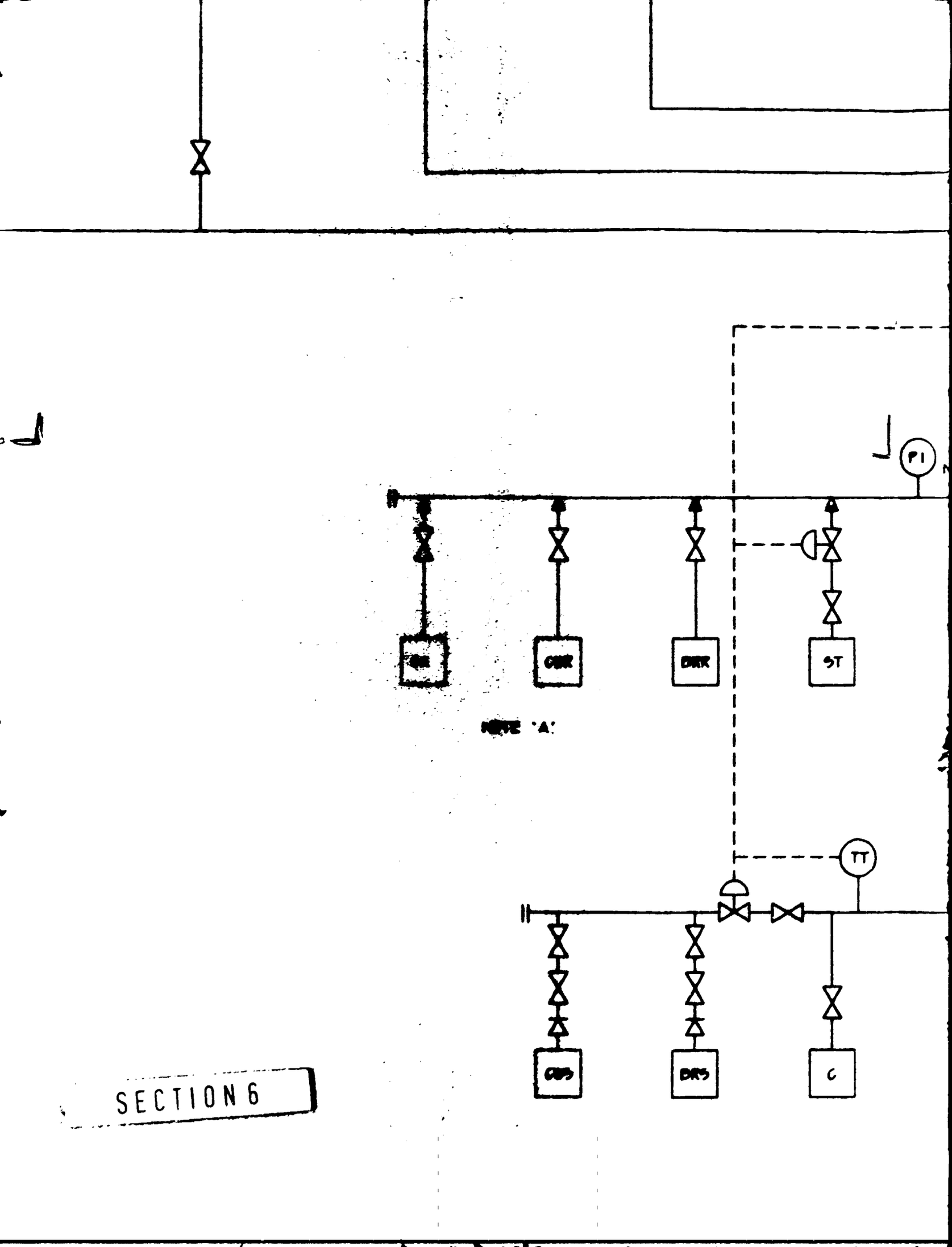
NOTE D

MAXIMUM
4 OFF

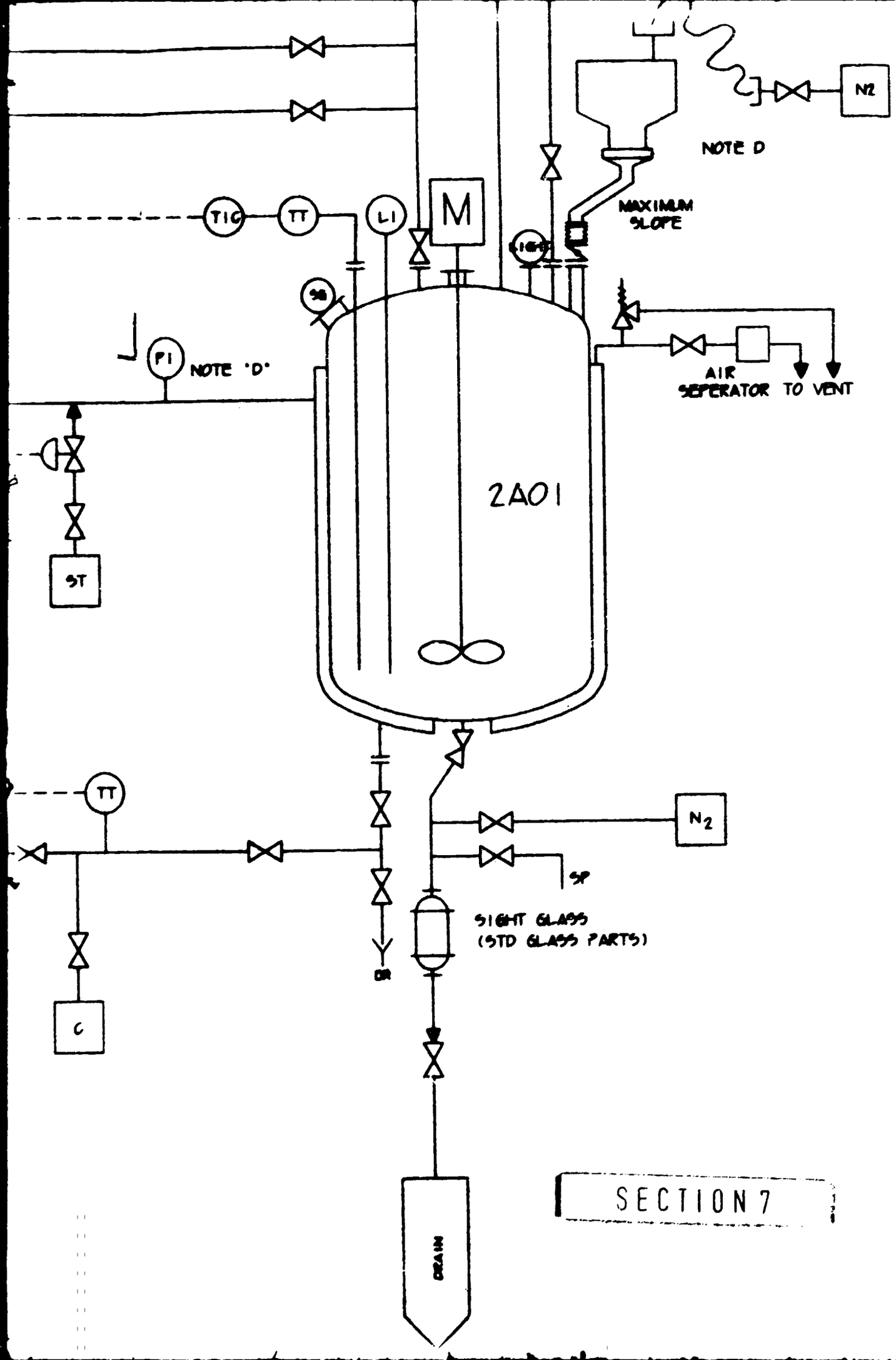
SECTION 4

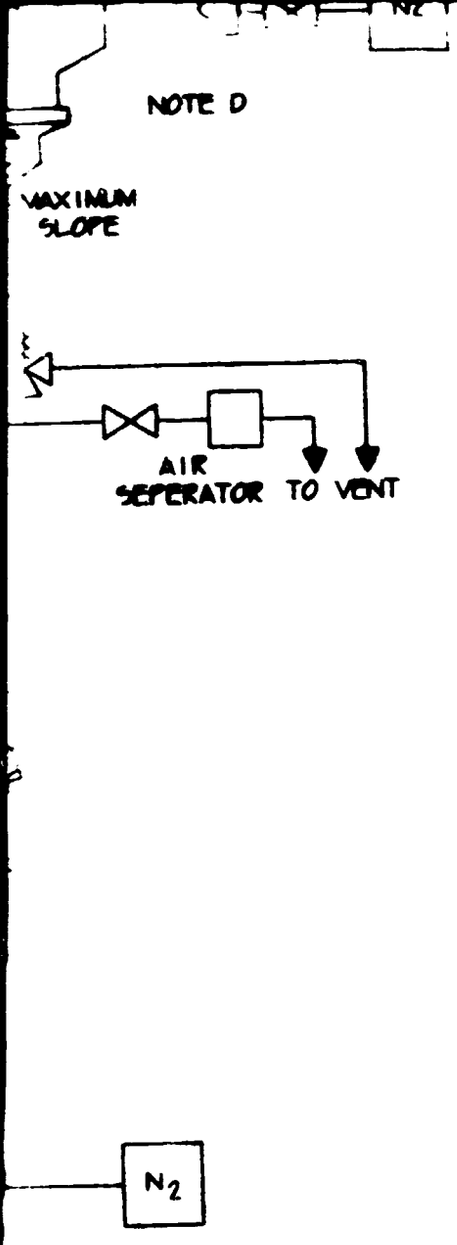


SECTION 5



SECTION 6


N2
NOTE D
MAXIMUM SLOPE
TIC
TT
LI
M
SG
PI
NOTE 'D'
AIR SEPERATOR TO VENT
2A01
ST
TT
N2
SP
SIGHT GLASS (STD GLASS PARTS)
DR
C
DRAIN
SECTION 7



SECTION 8

Rev	Date	Description	By
A	14/12/92	ISSUED WITH REPORT	HG

Client

UNIDO
P.O. BOX 300, A-1400 VIENNA,
AUSTRIA, FAX:232156

Project

ALKALOIDA 2
TF/HUN/90/910

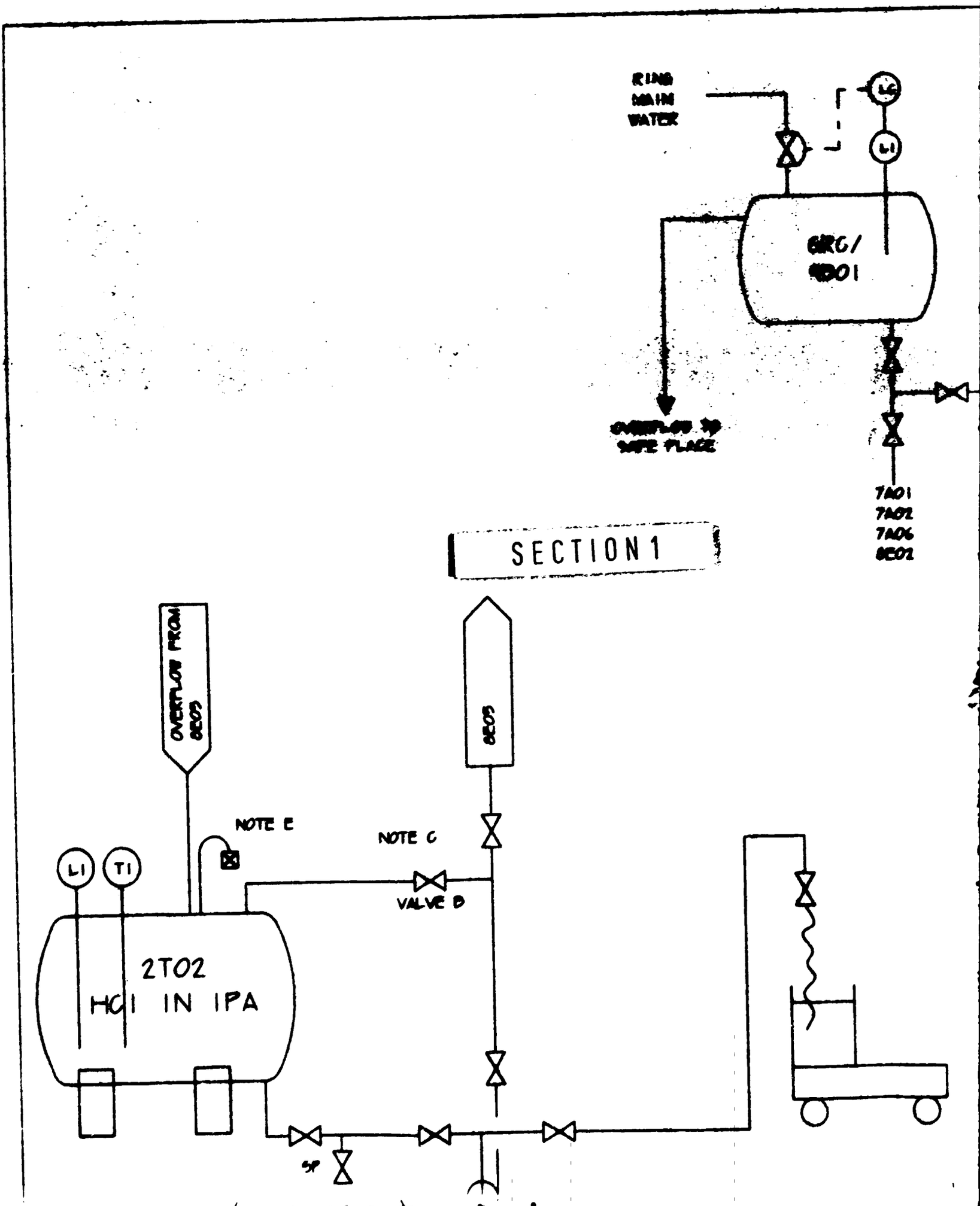
Drawing Title

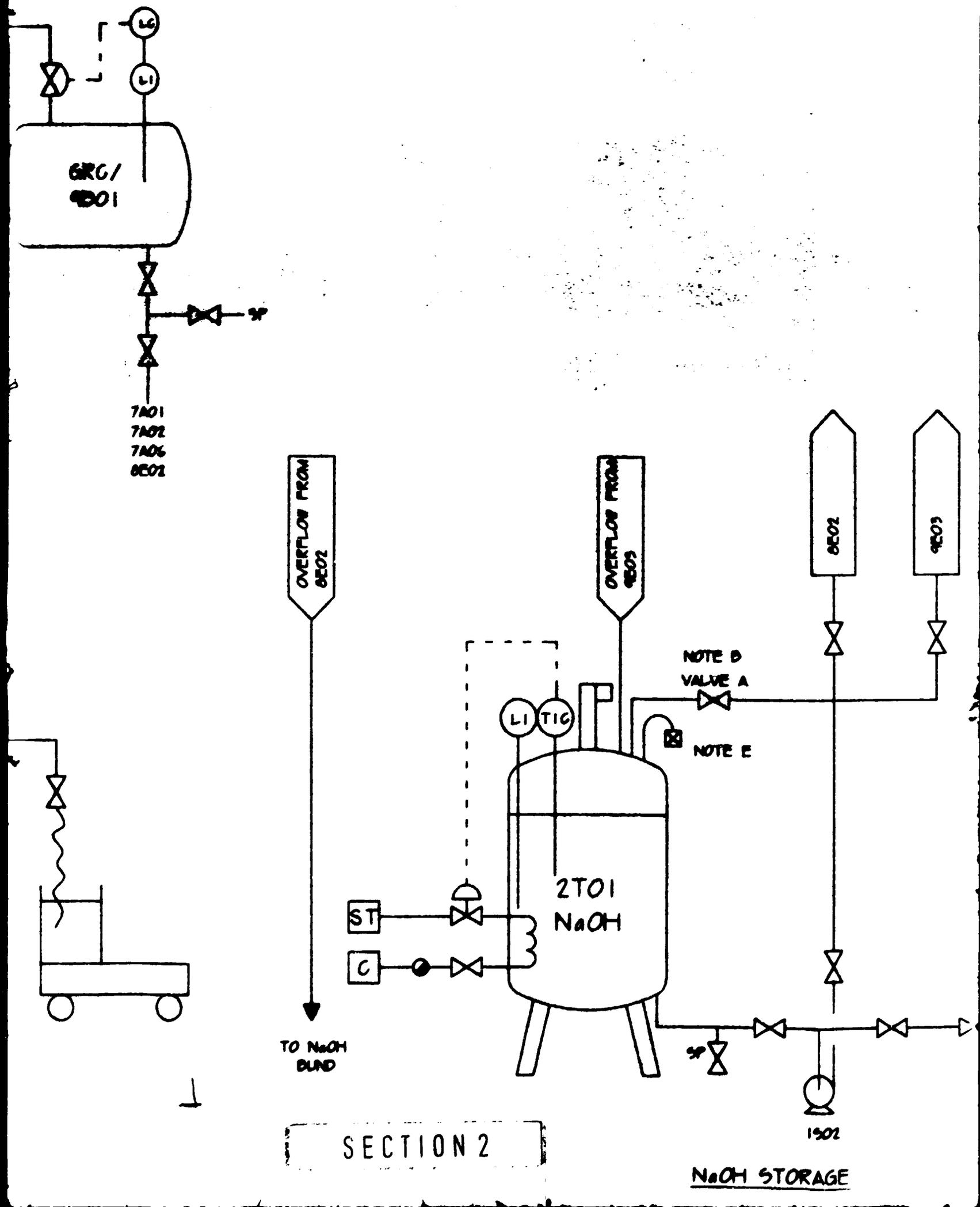
SUBSYSTEM 11
ENGINEERING LINE
DIAGRAM

GRC CONSULTANTS

WATERCRESS HOUSE
1 THE WINDMILLS ST MARY'S CLOSE,
ALTON HANTS GU34 1EF
TEL: 0420 89847 FAX: 0420 89427

Drawing Number	Scale	Revision
92/0:3/240	NTS	A


RING MAIN WATER
LC
LI
6RG/ 4D01
OVERFLOW TO WASTE PLACE
7A01
7A02
7A06
8E02
SECTION 1
OVERFLOW FROM 8E05
8E05
NOTE E
NOTE C
LI
TI
VALVE D
2T02
HCl IN IPA
SP



SECTION 2

NaOH STORAGE

NOTES:-

A. TEMPERATURE CONTROLLER MAINTAINS TEMPERATURE ABOVE MAIN FREEZING POINT

B. VALVE A OPEN WHEN PUMP 1502 OFF, TO DRAIN LINE

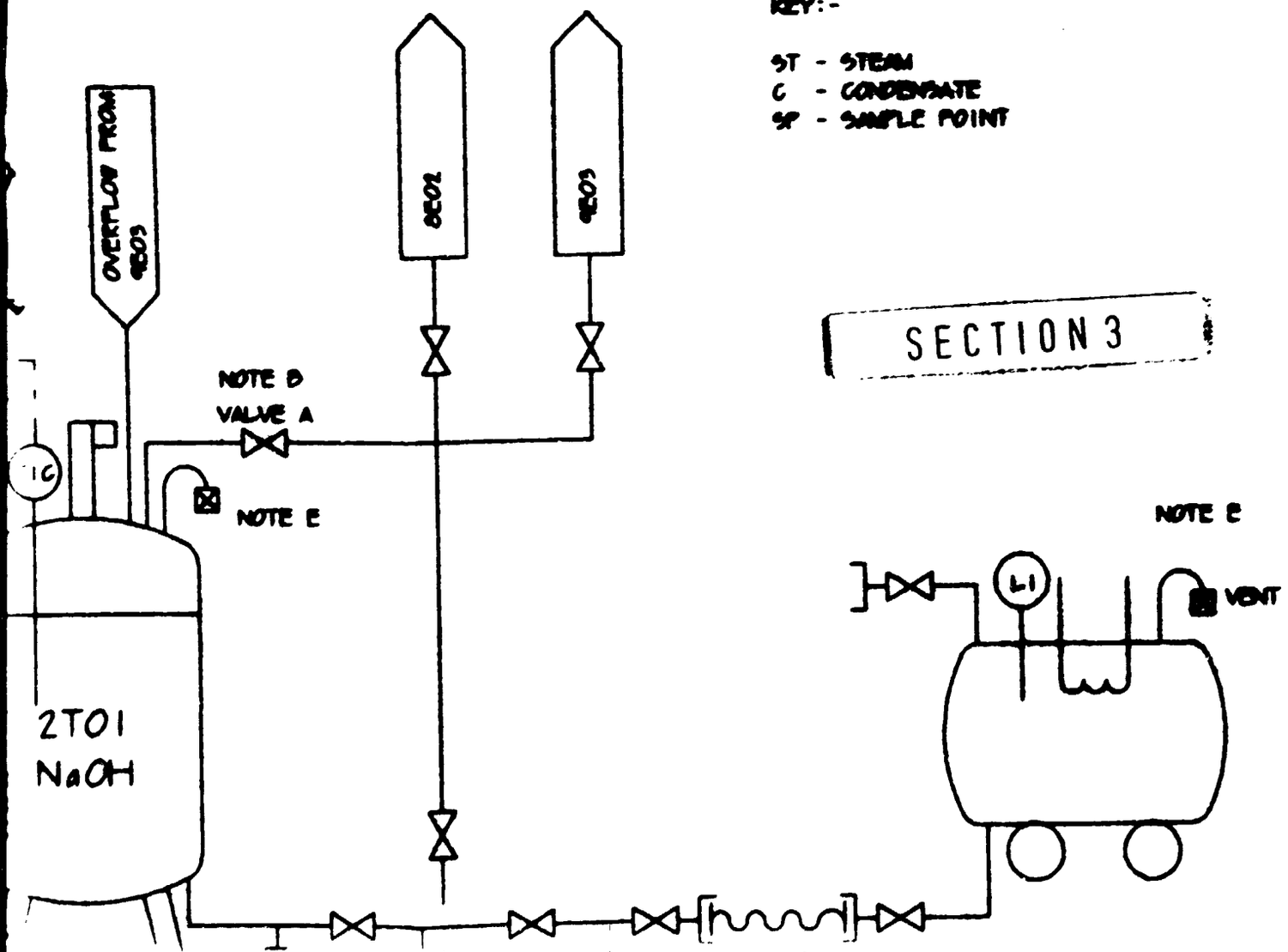
C. VALVE B OPEN WHEN PUMP 1503 OFF, TO DRAIN LINE

D. VESSELS STEAM JACKETED IN DISTILLATE SECTION

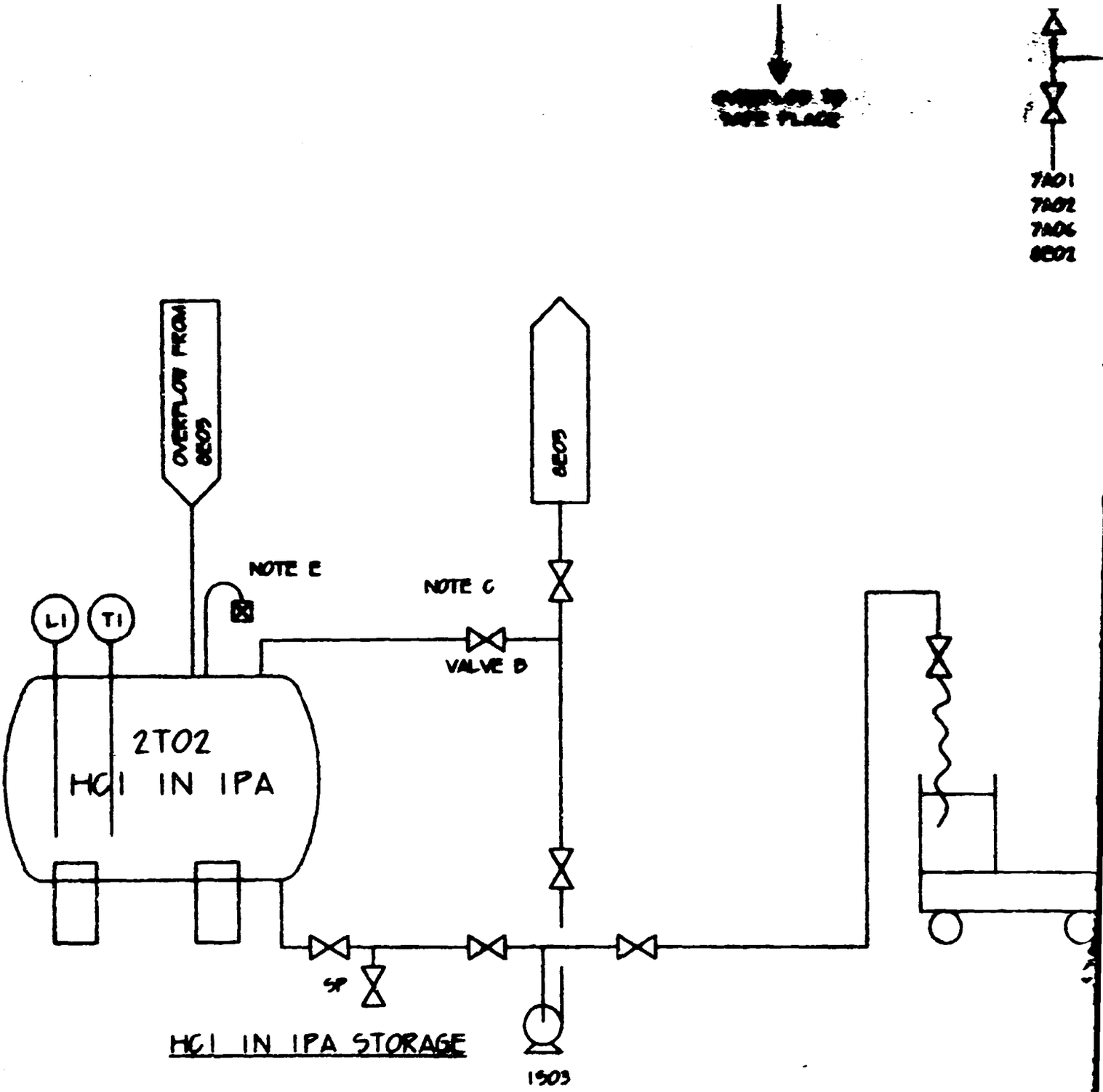
E. FLAME ARRESTING BREATHER ON VENT LINES

KEY:-

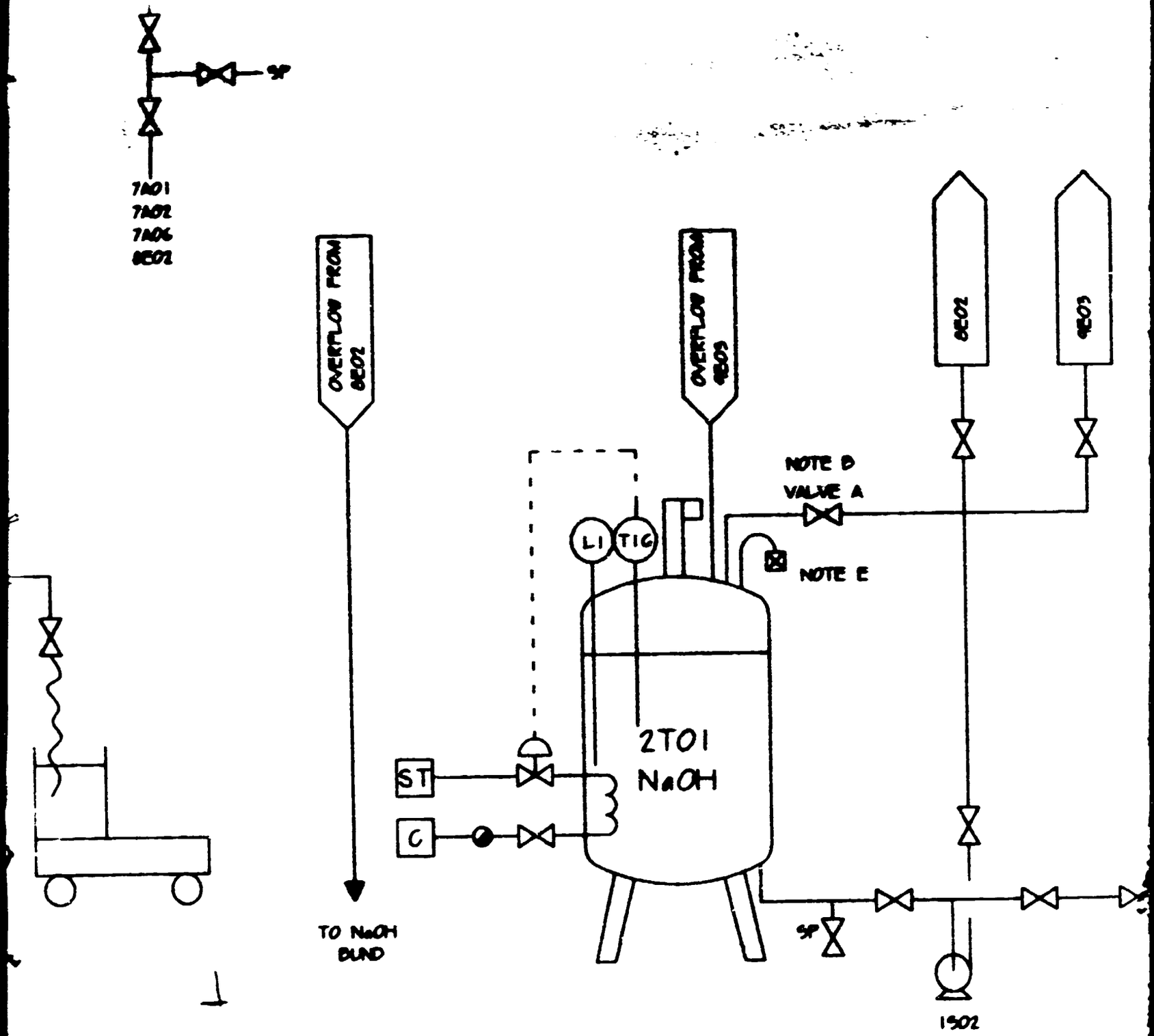
ST - STEAM
C - CONDENSATE
SP - SAMPLE POINT



SECTION 3



CHECKED							GF
APPROVED							
DRAWN BY				ISSUED WITH REPORT	A	14/12/92	WATERCRE
				MODIFICATION	ISSUE	DATE	ST MARY TEL:-04



NaOH STORAGE

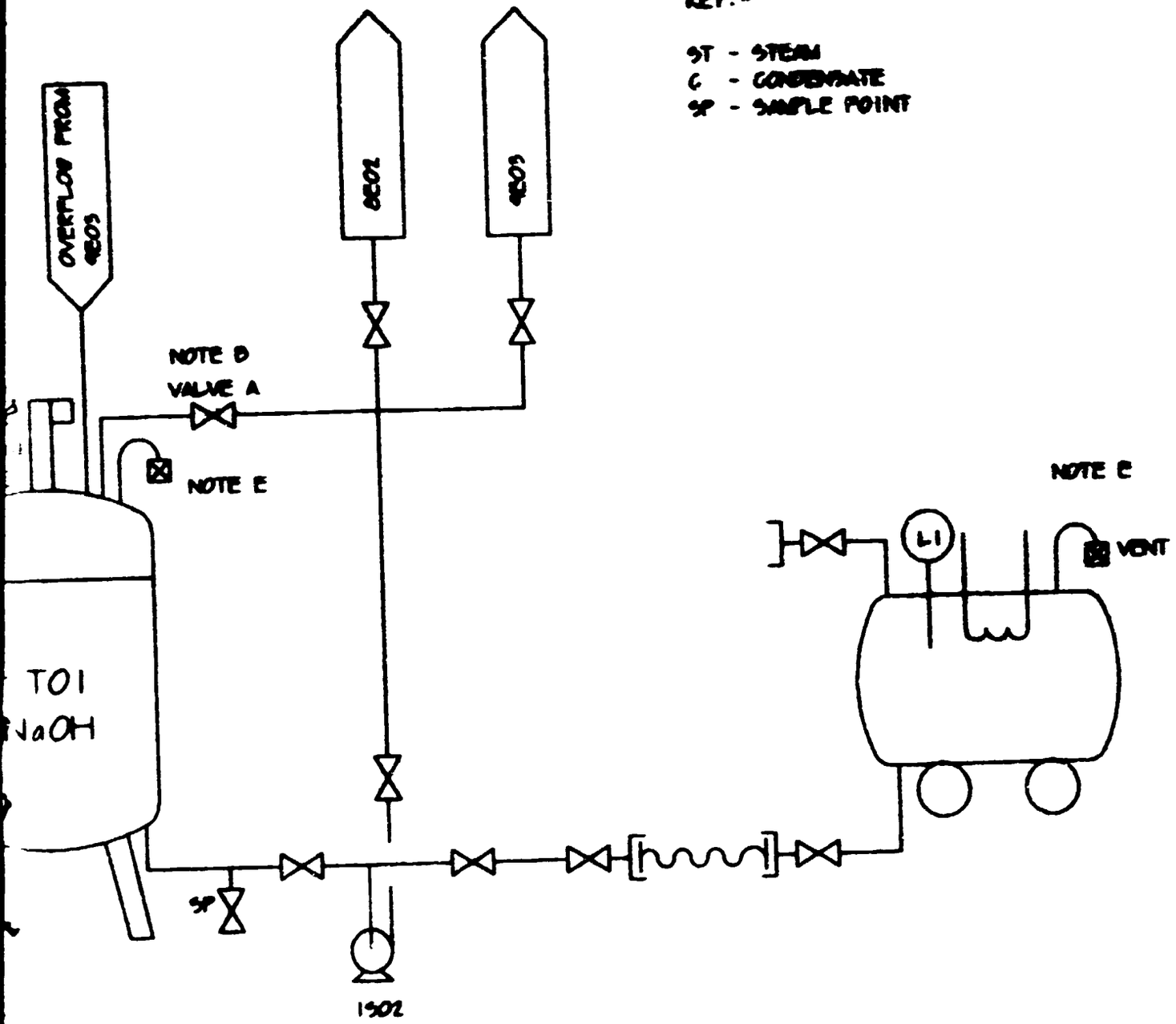
GRC CONSULTANTS WATERCRESS HOUSE 1 THE WINDMILLS ST MARY'S CLOSE ALTON HANTS TEL: -0420 89847 FAX: -0420 89427	CLIENT UNIDO P.O. BOX 300, A-1400 VIENNA, AUSTRIA FAX: 232156	PROJECT ALKALOIDA 2 TF/HUN/90/910
/12/92	DATE: SCALE: DIMENSIONS IN:	

SEPARATE BUNDS

E. [redacted]

KEY:-

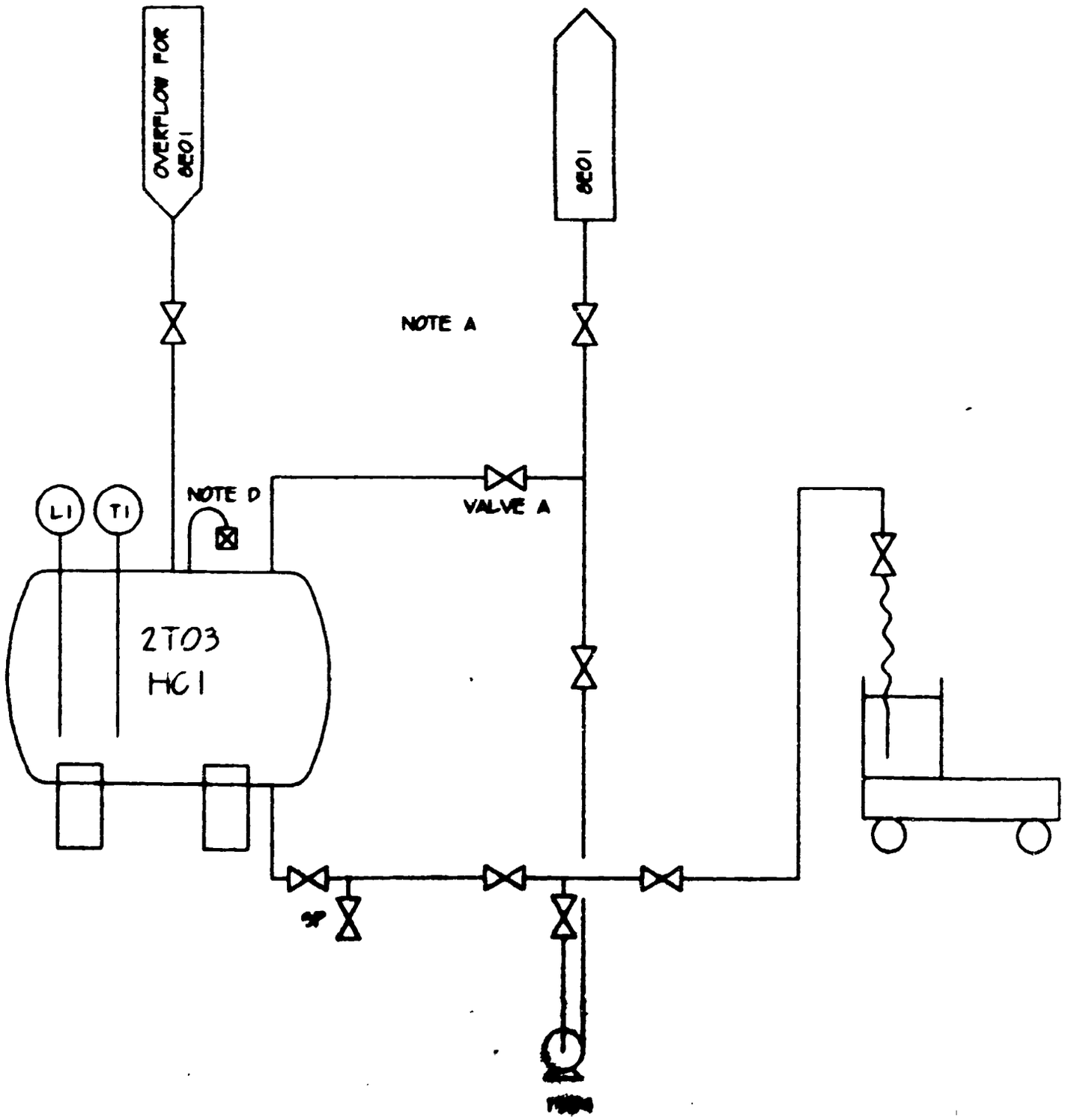
ST - STEAM
C - CONDENSATE
SP - SAMPLE POINT



NaOH STORAGE

x 300, IENNA, AUSTRIA :156	PROJECT ALKALOIDA 2 TF/HUN/90/910	TITLE SUBSYSTEM 12 ENGINEERING LINE DIAGRAM	
		DRAWING NUMBER 92/013/241	REV A

SECTION 1



HCl STORAGE

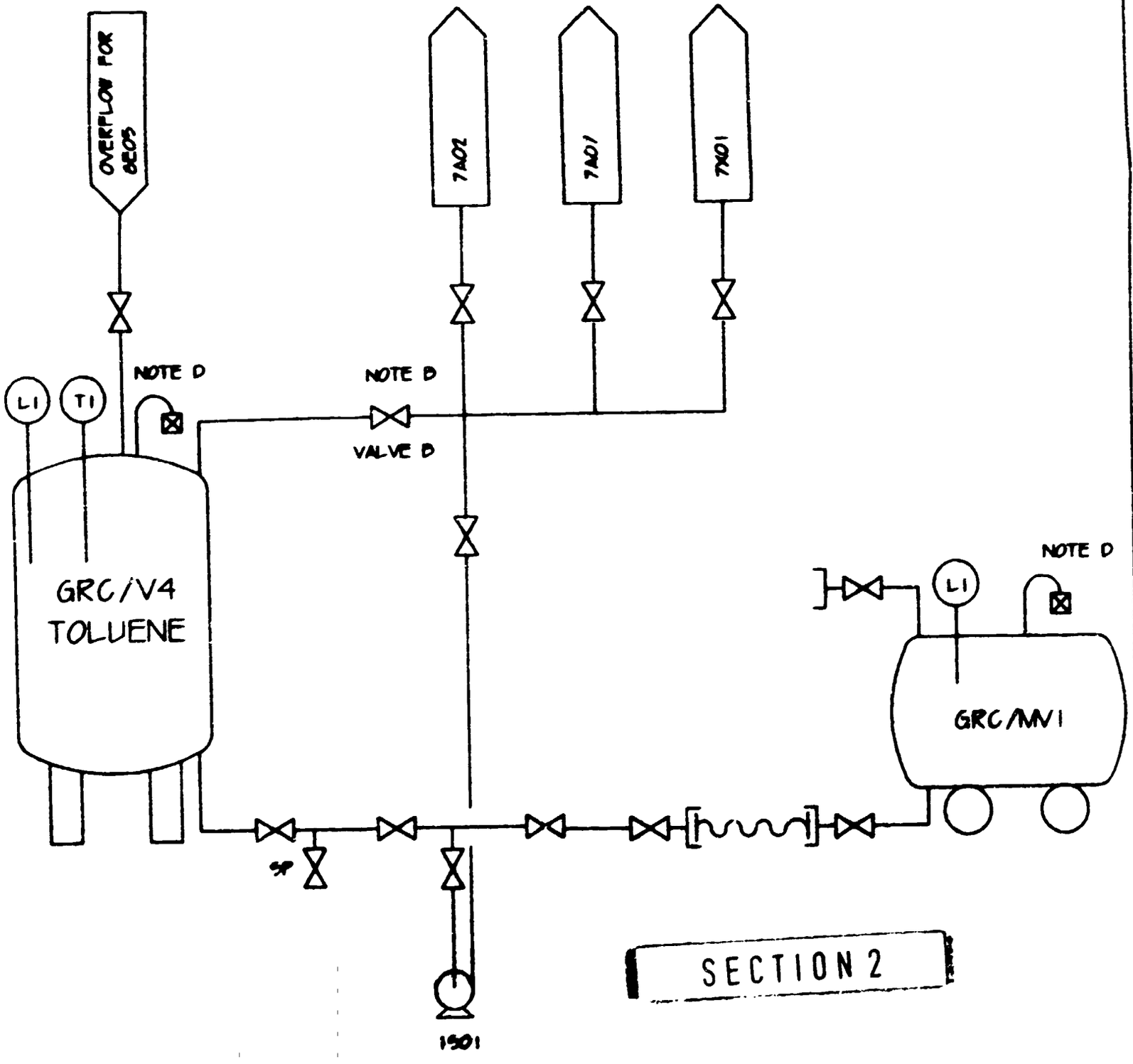
NOTES:-

A. VALVE A OPEN WHEN PUMP 1504 OFF TO DRAIN LINE

B. VALVE B OPEN WHEN PUMP 1501 OFF TO DRAIN LINE

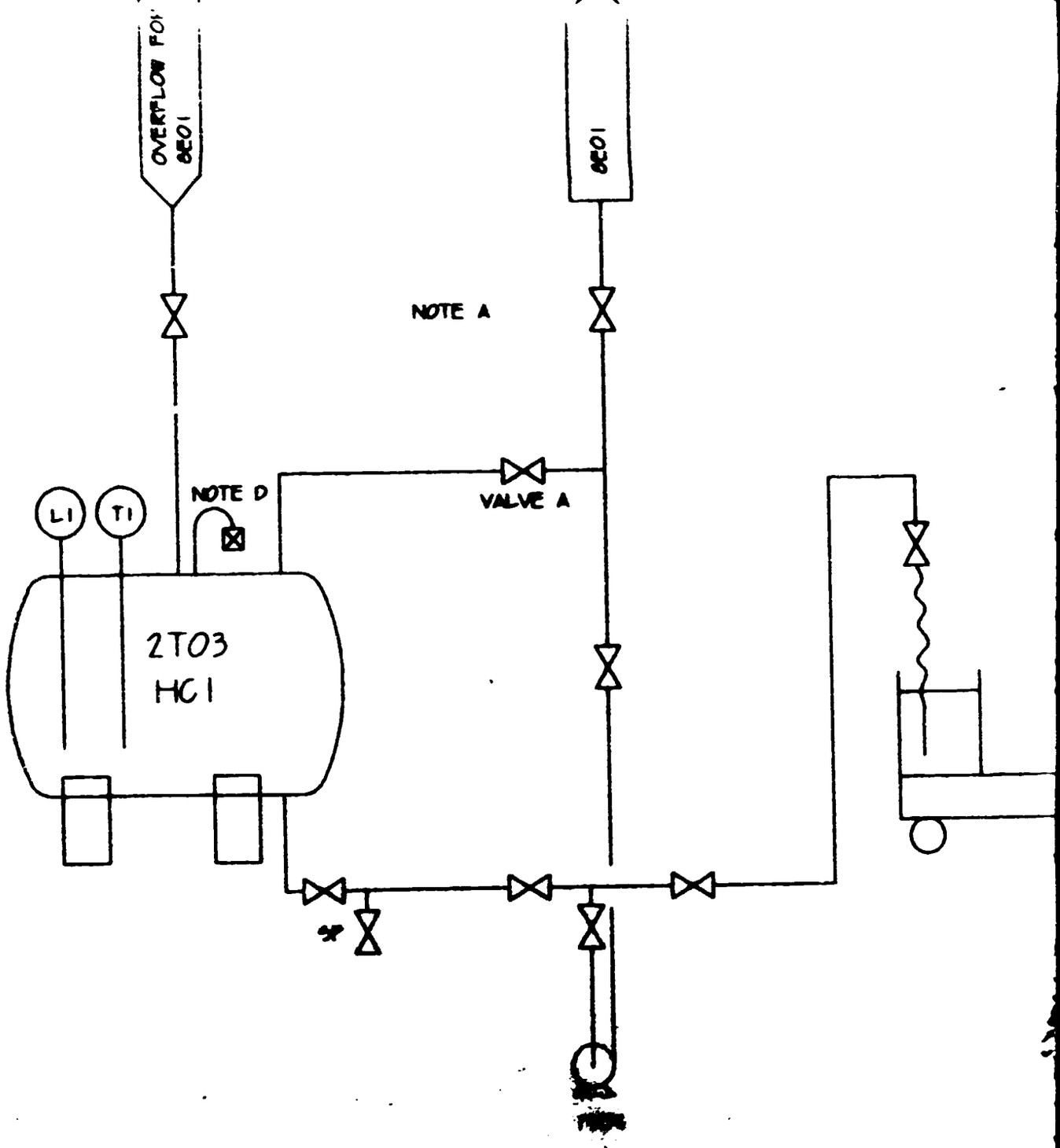
C. VESSEL 2T03 AND GRC/V4 LOCATED IN SEPARATE BUNDS

D. FLAME ARRESTER INSTALLED ON VENT LINES



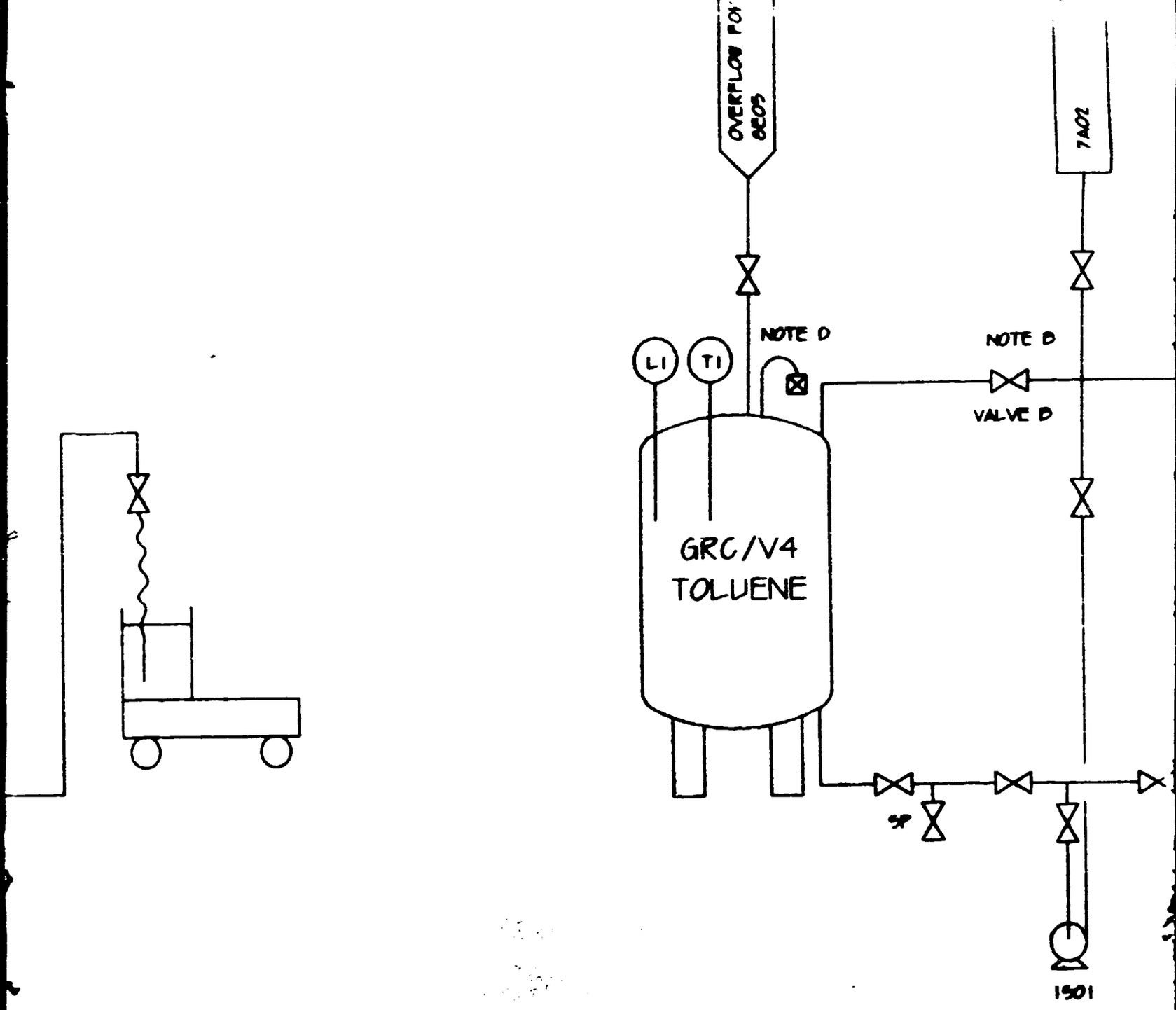
SECTION 2

TOLUENE STORAGE



HCl STORAGE

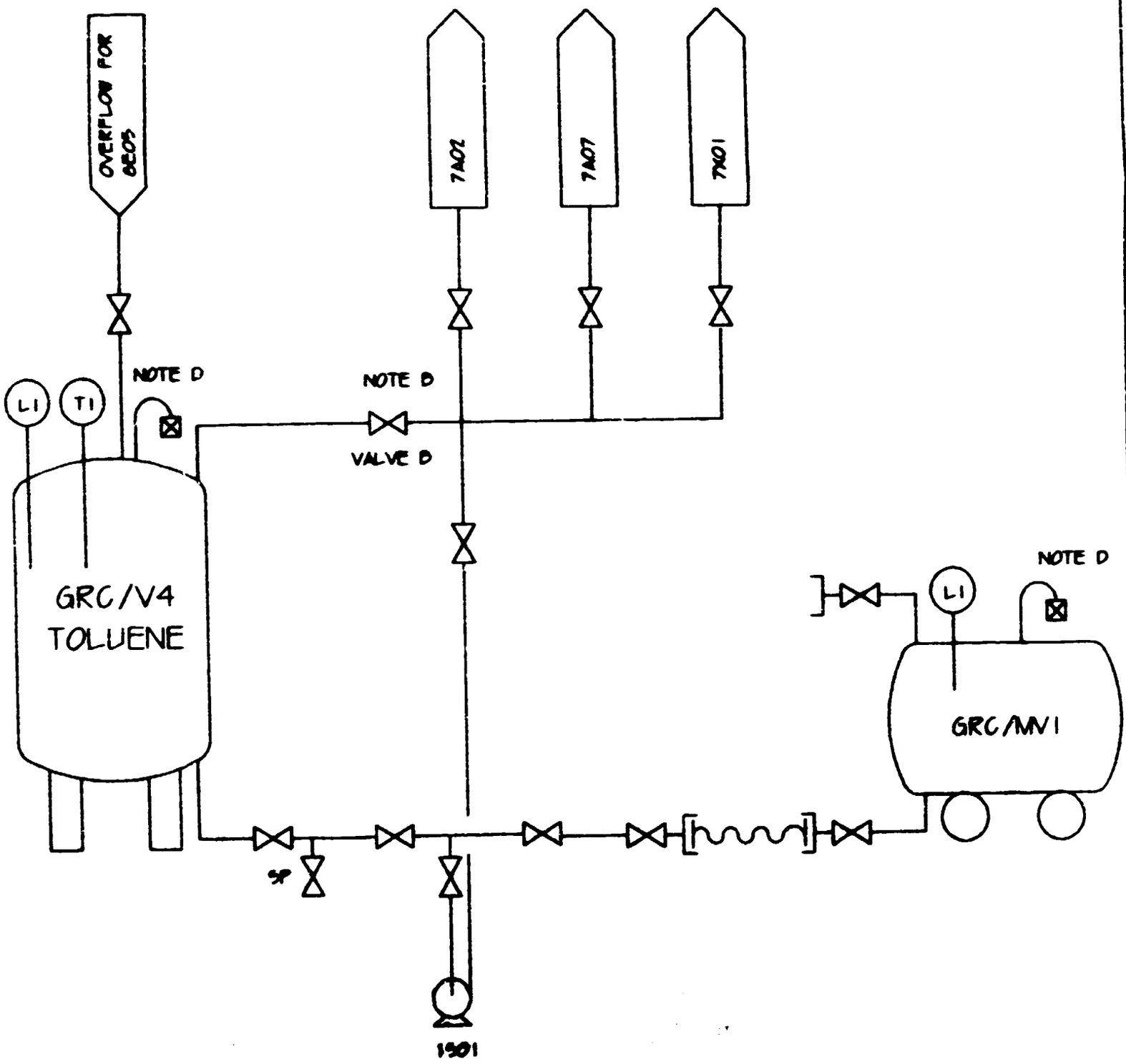
CHECKED							GRC
APPROVED							
DRAWN BY				ISSUED WITH REPORT	A	14/12/92	WATERCRESS ST MARY'S TEL: -0420
				MODIFICATION	ISSUE	DATE	



TOLUENE STORAGE

	GRC CONSULTANTS WATERCRESS HOUSE 1 THE WINDMILLS ST MARY'S CLOSE ALTON HANTS TEL: -0420 84847 FAX: -0420 84427	CLIENT UNIDO P.O. BOX 300, A-1400 VIENNA, AUSTRIA FAX: 232156	PROJECT ALKALOIDA 2 TF/HUN/90/910
4/12/92 DATE		DATE:	
		SCALE:	
		DIMENSIONS IN:	

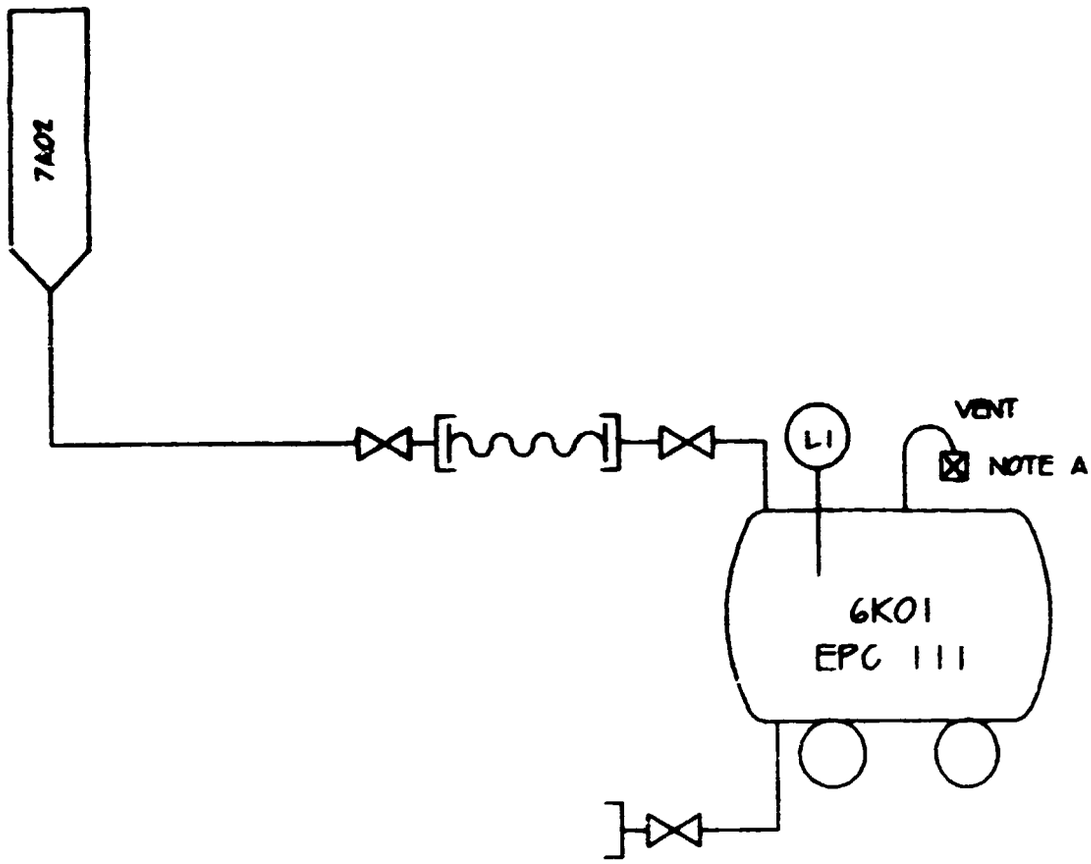
SECTION 4



TOLUENE STORAGE

KEY: SP - SAMPLE POINT

CLIENT UNIDO P.O. BOX 300, A-1400 VIENNA, AUSTRIA FAX: 232156	PROJECT ALKALOIDA 2 TF/HUN/90/910	TITLE SUBSYSTEM 13 ENGINEERING LINE DIAGRAM
DATE: ALE DIMENSIONS IN:		DRAWING NUMBER 92/0 [illegible]
		REV



SECTION 1

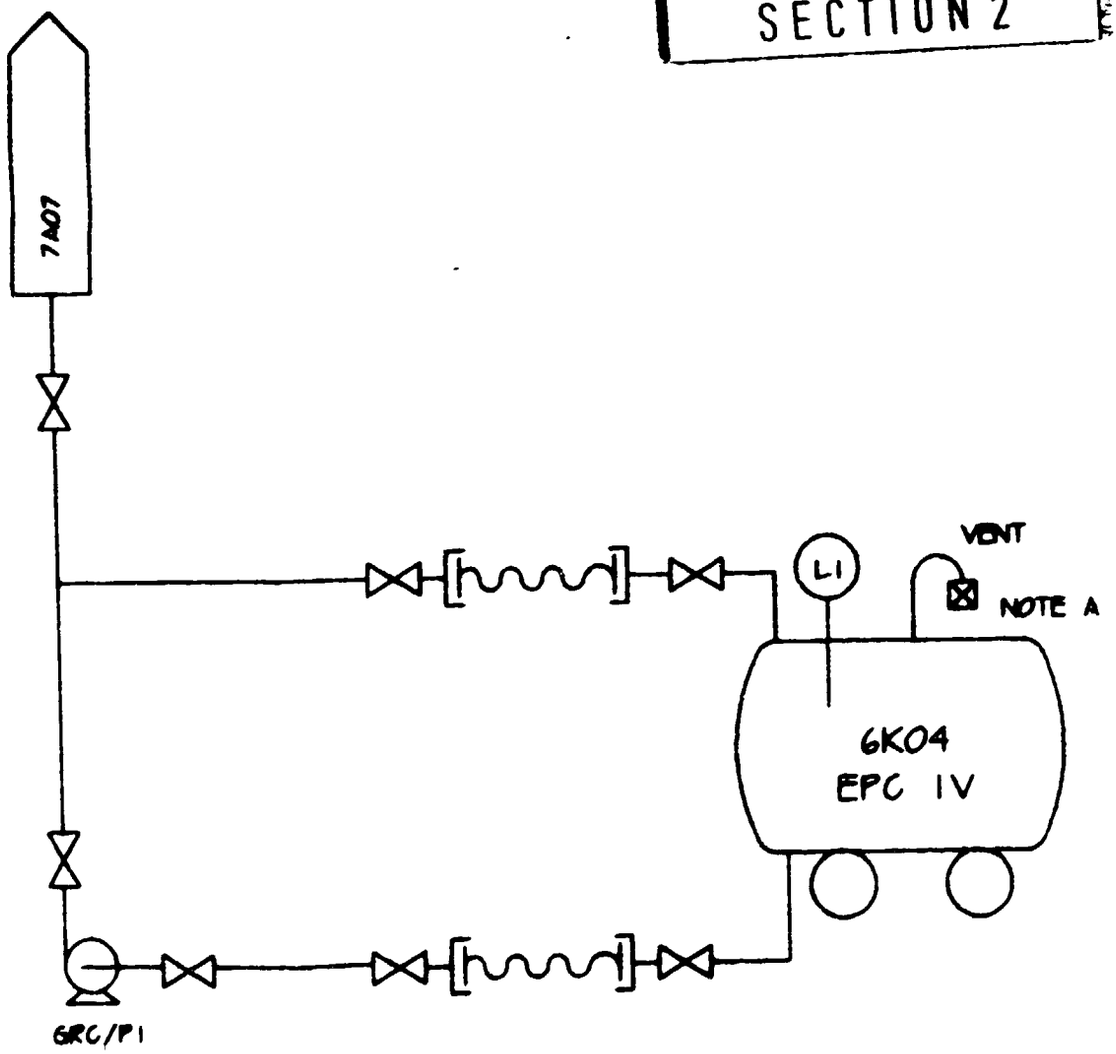
CHECKED						GRC CO
APPROVED						
DRAWN BY				ISSUED WITH REPORT	A	14/12/92

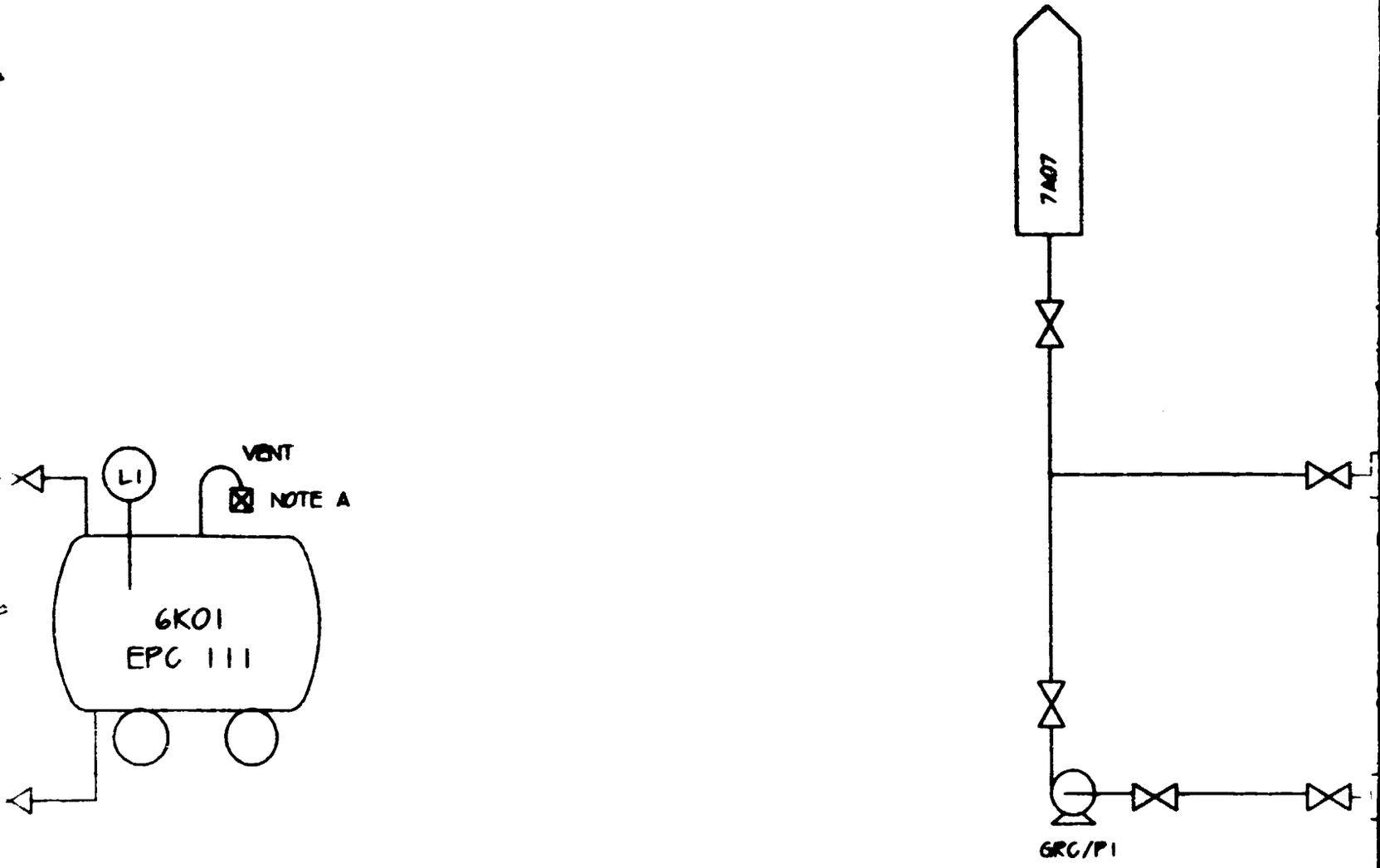
WATERCRESS HO
ST MARY'S CLO

NOTE:-

A. FLAME ARRESTER INSTALLED ON VENT LINES

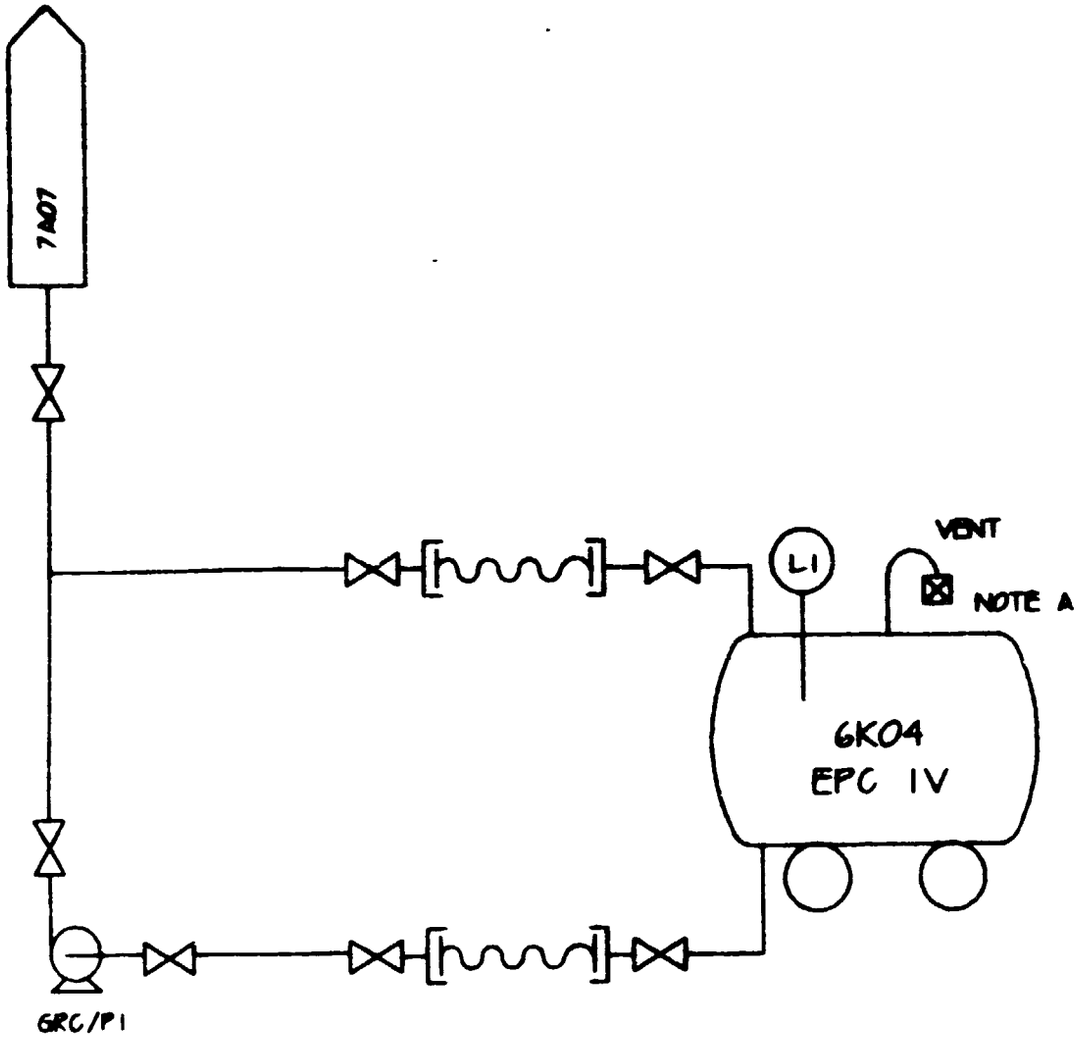
SECTION 2





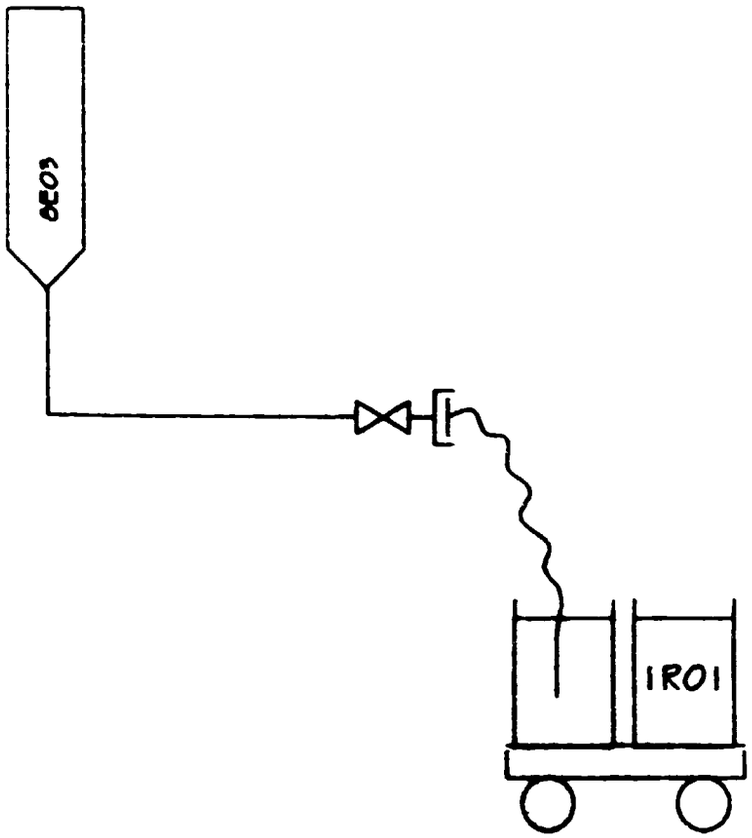
		GRC CONSULTANTS	CLIENT UNIDO P.O. BOX 300, A-1400 VIENNA, AUSTRIA FAX: 232156	PROJECT ALKALOIDA TF/HUN/90/
		WATERCRESS HOUSE 1 THE WINDMILLS	DATE:	
A	14/12/92	ST MARY'S CLOSE ALTON HANTS	SCALE:	
ISSUE	DATE	TEL:-0420 89847 FAX:-0420 89427	DIMENSIONS IN:	

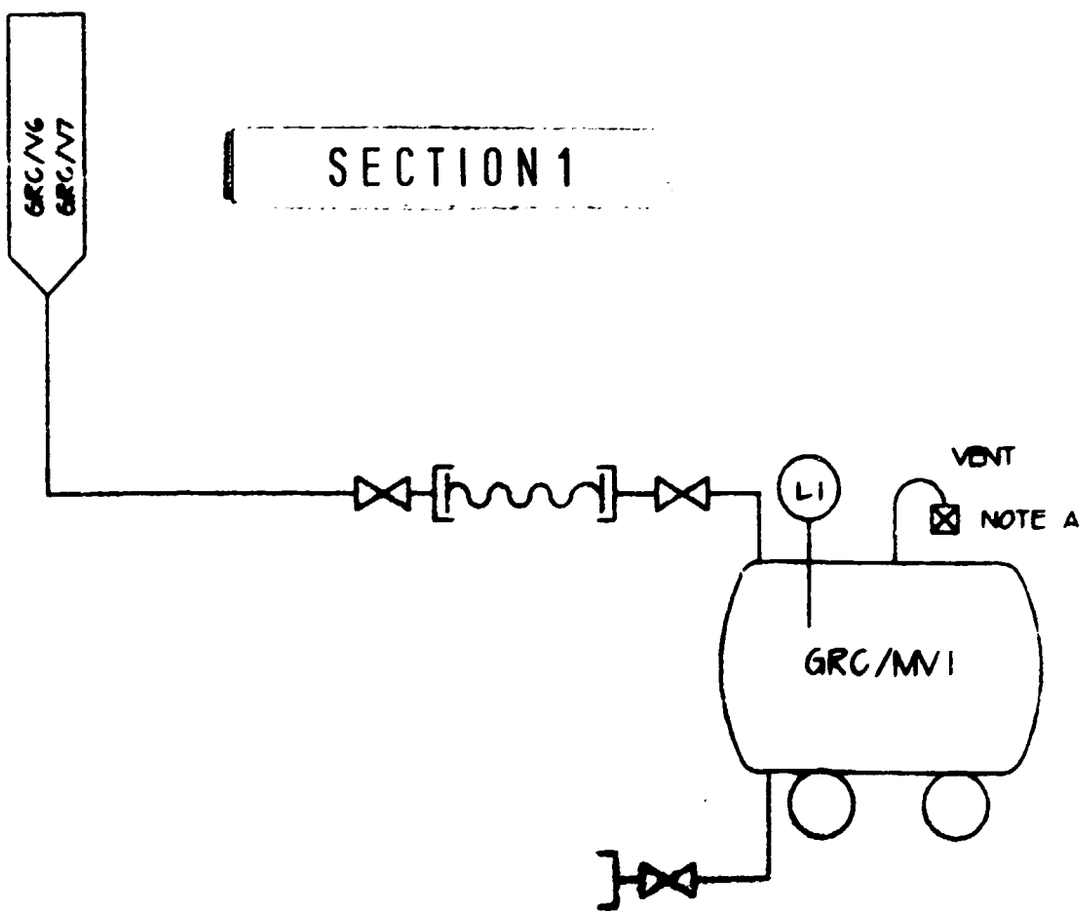
SECTION 3



SECTION 4

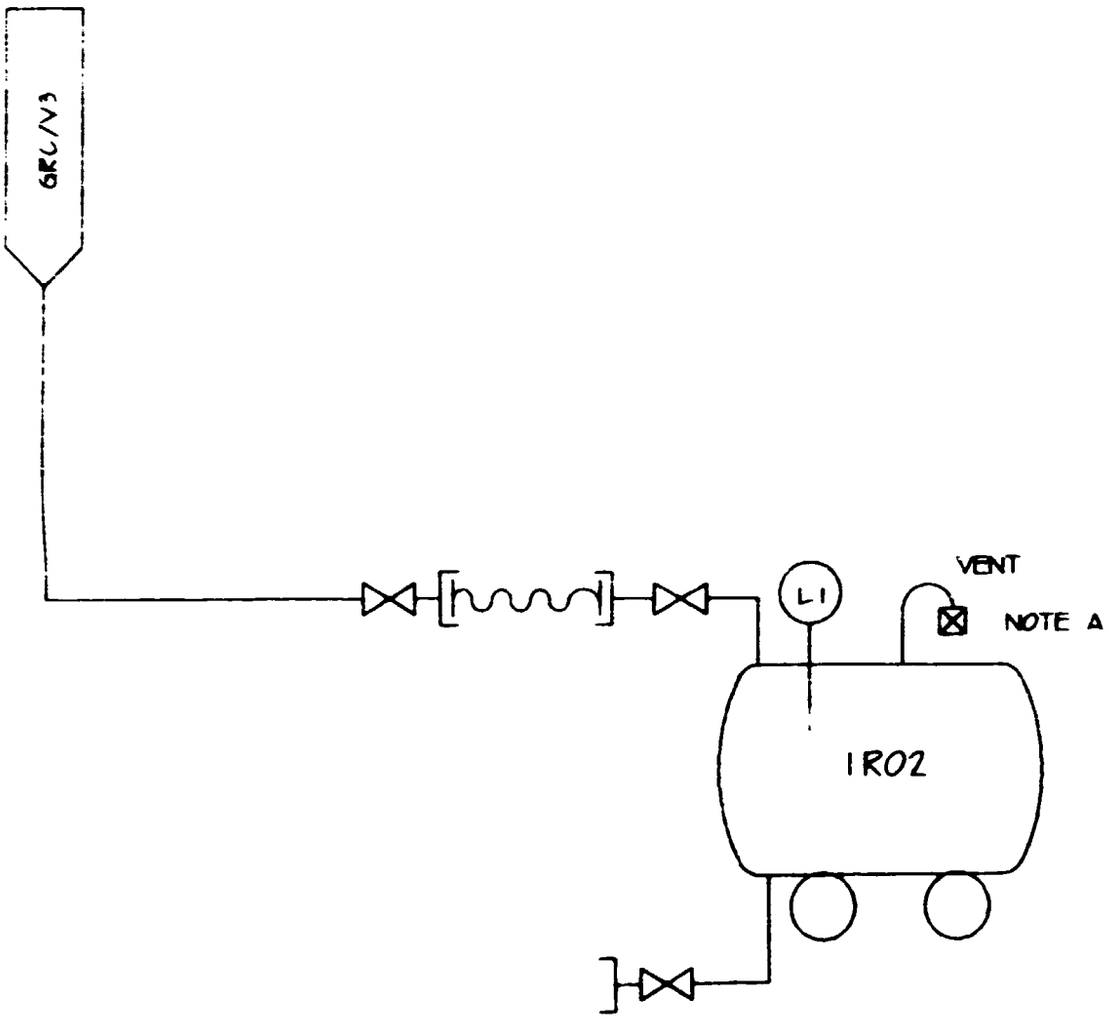
ox 300, VIENNA, AUSTRIA 2156	PROJECT ALKALOIDA 2 TF/HUN/90/910	TITLE SUBSYSTEM 14 ENGINEERING LINE DIAGRAM	
		DRAWING NUMBER 92/013/243	REV A
ONS IN:			

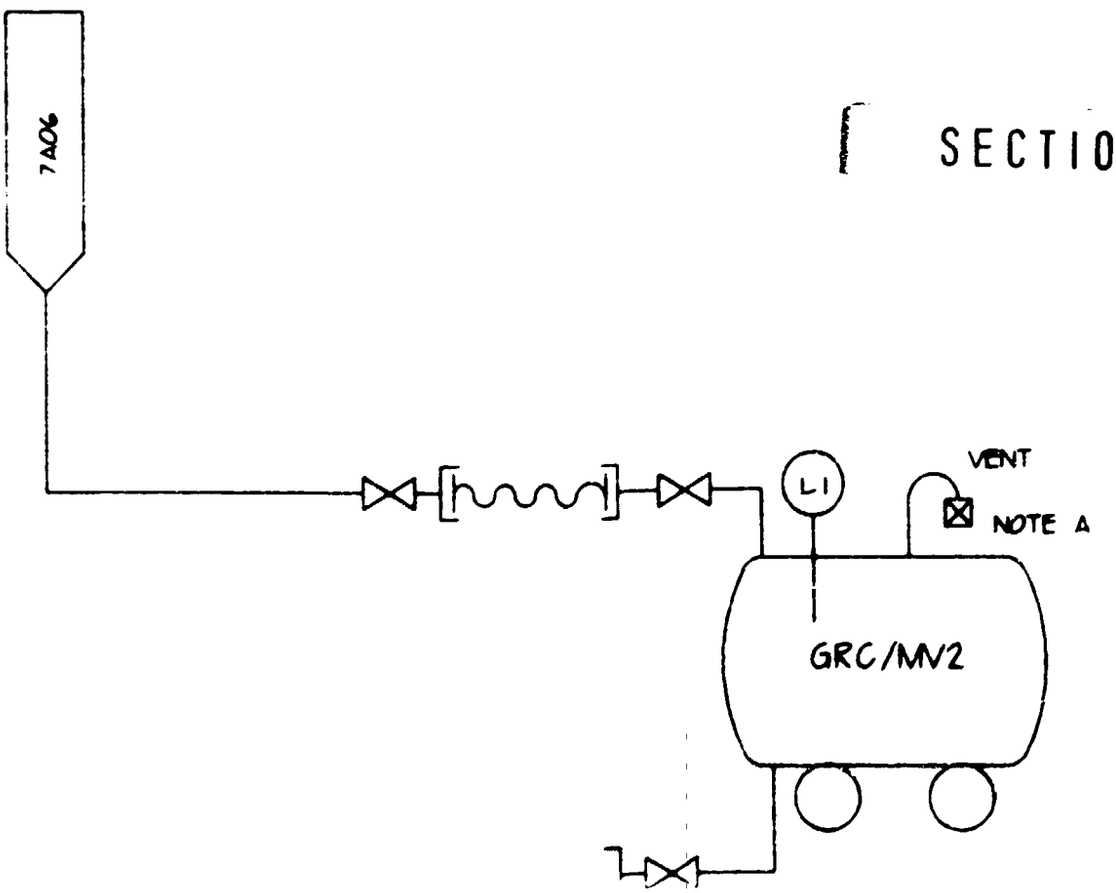

GEO3
1R01


GRC/V6
GRC/V7
SECTION 1
LI
VENT
NOTE A
GRC/MV1

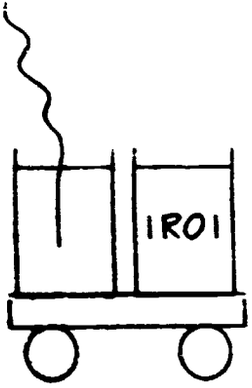
NOTE -

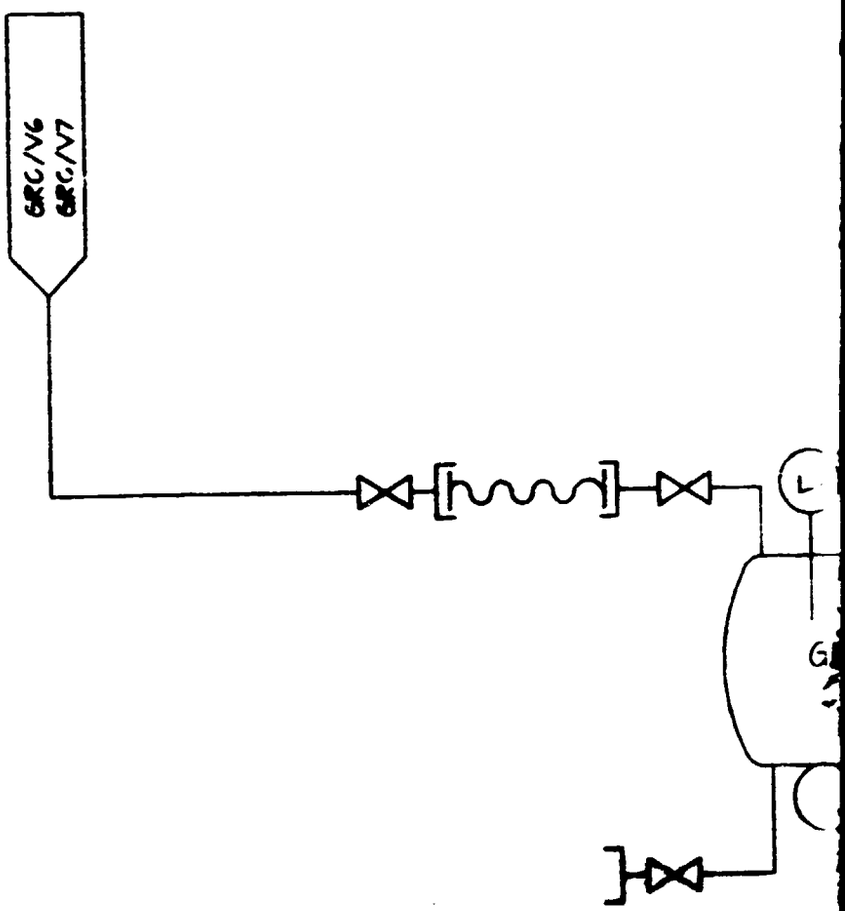
1 FLAME ARRESTER INSTALLED ON VENT LINES





SECTION 2

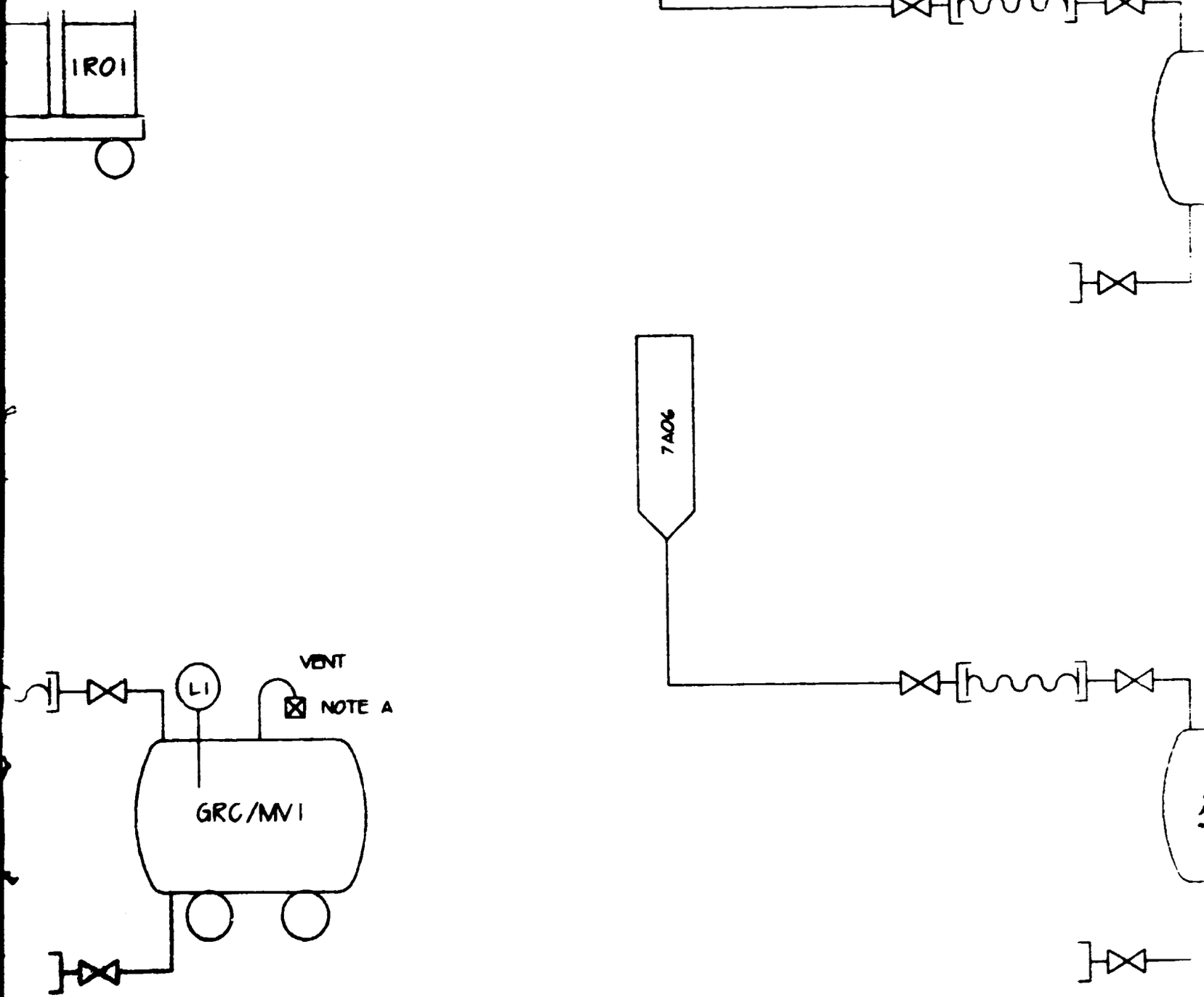




CHECKED						
APPROVED						
DRAWN BY				ISSUED WITH REPORT	A	24/12/92
				MODIFICATION	MARK	DATE

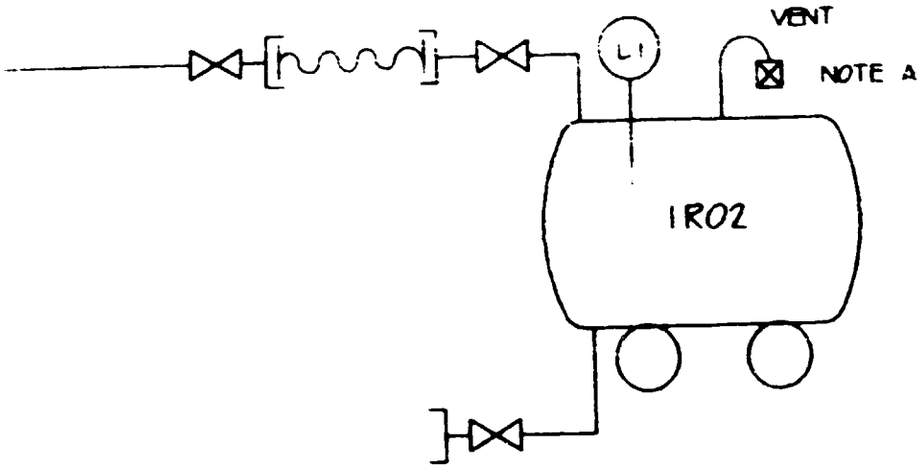
WATER
ST MA
TEL:

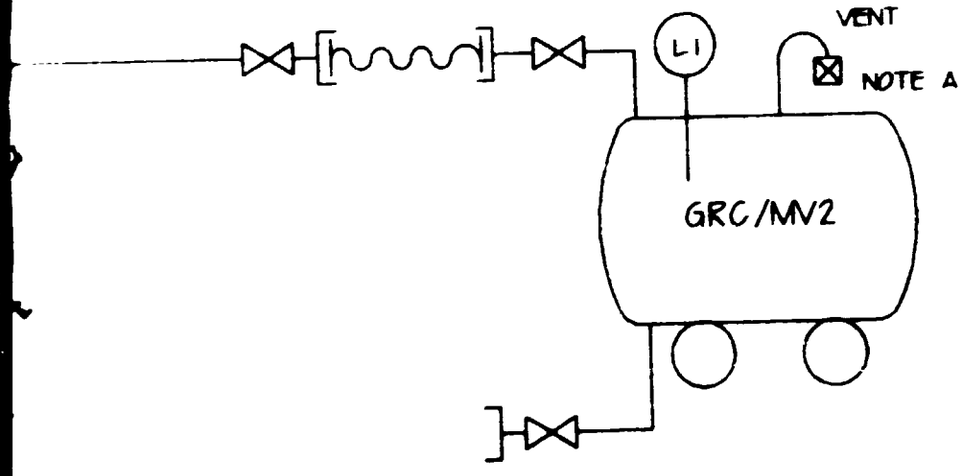
SECTION 3



	GRC CONSULTANTS WATERCRESS HOUSE 1 THE WINDMILLS ST MARY'S CLOSE ALTON HANTS TEL -0420 89847 FAX -0420 89427	CLIENT UNIDO P.O. BOX 300, A-1400 VIENNA, AUSTRIA FAX: 232156	PROJECT ALKALOIDA 2 TF/HUN/90/91
		DATE:	
		SCALE:	
		DIMENSIONS	

SECTION 4

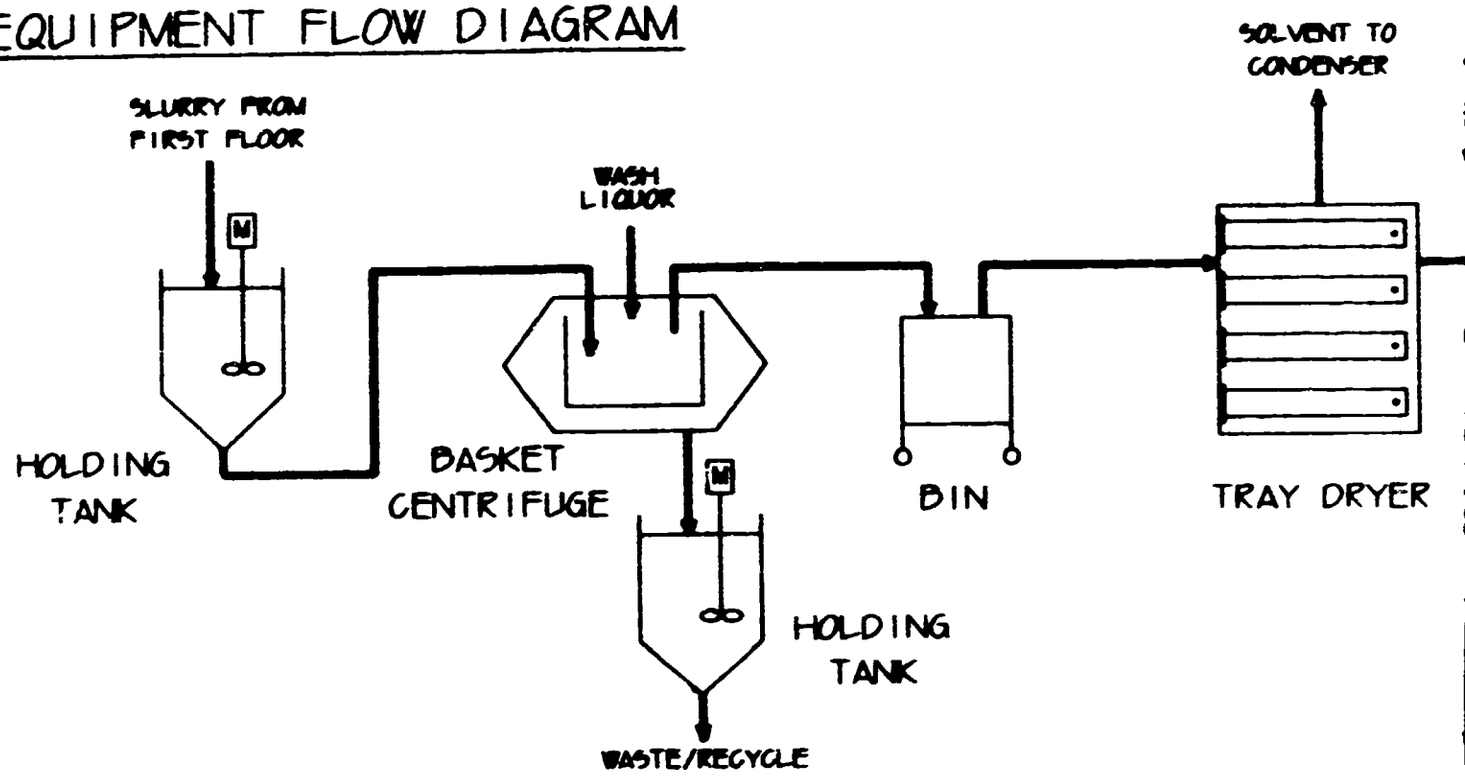




300, ENNA, AUSTRIA 156	PROJECT ALKALOIDA 2 TF/HUN/90/910	TITLE SUBSYSTEM 15 ENGINEERING LINE DIAGRAM
		DRAWING NUMBER 92/013/244 — REV A

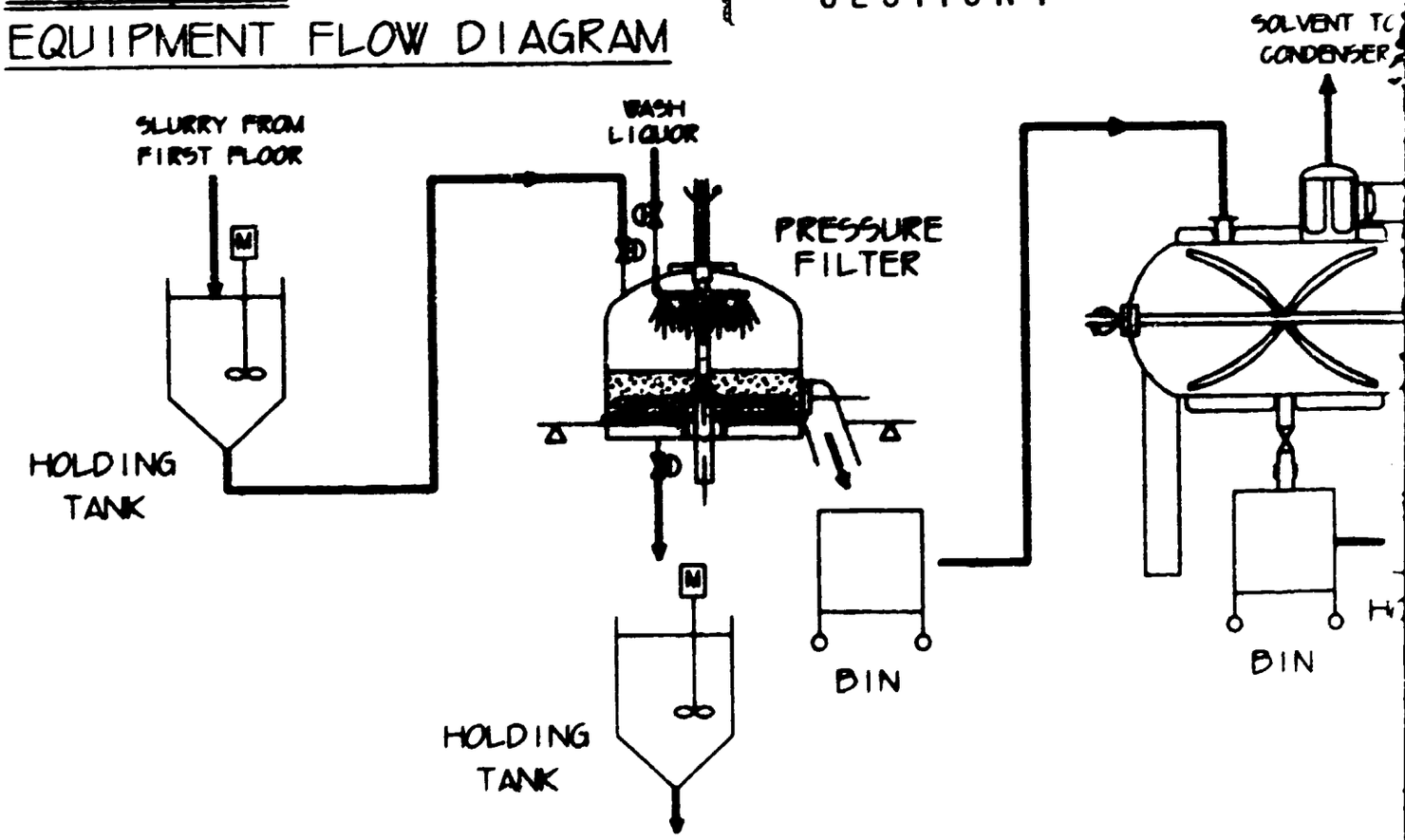
SECTION 5

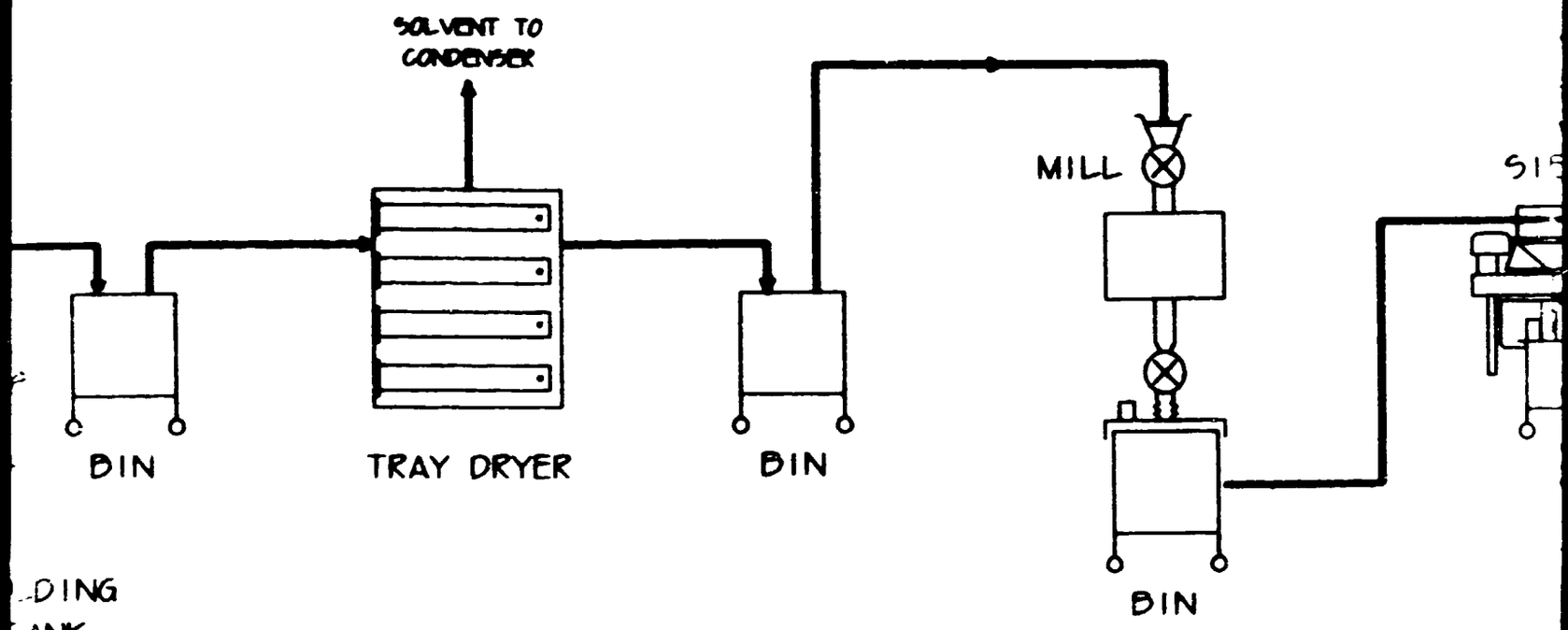
PROCESS 1
EQUIPMENT FLOW DIAGRAM



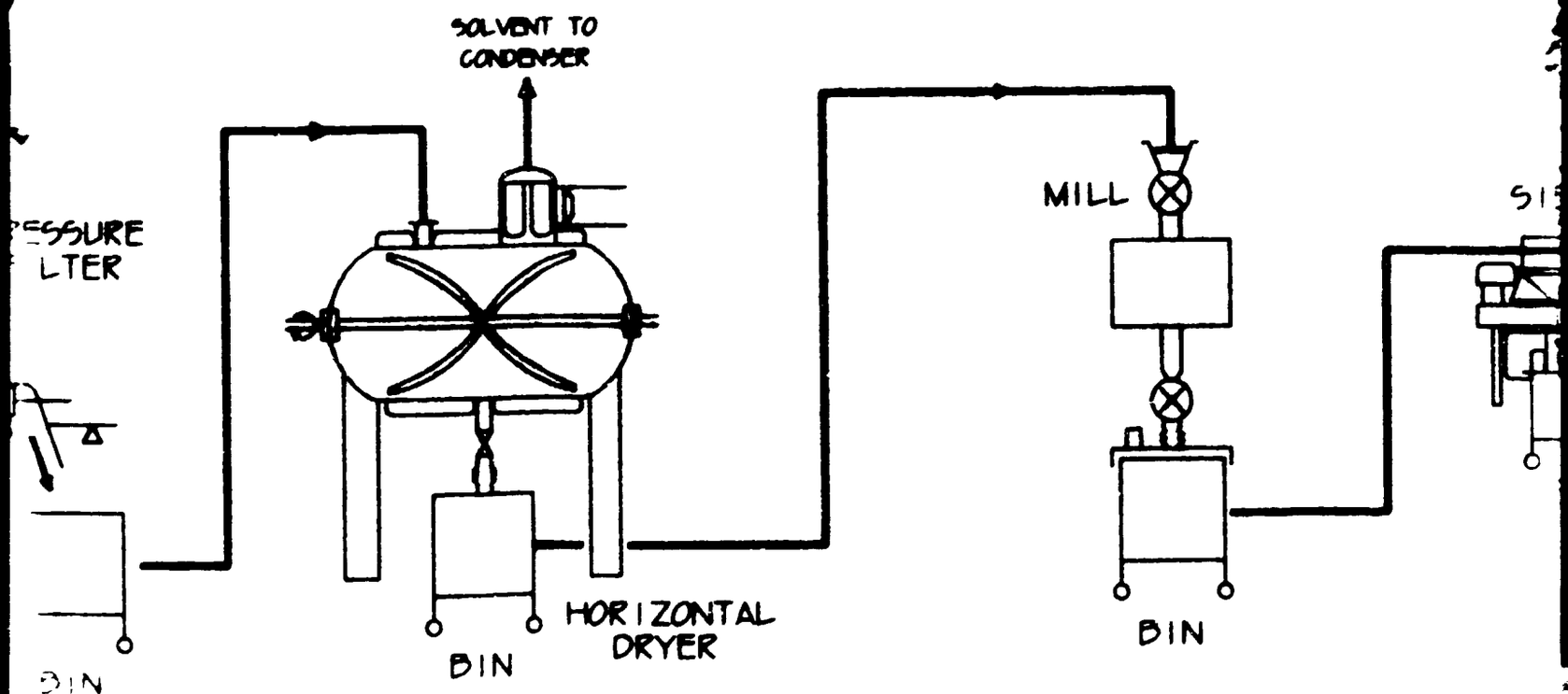
PROCESS 2
EQUIPMENT FLOW DIAGRAM

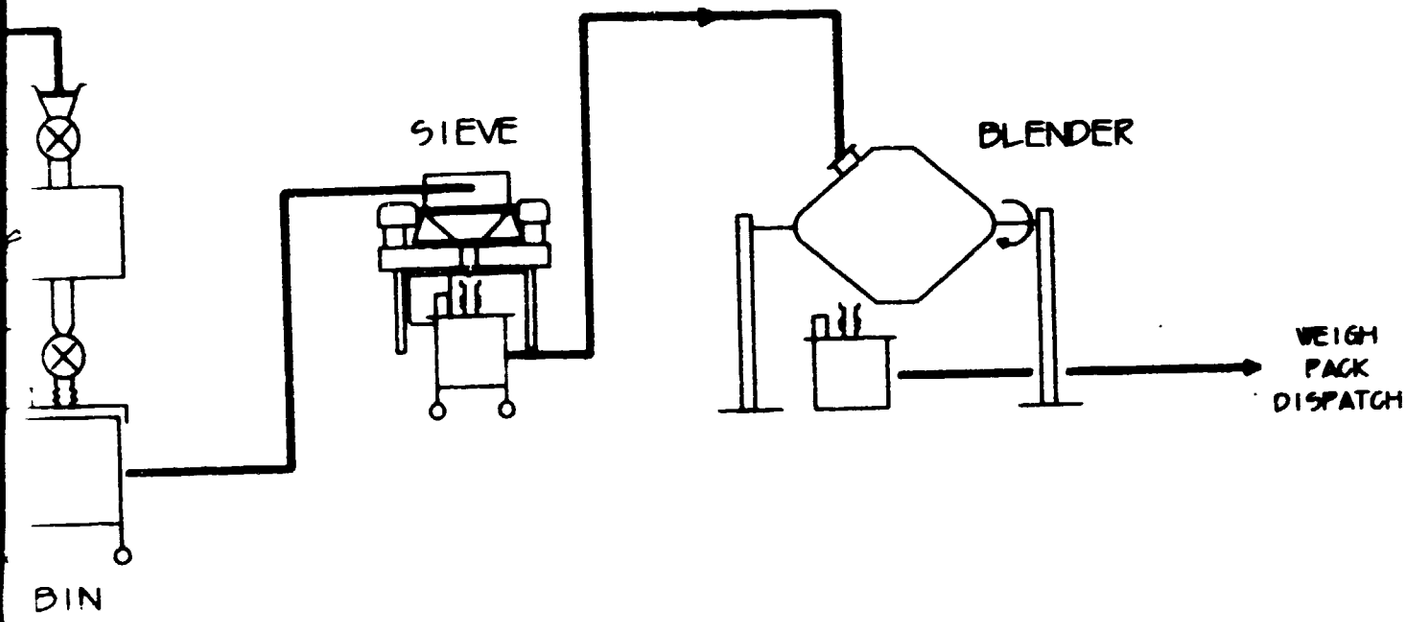
SECTION 1



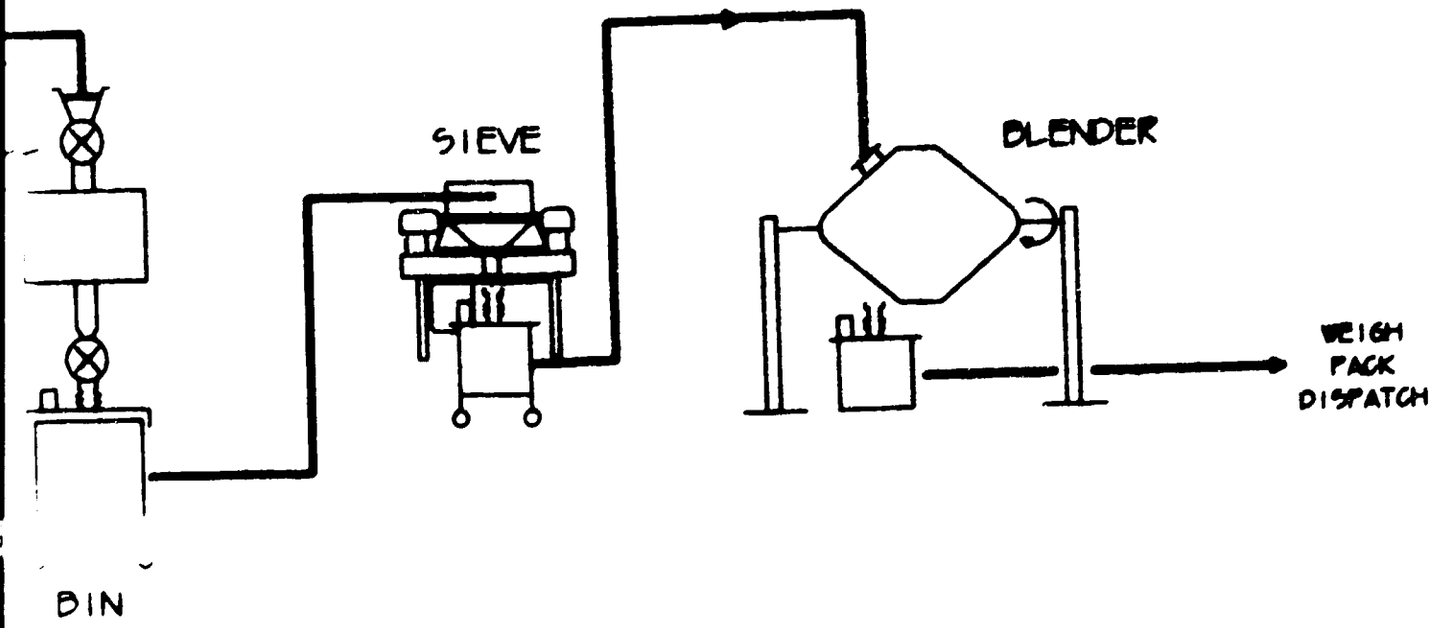

SOLVENT TO CONDENSER
MILL
BIN
TRAY DRYER
BIN
BIN

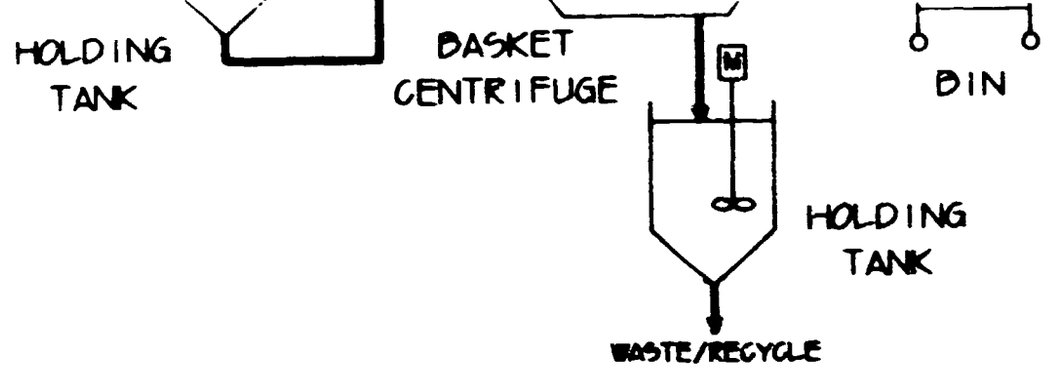
SECTION 2


SOLVENT TO CONDENSER
MILL
BIN
BIN
HORIZONTAL DRYER
BIN

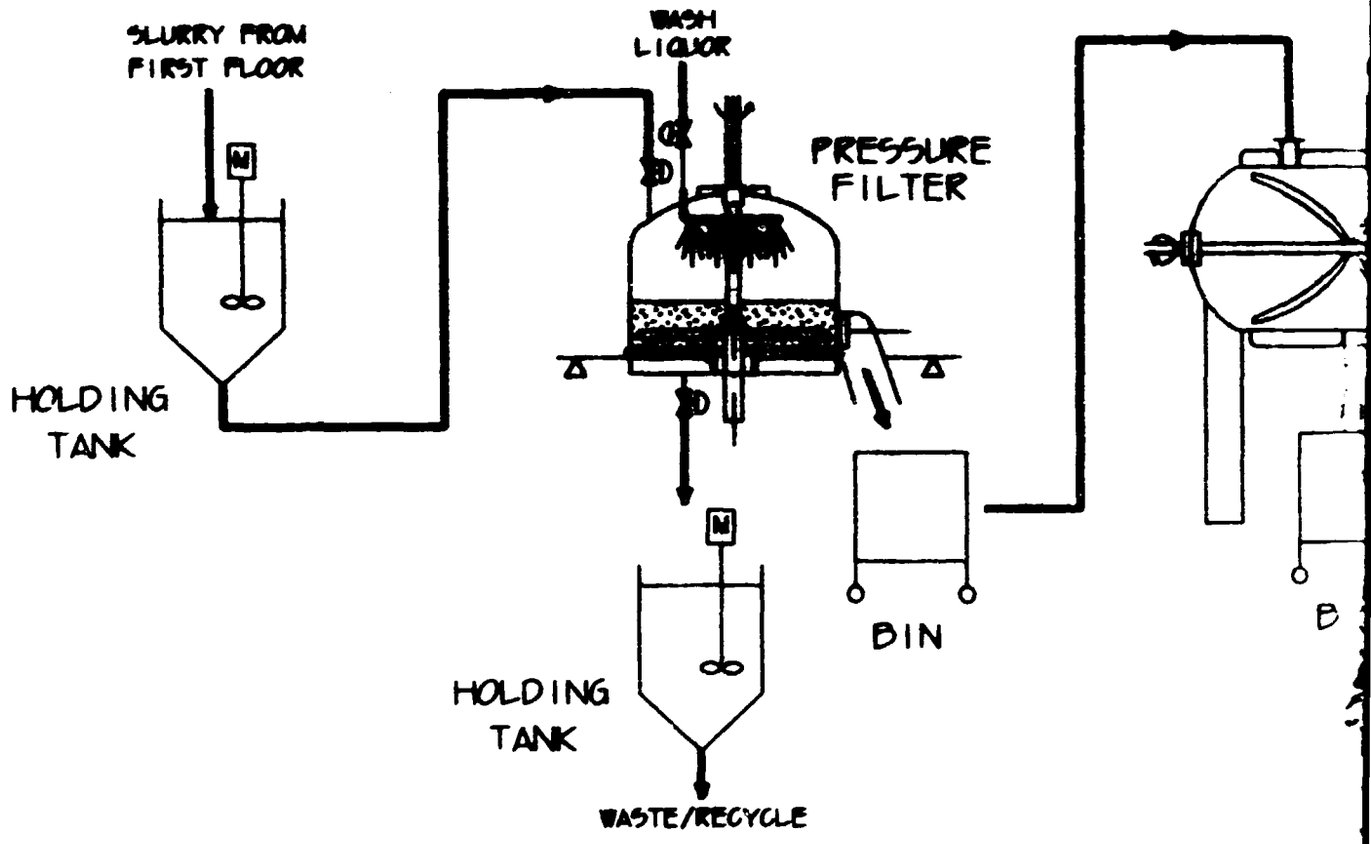

SIEVE
BLENDER
WEIGH
PACK
DISPATCH
BIN

SECTION 3

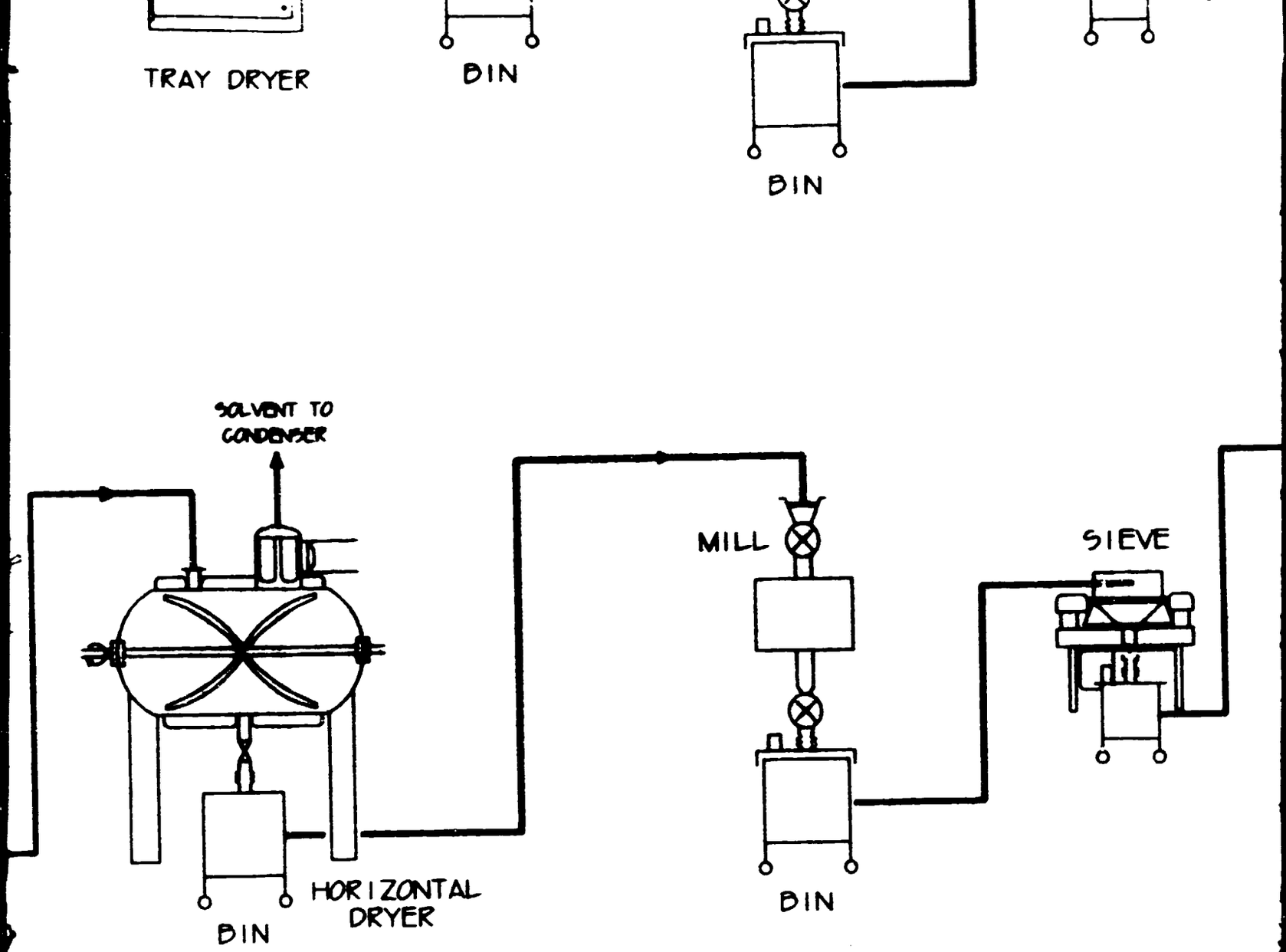

SIEVE
BLENDER
WEIGH
PACK
DISPATCH
BIN



PROCESS 2
EQUIPMENT FLOW DIAGRAM

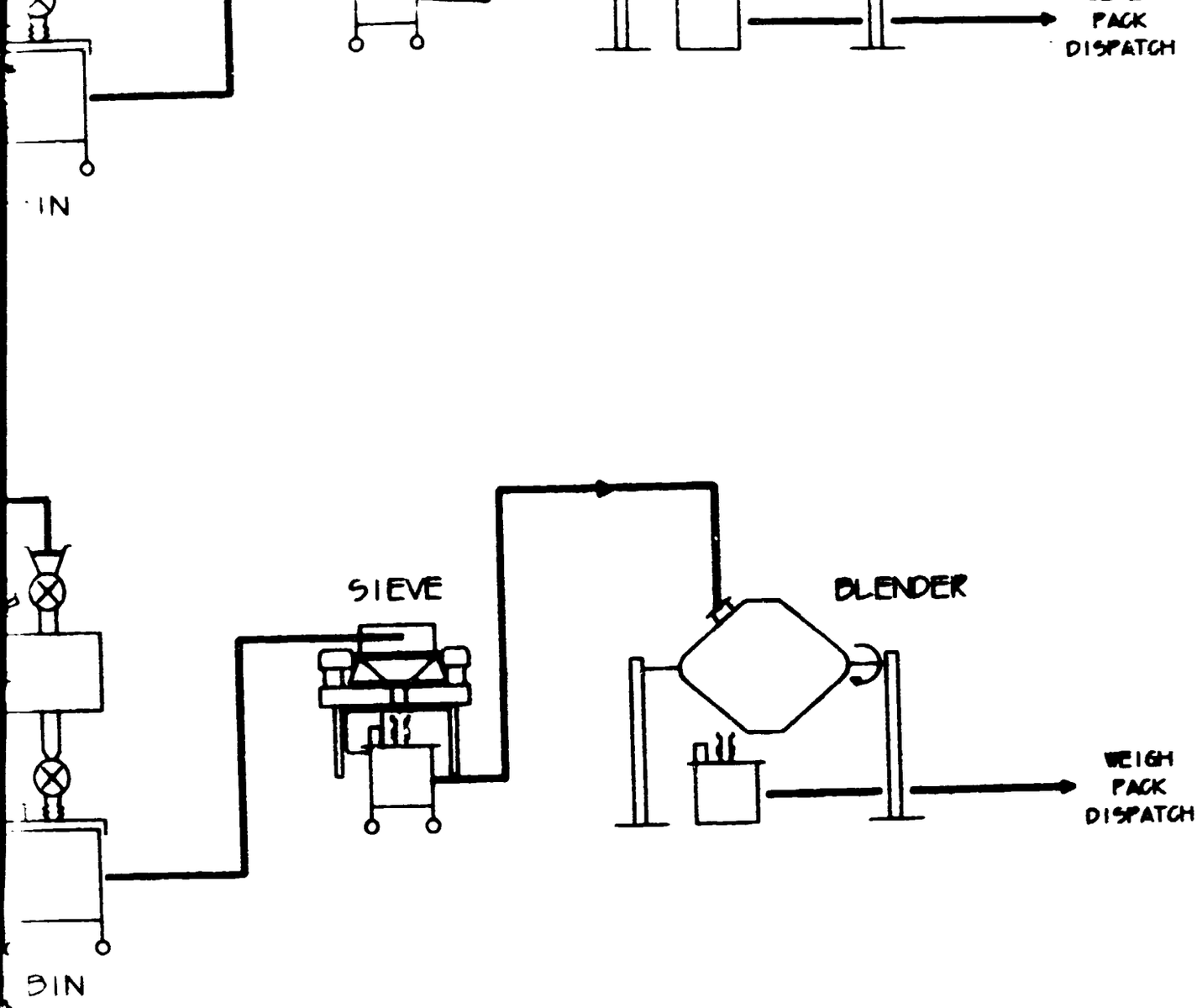


CHECKED							
APPROVED JD							
DRAWN BY CS				ISSUED FOR REPORT	D	7/1 2/92	WATER ST MAR TEL C
				MODIFICATION	ISSUE	DATE	



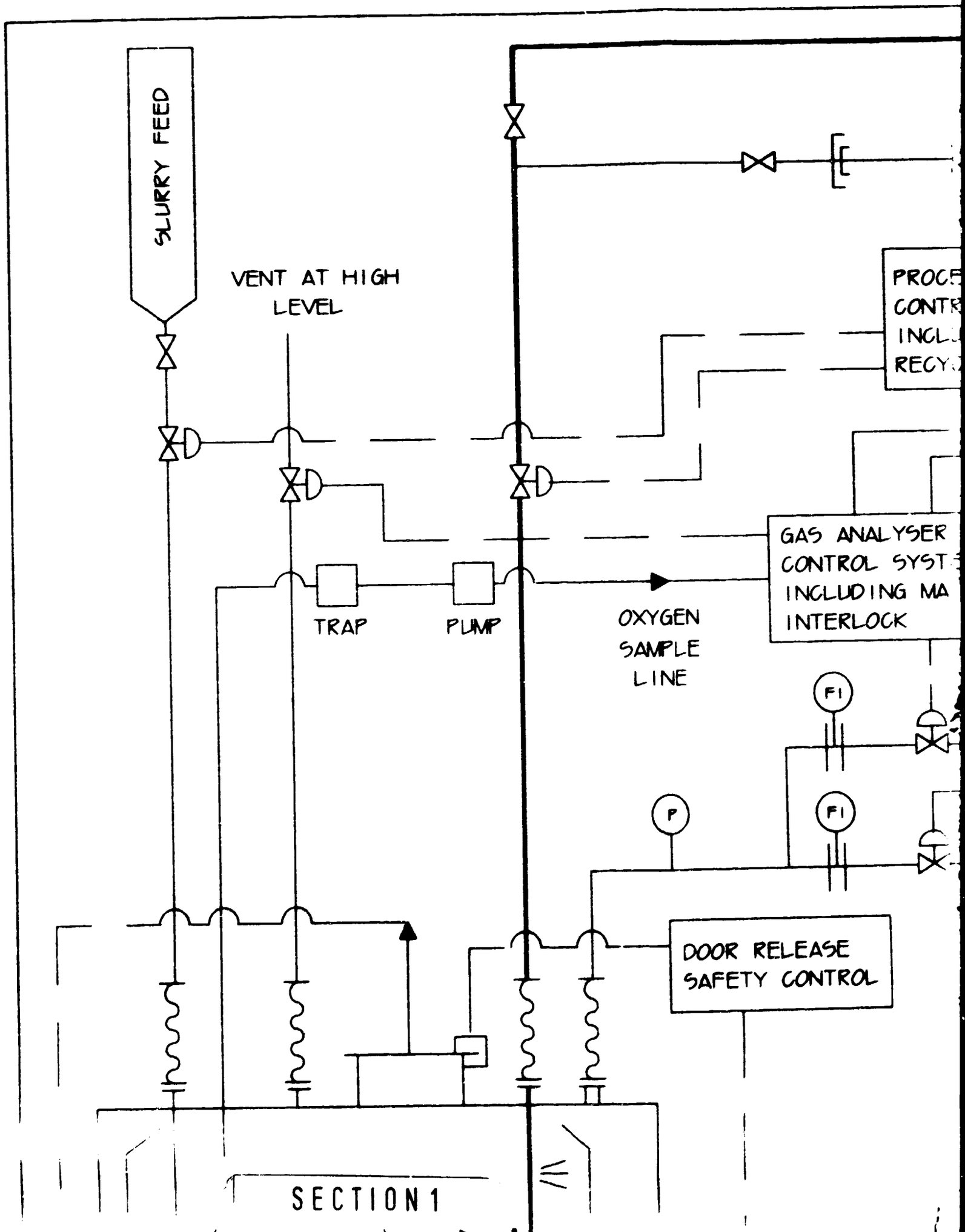
	GRC CONSULTANTS WATERCRESS HOUSE 1 THE WINDMILLS ST MARY'S CLOSE ALTON HANTS TEL 0420 89847 FAX 0420 89427	CLIENT UNIDO, P.O.BOX 300, A-1400 VIENNA, AUSTRIA, FAX: 2321 56	PROJECT ALKALI TF/HUN
7/12/92		DATE: JUNE 1992	
DATE		SCALE: N.T.S.	
		DIMENSIONS IN: METRES	

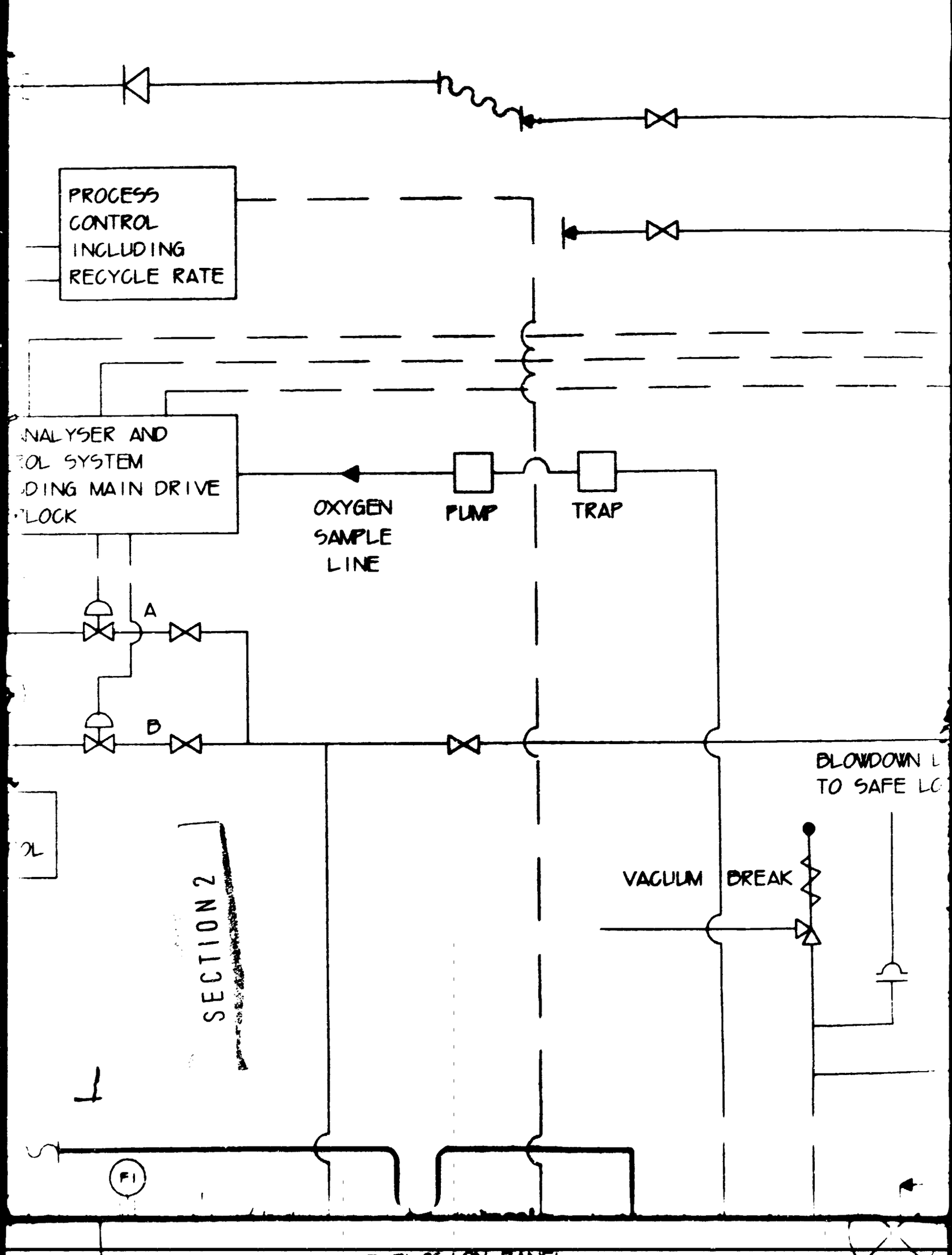
SECTION 5

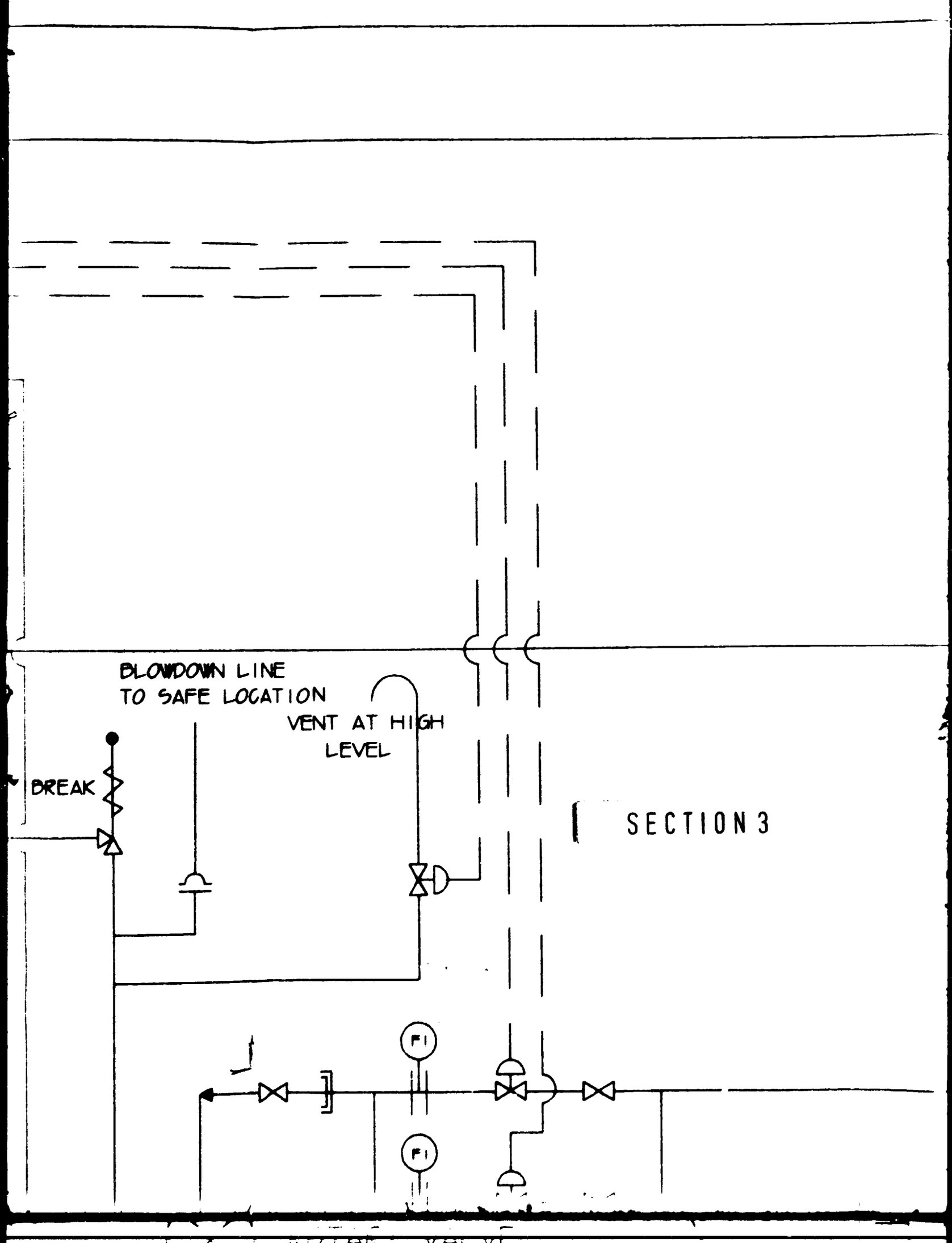


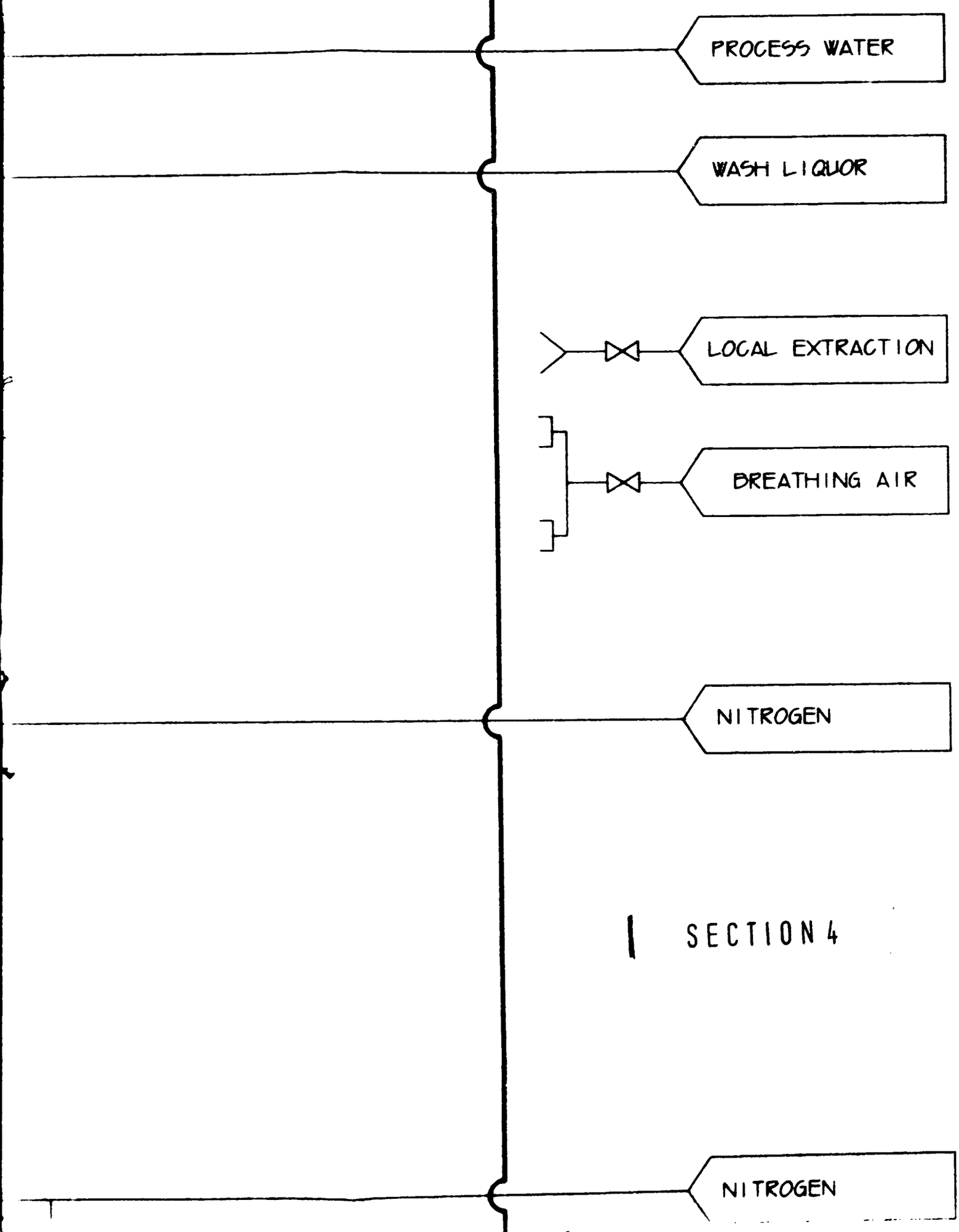
P O BOX 300, VIENNA, ., FAX 2321 56	PROJECT ALKALOIDA I TF/HUN/90/907	TITLE DSP EQUIPMENT FLOW DIAGRAM	
JUNE 1992 N.T.S. S IN METRES		DRAWING NUMBER 92/005/214	REV B

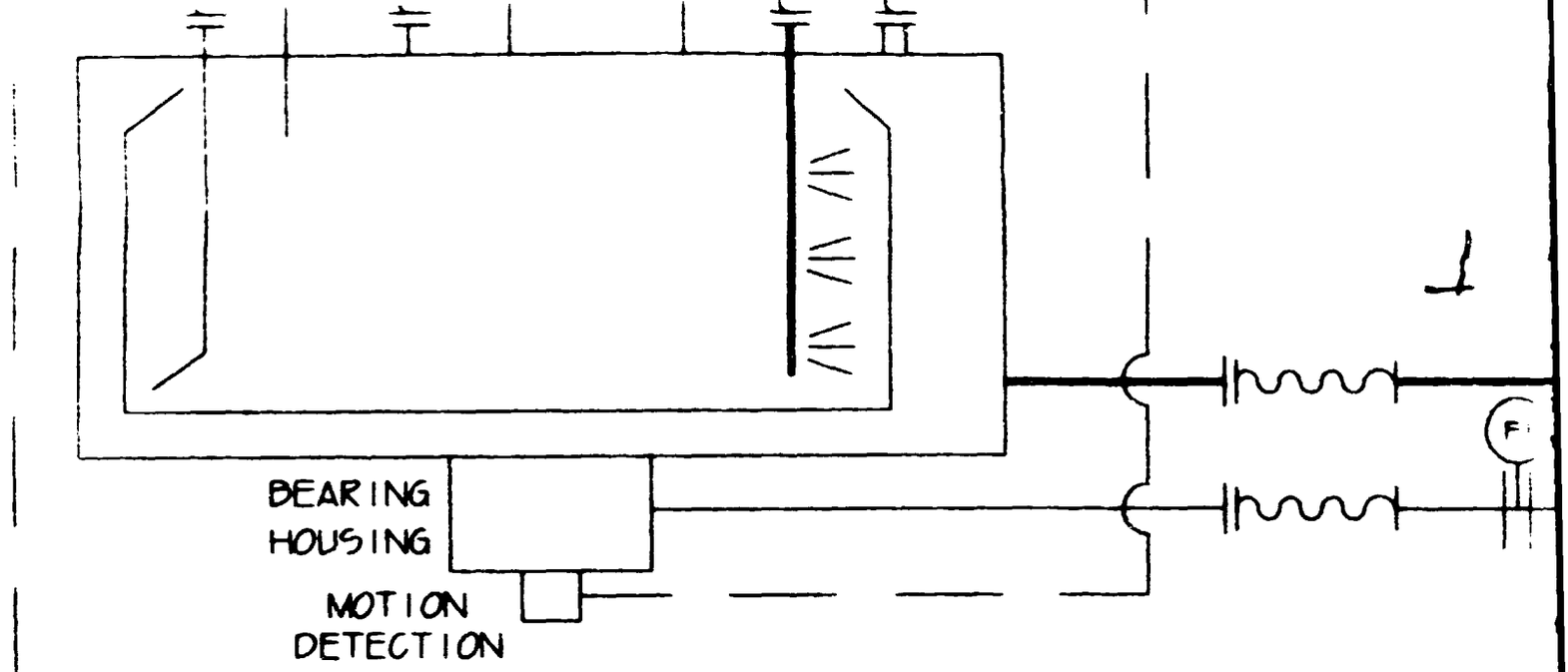
SECTION 6


SLURRY FEED
VENT AT HIGH LEVEL
PROCE
CONTR
INCL
RECY
GAS ANALYSER
CONTROL SYST
INCLUDING MA
INTERLOCK
TRAP
PUMP
OXYGEN SAMPLE LINE
FI
P
FI
DOOR RELEASE SAFETY CONTROL
SECTION 1

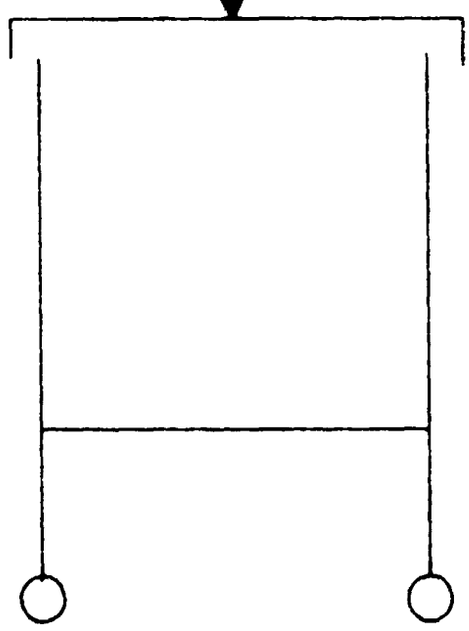

PROCESS
CONTROL
INCLUDING
RECYCLE RATE
NALYSER AND
OL SYSTEM
DING MAIN DRIVE
LOCK
OXYGEN
SAMPLE
LINE
PUMP
TRAP
A
B
BLOWDOWN L
TO SAFE LO
VACUUM BREAK
SECTION 2
F1


BLOWDOWN LINE
TO SAFE LOCATION
VENT AT HIGH
LEVEL
BREAK
SECTION 3
FI
FI


PROCESS WATER
WASH LIQUOR
LOCAL EXTRACTION
BREATHING AIR
NITROGEN
SECTION 4
NITROGEN



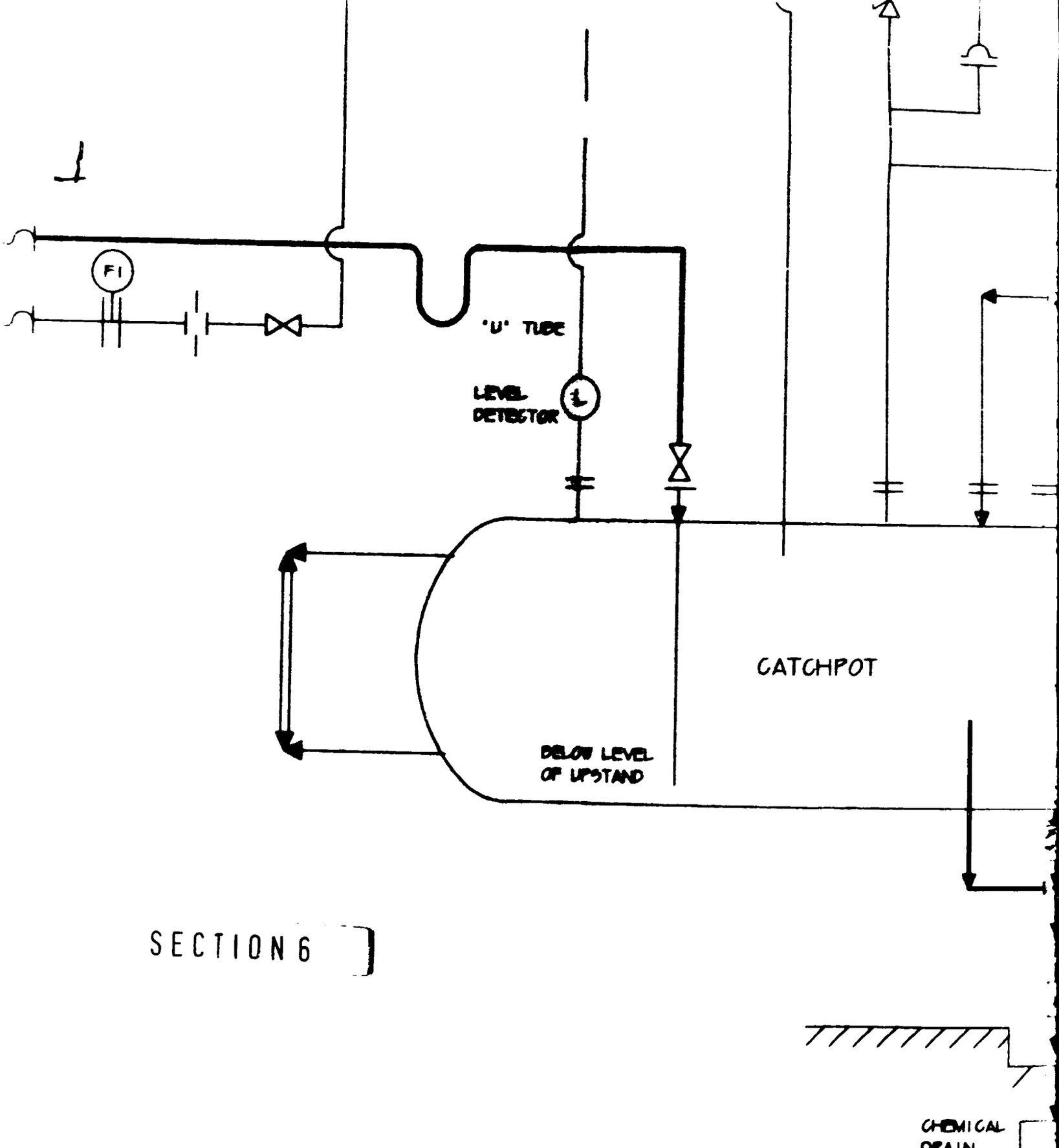
MANUAL CAKE DISCHARGE



SECTION 5

SOLIDS TRANSFER
BIN

CHECKED								
APPROVED JD								
DRAWN BY CS								ISSUED FOR REP



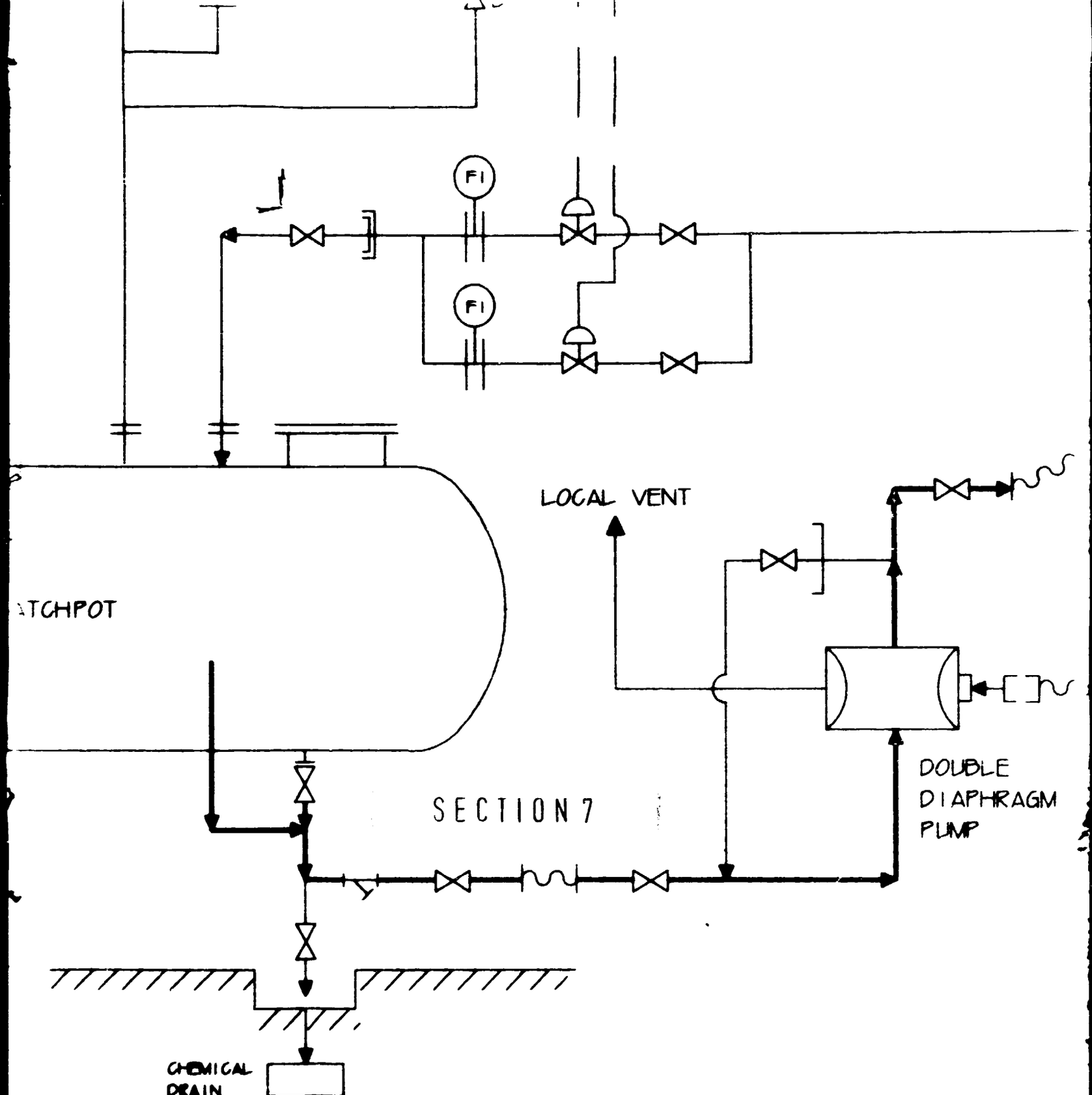
SECTION 6

SUED FOR REPORT	A	23/6/9
DIFICATION	ISSUE	DATE

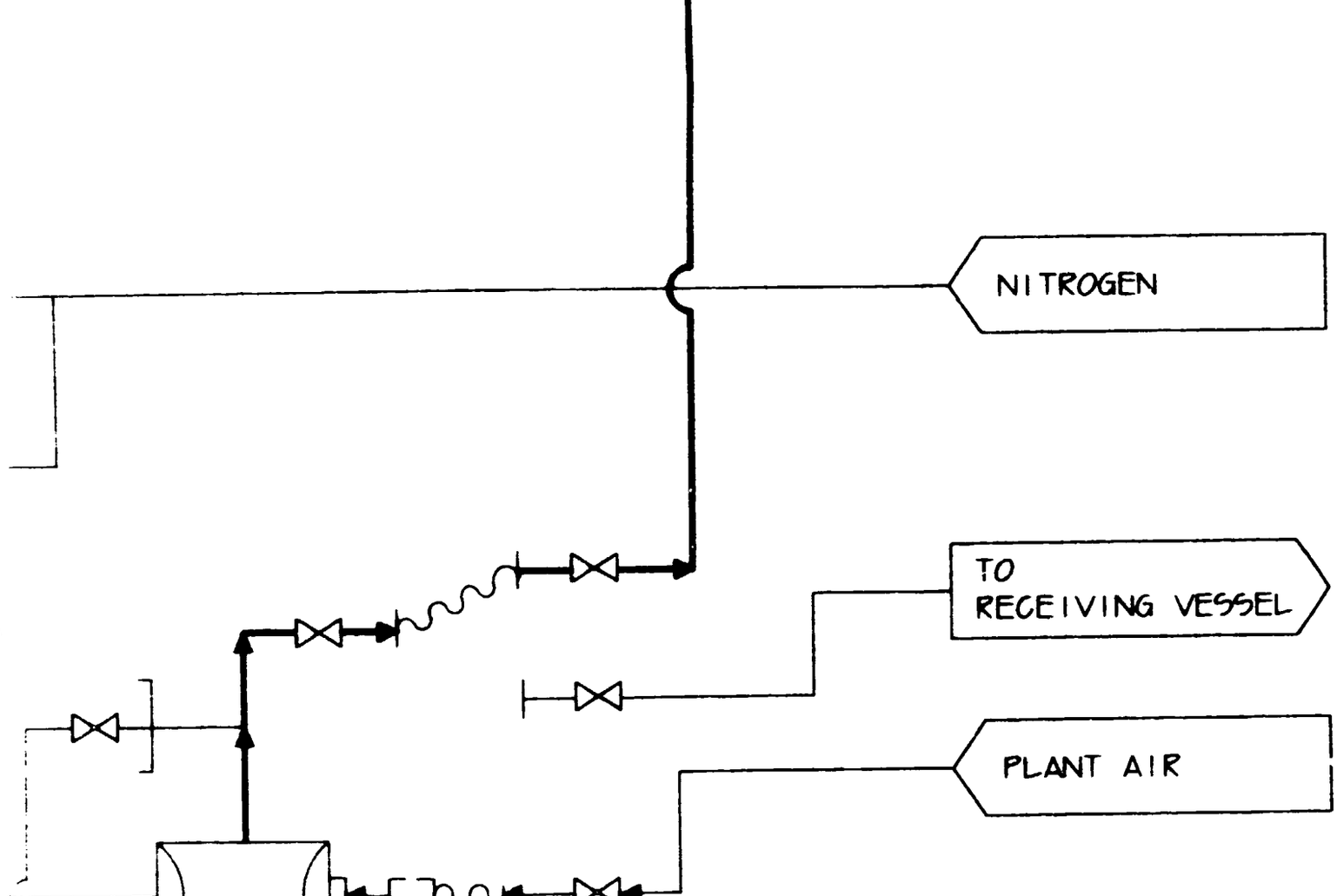
GRC CONSULTANTS
WATERCRESS HOUSE 1 THE WINDMILLS
ST MARY'S CLOSE ALTON HANTS
TEL:- 0420 89847 FAX:- 0420 89427

CLIENT
UNIDO, P
A-1400 VIE
AUSTRIA

DATE:
SCALE:
DIMENSIONS



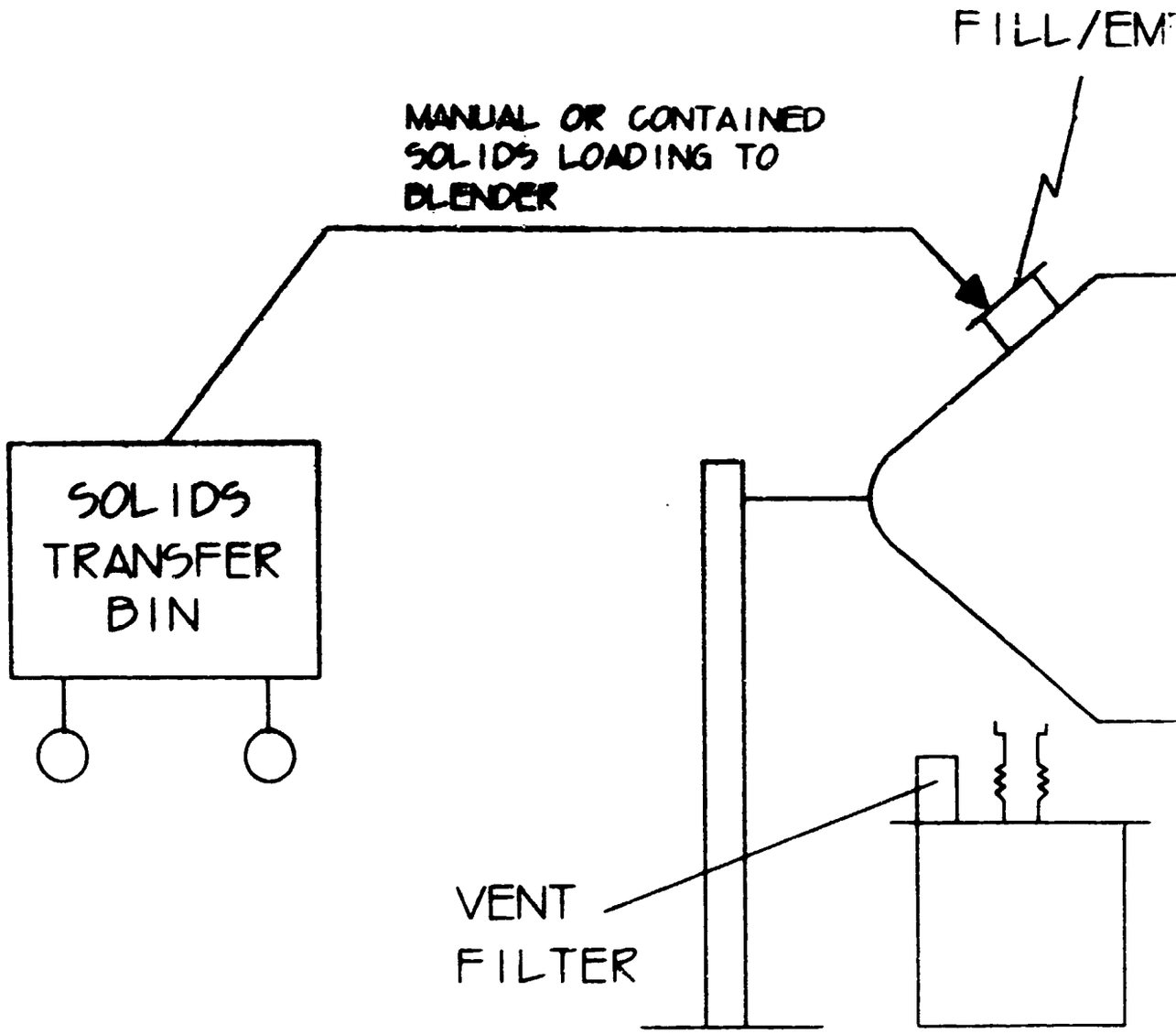
	CLIENT UNIDO, P.O.BOX 300, A-1400 VIENNA. AUSTRIA. FAX:232156	PROJECT ALKALOIDA I TF/HUN/90/907
MILLS TS 89427	DATE: MAY 1992 SCALE: N.T.S DIMENSIONS IN N/A	



NOTES

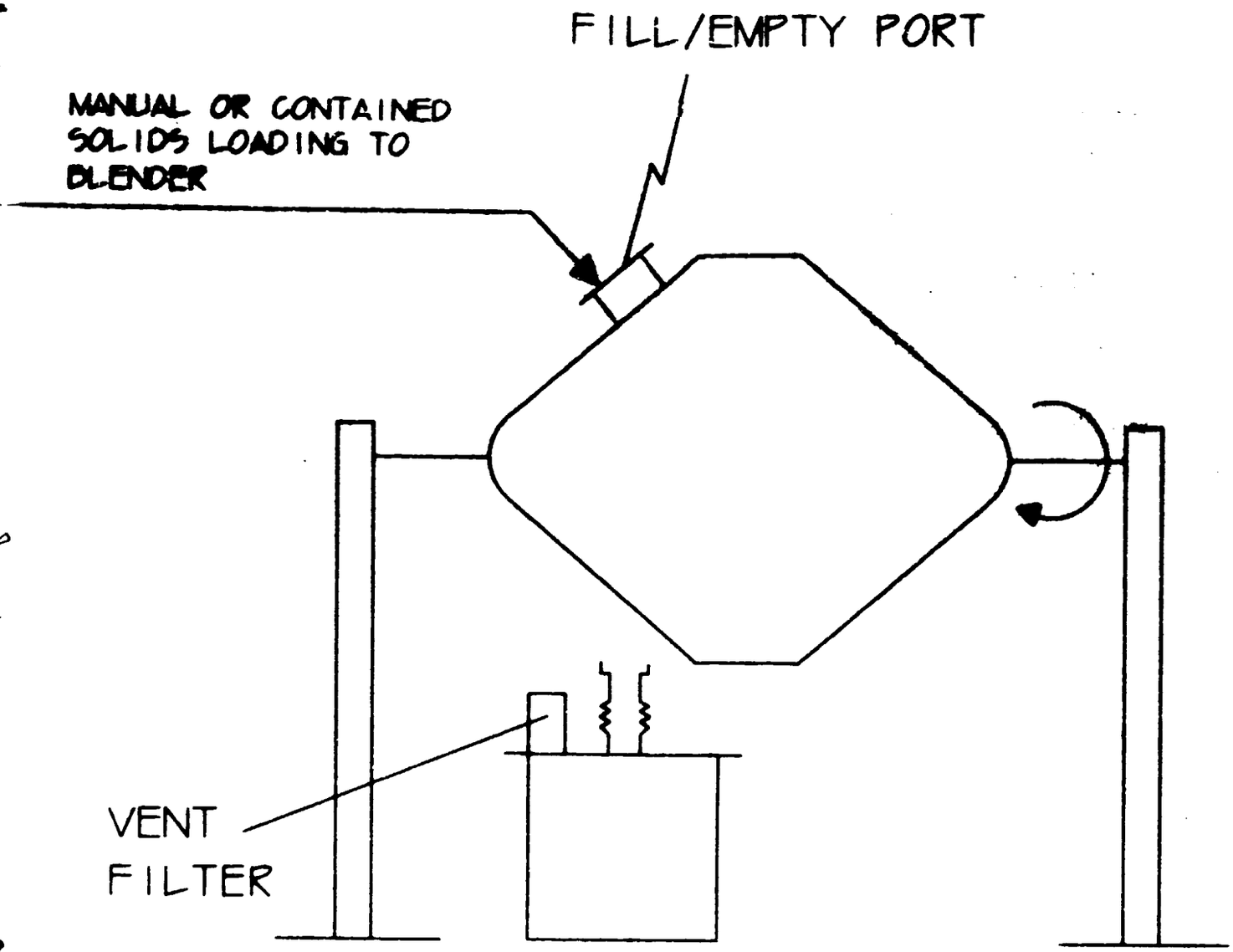
1. ALL HIGH LEVEL VENTS TO BE TERMINATED 2M ABOVE ROOF APEX.
2. ON NITROGEN PURGE SYSTEM FOR BOTH CENRIFUGE AND CATCHPOT
   VALVE 'A' FOR NORMAL FLOWRATE.
   VALVE 'B' FOR INITIAL PURGE AND EMERGENCY NITROGEN FLOW.
3. FEED TANK NOT SHOWN BUT SHOULD ALSO BE UNDER NITROGEN PURGE.

ALKALOIDA I =/HUN/90/907	TITLE ENGINEERING FLOW DIAGRAM - CENTRIFUGE
	DRAWING NUMBER: 92/005/201 — REVISION:



SECTION 1

CHECKED							GRC
APPVD JD							
CS				ISSUED FOR REPORT	A	25/6/92	ST MARY'S TEL - 0420
				MODIFICATION	ISSUE	DATE	



BLENDER

SECTION 2

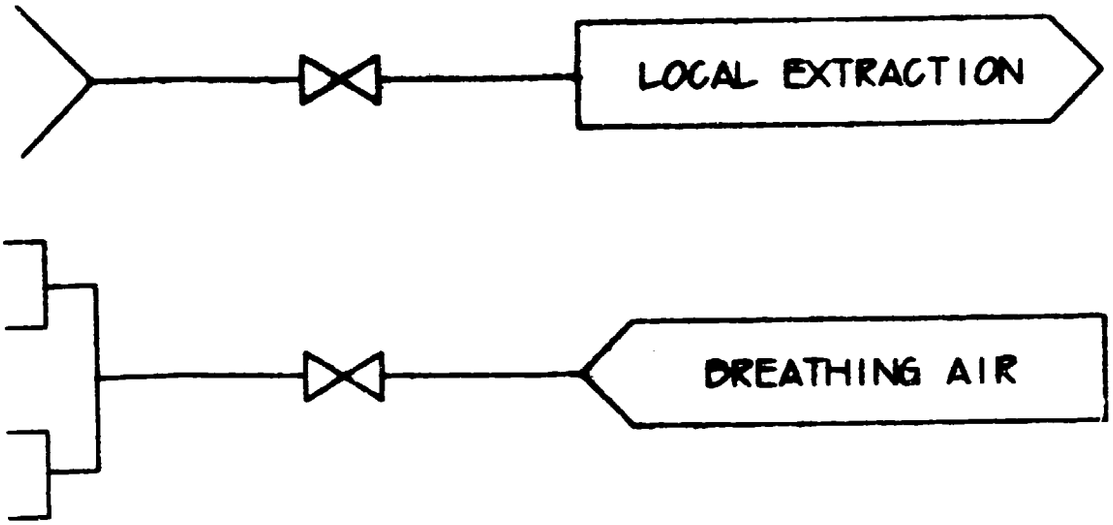
	ISSUED FOR REPORT	A	25/6/92
	MODIFICATION	ISSUE	DATE

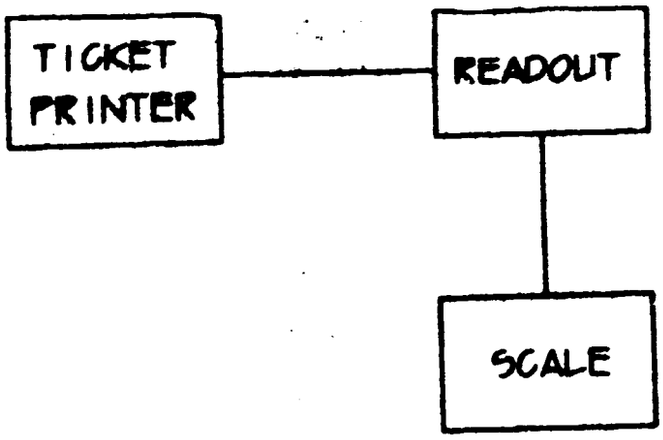
GRC CONSULTANTS

WATERCRESS HOUSE 1 THE WINDMILLS
ST MARY'S CLOSE ALTON HANTS
TEL - 0420 89847 FAX - 0420 89427

CLIENT
UNIDO, P.O.B
A-1400 VIEN
AUSTRIA, FAX

DATE: APR
SCALE:
DIMENSIONS IN



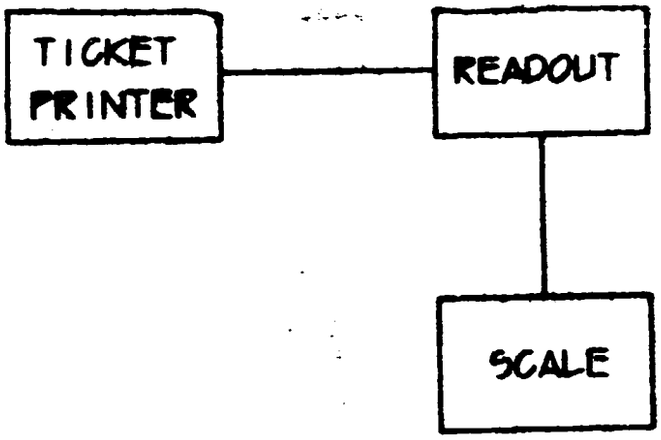


BALANCE

SECTION 3

NOTES

1 BLENDER TO BE SITED IN SAFETY CAGE. THE CAGE DOOR WILL BE INTERLOCKED WIYH BLENDER MOTOR AND THE BLENDER START CONTROLS FITTED OUTSIDE

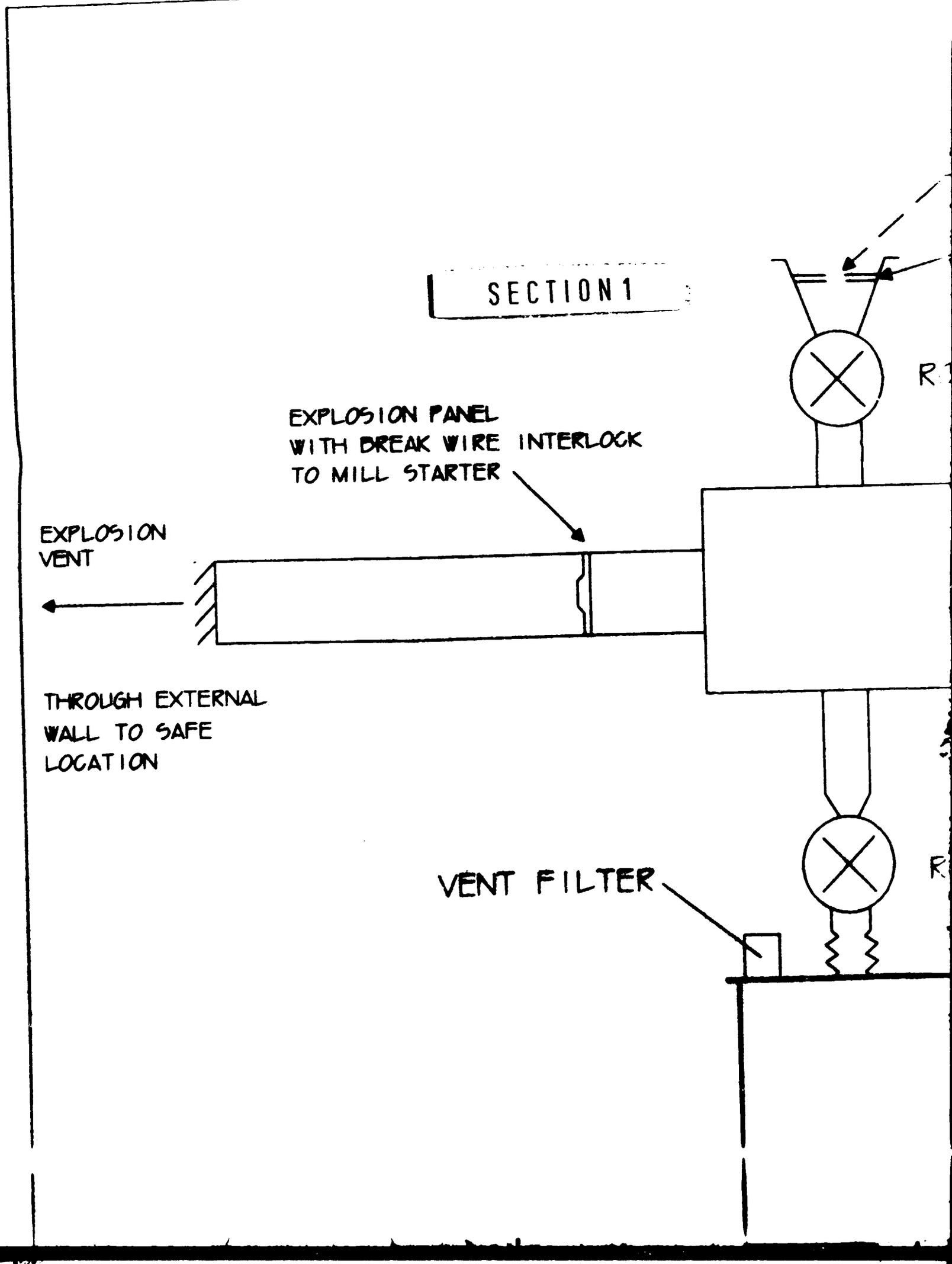


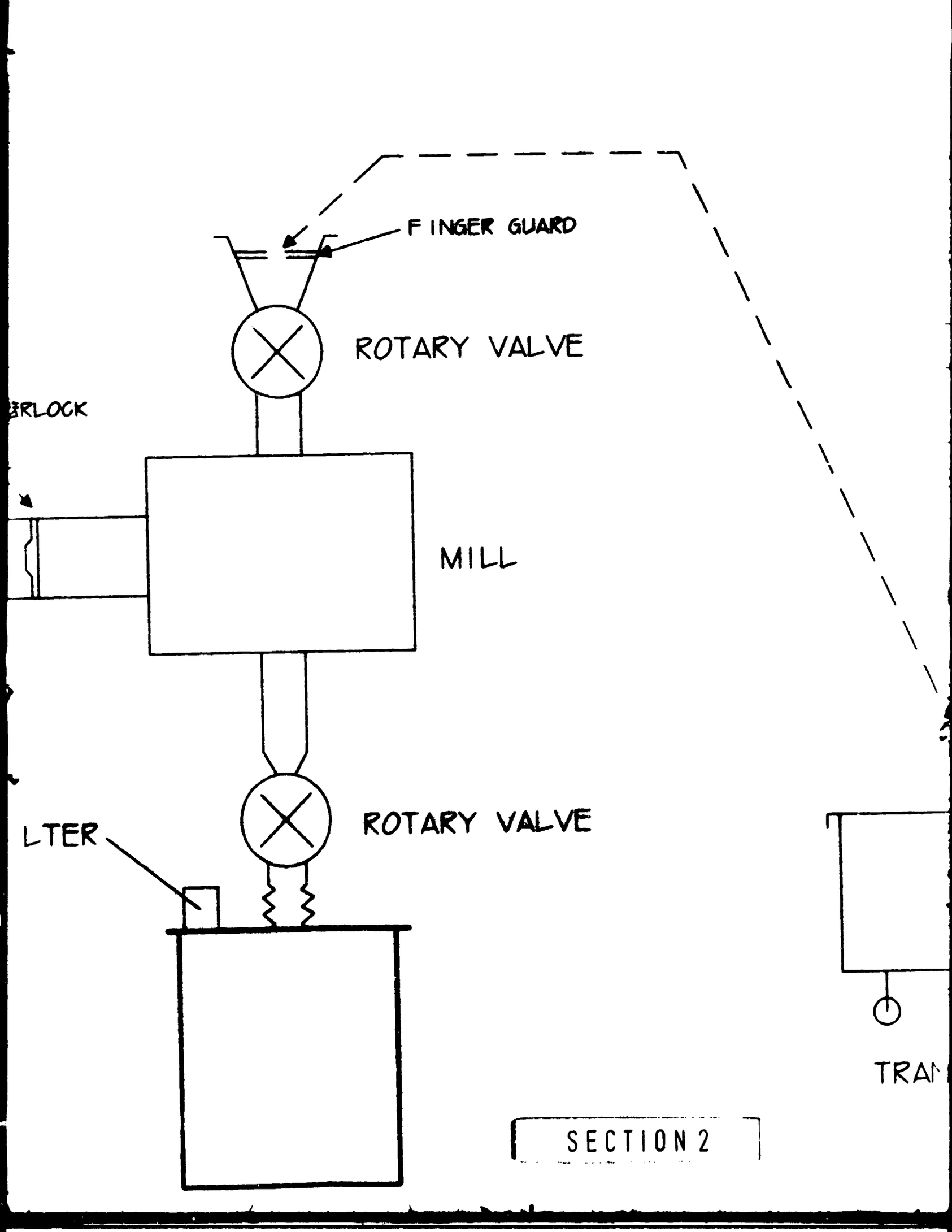
BALANCE

NOTES

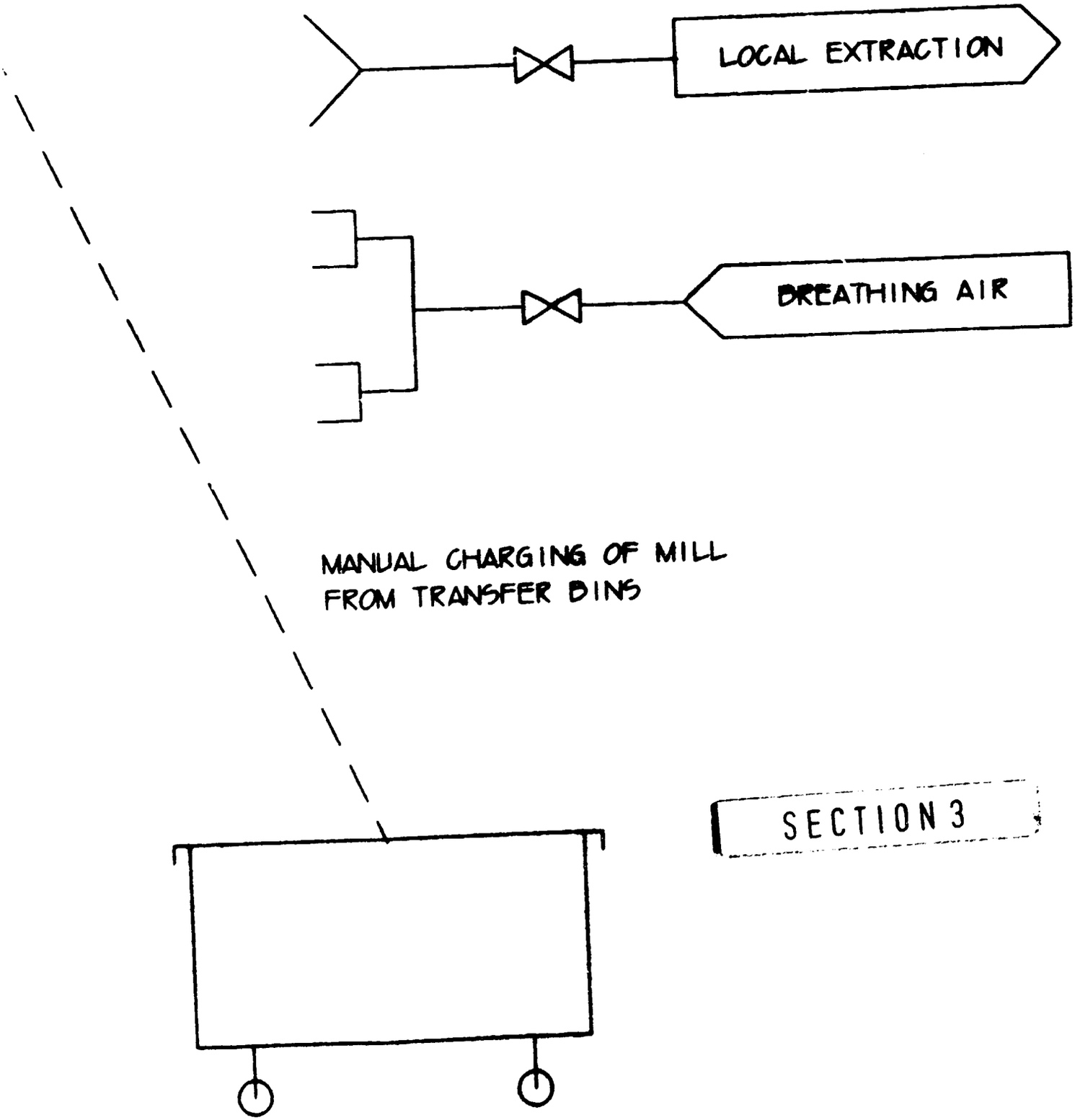
1. BLENDER TO BE SITED IN SAFETY CAGE. THE CAGE DOOR WILL BE INTERLOCKED WIYH BLENDER MOTOR AND THE BLENDER START CONTROLS FITTED OUTSIDE THE CAGE.
2. ASSUME DESIGNED FOR CONTROL OF EXPLOSION
3. EXACT DETAILS OF LOADING/UNLOADING NOT SHOWN UNLOADING PROCEDURES MAY DEPEND ON HEIGHT. UNLIMITED HEIGHT MAY NECESSITATE THE USE OF A MATERIAL TRANSFER SYSTEM SUCH AS A VACUMAX

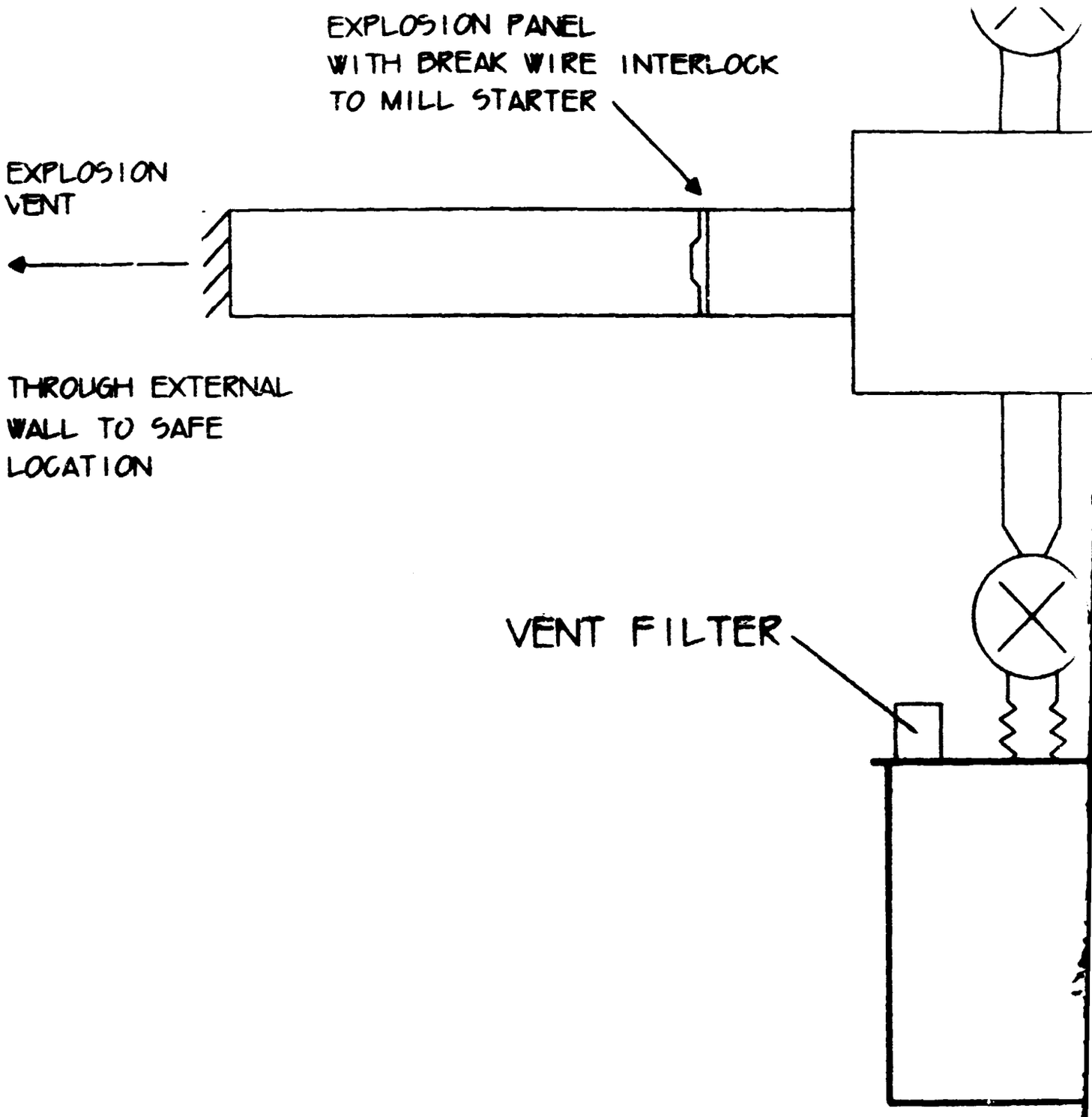
O BOX 300, IENNA, FAX 232156	PROJECT ALKALOIDA I TF/HUN/90/907	TITLE ENGINEERING FLOW DIAGRAM - BLENDER
APRIL 1992	SECTION 4	DRAWING NUMBER 92/005/202 REV A
N/A		
S IN: N/A		


SECTION 1
EXPLOSION PANEL
WITH BREAK WIRE INTERLOCK
TO MILL STARTER
EXPLOSION
VENT
THROUGH EXTERNAL
WALL TO SAFE
LOCATION
VENT FILTER



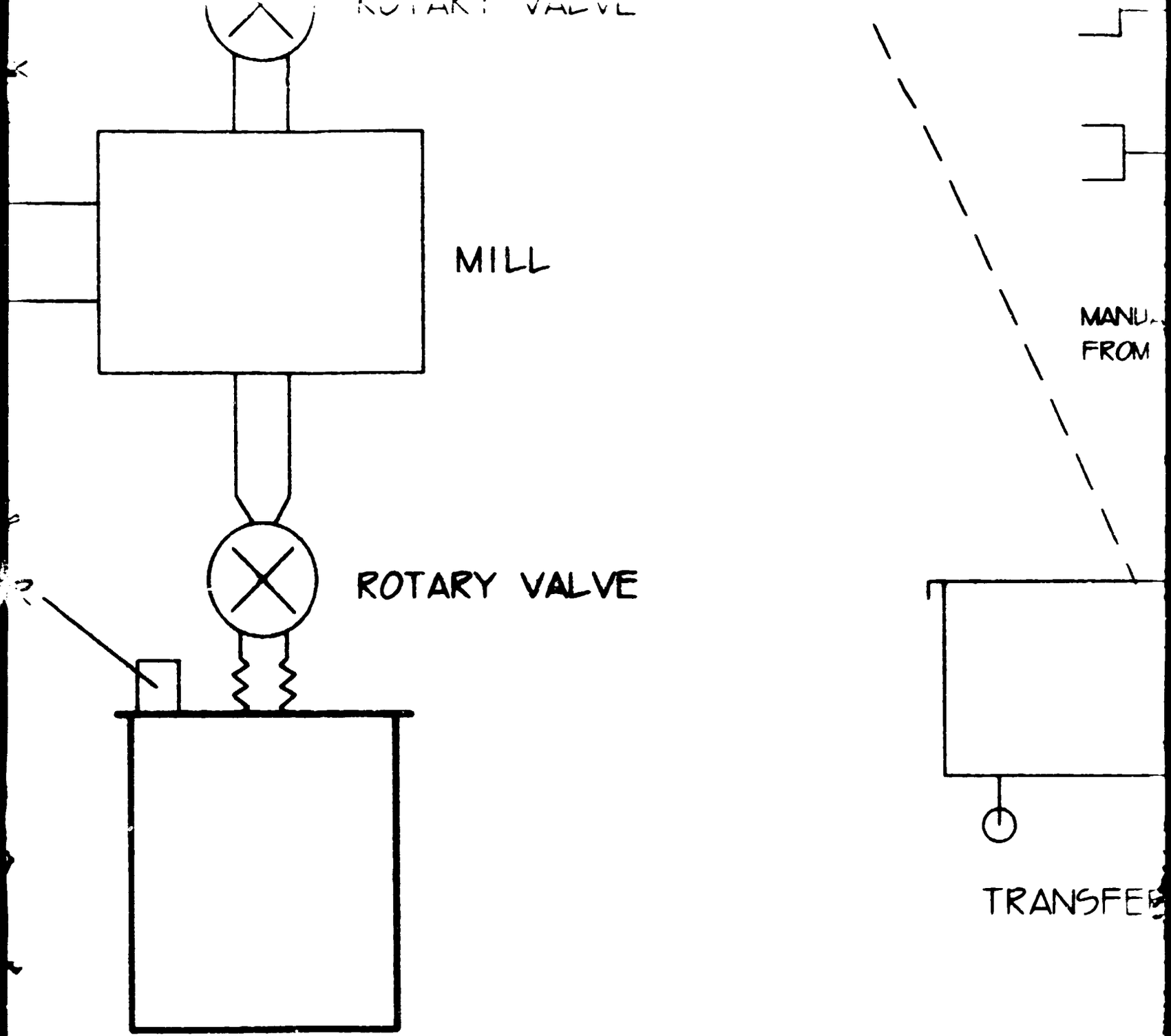
SECTION 2


LOCAL EXTRACTION
BREATHING AIR
MANUAL CHARGING OF MILL
FROM TRANSFER BINS
SECTION 3
TRANSFER BINS



SECTION 4

CHECKED							GF
APP'D JD							
							WATER
DRAWN CS							ST MA
				ISSUED FOR REPORT	A	25/6/92	TEL -
				MODIFICATION	ISSUE	DATE	



SECTION 5

A	25/6/92	
ISSUE	DATE	

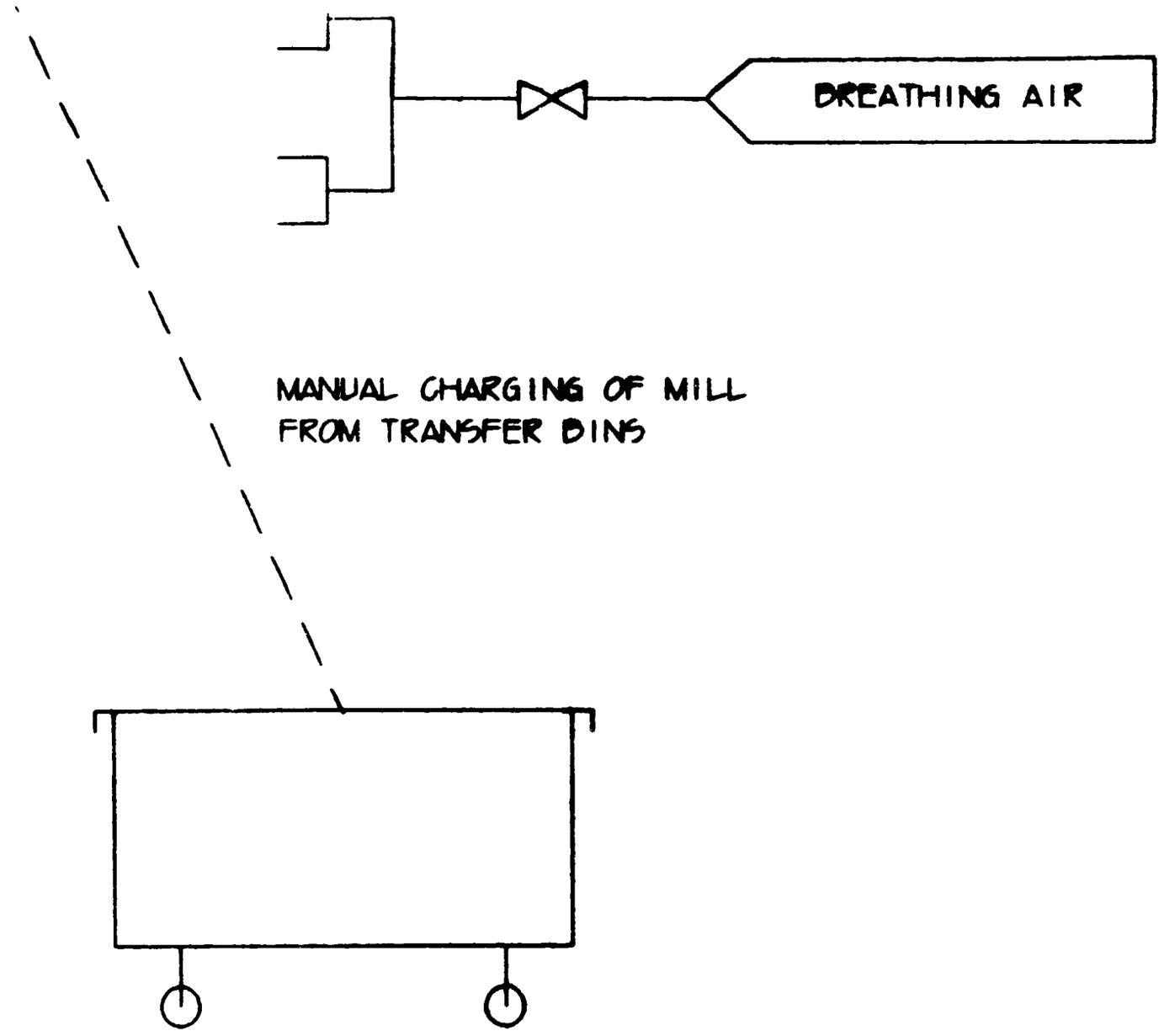
GRC CONSULTANTS

WATERCRESS HOUSE 1 THE WINDMILLS
ST MARY'S CLOSE ALTON HANTS
TEL - 0420 89047 FAX:- 0420 89423

CLIENT
UNIDO, [illegible] 300,
A-1400 [illegible],
AUSTRIA, FAX: 232156

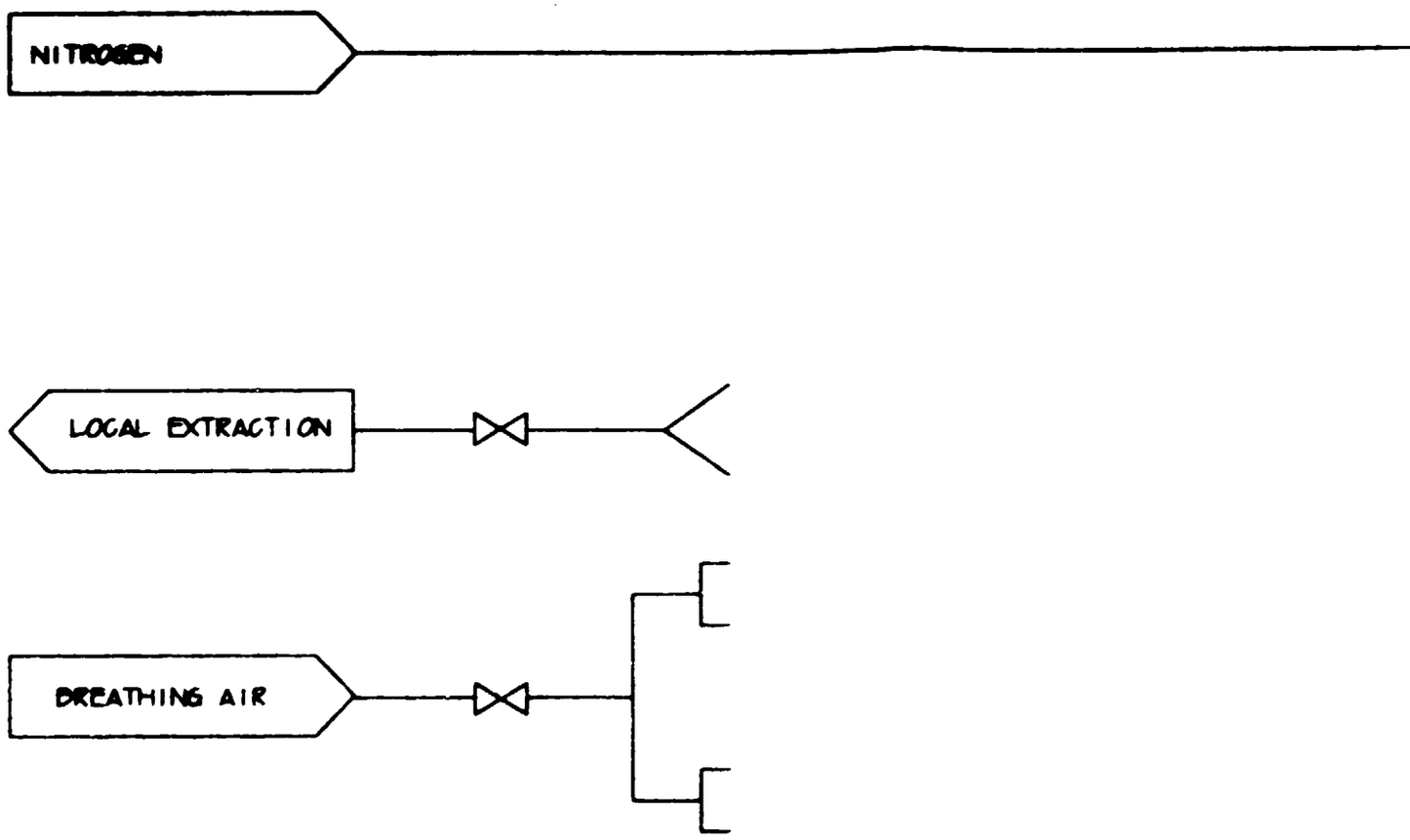
DATE: APRIL 1992
SCALE: N/A
DIMENSIONS IN: N/A

PROJECT
TF

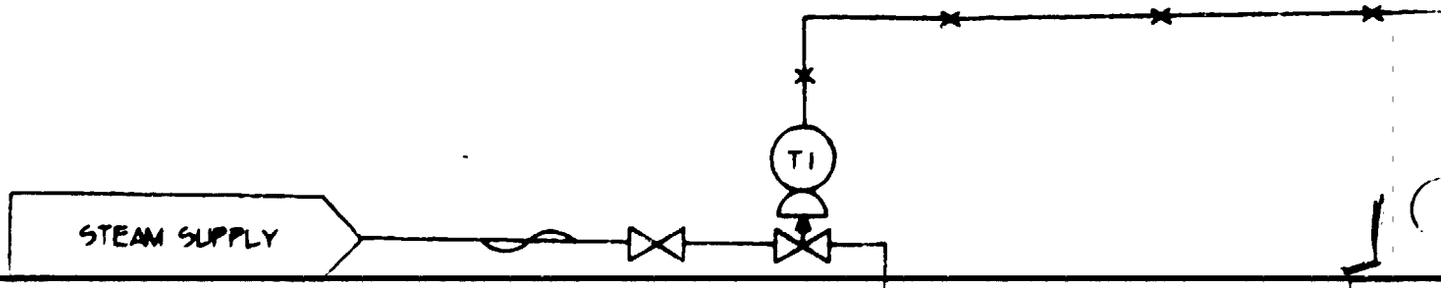


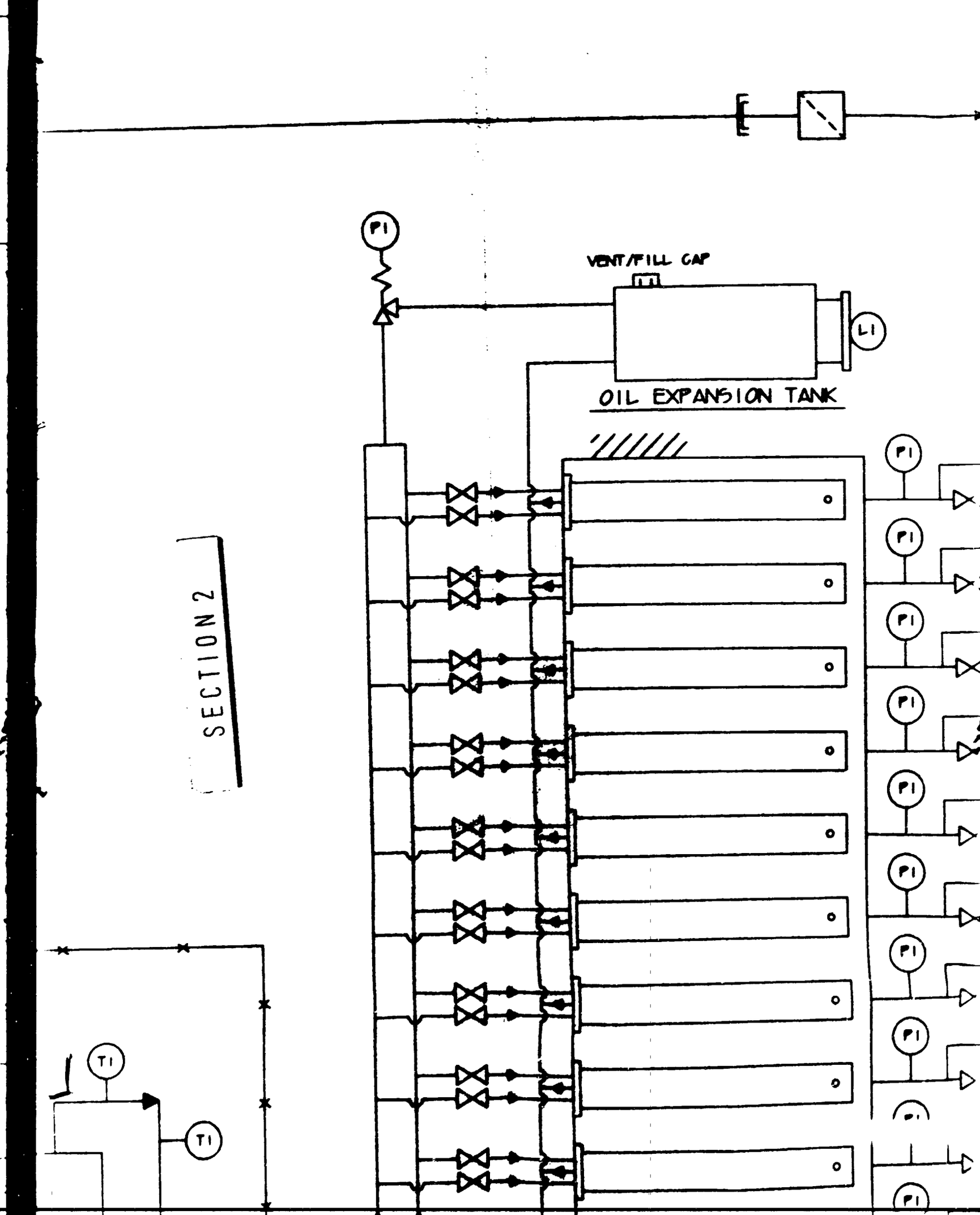
SECTION 6

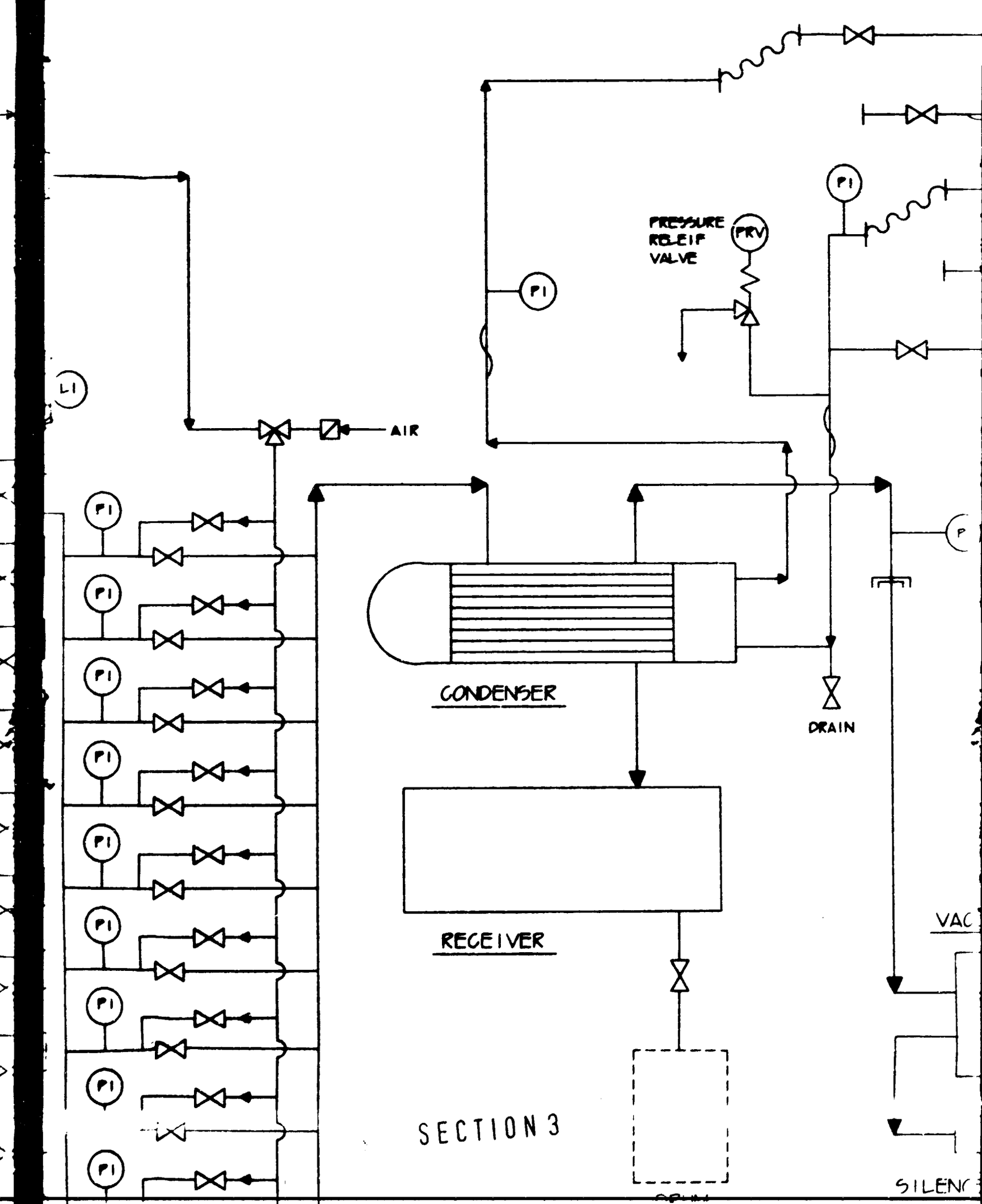
O.BOX 300, IENNA, FAX: 232156	PROJECT ALKALOIDA I TF/HUN/90/907	TITLE ENGINEERING FLOW DIAGRAM - MILL
APRIL 1992 N/A IS IN: N/A		DRAWING NUMBER REV 92/005/203 A

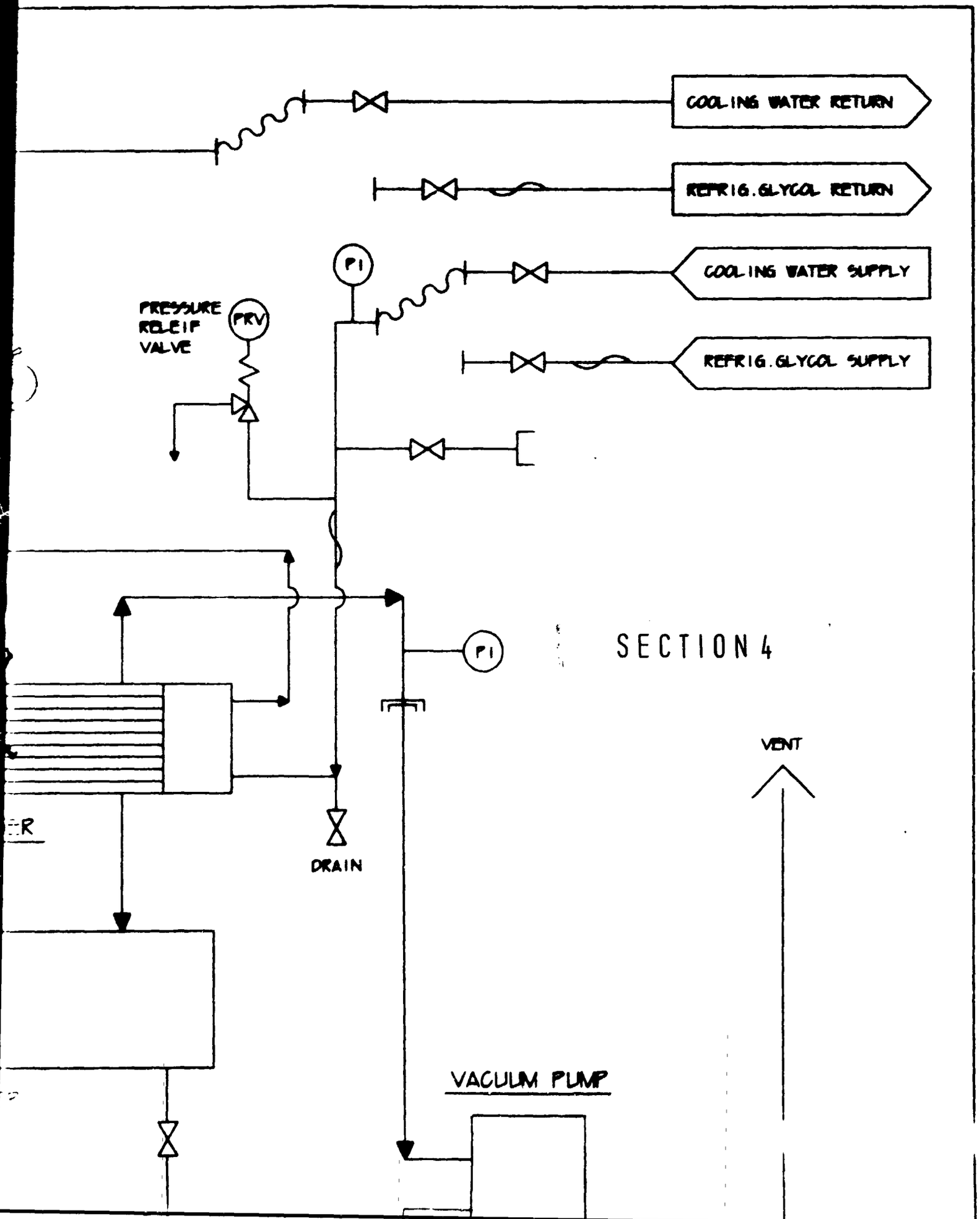


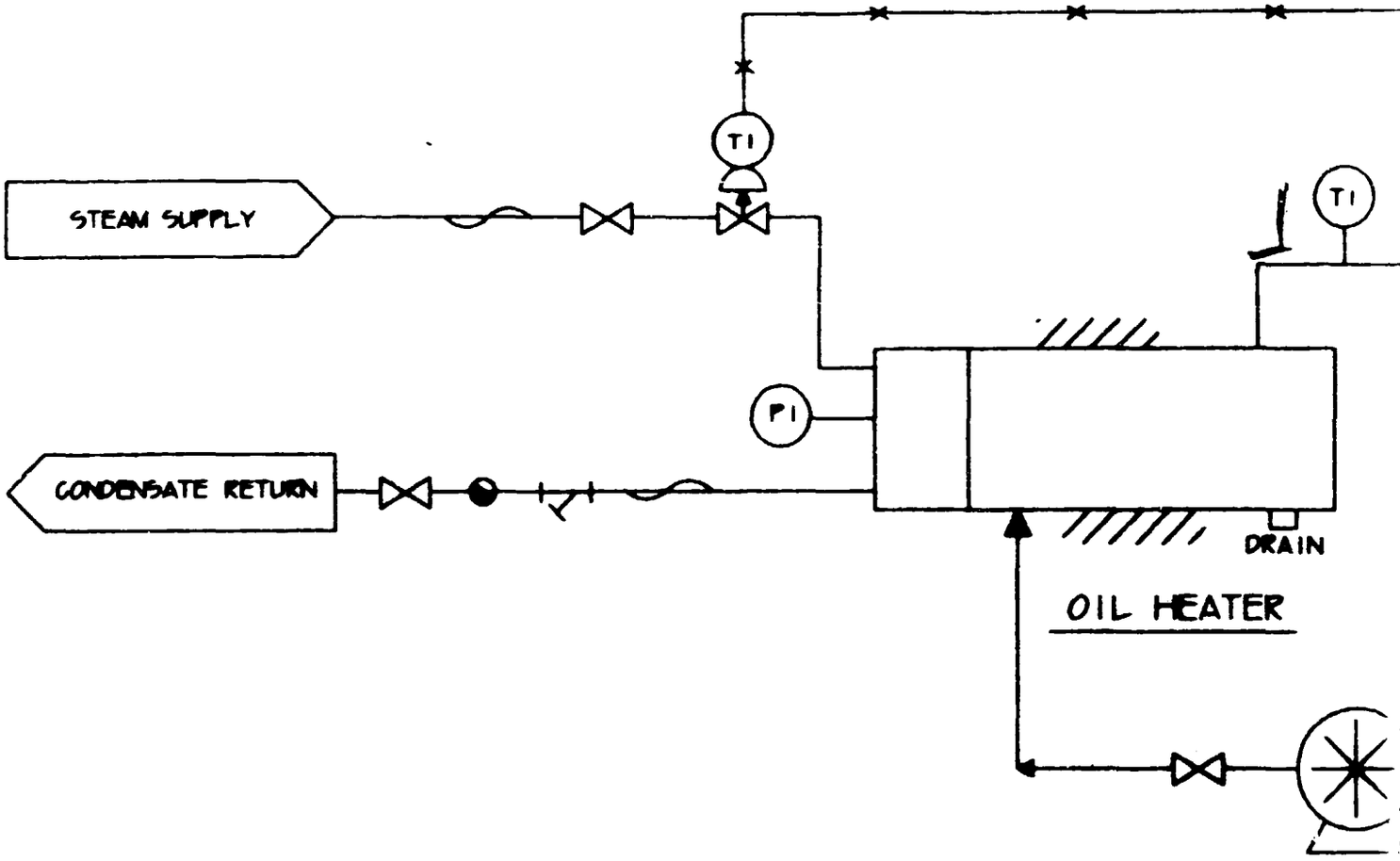
SECTION 1

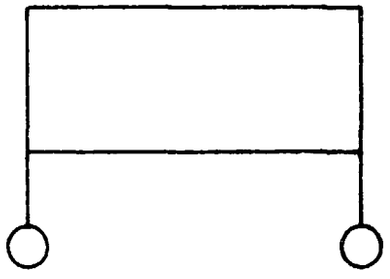



PI
VENT/FILL CAP
LI
OIL EXPANSION TANK
SECTION 2
TI
TI


PRESSURE
RELEIF
VALVE
PRV
PI
LI
AIR
CONDENSER
DRAIN
RECEIVER
VAC
SECTION 3
SILENC


COOLING WATER RETURN
REFRIG. GLYCOL RETURN
COOLING WATER SUPPLY
REFRIG. GLYCOL SUPPLY
PI
PRESSURE RELEIF VALVE
PRV
PI
SECTION 4
VENT
DRAIN
VACUUM PUMP

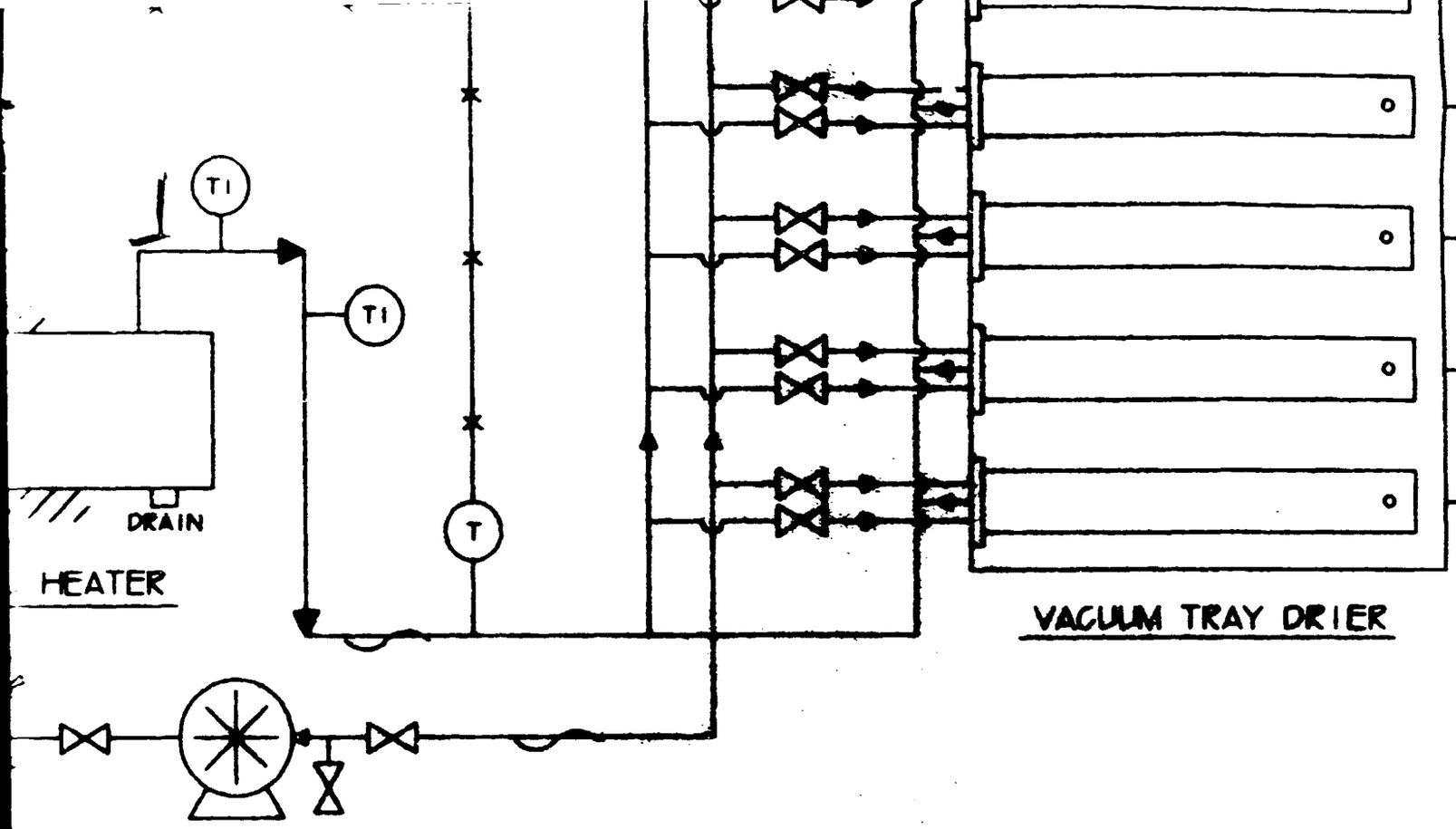




SOLIDS TRANSFER BINS

SECTION 5

CHECKED								
APPROVED								
JD								
CS								ISSUED FOR K
								MODIFICATION



SECTION 6

INS

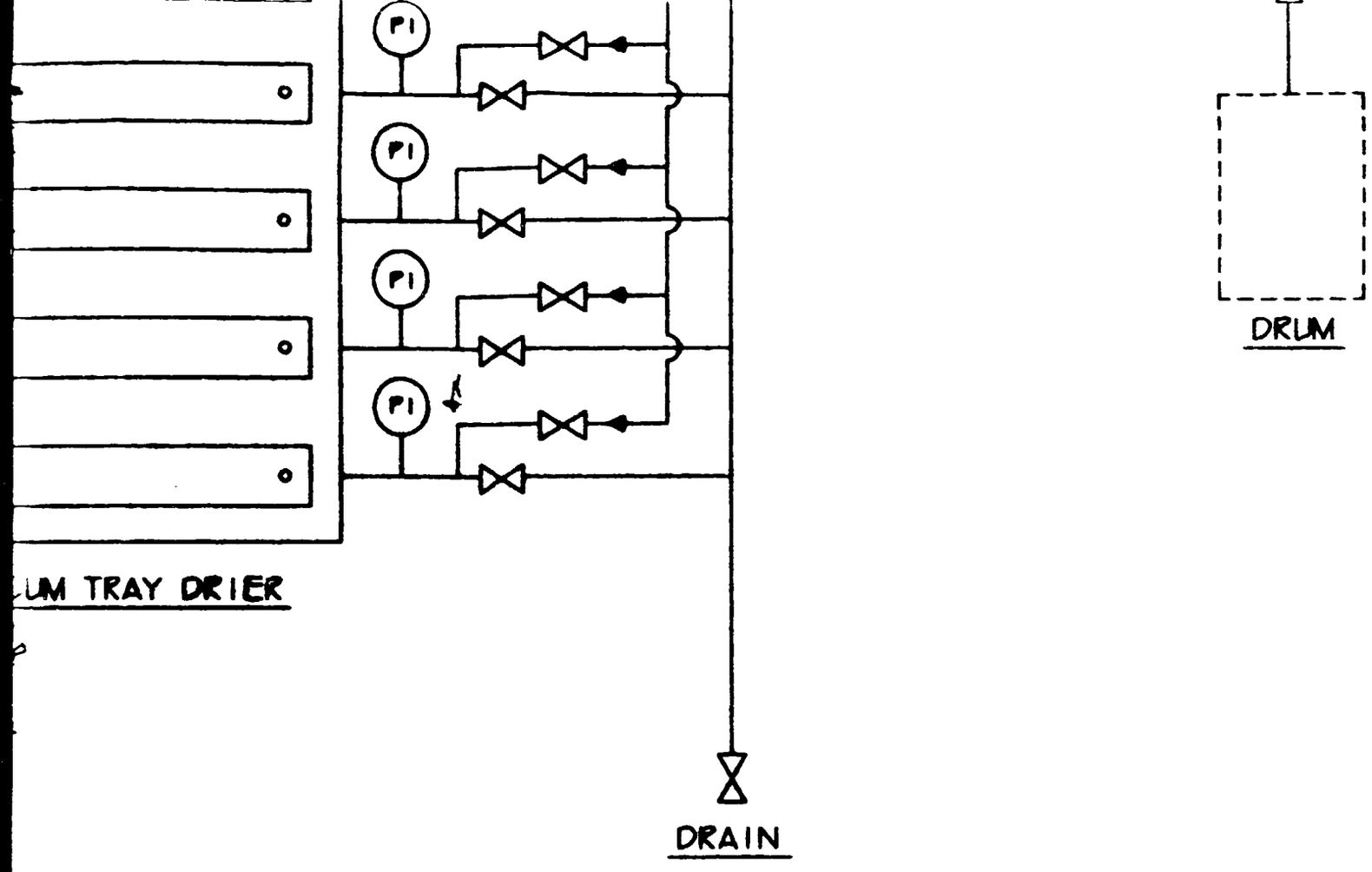
MODIFICATION	ISSUE	DATE
	A	25/6/92

GRC CONSULTANTS
WATERSIDE HOUSE 1 THE WINDMILLS
ST MARY'S CLOSE
TEL:- 0420 69427 FAX:- 0420 69427

CLIENT
UNIDO,
A-1400
AUSTRIA

DATE

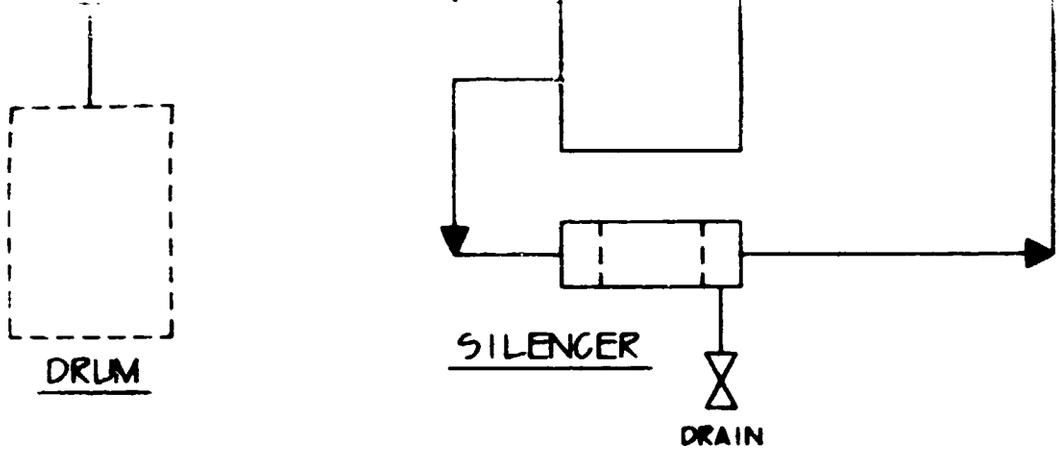
DIMENSIONS



UM TRAY DRIER

SECTION 7

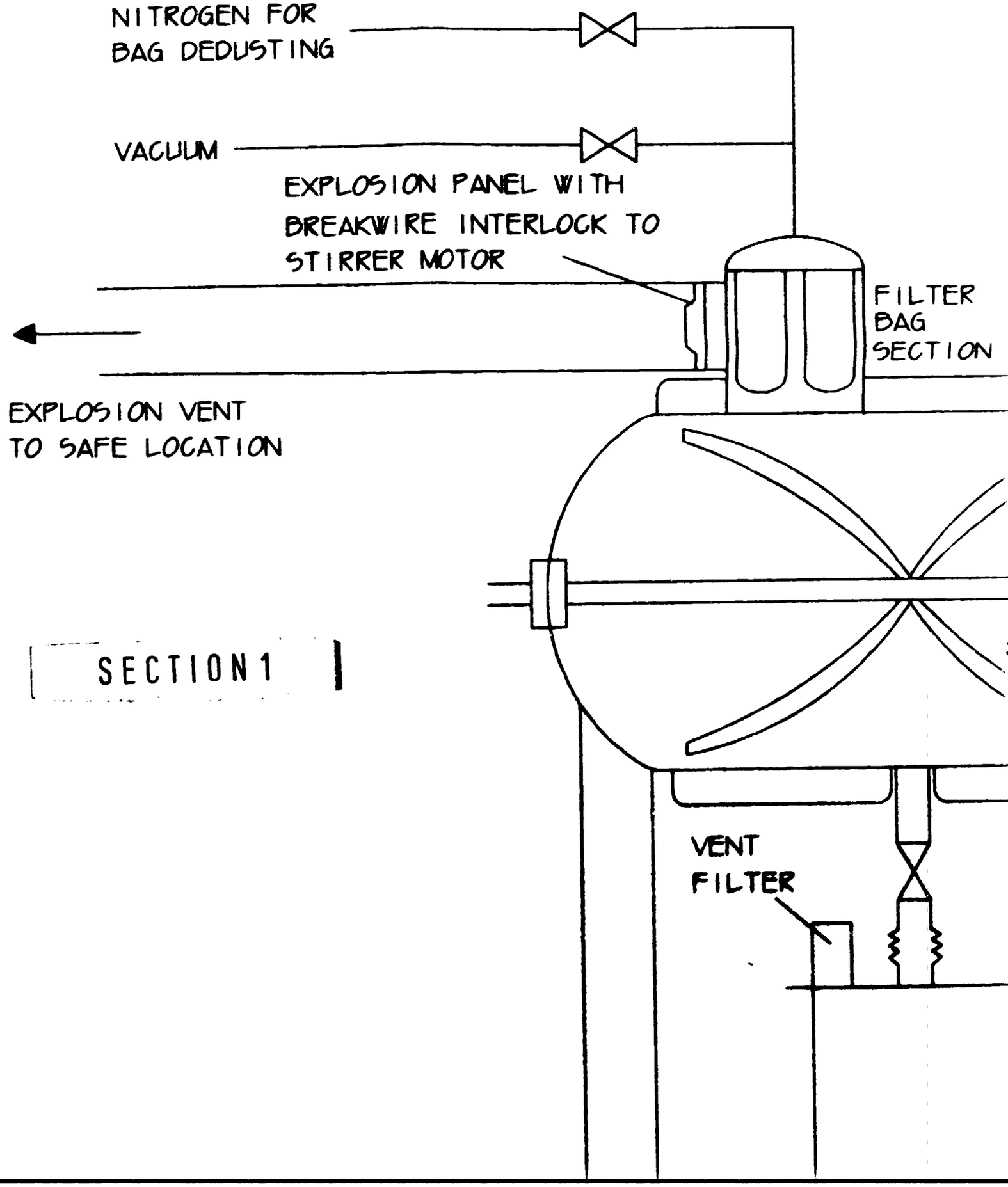
TS	CLIENT UNIDO, P.O.BOX 300, A-1400 VIENNA. AUSTRIA. FAX:232156	PROJECT ALKALOIDA I TF/HUN/90/907
WINDMILLS	DATE: MAY 1992	
	SCALE N.T.S.	
4LU 04921	DIMENSIONS IN N/A	

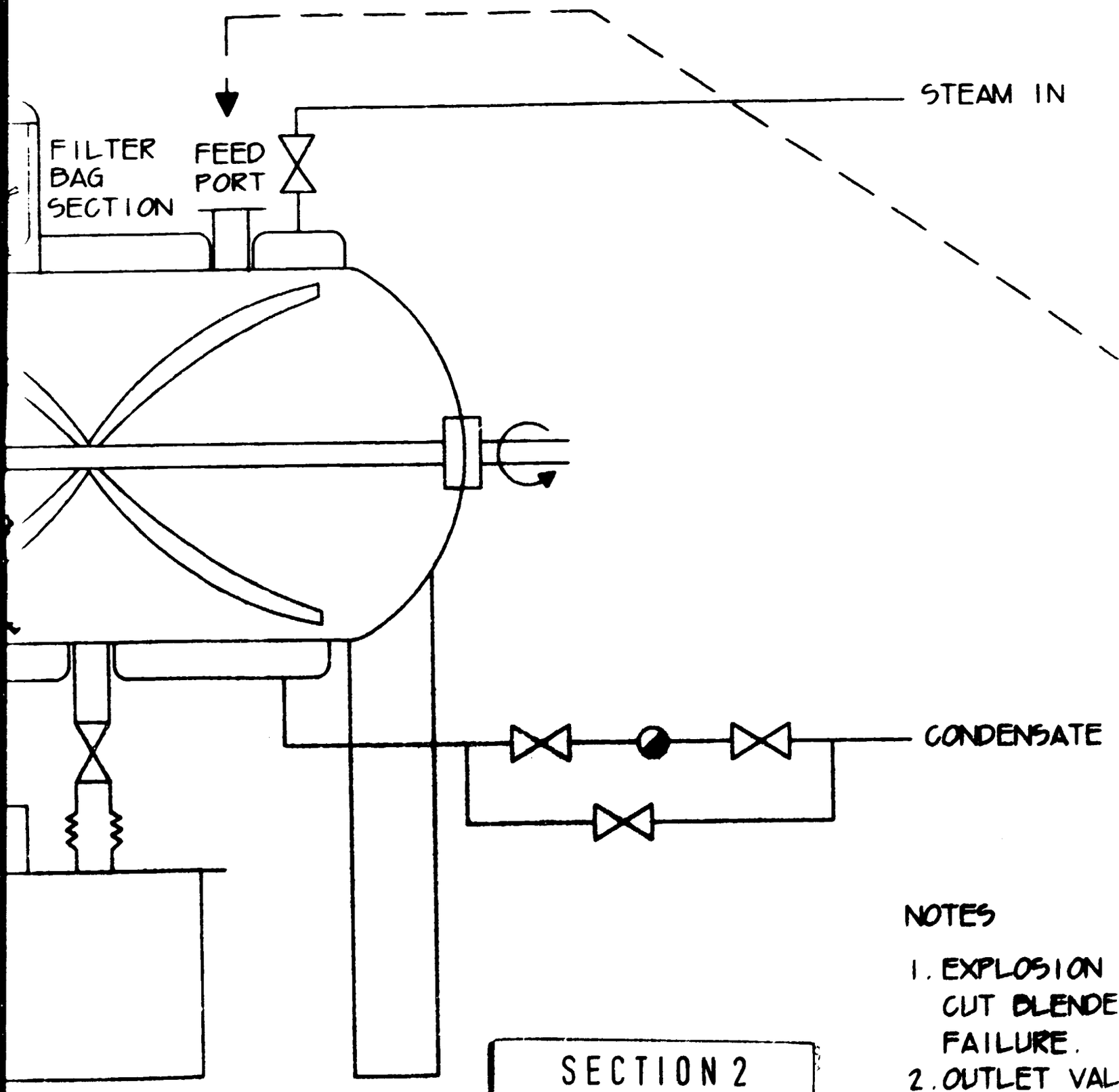


SECTION 8

NOTES
1 VENT TO TERMINATE 2M ABOVE LOCAL ROOF APEX.

KALOIDA I JN/90/907	TITLE ENGINEERING FLOW DIAGRAM - VACUUM TRAY DRIER
	DRAWING NUMBER 92/005/204 — REVISION

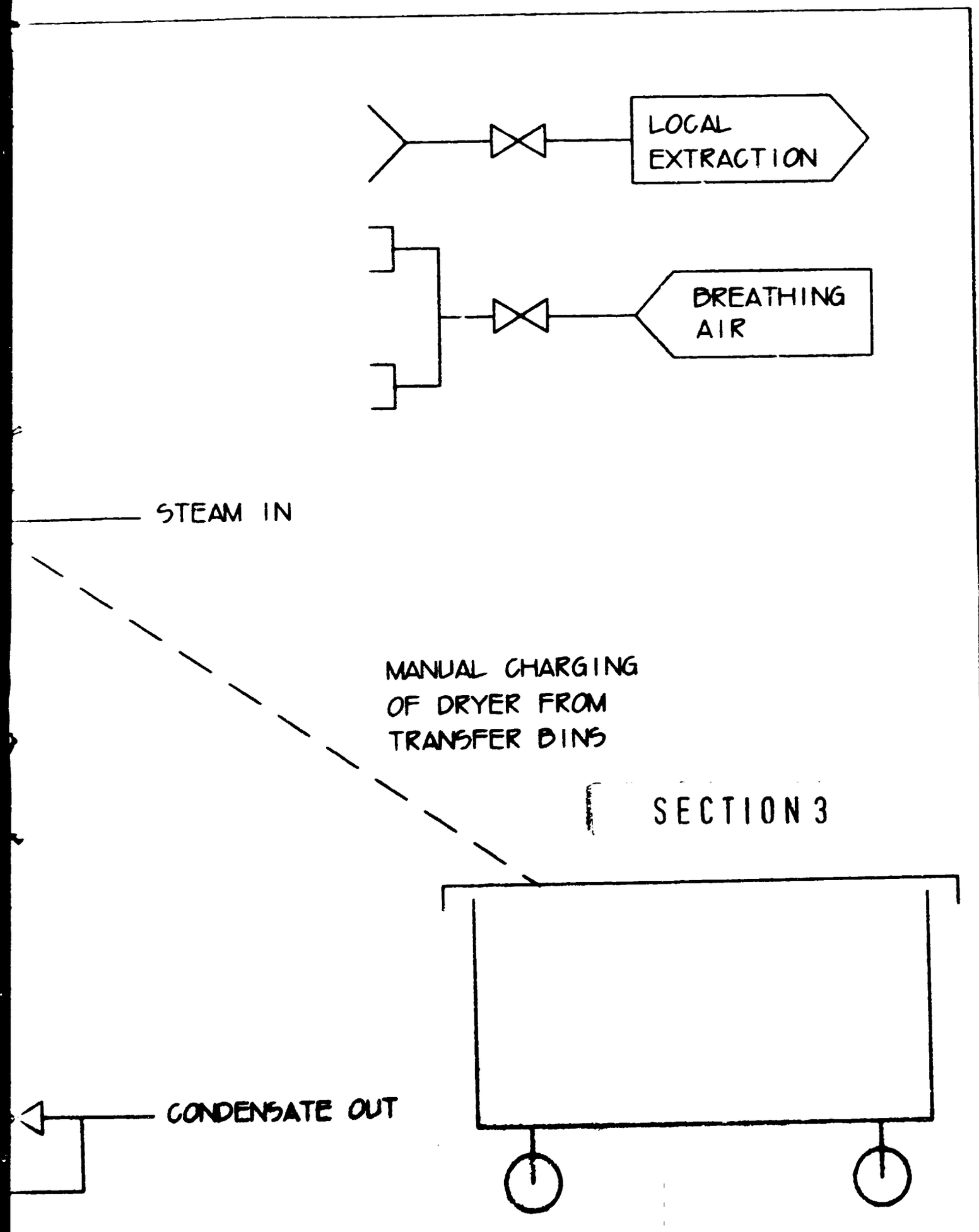

NITROGEN FOR
BAG DEDUSTING
VACUUM
EXPLOSION PANEL WITH
BREAKWIRE INTERLOCK TO
STIRRER MOTOR
FILTER
BAG
SECTION
EXPLOSION VENT
TO SAFE LOCATION
SECTION 1
VENT
FILTER



SECTION 2

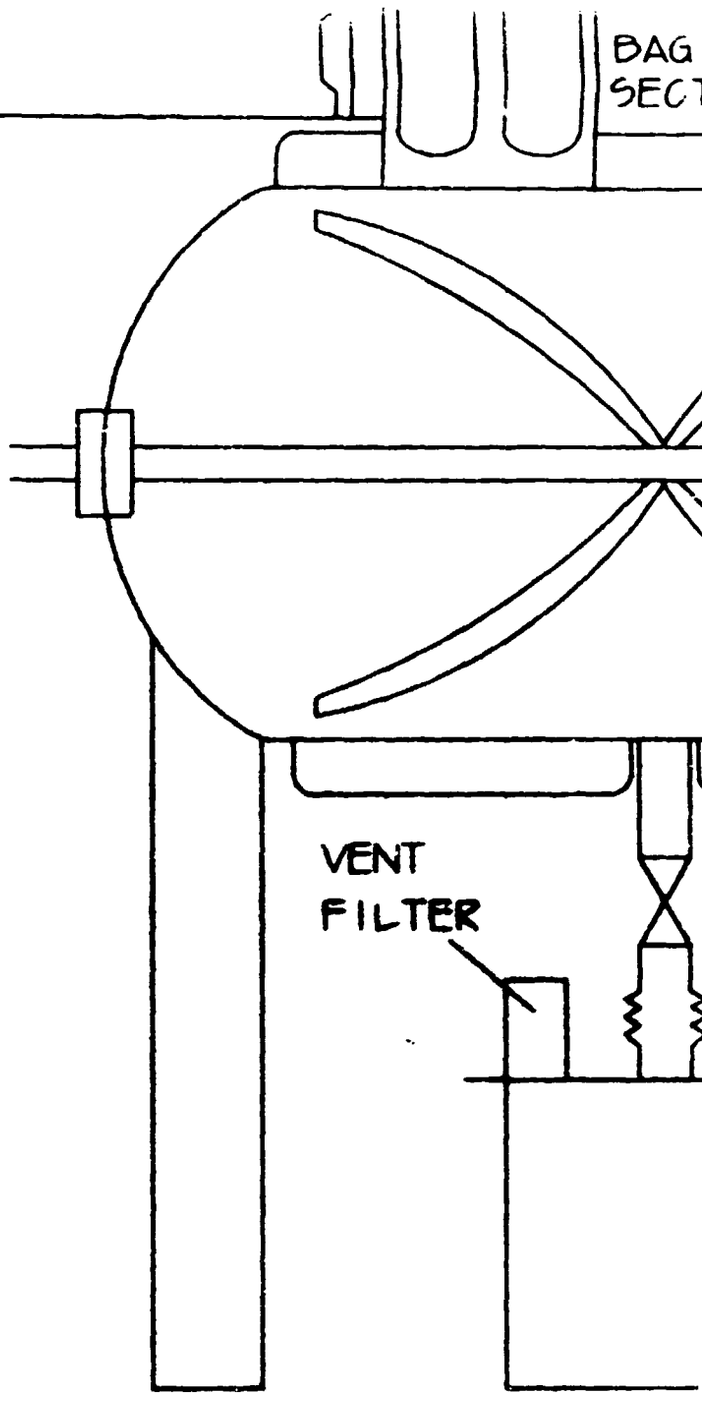
NOTES

1. EXPLOSION CUT BLENDE FAILURE.
2. OUTLET VAL EXPLOSION


LOCAL EXTRACTION
BREATHING AIR
STEAM IN
MANUAL CHARGING OF DRYER FROM TRANSFER BINS
SECTION 3
CONDENSATE OUT

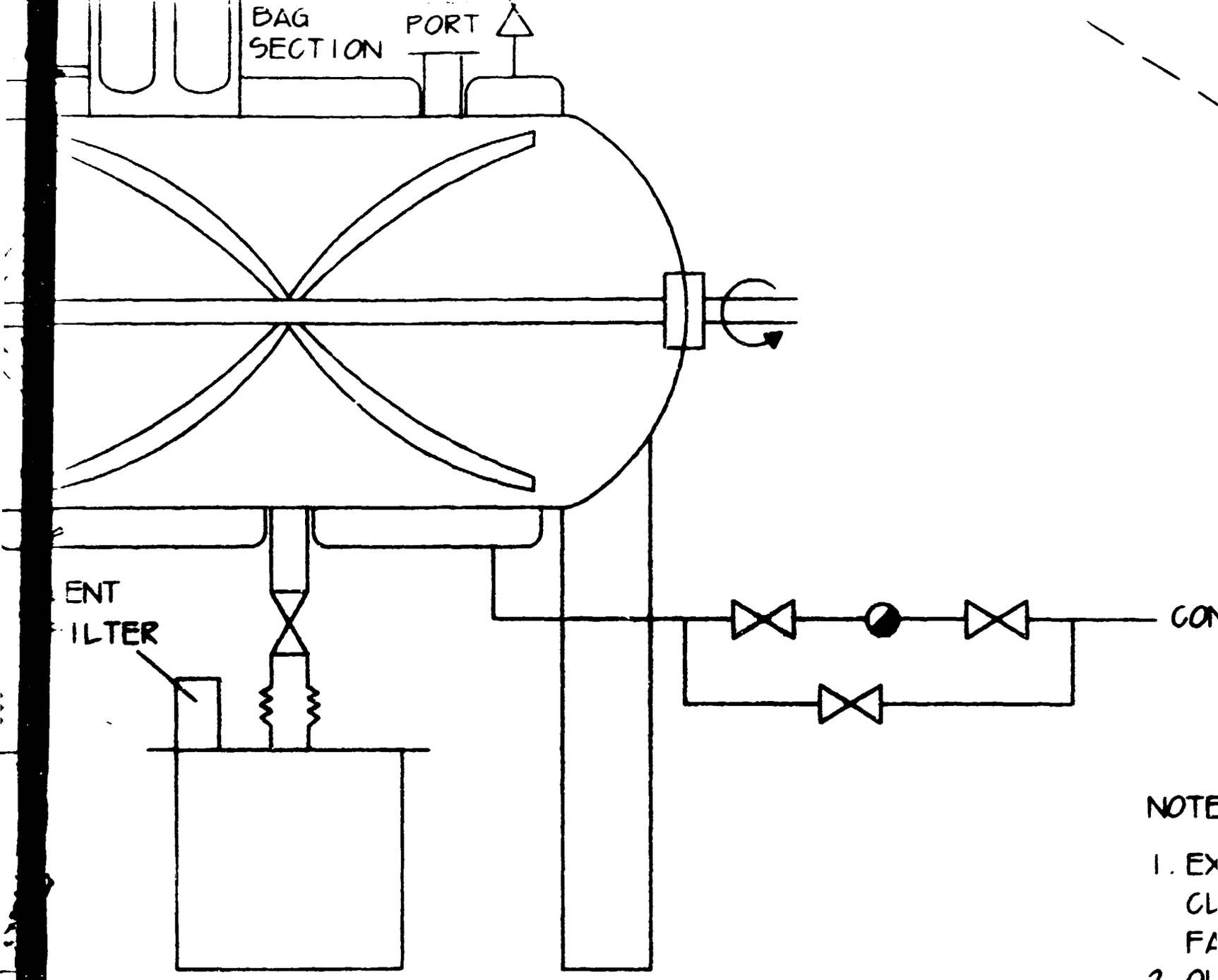
NOTES

EXPLOSION VENT
TO SAFE LOCATION



SECTION 4

CHECKED							
APPVD JD							
DRAWN							
				ISSUED FOR REPORT		A	23/6/92



NOTE

1. EX
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2. OL
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3. IF
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SECTION 5

T	A	23/6/92

GRC CONSULTANTS

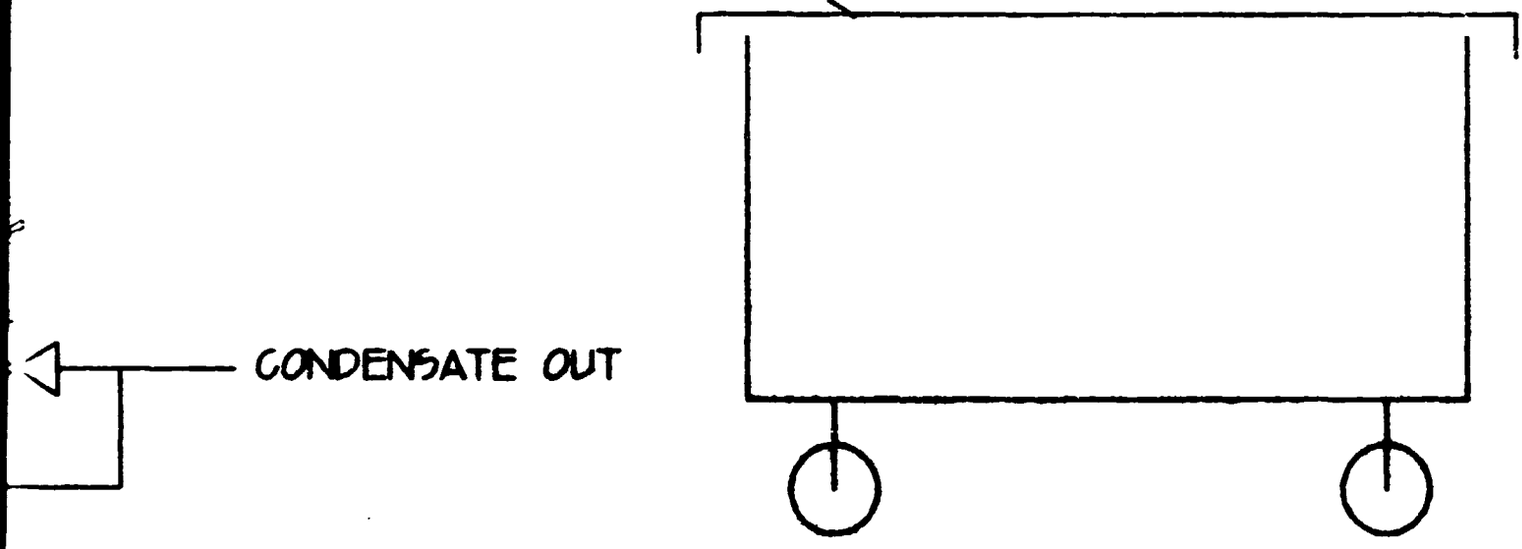
WATERCRESS HOUSE I THE WINDMILLS
ST MARY'S CLOSE ALTON HANTS
TEL:- 0420 89847 FAX:- 0420 89427

CLIENT
UNIDO, P.O.BOX 300,
A-1400 VIENNA,
AUSTRIA, FAX: 232156

DATE: APRIL 1992
SCALE: N/A

PROJ

MANUAL CHARGING
OF DRYER FROM
TRANSFER BINS



NOTES

1. EXPLOSION PANEL INTERLOCKED ELECTRICALLY TO CUT BLENDER BLADE MOTOR AND VACUUM PUMP ON FAILURE.
2. OUTLET VALVE AND SEALS SPECIFIED TO WITHSTAND EXPLOSION PANEL BURST PRESSURE
3. IF HEIGHT ALLOWS DRYER MAY DISCHARE DIRECTLY TO BINS OR ALTERNATIVELY BE TRANSFERED VIA AN AIRSLIDE MECHANISM

SECTION 6

BOX 300, NA, X: 232156 IL 1992 N/A	PROJECT ALKALOIDA I TF/HUN/90/907	TITLE ENGINEERING FLOW DIAGRAM - HORIZONTAL VACUUM DRYER
		DRAWING NUMBER 92/005/206 REV A

CE
AL
1
2
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4
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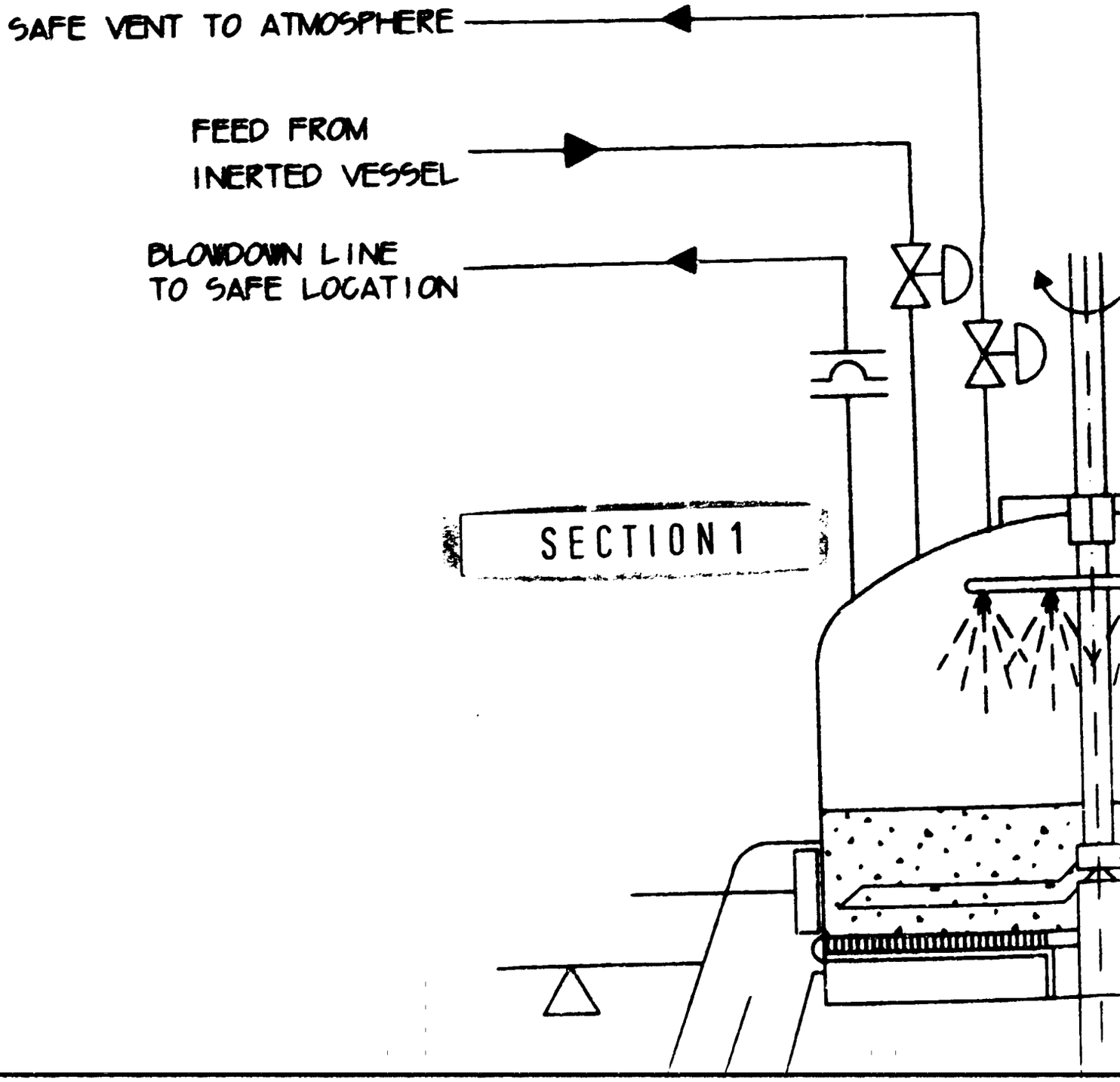
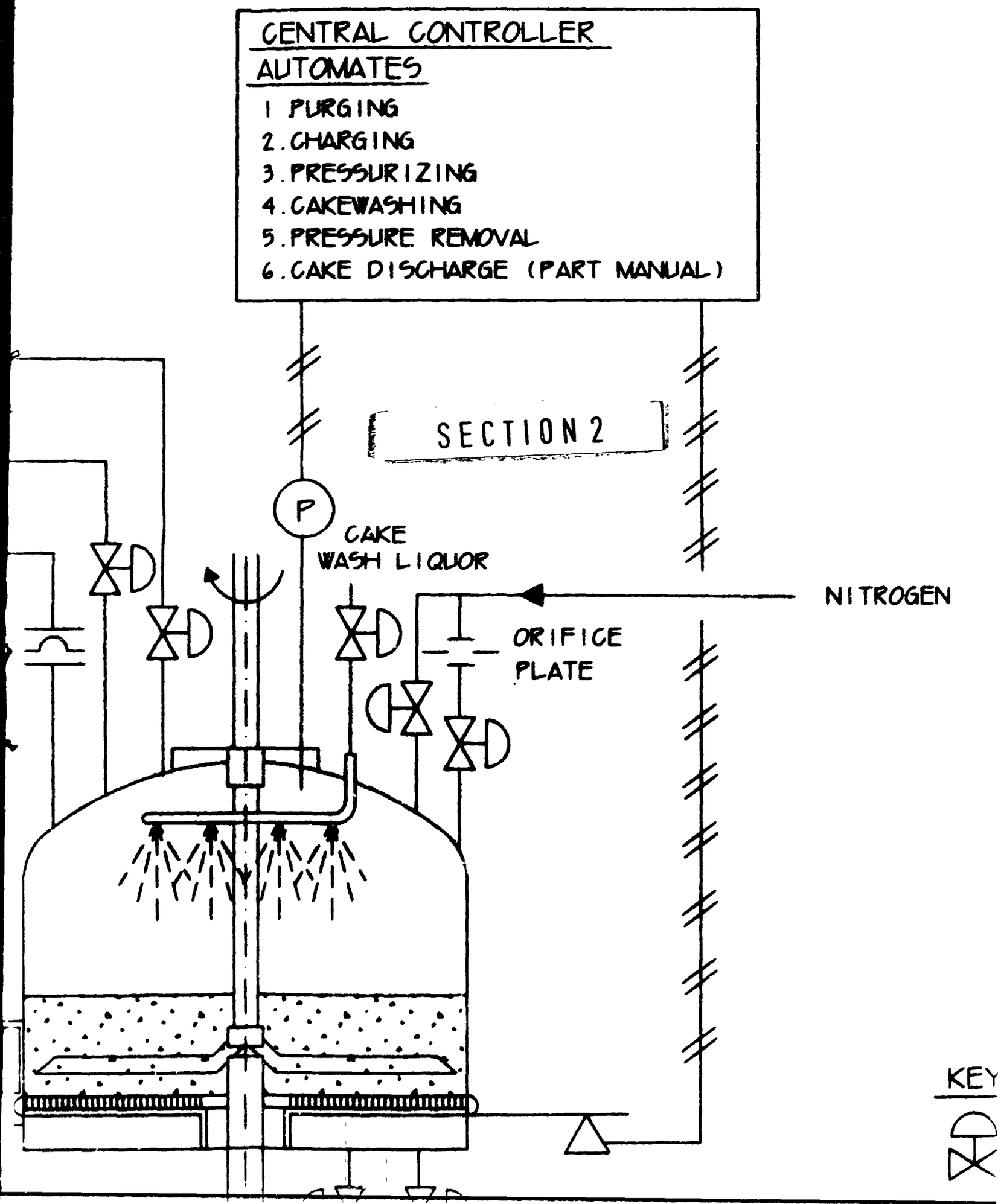
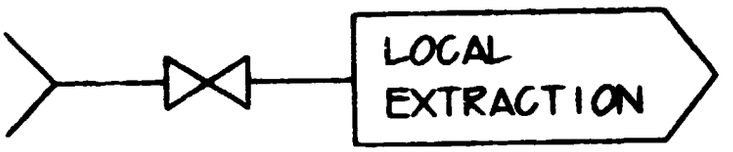
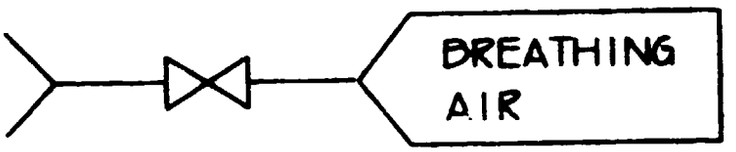

SAFE VENT TO ATMOSPHERE
FEED FROM
INERTED VESSEL
BLOWDOWN LINE
TO SAFE LOCATION
SECTION 1


CENTRAL CONTROLLER
AUTOMATES
1 PURGING
2. CHARGING
3. PRESSURIZING
4. CAKEWASHING
5. PRESSURE REMOVAL
6. CAKE DISCHARGE (PART MANUAL)
SECTION 2
P
CAKE
WASH LIQUOR
NITROGEN
ORIFICE
PLATE
KEY





NITROGEN

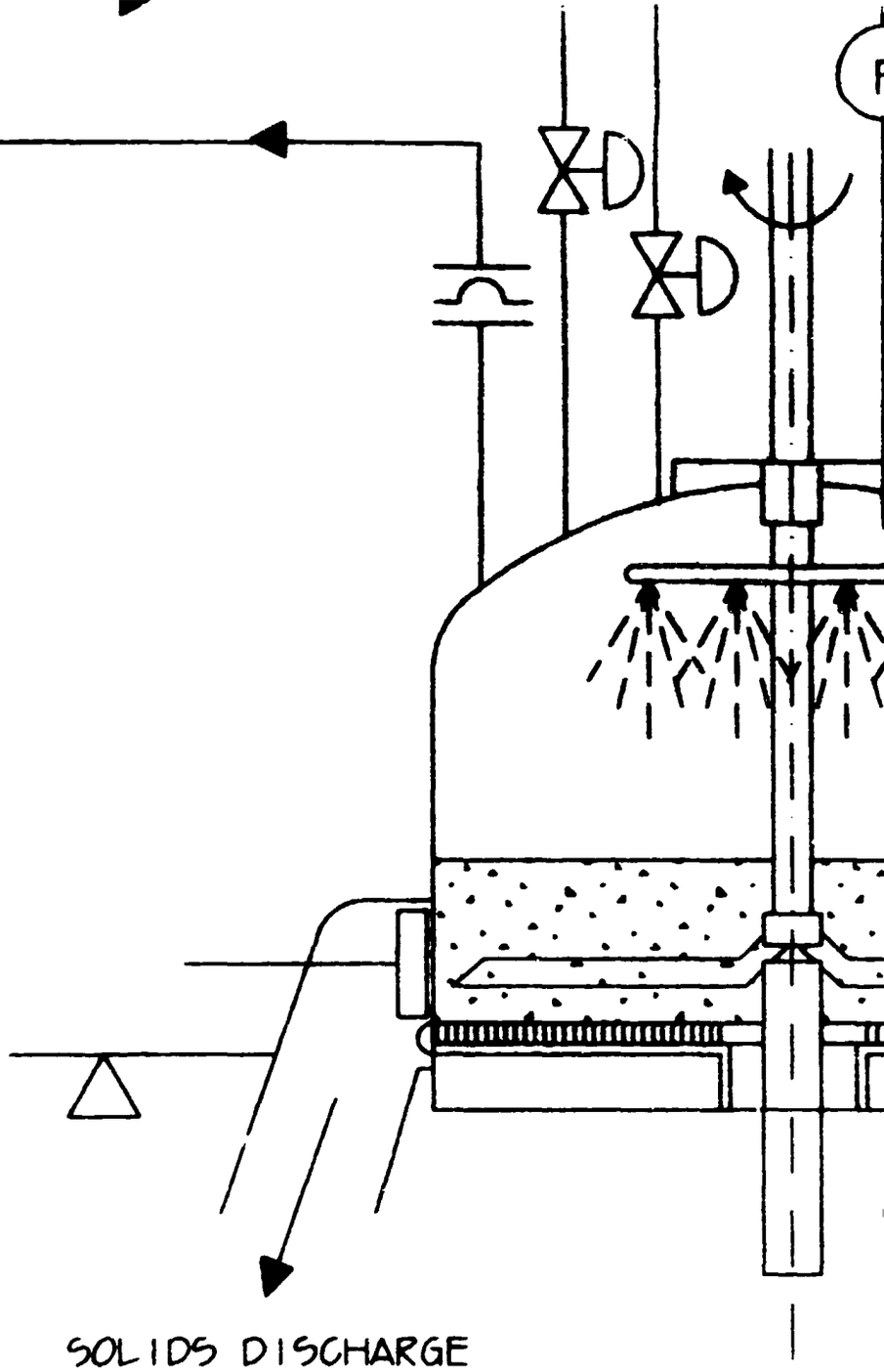
SECTION 3

KEY

VALVE CONTROLLED BY CENTRAL CONTROLLER

INERTED VESSEL

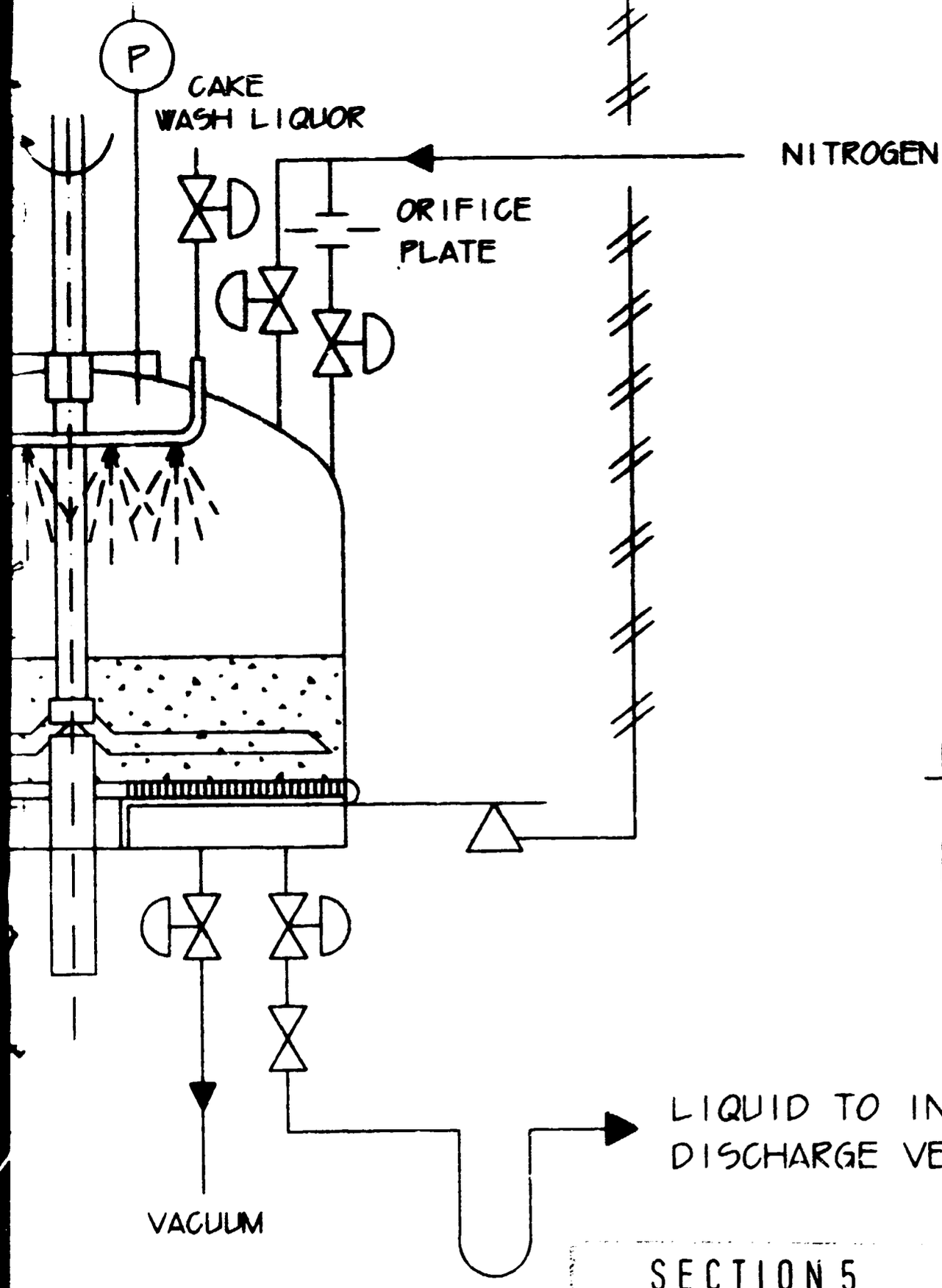
BLOWDOWN LINE
TO SAFE LOCATION



SOLIDS DISCHARGE

SECTION 4

CHECKED							GR
APPVD JD							
DRAWN CS				ISSUED FOR REPORT	A	25/6/92	WATERCR ST MARY TEL: - (
				MODIFICATION	ISSUE	DATE	



SECTION 5

GRC CONSULTANTS

WATERCRESS HOUSE 1 THE WINDMILLS
ST MARY'S CLOSE ALTON HANTS
TEL:- 0420 89847 FAX:- 0420 89427

CLIENT
UNIDO, P.O.BOX 300,
A-1400 VIENNA,
AUSTRIA, FAX: 232156

DATE: APRIL 1992
SCALE: N/A
DIMENSIONS IN: N/A

PROJECT
ALKALOID
TF/HUN/90

ITROGEN

KEY

VALVE CONTROLLED BY CENTRAL CONTROLLER

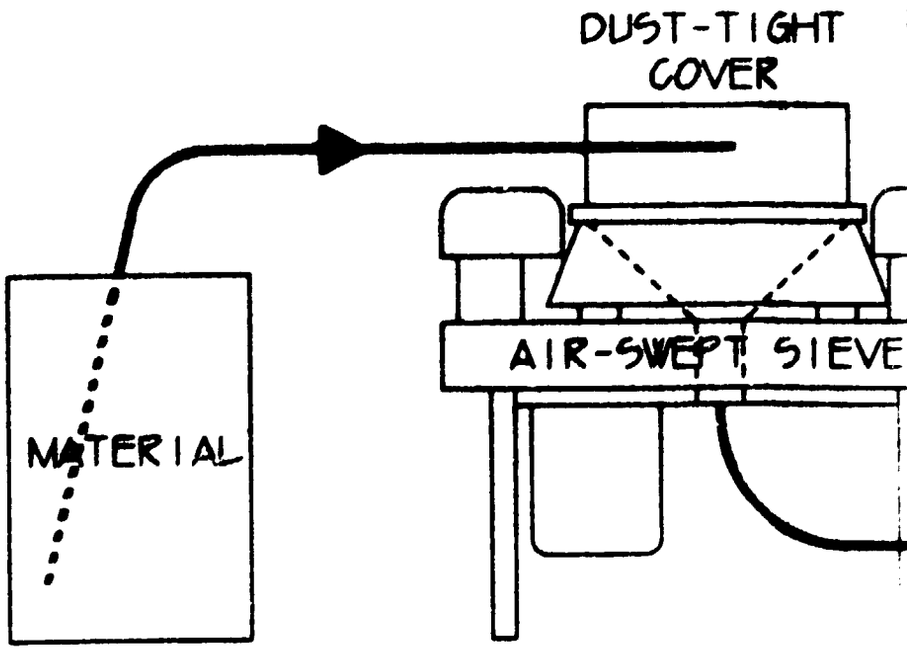
TO INERTED
ARGE VESSEL

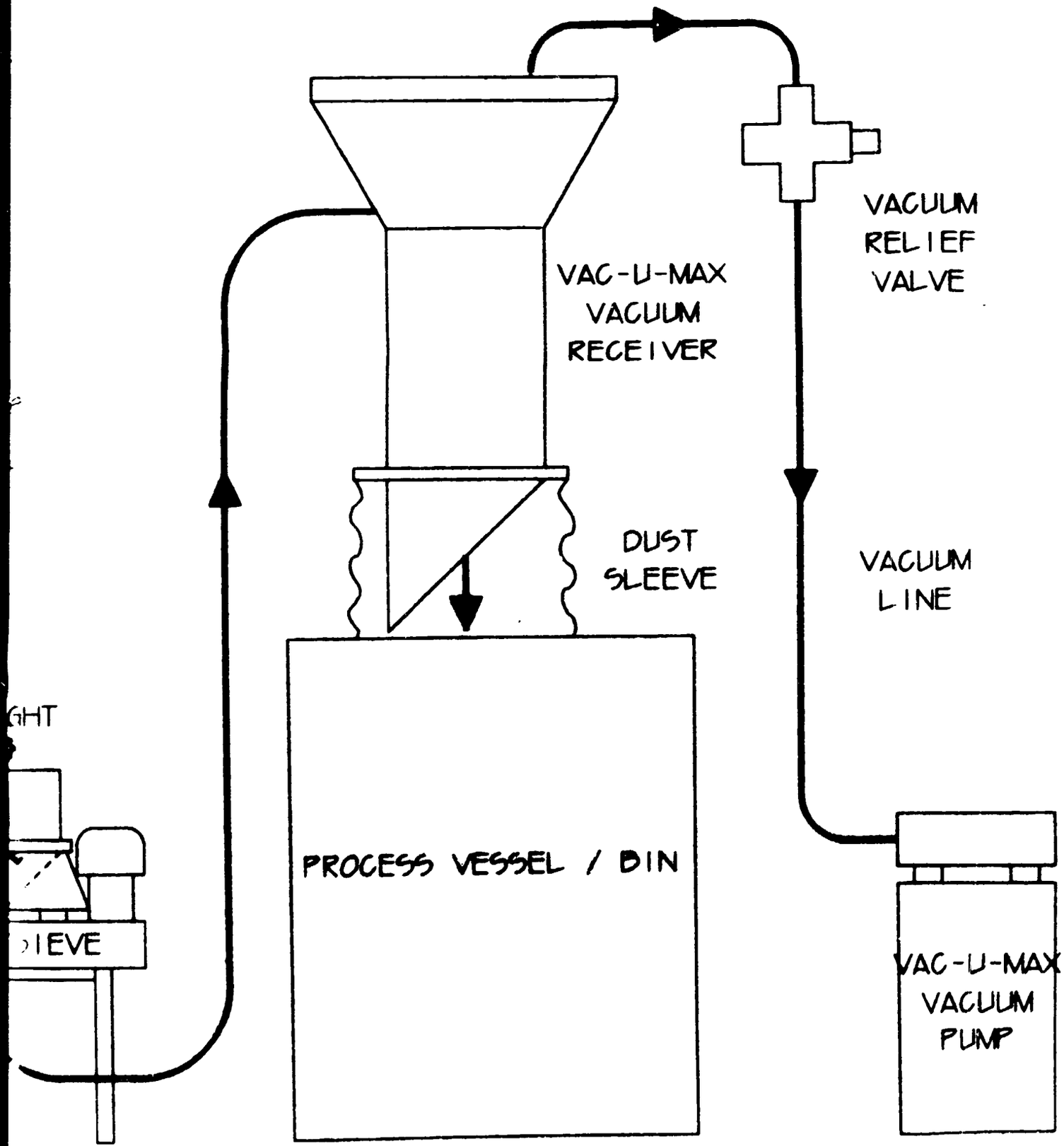
SECTION 6

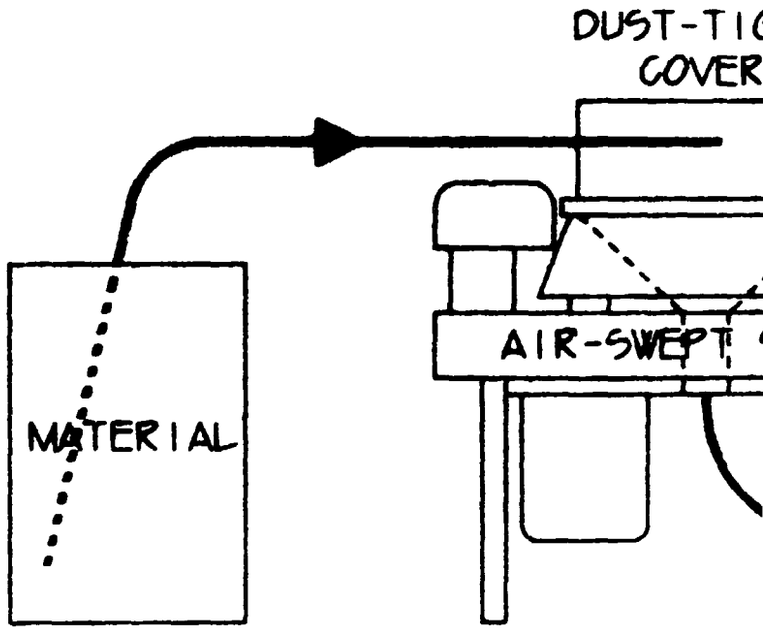
OX 300, A, 232156 - 1992 /A	PROJECT ALKALOIDA I TF/HUN/90/907	TITLE ENGINEERING FLOW DIAGRAM - PRESSURE FILTER
		DRAWING NUMBER 92/005/207 REV A


LOCAL
EXTRACTION

SECTION 1


DUST-TIGHT
COVER
AIR-SWEPT SIEVE
MATERIAL


VACUUM
RELIEF
VALVE
VAC-U-MAX
VACUUM
RECEIVER
DUST
SLEEVE
VACUUM
LINE
PROCESS VESSEL / BIN
VAC-U-MAX
VACUUM
PUMP



SECTION 3

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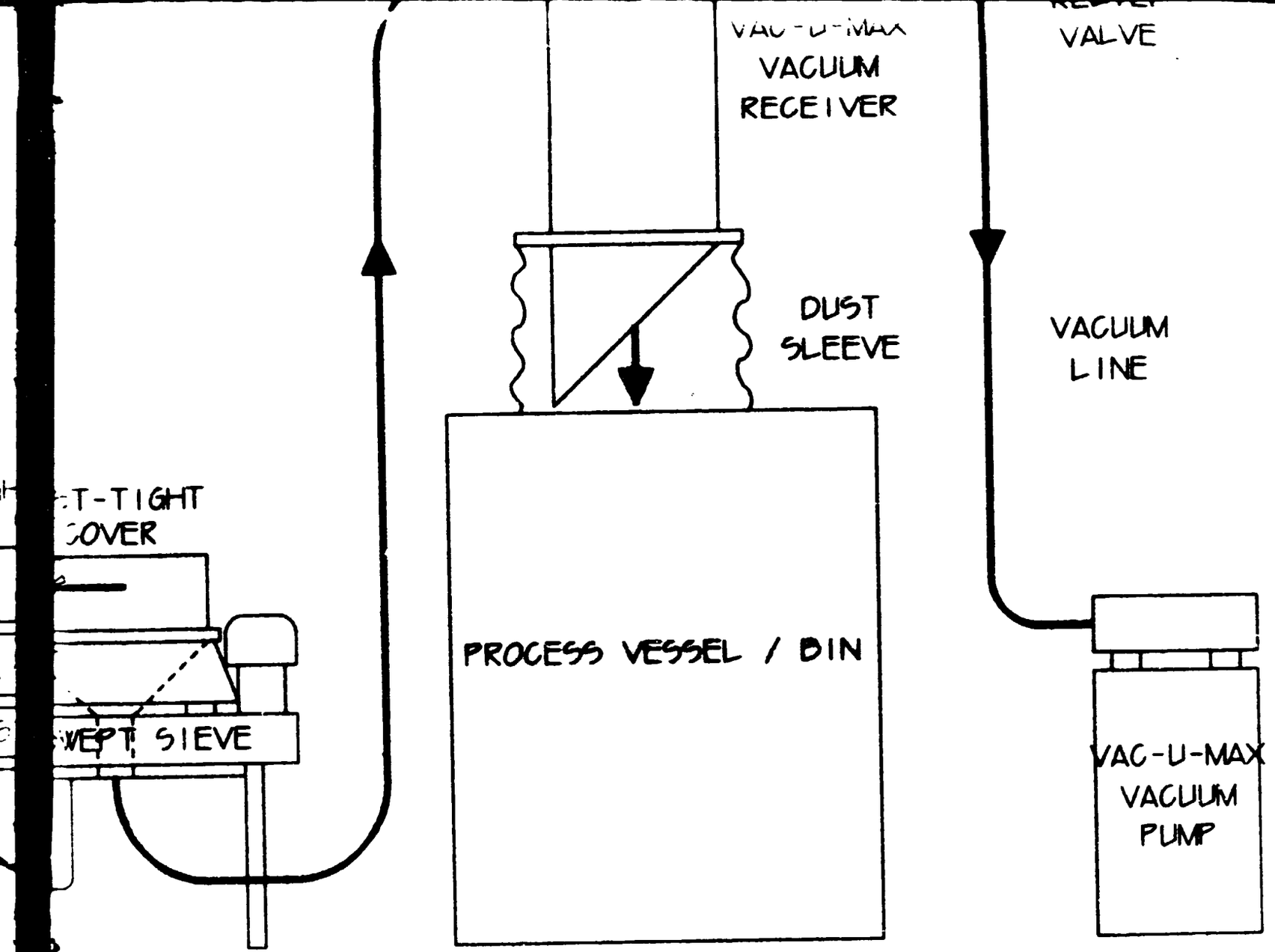

SECTION 4

GRC CONSULTANTS

WATERCRESS HOUSE | THE WINDMILLS
ST MARY'S CLOSE ALTON HANTS
TEL - 0420 89847 FAX - 0420 89427

CLIENT
UNIDO, P.O.BOX 300,
A-1400 VIENNA,
AUSTRIA, FAX: 232156

DATE: APRIL 1992
SCALE: N/A

PROJECT
ALKA
TF/HU

-MAX
UM
VER

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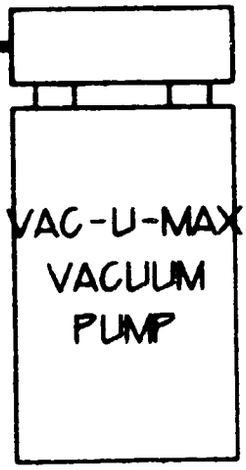

SECTION 5

BOX 300, NA, X 232156	PROJECT ALKALOIDA I TF/HUN/90/907	TITLE ENGINEERING FLOW DIAGRAM - SIEVE
		DRAWING NUMBER 91/005/213
RIL 1992 N/A		REV A

APPENDICES

I EQUIPMENT SUPPLIERS

II VAPOUR SAMPLING AND MONITORING

III SAFETY DATA SHEETS AND PROPERTIES OF MATERIALS

IV ENGINEERING STANDARDS AND SPECIFICATIONS

APPENDIX I

EQUIPMENT SUPPLIERS

APPENDIX I

EQUIPMENT SUPPLIERS

PRESSURE FILTER SUPPLIERS

Rosenmund AG
Gestadeckplatz 6
CH-4410 Liestal
Switzerland

Tel: 061 925 1111
Fax: 061 921 4893
Telex: 966 010 ros ch

Schenk Filterbau GmbH
Postfach 20
D-7076 Waldstetten
Germany

Tel: 07171 4010
Fax: 07171 401017
Telex: 7248 8818

Seitz Enzinger Noll
D-6800 Mannheim 1
Postfach 645
Germany

Tel: 0621 81071
Fax: 0621 8107 223
Telex: 463129 senma d

BASKET CENTRIFUGE SUPPLIERS

Broadbent Incorporated
PO Box 185249
2684 Gravel Drive
Fort Worth
Texas 76118
USA

Tel: 817 595 2411
Fax: 817 595 0415
Telex: 910 893 4070

Rousselet
17 Rue Montalivet
07104 Annonay
Cedex
France

Tel: 7567 0307
Fax: 7567 6980
Telex: 345670

Krauss-Maffei
Verfahrenstechnik GmbH
Krauss-Maffei-Strasse 2
D-8000 Munchen 50
Germany

Tel: 89 88990
Fax: 89 8899 3299
Telex: 5216 504

HORIZONTAL VACUUM DRIER SUPPLIERS

Buss AG. Basel
Hohenrainstrasse 10
CH-4133 Prattein
Switzerland

Tel: 061 8256 111
Fax: 061 8256 699
Telex: 968080

Calmic Euro-Vent Ltd
Govan Road
Fenton Industrial Estate
Fenton
Stoke-on-Trent
Staffs
ST4 2RS
England

Tel: 0782 744242
fax: 0782 744475

APV Pasilac Ltd
Denton Holme
Carlisle
Cumbria
CA2 5DU
UK

Tel: 0228 34433
Fax: 0228 401060
Telex: 64139

VACUUM TRAY DRIER SUPPLIERS

Calmic Euro-Vent Ltd
Govan Road
Fenton Industrial Estate
Fenton
Stoke-on-Trent
Staffs
ST4 2RS
England

Tel: 0782 744242
fax: 0782 744475

Apex Engineering Industries Ltd
Apex House
95 Kent Road
Dartford
Kent
DA1 2AJ
England

Tel: 0322 288256
Fax: 0322 288103
Telex: 918951 APEXCO G

APV Pasilac Ltd
Denton Holme
Carlisle
Cumbria
CA2 5DU
UK

Tel: 0228 34433
Fax: 0228 401060
Telex: 64139

DOUBLE CONE BLENDER SUPPLIERS

Gardner Products
Kemutec Group Ltd
Hulley Road
Hurdsfield Industrial Estate
Macclesfield
Cheshire
SK10 2ND
England

Tel: 0625 428733
Fax: 0625 427319
Telex: 668623

Apex Engineering Industries Ltd
Apex House
95 Kent Road
Dartford
Kent
DA1 2AJ
England

Tel: 0322 288256
Fax: 0322 288103
Telex: 918951 APEXCO G

APV Pasilac Ltd
Denton Holme
Carlisle
Cumbria
CA2 5DU
UK

Tel: 0228 34433
Fax: 0228 401060
Telex: 64139

HAMMER MILL SUPPLIERS

Apex Engineering Industries Ltd
Apex House
95 Kent Road
Dartford
Kent
DA1 2AJ
England

Tel: 0322 288256
Fax: 0322 288103
Telex: 918951 APEXCO G

Hosokawa Micron Ltd
Rivington House
Whitehouse Industrial Estate
Runcorn
Cheshire
WA7 2DS
England

Tel: 0928 710101
Fax: 0928 714325
Telex: 628051

A Christison (Scientific Equipment) Ltd
Albany Road
East Gateshead Industrial Estate
Gateshead
NE38 3AT
England

Tel: 091 477 4261
Fax: 091 490 0549
Telex: 537426

SIEVE SUPPLIERS

Russell Finex NV
Zandvoortstraat-Industriepark Noord 2
B-2800 Mechelen
Belgium

Tel: 015 21 8720
Fax: 015 21 9335
Telex: 27084

Apex Engineering Industries Ltd
Apex House
95 Kent Road
Dartford
Kent
DA1 2AJ
England

Tel: 0322 288256
Fax: 0322 288103
Telex: 918951 APEXCO G

Hosokawa Micron Ltd
Rivington House
Whitehouse Industrial Estate
Runcorn
Cheshire
WA7 2DS
England

Tel: 0928 710101
Fax: 0928 714325
Telex: 628051

SCALE SUPPLIERS

GEC Avery Ltd
Smethwick
Warley
West Midlands
B66 2LP
England

Tel: 021 558 1112
Fax: 021 555 6062
Telex: 336390

Sartorius GmbH
PO Box 3243
Weender Landstrasse 94-108
3400 Goettingen
Germany

Tel: 551 3080
Fax: 551 308289
Telex: 96723

Nova Weigh Ltd
Colemeadow Road
North Moons Moat
Redditch
Worcs
B98 9PB
England

Tel: 0527 67557
Fax: 0527 60213

SCRUBBER SUPPLIERS

Plastic Constructions (Fabrications) Ltd
Evelyn Road
Sparkhill
Birmingham
B11 3JJ

Tel: 021 773 4951
Fax: 021 772 3588
Telex: 336747

Chem-Resist
Britannia House
Lockway
Ravensthorpe Industrial Estate
Dewsbury
West Yorkshire
WF13 3SX

Tel: 0924 499466
Fax: 0924 490334
Telex: 556368

Forbes Plastics Ltd
Denver
Downham Market
Norfolk
PE38 0DR

Tel: 0366 388941
Fax: 0366 385274
Telex: 81346

REACTOR SUPPLIERS

Pfaudler-Balfour Ltd
Leven
Fife
Scotland
KY8 4RW

Tel: 0333 23020
Fax: 0333 27432
Telex: 72304

De Dietrich
Division Equipement Chimique
F67110
Niederbronn-les-Bans
France

Tel: 88 090027
Telex: 870758F

Lampart
H-1105 Budapest X
Gergel u.27

Tel: 00361 1570111
Fax: 1572029
Telex: 225365

APPENDIX II

VAPOUR SAMPLING AND MONITORING

APPENDIX II

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 necessarily 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.

Continuous room monitoring is increasingly being used to ensure a non toxic and non flammable working atmosphere. This has been brought about in part by the identification of previously thought of safe compounds as potentially toxic.

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 III

SAFETY DATA SHEETS AND PROPERTIES OF MATERIALS

APPENDIX III

SAFETY DATA SHEETS AND PROPERTIES OF MATERIALS

ACETONE

Form

Colourless mobile liquid, characteristic odour.

Fire/Explosion Hazard

Extremely flammable, vapour/air mixture explosive.

Health Hazard

Can cause serious damage if splashed in eyes.
Degreases skin possibly causing dermatitis.
Vapour narcotic in high concentration.

First Aid Measures

Eyes	Irrigate thoroughly with water for at least 10 minutes, obtain medical attention.
Lungs	Remove from exposure, rest and keep warm.
Skin	Wash thoroughly with water. Wash contaminated clothing before reuse. In severe cases, obtain medical attention.
Mouth	Wash out mouth thoroughly with water and give plenty of water to drink.

Personal Protection

Breathing apparatus, flame proof fume cupboard, nitrate gloves, goggles/face shield, plastic apron, sleeve, boots are recommended for protection depending on quantity handled.

Spillages

Shut off sources of ignition, inform others to keep a safe distance and wear appropriate protective clothing. If local regulations permit, mop up with plenty of water and run to

waste diluting greatly with running water. If material enters surface drains it may be necessary to inform the local authorities, including fire services. Otherwise absorb on to inert absorbent, transfer to container for disposal.

Storage

Local flammable material regulations may cover this material. Generally plant and vessel should be effectively bonded and earthed and electrical equipment should be flameproofed.

BUTAN-1-OL/BUTAN-2-OL

Form

Colourless liquid, characteristic odour.

Fire/Explosion Hazard

Flammable.

Health Hazard

Harmful by ingestion and inhalation. If swallowed can cause headache, dizziness and narcosis.

First Aid Measures

Eyes — Irrigate thoroughly with water for at least 10 minutes. If discomfort persists, obtain medical attention.

Lungs — Remove from exposure, rest and keep warm. In severe cases obtain medical attention.

Skin — Wash off skin thoroughly with water. Remove contaminated clothing and wash before re-use. In severe cases, obtain medical attention.

Mouth — Wash out mouth thoroughly with water and give plenty of water to drink. Obtain medical attention.

Personal Protection

Breathing apparatus, flame proof fume cupboard, rubber/plastic gloves, goggles/face shield, plastic apron, sleeves and boots are recommended for protection depending on quantity handled.

Spillages

Shut off sources of ignition, inform others to keep a safe distance and wear appropriate protective clothing. If local regulations permit, mop up with plenty of water and run to waste diluting greatly with running water. If material enters surface drains it may be necessary to inform the local authorities, including fire services. Otherwise absorb on to inert absorbent, transfer to container for disposal.

Storage

As required by local flammable material regulations.

ETHANOL

Form

Colourless liquid, slight characteristic odour.

Fire/Explosion Hazard

Highly flammable, vapour/air mixture explosive.

Health Hazard

Intoxicating if inhaled or ingested, irritating to eyes. If ingested in undiluted form has a severe drying effect on mucus membranes of mouth and throat. Can be damaging if splashed in eyes.

First Aid Measures

Eyes	Irrigate thoroughly with water for at least 10 minutes. If discomfort persists, obtain medical attention.
Lungs	Remove from exposure, rest and keep warm. In severe cases obtain medical attention.
Skin	Wash off skin thoroughly with water. Remove contaminated clothing and wash before re-use. In severe cases, obtain medical attention.
Mouth	Wash out mouth thoroughly with water and give plenty of water to drink. Obtain medical attention.

Personal Protection

Breathing apparatus, flame proof fume cupboard, rubber/plastic gloves, goggles/face shield, plastic apron, sleeves and boots are recommended for protection depending on quantity handled.

Spillages

Shut off sources of ignition, inform others to keep a safe distance and wear appropriate protective clothing. If local regulations permit, mop up with plenty of water and run to waste diluting greatly with running water. If material enters

surface drains it may be necessary to inform the local authorities, including fire services. Otherwise absorb on to inert absorbent, transfer to container for disposal.

Storage

As required by local flammable material regulations.

ISO-PROPYL ALCOHOL

Form

Colourless liquid, characteristic odour.

Fire/Explosion Hazard

Highly flammable, vapour/air mixture explosive.

Health Hazard

Inhalation of high concentrations of vapour or ingestion of liquid may result in headache, dizziness, mental depression, nausea, vomiting, narcosis, anaesthesia and coma. Fatal dose is about 100ml. Can cause severe damage if splashed in eyes.

First Aid Measures

Eyes	Irrigate thoroughly with water for at least 10 minutes. If discomfort persists, obtain medical attention.
Lungs	Remove from exposure, rest and keep warm. In severe cases obtain medical attention.
Skin	Wash off skin thoroughly with water. Remove contaminated clothing and wash before re-use. In severe cases, obtain medical attention.
Mouth	Wash out mouth thoroughly with water and give plenty of water to drink. Obtain medical attention.

Personal Protection

Breathing apparatus, flame proof fume cupboard, nitrate gloves, goggles/face shield, plastic apron, sleeves and boots are recommended for protection depending on quantity handled.

Spillages

Shut off sources of ignition, inform others to keep a safe distance and wear appropriate protective clothing. If local regulations permit, mop up with plenty of water and run to waste diluting greatly with running water. If material enters

surface drains it may be necessary to inform the local authorities, including fire services. Otherwise absorb on to inert absorbent, transfer to container for disposal.

Storage

Local flammable material regulations may cover this material. Generally plant and vessel should be effectively bonded and earthed and electrical equipment should be flameproofed. Note that this chemical can form explosive peroxides on prolonged storage.

METHANOL

Form

Colourless volatile liquid, characteristic odour.

Fire/Explosion Hazard

Highly flammable, vapour/air mixture explosive.

Health Hazard

Toxic by ingestion. Damaging if splashed in eyes. Vapour in high concentration may cause dizziness, stupor, cramps and digestive disturbances. Lower levels may cause headache and nausea. Chronic effects - damages the central nervous system, particularly the optic nerve and internal organs.

First Aid Measures

Eyes	Irrigate thoroughly with water for at least 10 minutes. If discomfort persists, obtain medical attention.
Lungs	Remove from exposure, rest and keep warm. In severe cases obtain medical attention.
Skin	Wash off skin thoroughly with water. Remove contaminated clothing and wash before re-use. In severe cases, obtain medical attention.
Mouth	Wash out mouth thoroughly with water and give plenty of water to drink. Obtain medical attention.

Personal Protection

Breathing apparatus, flame proof fume cupboard, rubber/plastic gloves, goggles/face shield, plastic apron, sleeves and boots are recommended for protection depending on quantity handled.

Spillages

Shut off sources of ignition, inform others to keep a safe distance and wear appropriate protective clothing. If local regulations permit, mop up with plenty of water and run to waste diluting greatly with running water. If material enters

surface drains it may be necessary to inform the local authorities, including fire services. Otherwise absorb on to inert absorbent, transfer to container for disposal.

Storage

As required by local flammable material regulations.

TOLUENE

Form

Colourless liquid, Benzene-like odour.

Fire/Explosion Hazard

Highly flammable, vapour/air mixture explosive.

Health Hazard

Inhalation may cause dizziness, headache, nausea and mental confusion. Vapour irritating to the eyes and mucus membranes. Harmful by ingestion and skin contact. If Benzene is present as an impurity, prolonged use may cause blood disease. Prolonged use may cause dermatitis.

First Aid Measures

Eyes	Irrigate thoroughly with water for at least 10 minutes. If discomfort persists, obtain medical attention.
Lungs	Remove from exposure, rest and keep warm. In severe cases obtain medical attention.
Skin	Drench the skin thoroughly with water. Remove contaminated clothing and wash before re-use. Unless contact has been slight, obtain medical attention.
Mouth	Wash out mouth thoroughly with water and give plenty of water to drink. Obtain medical attention.

Personal Protection

Breathing apparatus, flame proof fume cupboard, nitrate gloves, goggles/face shield, plastic apron, sleeves and boots are recommended for protection depending on quantity handled.

Spillages

Shut off sources of ignition, inform others to keep a safe distance and wear appropriate protective clothing. If local regulations permit, mop up with plenty of water and run to

waste diluting greatly with running water. If material enters surface drains it may be necessary to inform the local authorities, including fire services. Otherwise absorb on to inert absorbent, transfer to container for disposal.

Storage

As required by local flammable material regulations.

TABLE A3.1

PHYSICAL PROPERTIES OF SOLVENTS

SUBSTANCE	MELTING POINT °C	BOILING POINT °C	SPECIFIC GRAVITY	VAPOUR PRESSURE mmHg	VAPOUR[1] DENSITY	FLASH[2] POINT °C	EXPLOSION[3] LIMITS % VOL LOWER	UPPER
ACETONE	-95	56	0.79	185 @ 20°C	2.0	-20	3	13
BUTAN-I-OL	-89	118	0.81	6 @ 20°C	2.55	29	1.4	11
BUTAN-2-OL	-115	99	0.81	10 @ 20°C	2.55	24	1.7	10
ETHANOL	-117	78	0.80	43 @ 20°C	1.59	13	3.3	19
ISOPROPYL ALCOHOL	-89	82	0.78	33 @ 20°C	2.07	12	2.3	12
METHANOL	-98	65	0.79	100 @ 21°C	1.11	12	7.3	37
TOLUENE	-95	111	0.86	37 @ 30°C	3.14	7	1.4	7

1. AIR = 1.0

2. CLOSED CUP FIGURES

3. % BY VOLUME IN AIR AT ROOM TEMPERATURE

4. OCCUPATIONAL EXPOSURE LIMITS FROM BRITISH HSE OCCUPATIONAL EXPOSURE LIMITS 1992
   TWA = TIME WEIGHTED AVERAGE

APOUR[1] ENSITY	FLASH[2] POINT °C	EXPLOSION[3] LIMITS % VOL LOWER	UPPER	AUTO IGNITION TEMP °C	TOXICITY LD50	OCCUPATIONAL LIMITS LONG TERM (8HR TWA) ppm	mg/m³	EXPOSURE[4] SHORT TERM (10 MINS) ppm	mg/m³	MUTA/ TERATO/ CARCINO/ GENICITY
.0	-20	3	13	538	5800mg/kg ORAL RAT	750	1780	1500	3560	NO EVIDENCE
.55	29	1.4	11	365	790mg/kg ORAL RAT	-	-	50	150	NO EVIDENCE
.55	24	1.7	10	406	6480mg/kg ORAL RAT	100	300	150	450	NO EVIDENCE
.59	13	3.3	19	425	7060MG/KG ORAL RAT	1000	1900	-	-	NO EVIDENCE
.07	12	2.3	12	425	5045mg/kg ORAL RAT	400	980	500	1225	NO EVIDENCE
.11	12	7.3	37	464	5628mg/kg ORAL RAT	200	260	250	310	NO EVIDENCE
.14	7	1.4	7	335	5000mg/kg ORAL RAT	50	188	150	560	NO EVIDENCE

CUPATIONAL

SECTION 2

APPENDIX IV

ENGINEERING STANDARDS AND SPECIFICATIONS

GENERAL SPECIFICATIONS AND STANDARDS FOR NON STERILE SERVICE

GENERAL SPECIFICATION FOR VESSEL FABRICATION IN AUSTENITIC STAINLESS STEEL

SUPPLEMENTARY REQUIREMENTS FOR VESSEL FABRICATION IN AUSTENITIC STAINLESS STEEL

GENERAL SPECIFICATIONS FOR MILD STEEL ENAMELLED VESSELS

PIPING SPECIFICATION SUMMARIES

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 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.

GENERAL SPECIFICATIONS

FOR

MILD STEEL ENAMELLED VESSELS

MILD STEEL ENAMELLED VESSELS

1. GENERAL

Vessels are to conform generally to the standards laid down by the Pfaudler Balfour Group, or equivalent, unless otherwise specified.

2. PREFERRED TYPES

The following are details of the preferred types for use.

2.1 Sizes

50 gal	(225 litres)
100 gal	(450 litres)
150 gal	(680 litres)
300 gal	(1,350 litres)
500 gal	(2,260 litres)
1,000 gal	(4,500 litres)
2,000 gal	(9,090 litres)
3,000 gal	(13,500 litres)

2.2 Maximum Working Pressures

50-500 gal inclusive:
Jacket 5 bars (4 bars if vacuum in vessel)
Vessel 2.8 bars

1,000-3,000 gal inclusive:
Jacket 6 bars (5 bars if vacuum in vessel)
Vessel 6.9 bars

2.3 Enamel

The required enamel grade is Pfaudler Blue type 3115, or equivalent, acid/alkali resistant glass, spark tested.

2.4 Enamel Defects

The numbers and positions of acceptable plugged defects are laid down by Balfour's Quality Control and are as follows:

Capacity	Vessel*	Cover*	Agitator	Baffle	Pocket
50	Nil	Nil	Nil	Nil	Nil
100	Nil	Nil	Nil	Nil	Nil
150	Nil	Nil	Nil	Nil	Nil
300	1	1	Nil	Nil	Nil
500	2	1	1	1	Nil
1,000	5	Nil	1	1	1
2,000	6	Nil	1	1	1
3,000	10	Nil	2	2	1

* No plugs allowed in centre nozzles or in centre run-offs.

2.5 Agitators

Agitators shall be either 47 rpm Anchor Type with separate thermometer pocket or 90 rpm Impeller Type with thermotip baffle.

Thermotips shall be in Tantalum and the inside of the baffle provided with a fair lead to facilitate entry of the element into the tip.

2.6 Shaft Closures

Capacity (gal)	Closure Type
50	Low duty
100	Split
150	Split
300	Split
500	Split
1,000	High Duty
2,000)	High Duty or Mechanical
3,000)	Seal - VS Drive

2.7 Gaskets

Fluon sheathed gaskets shall be provided for all joints.

2.8 Inspection Light

An inspection light to BSS 4683 Part 2, 1971, or equivalent, Group II B shall be provided.

3. SUPPORTS

Undrilled bracket pads shall be provided on all vessels in addition to the standard leg sockets. The leg sockets shall be closed with plastic plugs. Four standard brackets shall be supplied loose with each vessel.

4. TESTS AT MAKER'S WORKS

A certificate of test shall be provided by the Makers of each vessel in respect of:

Hydraulic test of jacket and vessel

Spark test of enamel

Number and positions of tantalum plugs inserted.

5. TESTS AFTER DELIVERY

All vessels received into client's works shall within 48 hours, be thoroughly examined and spark tested, so that any claim arising may be made on the carrier and/or maker within 3 days of receipt.

6. NOTIFICATION OF DELIVERY

The makers are to notify the client by Telex on the day of despatch.

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.

REFERENCES

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

(2) TF/HUN/90/907 - Technical Assistance for upgrading a small scale multiproduct medicinal chemical plant

(3) TF/HUN/90/910 - Upgrading of Quality Assurance and Good Manufacturing Practices in the Multipurpose Medicinal Chemical Pilot Plant of Alkaloida - Contract No. 92/114

(4) TF/HUN/90/910 - Visit Report and Discussion Notes. Alkaloida Company, Tiszavasvari, 27-29 July 1992, August 1992

(5) TF/HUN/90/907 - Quality Control Audit and Good Manufacturing Practice Critique of Small Scale Production Unit of Alkaloida, November 1992

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