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# GRC Consultants

20877

PROJECT REPORT TO UNIDO

ON

ENHANCEMENT OF CONSULTANCY CAPABILITIES

IN

DESIGN AND CONSTRUCTION

OF

PHARMACEUTICAL, BIOCHEMICAL AND FOOD

PROCESSING PLANTS

FOR

VEGYTERV, BUDAPEST

(TF/HUN/90/908/21-01)

# SYNOPSIS

## GENERAL

The general market conditions in the chemical and pharmaceutical industries in Hungary remain uncertain. With one or two notable exceptions, capital investment by Hungarian companies remains at a low level, a situation which is further exacerbated by the general lack of inward investment by foreign companies.

The market conditions have seriously affected Vegyterv's turnover which has led to a general reduction in staff levels and a relatively poor financial status for the company.

The management at Vegyterv clearly recognise the difficulties which they face and are seeking every means possible to improve their company's organisation, skill base and trading position in order that the company can compete for and secure contracts in the marketplace. The free market has spawned a large number of small design and management companies which pose serious competition to Vegyterv particularly when they are bidding for smaller projects.

The pharmaceutical, chemical and food industries remain the key target markets for the foreseeable future and provided adjustments are made to the organisation, Vegyterv can compete and win business in these fields.

The loss of project activity which started to occur prior to 1990 has not improved principally because the investment in projects imposed by central Government has not been replaced with projects sponsored and financed by the free market economy.

This assignment was carried out with the aim of assisting Vegyterv to understand the standards of design, construction and overall qualification required for processing plants in the food, pharmaceutical and biochemical industries. Particular emphasis was placed on the understanding of current Good Manufacturing Practice (cGMP) and the need for validation of manufacturing plant, particularly in the pharmaceutical industry. The above was demonstrated in considerable detail during the study tour of pharmaceutical, biochemical, fine chemical and equipment manufacturing companies located in the United Kingdom.

The management, design, specification, construction and validation of pharmaceutical plants was explored in considerable detail at a series of lectures and workshops held in Budapest.

The training which took place during this period of intensive instruction covered all of the main features of pharmaceutical plant design and construction including the following:-

(a) An introduction to cGMP and Regulatory Matters
(b) The International Contracting Industry
(c) Product Segregation and Cross Contamination
(d) Plant Layout
(e) Clean Room Design
(f) Validation
(g) High Quality Utility Services
(h) Hygienic Standards
(i) Environmental Standards
(j) Cleaning in Place (CIP)
(k) Sterilising in Place (SIP)
(l) Marketing and Tendering
(m) Commercial Matters

In addition to these key technical subjects, a seminar for manufacturing companies in the pharmaceutical industry was organised by Vegyterv and GRC Consultants. During the seminar, lectures were given on key subjects including Validation and GMP. The seminar was also supported by the Hungarian Medicines Inspection Agency (OGI), who provided a lecture on regulatory matters as applied in Hungary.

The general programme concluded in Vegyterv and GRC Consultants signing a protocol for continuing technical assistance. This protocol has already led to both companies co-operating on a feasibility study for a pharmaceutical plant expansion and upgrade.

## ACKNOWLEDGEMENTS

GRC Consultants wishes to acknowledge the support and help provided by the following organisations:-

APV Baker Perkins Ltd
Association of Hungarian Pharmaceutical Manufacturers
Atomic Energy Authority
British Biotechnology Ltd
BWI Manesty Ltd
Clean Room Construction (London) Ltd
Evans Medical Ltd
Genzyme UK Ltd
Glaxo Group Research Ltd
National Institute of Pharmacy (Orszigos Gyogyszersziti Intezet)
Rhone Poulenc Rorer Ltd
VPX Technoconsult Rft

In addition GRC Consultants and Vegyterv wish to thank the following Hungarian pharmaceutical manufacturers for their interest and participation in a seminar hosted by Vegyterv on the subject of Good Manufacturing Practice in the pharmaceutical industry:-

Alkaloida
Biogal
Chinoin
Egis
Human
Pharmavit Rt
Vepex Consulting Ltd
Trigon

# INDEX

# 1 INTRODUCTION

Contract No. 93/142 between the United Nations Industrial Development Organisation (UNIDO) and GRC Consultants (GRC) has been carried out in accordance with the Terms of Reference (Technical) issued under Project No. TF/HUN/90/908 (Activity Code J13312). The Terms of Reference were revised and agreed in June 1993 and issued on 29th June 1993.

The project was commenced in mid August 1993 with all field work effectively completed by the end of November 1993. Throughout the contract period GRC Consultants was given every support and assistance by Vegyterv. Vegyterv's wholehearted support of the programme of activities made all phases of the project worthwhile and valuable in all aspects of the work carried out.

Some delay occurred to the overall programme due principally to the difficulties experienced in combining a relatively complex set of activities both in the United Kingdom and Hungary.

The project took place in accordance with the scope of work contained in the Terms of Reference which were as follows:-

(a) Audit and review of Vegyterv's procedures

(b) Organisation of a one week study visit to the UK for a small group of Vegyterv key staff

(c) GRC Consultants to accompany the study tour to give adequate guidance and explanation of all stages of the visit

(d) Intensive instruction in Hungary to a larger group of Vegyterv staff on:
- Modern techniques of GMP and Validation
- Techniques of project contracting in the pharmaceutical industry

It should be noted that the study tour in the United Kingdom was supported by a number of major manufacturing companies. GRC Consultants and Vegyterv wish to thank all of the companies for their assistance in carrying out the study tour and in particular the time set aside by their staff and senior management in providing lecturers, guided tours of manufacturing plant and technical documentation.

# 2 PRELIMINARY REVIEW OF THE VEGYTERV ORGANISATION

## 2.1 INTRODUCTION

The following section provides a general overview of Vegyterv since it was established in 1950 until the present day. The information was obtained from documentation handed over to GRC and also from a series of meetings with senior management of the company at the start of the project and also from meetings which took place in 1990 during the exploratory mission on behalf of UNIDO. In particular, the history of the company and its change in structure and size are discussed because they are relevant not only to how Vegyterv will develop in the future, but also give a good indication as to the general state of the chemical, pharmaceutical, petrochemical, and fine chemical industries in Hungary at present.

## 2.2 COMPANY HISTORY

Vegyterv was established in 1950 as a State owned design institute to carry out a wide range of engineering activities as part of the general reconstruction and development of the chemical industry in Hungary following the second World War. The company's development followed a similar path to that of other design institutes not only in Hungary but throughout the former communist region. Its scope of activities were principally defined by the State and these included design of facilities for the petrochemical, chemical, fine chemical and pharmaceutical industries.

During its peak period of activity, Vegyterv had a staff of over 3,000 people with departments covering all aspects of detailed engineering design.

Although the company concentrated on design, by 1981 it had established a capability to provide turnkey plant by acting as a main contractor. However, unlike its counterparts in Western Europe and the USA, the method of project execution substantially diverged from the techniques employed in the competitive contracting industry. In common with all State run industries, competition was practically unknown and therefore the need for establishing efficient and competitive systems of operation was not forced upon Vegyterv. Until the mid 1980's, the principal activities of the company and the markets which it served were all directed by central government and therefore the general management and organisation of the company followed largely predictable and undynamic patterns.

Whilst the company claimed turnkey capability, this depended upon working with other State owned and State directed construction companies. In view of the manner in which projects were established, it is questionable whether Vegyterv had any real control over construction aspects of projects other than to provide design information and resolve design problems encountered during the construction phase.

Until 1990, the company had designed in excess of 1,000 chemical plants which had been commissioned and were in operation in Hungary and other Eastern European communist states. In addition to plants being designed using technology developed in Hungary, the company also gained experience from working with Western companies who were supplying process know-how and technology through the State owned import corporations.

In addition to its classic role as a chemical plant designer, Vegyterv became involved in the development of process equipment for the chemical industry, principally because of the difficulties of purchasing advanced equipment required which was only available from Western Europe or the USA.

Often in support of politically driven initiatives, Vegyterv were employed from time to time to provide design for facilities to be built in developing nations where the investments were supported either by Central Government or the World Bank.

Since 1990 the company has considerably reduced in size, reflecting the generally low level of activity in the chemical and related fields. In spite of the reduction of the workforce, Vegyterv still remains one of the only Hungarian based companies capable of undertaking a multi-discipline process plant project of any significant scale in the chemical and fine chemical industries.

## 2.3 BUSINESS SECTORS

Vegyterv has undertaken projects in the following sectors of the chemical industry:

- heavy chemical
- petrochemical
- pharmaceutical
- organic chemical

- inorganic chemical
- plastics and rubber
- fine chemical
- biochemical

Within the target industries Vegyterv has carried out design work which has included all aspects of pharmaceutical, fine chemical and biochemical plant design. This work has included the following main technologies:

- feedstock preparation
- fermentation
- chemical synthesis
- extraction
- product recovery and purification
- formulation
- sterile and non-sterile finishing
- packaging

## 2.4 PROJECT WORKLOAD

In common with most of the previously State owned engineering design institutes, Vegyterv have suffered from a serious decline in capital plant investment in Eastern Europe. Currently the company has no major projects underway and is supporting its workforce with a series of minor projects in the pharmaceutical, chemical and fine chemical industries. The current capacity of Vegyterv is approximately 250,000 manhours per annum whereas the actual workload is probably not in excess of 100,000 manhours. The reason for the uncertainty is the lack of clear definition of the balance between productive and non-productive manhours in terms of fee earning. It should also be recognised that Vegyterv in common with other state owned industries appear to have a large number of supernumerary staff that are not directly involved with contracting operations. (See Section 4.4 where the subject of staffing is dealt with in greater depth).

The decline in workload and staff numbers can be clearly demonstrated in the following tabulations which indicate the decline in the company's size which has occurred during the last 10 years.

| Details | 1985 | 1990 | 1994 |
|---|---|---|---|
| Total Staff | 1300[1] | 610 | 150[2][4] |

(1) Within the figure stated for the gross numbers of staff over 600 were qualified graduate engineers or scientists.

(2) This figure excludes electrical engineering staff which now are employed by Vegyterv - VIV Elektroprojekt Kft in which Siemens the German conglomerate has a major interest.

(3) A detailed breakdown of the staff numbers and personnel is provided in Appendix 4.

(4) In addition to the technical staff of 150, Vegyterv also had approximately 25 personnel employed to provide maintenance, cleaning and security services for the office complex.

## 2.5 COMPANY ORGANISATION

The Vegyterv organisation has changed significantly during the last 10 years. In order that a full appreciation of the radical changes made in order to respond to the market situation two organisation charts are included in this section. Chart 1 represents the organisation of the company during the period of its most intense workload, Chart 2 shows the current organisation. The differences are such that in many respects the company which exists today is entirely different to that which existed during the former Communist era.

In its original form the company had a very bureaucratic organisation but one which was not significantly different to many of the major western contractors. During the period of its highest workload the company was operated with speciality departments serving the organic, inorganic and petrochemical industries. In addition the speciality fields of pharmaceuticals, pesticides and intermediates (chemicals) were considered to be of sufficient size and importance to warrant a Deputy General Manager in control.

It can be seen that in spite of the company's change in fortunes no appreciable change in organisation took place up to 1992/3. Chart 2 clearly indicates a similar structure to Chart 1 but by this time the management was extremely large in comparison with the workload being handled. Whether it was felt that the free market would induce higher turnover within a short time or that the company was slow to react to changing conditions is not clear.

Since 1992 when the need to scale down the company became very apparent, the organisation has substantially changed. Vegyterv now effectively operates a matrix system which is as shown on Chart 3. This form of organisation is considered to be the most flexible particularly when handling a large number of small to medium sized projects.

# VEGYTERV ORGANISATION UP TO 1990

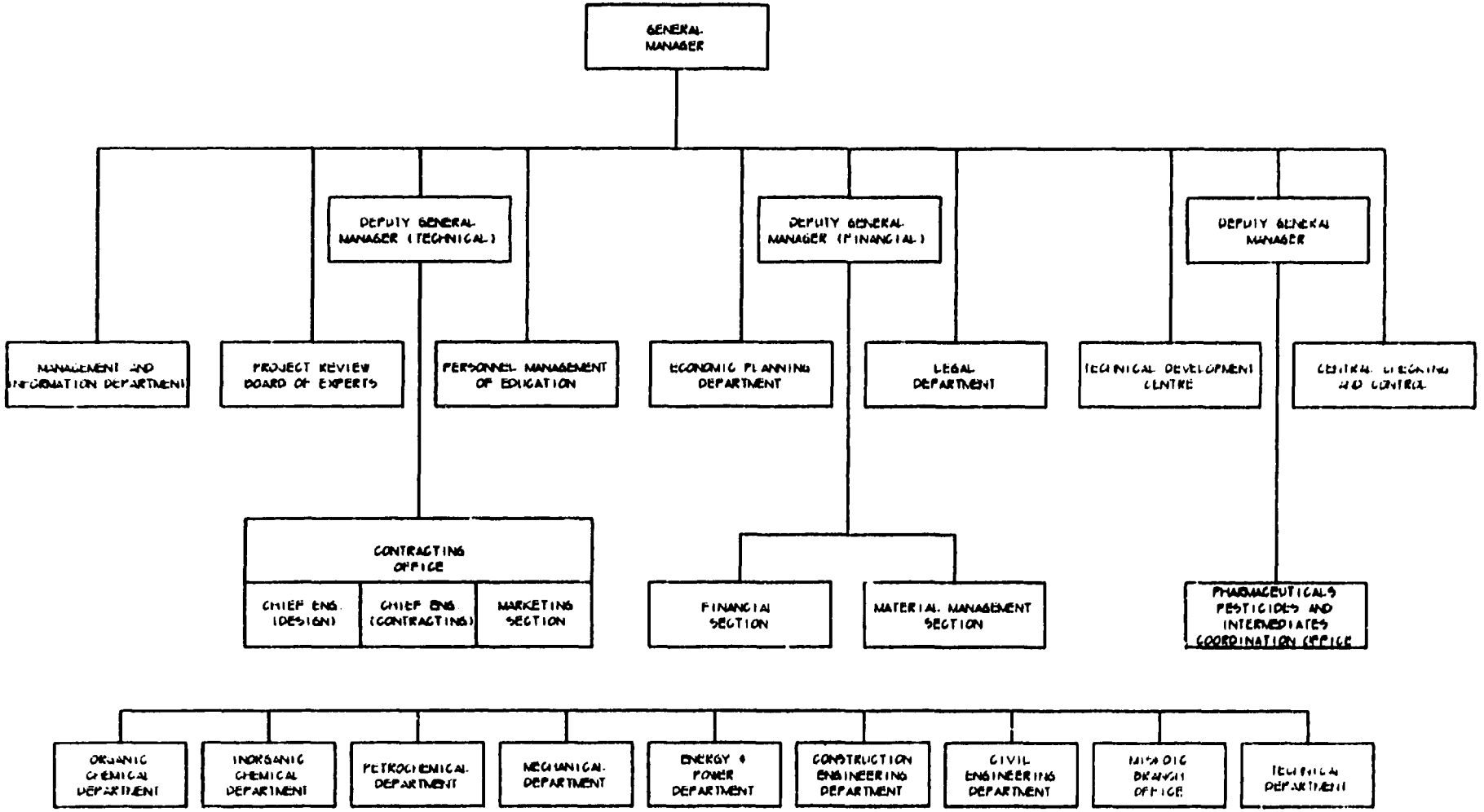


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CHART 1

94/001/TS1

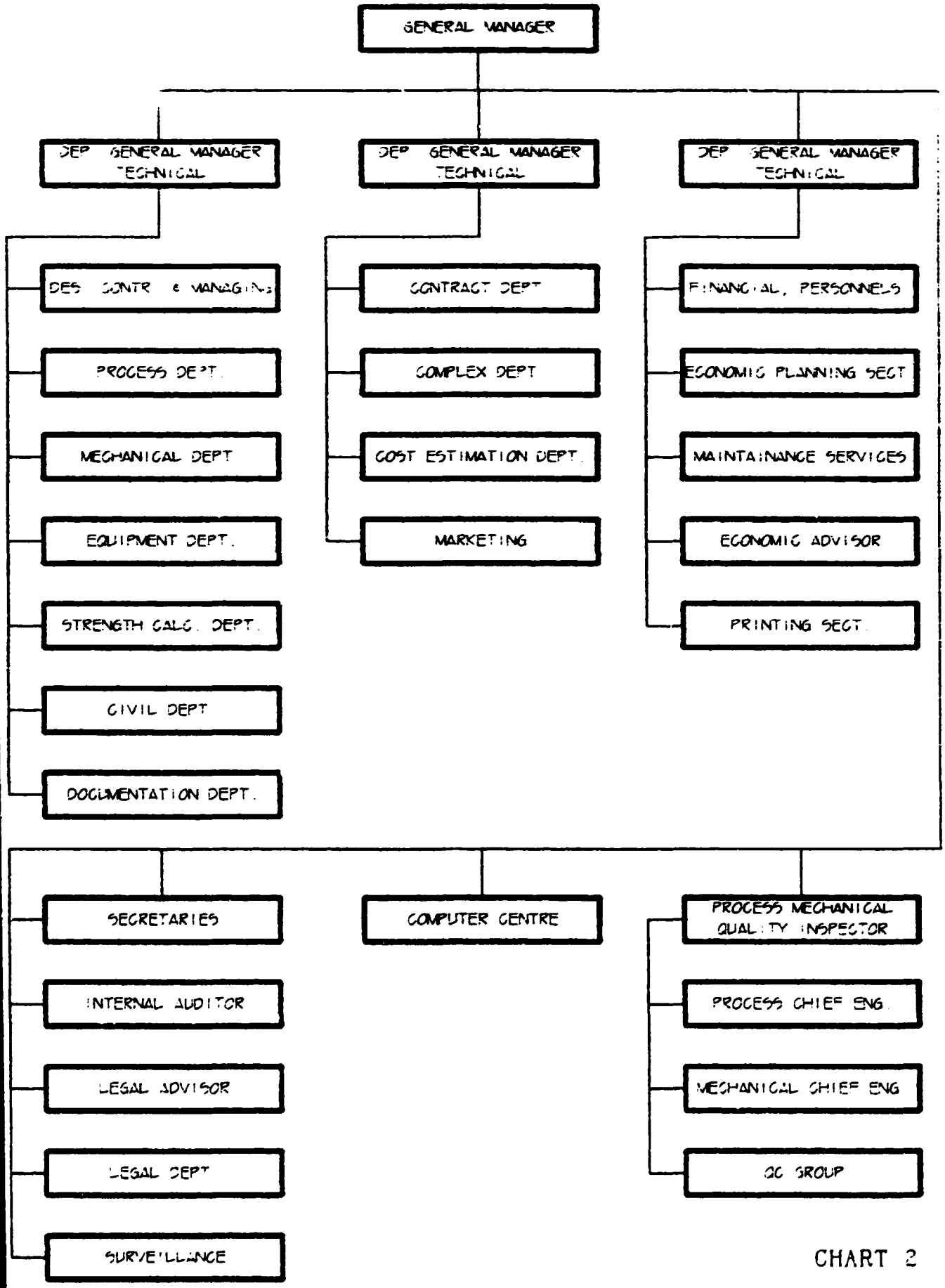
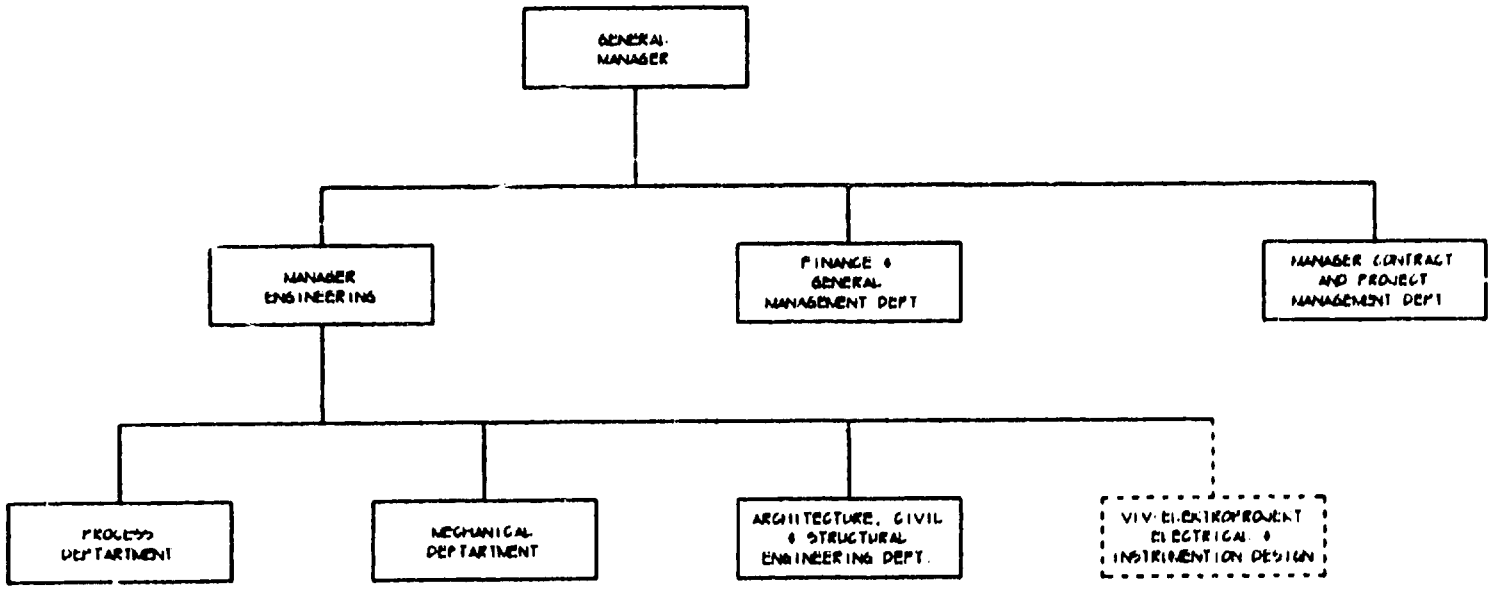



CHART 2

VESYTERV ORGANISATION CHART 20 04 92

# VEGYTERV ORGANISATION 1993




GRC CONSULTANTS

CHART 3

91/021/XG

The departments shown on the organisation shown on Chart 3 currently carry out the following activities:-

**Process Department**

- Process Flow Diagrams
- Process Data Sheets
- Instrument Data Sheets
- Process Description
- Safety and Hazard Analysis
- Preliminary Plant Operating Instructions
- Support to Mechanical Department on Layout

**Mechanical Department**

- Plant Layout
- Process and Instrumentation Diagrams (P&IDs)
- Utility Line Diagrams (ULDs)
- Vessel and Equipment Data Sheets
- Equipment List
- General Design Co-ordination
- Detailed Piping and Building Services Design
- Equipment Layout

It should be noted that this department also has overall responsibility for GMP activities.

**Architecture, Civil and Structural Design**

This department is responsible for the following:-

- Overall Site Development
- Site Infrastructure
- External building architectural design
- Internal building layout and design

- Specification of external and internal building finishes
- Detailed civil engineering design
- Detailed structural engineering design
- Quantity surveying activities

**Project Management and Contracting**

This department is responsible for the overall project management including the following:-

- Project co-ordination
- Cost control
- Planning
- Manpower control
- Project documentation
- Construction management

**Financial and General Management**

This department currently reports direct to the General Manager and is responsible for the following:-

- Personnel management
- Building (office) management
- Project financing
- Accounts

In general personnel are made available to the Project Management Department by each of the technical departments on an as needs basis. Due to the currently low level of project activity, most personnel work from within their own departments and are not seconded to project task force groups.

## 2.6 PERSONNEL

Regarding the quality of personnel, it was not possible to interview a large number of Vegyterv's more junior staff as most of the technical information was discussed and conveyed to senior personnel either at general manager, department manager or senior engineer level. It must be said that in most cases the personnel met were very well qualified and capable, exhibiting all the basic skills necessary in their particular professions. It is likely, however, that many of the more junior staff are not used to taking decisions by themselves and will always wish make reference to more senior staff. This is may be a remnant of the management methods which the company employed during the Communist era and it is important that the staff are urged to take greater responsibility for what they do, particularly if the company is to work efficiently and with any level of dynamism.

Provided in Appendix 4 is a detailed breakdown of the staffing numbers between 1990 to 1992. It should be noted that the numbers of staff have declined further and currently Vegyterv employ approximately 150 personnel.

It will be critical to Vegyterv's future that they maintain a core of highly capable and committed engineers and managers if the company is to grow and establish itself on the international market.

## 2.7 PRINCIPAL DEPARTMENTS

### 2.7.1 Process Department

Currently Vegyterv have a relatively small process department consisting of approximately 7 people, of which 3 are chemical engineers, 2 chemists and 2 instrumentation specialists. To date process departments operated in Hungarian engineering design companies have generally been different from those of Western European companies. In addition to the activities which were described in Section 2.5, the department operates in the two principal roles as described below.

(a) The upgrading of existing processes, particularly where clients in Hungary are unable to purchase new processes from overseas or have insufficient capability to develop new processes in house.

(b) The client company purchases new process technology, in which case the process department takes the role of checking and assisting with the development of basic data into a full engineering package.

The process department, in addition to its basic design role, is also responsible for carrying out all hazard and operability studies for projects which Vegyterv undertake.

It is noted that in Hungary most of the pharmaceutical companies are operating their own process design groups and in certain circumstances have total design capacity in house, from this point of view Vegyterv have limited opportunity to develop in depth process engineering capability in these fields. It was noted during discussions with the process department that for specialist utilities the process department does not play a significant role and would require external support if process information or documentation was not available from the client.

Although Vegyterv have undertaken pharmaceutical projects during the last 5 years, the process department have not been involved with these projects and therefore have not been developing their skills in the pharmaceutical and fine chemical areas. This situation may prove to be a serious deficiency in Vegyterv's capability, particularly where foreign investment is concerned in so far that most major pharmaceutical companies would expect the process or chemical engineering department to lead much of the design activity.

### 2.7.2 Mechanical Engineering Department

The mechanical engineering department appears to be the most experienced and knowledgeable of all the departments in Vegyterv regarding the design and construction of pharmaceutical, fine chemical and biochemical plant. For the reasons explained in Section 2.7.1, the mechanical engineering department tends to take the lead when establishing the scope of work and the general technology because it is the department which interfaces with the client process team. The department acts as the power house of all the project work undertaken and is responsible for feasibility, concept and detailed design of all of the production plant within a project.

The department also has a co-ordination role between all of the departments, taking and collating information not only from Vegyterv's departments but also from external groups such as VIV Elektropojekt who provide the electrical engineering design.

It is envisaged that the mechanical department will remain the most important element of Vegyterv's organisation when seeking work in the pharmaceutical, fine chemical and biochemical industries. This department has considerable experience of modern pharmaceutical plant design techniques, equipment and systems but recognises that until recently have had little absolute control over the choice of equipment and design. Again it must be noted that client companies have taken a very strong lead in determining details of design and therefore Vegyterv's key departments such as mechanical and process have not been able to expand their skills or to maintain contact with the latest technology which has been developing in Western European and USA based companies. In spite of the above comments, the department has considerable capability and with appropriate direction will be able to design all aspects of pharmaceutical, fine chemical, biochemical plant to the latest design standards.

### 2.7.3 Architecture, Civil and Structural Design Department

In spite of this department being responsible for detailed building design, the lead on GMP aspects of design has normally rested either with the client or the mechanical engineering department. It is clear from discussions held with the heads of department that considerable development of skills in all aspects of Good Manufacturing Practice would be required. In particular, the following aspects appeared to be deficient.

(a) Lack of clear understanding of material and personnel flow.

(b) Very limited exposure to high quality internal finishes for pharmaceutical plant.

(c) Little involvement with the choice and management of contractors on site. It should be noted that although the department is called to undertake inspection of works, these visits are normally only made on request of the client or the main construction contractor. In the past on major projects designers visited site regularly and had weekly meetings with the client, more recently this practice seems to have disappeared and as a

result Vegyterv's department have had little control over the quality of work particularly in the architectural field which has been installed.

(d) Due to the generally poor quality of architectural components available within Hungary, the architects department has limited experience of what is available in Western Europe in this field.

As a result of the above findings, it was considered that the architects department in particular would benefit from the study tour in the United Kingdom as it would be possible for them to see some very modern "state of the art" clean room facilities.

### 2.7.4 Electrical Engineering

The Vegyterv electrical engineering department has been partially privatised. A company called VIV Elektroproject Kft was formed which has a shareholding of 56% Vegyterv and 35% shareholding by the employees. This company carries out all of the main electrical, instrumentation and control engineering design not only for Vegyterv but for external companies. Vegyterv have the majority shareholding in VIV Elektroprojekt, approximately 76%.

The company appear to be capable of handling projects from full automation, low voltage distribution systems up to 35 kv systems and are fully conversant with IEC regulations, Hungarian standards and codes of practice and DIN standards.

The company currently has 15 people working for it, of which there is 1 clerical staff and 1 draughtsperson. The remainder of the staff are either engineers, designers or technicians.

The company has adopted AutoCAD as their standard design tool and since purchasing the system have completed a number of projects.

Due to its proximity (in the same office as Vegyterv) and its historical involvement with company, all staff are ex-Vegyterv personnel, it is anticipated that VIV Elektroprojekt will continue to act as the main support for Vegyterv for electrical design for the foreseeable future.

## 2.7.5 Heating, Ventilating and Air Conditioning and Building Services

Due to the relatively low level of work in this field, Vegyterv no longer retain its own HVAC and building services department. The company has recognised that this is a potential weakness, particularly when pharmaceutical plant is designed and as a result have established external relationships with private designers and design companies who can be employed on an as needs basis for any of the project work to be undertaken. This clearly is a potential weakness for Vegyterv, however, provided the control of such design remains with the mechanical engineering department, any slight deficiencies caused by the fact that an external team is used can easily be overcome.

## 2.7.6 Project Management and Contracting Department

**Project Management**

The company has a number of project managers with experience of supervising the design and construction of full projects. It should be noted that there are only a limited number of personnel in the company who have direct experience of pharmaceutical plant project management and this may be a significant factor in the future when Vegyterv attempts to win major projects particularly from overseas companies intending to invest in Hungary.

**Project Teams**

It was explained that Vegyterv now operate a matrix system whereby project managers or project engineers are assigned to a project and then draw technical expertise from each of the main engineering departments. In the past the company had four main project management departments which were for the pharmaceutical, inorganic and organic chemical industries and petrochemical industries but since the downturn in project workload it has been necessary for the company to work in a very flexible manner and for the time being the more rigid project team organisations seem to have been abandoned. Nevertheless project control is maintained by senior deputy managers of the company to whom the departments report on general project execution.

**Estimating**

Currently Vegyterv do not have an estimating department and if a project requires an estimate to be undertaken this is usually the responsibility of certain key senior staff within the technology groups.

**Cost Control and Planning**

The company has a small cost control and planning group but this would need to be expanded in the future in the event that there is an upturn in workload and if Vegyterv are responsible for overall turnkey aspects of a major project.

In general, due to the relatively low workload within the company the senior project managers are involved in executing a series of small projects and it is important that an internal training and development programme for these senior staff is maintained to ensure that when projects are won the company is capable of executing them in a satisfactory and controlled manner.

## 2.8 COMPANY TURNOVER

Details of the company's turnover in 1987-1992 are provided in Appendix 5. The income and cost tend to reflect a more or less constant workload between 1987 to 1990 with a sudden reduction of sales income of approximately 35% in 1991 followed by a further 5.5% reduction in 1992.

One major concern which exists is that in spite of the falling workload the costs have not fallen proportionately and therefore in 1991 the company showed it was operating in deficit for the first time and it is suspect that in 1992 and 1993 a similar situation has occurred. The deficit at present appears to be manageable and steps are being taken by the company's senior management to reverse these losses. Detailed accounts have not been made available for the 1992 and 1993 periods.

# 3 STUDY TOUR

## 3.1 INTRODUCTION

A study tour was carried out in the United Kingdom for a small team of senior engineers from Vegyterv. The purpose of the study tour was to allow key staff from Vegyterv to inspect some of the latest manufacturing facilities to have been installed in the United Kingdom which are directly involved either with the pharmaceutical, biochemical, fine chemical and food industries. Particular note was to be made of the general quality of construction, validation requirements, construction techniques and design standards currently employed to meet Good Manufacturing Practice.

The duration of the study tour was 5 days, commencing on 4 October 1993 and finishing by 8 October 1993. On return to Hungary, the study tour team from Vegyterv were to complete written reports for internal consumption and to brief their respective departments in preparation for the intensive instruction which was to take place during week beginning 22 November 1993.

The general programme of each visit was arranged so that the host companies could provide a general description of the facilities to be visited which would be followed by a tour of the site. After visiting the specific areas of interest a review session would take place at the end of the visit. As can be seen from the study tour programme, generally two companies were visited each day followed in the evening by general discussions on key topics.

## 3.2 THE VEGYTERV TEAM

During the initial review meeting at the Vegyterv offices in Budapest, discussions took place with senior management to determine the best balance of personnel to form the team, in order that Vegyterv could maximise the assimilation and dissemination of the information and knowledge gained into their organisation. It was decided that the following personnel should participate:

Mr Gabor Szalay (Project Manager)
Mr Szalay had recently completed a multi purpose fine chemical production plant project in Iran undertaken on a turnkey basis and was for the present seconded to the embryonic

marketing team to act as a sales and marketing manager. His responsibilities as team leader were to organise the activities of the Vegyterv team throughout the UNIDO study and to act as the primary technical translator.

Kristina Toth (Head of Mechanical Engineering)
As one of the most experienced engineers within Vegyterv, particularly in the field of pharmaceutical, biochemical and fine chemical plant design, Mrs Toth was a key member of the team and is pivotal to Vegyterv's understanding of modern design and construction techniques in the field. Her department carry out all of the detailed mechanical design of the plants for which Vegyterv are responsible and therefore she will be key to Vegyterv's success in adopting modern design techniques in the organisation.

Katerina Molnar (Head of Process)
It is key that Mrs Molnar's group understand the role that process/chemical engineers have within a modern contractor working in the target industries. It was important that her department should gain knowledge of modern production techniques currently employed in the pharmaceutical industry. In addition, Mrs Molnar has a responsibility within Vegyterv for developing validation capability within Vegyterv.

Friges Greiner (Architect)
Mr Greiner's department is responsible for all external and internal design of buildings designed by Vegyterv. The general standards of internal fit-out in the pharmaceutical industry and related fields in Hungary would not be regarded as acceptable in Western Europe and therefore it is of key importance that Mr Greiner and his group fully understand the specifications and standards which are expected by modern GMP.

Zsolt Trosztal (Building Services Engineer)
At present Vegyterv have no permanent building services and ventilation engineering department due to the relatively low level of work which they have been undertaking in this field. Mr Trosztal is an external specialist whom Vegyterv will use in the event that they need this element of design in a project for which they are responsible. It was considered that as building internal environmental conditions within pharmaceutical factories are of key importance and mandatory in terms of certain products, it was important that the techniques currently adopted in Western Europe should be thoroughly investigated and understood if Vegyterv are to compete adequately in the pharmaceutical industry.

## 3.3 STUDY TOUR PROGRAMME

| Date | Day | Company Visited | Basic Activities |
|---|---|---|---|
| 4/10/93 | Monday a.m. | Clean Room Construction Ltd | Design and Construction of Clean Rooms |
| 4/10/93 | Monday p.m. | Rhone Poulenc Rorer Ltd | Pharmaceutical and Fine Chemical Manufacturer |
| 5/10/93 | Tuesday a.m. | Genzyme UK Ltd | Pharmaceutical, Fine Chemical and Biochemical Manufacturer |
| 5/10/93 | Tuesday p.m. | Atomic Energy Authority | Design and supply of Isolator Systems |
| 6/10/93 | Wednesday a.m. | Evans Medical Ltd | Manufacture of Human and Animal Vaccines |
| 6/10/93 | Wednesday p.m. | BWI Manesty Ltd | Manufacturer of Pharmaceutical Tabletting Machinery |
| 7/10/93 | Thursday a.m. | Glaxo Group Research Ltd | Research and Development of Pharmaceuticals |
| 7/10/93 | Thursday p.m. | APV Baker plc | Manufacturer of Food Manufacturing Plant and Equipment |
| 8/10/93 | Friday | British Biotechnology Ltd | Manufacture, research and development of biochemical products |

## 3.4 REPORTS ON VISITS TO MANUFACTURING COMPANIES

The following section provides a brief report on each of the companies visited, literature on those companies has been issued to Vegyterv and would be available on request. As the information is extensive it has not been included in the report. The following section is organised in the sequence in which the visits took place.

### 3.4.1 Visit 1 - Clean Room Construction (London) Ltd

Westminster Industrial Estate
Woolwich Road
London
SE18 5TA

(Note: this company has now moved its premises to the following address)

Unit H1
Eastmill
Imperial Business Park
Gravesend
Kent
DA11 0DL

CRC are design and construction specialists in contamination control facilities. The company has been established for 22 years mainly working in the United Kingdom and to a lesser extent within Western Europe. The company employs a significant engineering, design and project management base and undertakes work for all sectors of contamination control users, but especially the pharmaceutical and biotechnology industries.

CRC have worked with pharmaceutical companies such as Wellcome, Glaxo, ICI, Evans, Bayer, SmithKline Beecham, Roche, Pfizer, Macarthy and numerous smaller but less well known organisations.

The company employs project engineers and design details originate from the building services and architectural professions and embraces all aspects of contamination control facility design including structures, finishes and the integration of specialised HVAC systems, mechanical and electrical services and pharmaceutical equipment.

CRC specialise in providing the "realisation" aspect of clean rooms, i.e. physically designing and building the facility and normally take the project on-board after the initial conception, planning and layout of the facility has occurred, which would normally be the province of organisations such as GRC Consultants.

The creation and construction of successful pharmaceutical areas forms a significant part of Good Manufacturing Practice which is the requirement laid down by statutory agencies and is covered in a number of guides to GMP.

Design and construction of pharmaceutical clean rooms is a very important aspect of achievement of GMP, but of course many other aspects contribute to make the total achievement of GMP a very much broader subject.

The design and construction of the clean room elements is, however, an essential part of the process and is a very specialised area. Most pharmaceutical facilities represent a large capital investment and the importance of effective design and construction together with operational validation represents a significant capital cost.

The presentation was intended to provide a brief insight into the essential facility design and construction aspects.

The visit to Clean Room Construction's design offices was to enable the senior management of Clean Room Construction to present the activities in design and construction normally carried out by a specialist contracting company of this type. During the presentations sufficient time was allowed for discussion on points of detailed design of clean room facilities. The presentation included the following:

(a) A general introduction to the clean room construction industry in the United Kingdom. In particular it was noted that two methods are generally adopted for designing and constructing clean rooms.

    (i) Major multi discipline contractors tend to design the complete clean room facility and then release contracts to qualified sub-contractors for the construction of such units. The main contractor takes responsibility for procuring all equipment and material and the construction contractors responsibility for installing the plant.

    (ii) The clean room contractors only specialise in this field of activity and take full responsibility for detailed design, procurement and construction of all such facilities often using their own labour as part of the construction team.

(b) A general introduction was given to the types of construction adopted in the industry and the materials used for construction of the basic clean room areas.

(c) The standards and specifications adopted in the pharmaceutical industry including a description of the United States Federal Standard 209E which tends to be used in preference to most other standards on a worldwide basis.

(d) A description of the types of finishes used in clean rooms including the following:

(i) Vinyl sheet coating
(ii) Modular panels manufactured either from glass reinforced plastic, coated steel or sprayed glass reinforced plastic

(e) A description of techniques used for validating clean rooms including the following:

(i) Particle measurement
(ii) Air flow visualisation
(iii) Temperature
(iv) Relative humidity
(v) Microbiological testing

(f) A demonstration of computer aided design used in the design of clean rooms was provided. The system used by Clean Room Construction is called Generic CAD (sold by AutoCAD). It should be noted, however, that many companies are now moving solely towards the use of AutoCAD as an industry standard for this type of work.

It was noted that as Clean Room Construction had been employed as the main clean room contractor for the Evans Medical vaccines facility at Speke, Liverpool (subject to a visit later in the week) a number of detailed design drawings and documents were tabled for review by Vegyterv which would assist in the preparation for the visit to this factory.

(g) The design standards for clean rooms with particular regard to air change rates, temperature control were discussed in detail with particular emphasis being made of the fact that in most cases ventilation rates installed are generally significantly higher than the minimum required air change rates of 20 per hour. The air change rates in most clean rooms are determined principally on the basis of clean up rate and temperature control.

### 3.4.2 Visit 2 - Rhone Poulenc Rorer Ltd

Rainham Road South
Dagenham
Essex
RM10 7XS

Rhone Poulenc Rorer are a major international pharmaceutical company formed from two separate corporations, one the Rhone Poulenc Group of France and the Rorer Pharmaceutical Corporation USA. In the United Kingdom, Rhone Poulenc held a major stake in the British company May & Baker Ltd until the new company Rhone Poulenc Rorer was formed. The site at Dagenham was originally developed by May & Baker in 1920 and has been subjected to many changes in layout organisation since the original factory was built. The overall site has a wide variety of processing units including research and development laboratories, pilot plants, primary and secondary production facilities, plus a full infrastructure to support this.

The facility which was to be the subject of the visit is the pharmaceutical active ingredients plant (PAIP).

This unit was designed specifically to manufacture pharmaceutical grade fine chemicals and active ingredients and to be capable of being validated to European and USA standards as applied at the time of construction. The construction of the facility was completed in approximately 1987 although validation of the unit took a significant time to achieve. The plant is designed to be multi purpose and is controlled by a central computer system which also undertakes all data logging for batch record purposes. Many details of the facility remain confidential. However, it is in principle a multi reactor unit which has a number of glass lined stainless steel and hastelloy vessels all interconnected by a piping manifold system which enables the transfer of chemicals from reactor to reactor all under the control of the central computer system.

The facility also has a number of product separation units including filter driers, driers and filter systems capable of handling a wide range of product type.

External to the main production building is a tank farm in which all of the bulk solvents used in the processes are stored and then transferred into the process units as required.

After a tour of the plant the Vegyterv team were taken to the central control room and given demonstrations of the control and data logging system with a full description of the techniques adopted.

### 3.4.3 Visit 3 - Genzyme UK Ltd

37 Hollands Road
Haverhill
Suffolk
CB9 8PU

Genzyme UK Ltd is a wholly owned subsidiary of the Genzyme Corporation of USA. The site visited was originally built to produce laboratory chemical reagents and speciality chemicals. The site was developed and operated by a company called Kochlight Ltd. Genzyme Corporation purchased Kochlight in 1986 with a view to developing the site to produce pharmaceutical bulk chemicals.

Since the initial purchase Genzyme have invested steadily in the site including the following capital projects:

(a) Construction of a pharmaceutical chemical facility designed to FDA standards.

(b) Upgrading of the existing multipurpose fine chemical facility originally built by Kochlight Ltd.

(c) General upgrade of the site infrastructure including new boiler house, solvent storage and waste treatment systems.

(d) The construction of a biopharmaceutical facility which is designed to transform biomaterial produced at Genzyme's Maidstone factory into finished product form.

The purpose of visiting this site was as follows:-

(a) The facility constructed in 1986 (completed in 1987) successfully met the criteria of the FDA Inspectorate, however, since this facility was put into operation, the general standards required by the regulatory authorities have increased and as a result there are general features in the existing plant which if designed today would be improved.

(b) The new biopharmaceutical facility currently under construction adopts many advanced design features including high quality class 3.5 (Federal Standard 209E) clean rooms and advanced processing equipment. The new facility provides examples of high quality vessels, filtration systems, piping and high purity utility systems and demonstrates the standards of quality required in a modern pharmaceutical plant.

(c) At a critical stage in the process in the new biopharmaceutical facility, isolation technology is used, a technique which is increasingly being adopted in the chemical, biochemical and pharmaceutical industries when a controlled environment is required of a very high standard.

### 3.4.4 Visit 4 - Atomic Energy Authority

Chadwick House
Risley
Warrington
Cheshire
WA3 6AT

The Atomic Energy Authority is currently a Government organisation which has with the steady decrease in nuclear power research started to diversify its activities using many of the technologies developed during the nuclear programmes between 1950 and 1980. In particular the Atomic Energy Authority offer an engineering service to specific design and, if appropriate, supply isolators for the nuclear, chemical, defence industry, pharmaceutical, chemical and biochemical industries.

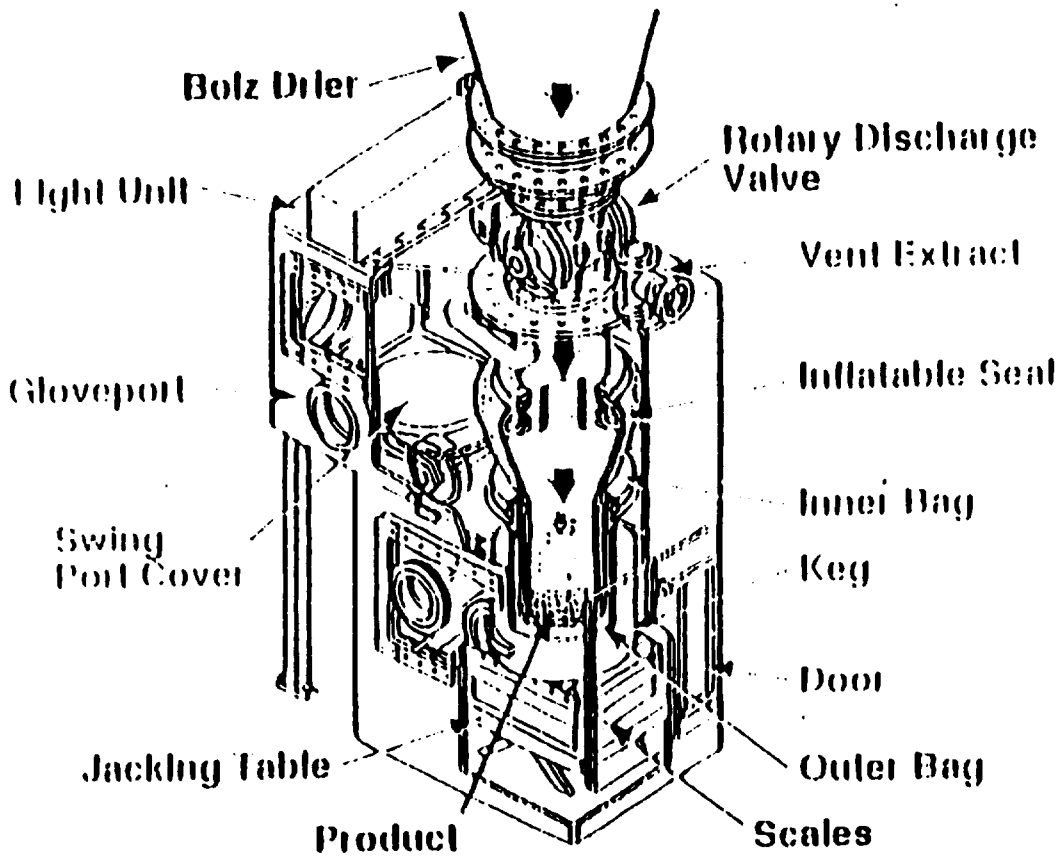
The company were chosen to supply an isolator for the Genzyme biopharmaceutical project after tendering against other qualified manufacturers and were therefore in an ideal position to demonstrate the application, design techniques and construction of such systems.

AEA provided a lecture and subsequent visit to the site to explain the details of the isolator. The subjects covered in the lectures were as follows:

(i) The general principles of isolator technology
(ii) The standards which are applicable to isolator design
(iii) The various methods of construction and the materials used
(iv) The conflicting requirements of containment and high quality environments within the isolators
(v) Methods of cleaning and sterilising the isolators
(vi) The theory of vortex valve design
(vii) Safe transfer ports and the general methods of transferring materials and equipment into and out of isolators

The above presentations were then followed by a general discussion on the likely development of isolator technology in the pharmaceutical and fine chemical industries.

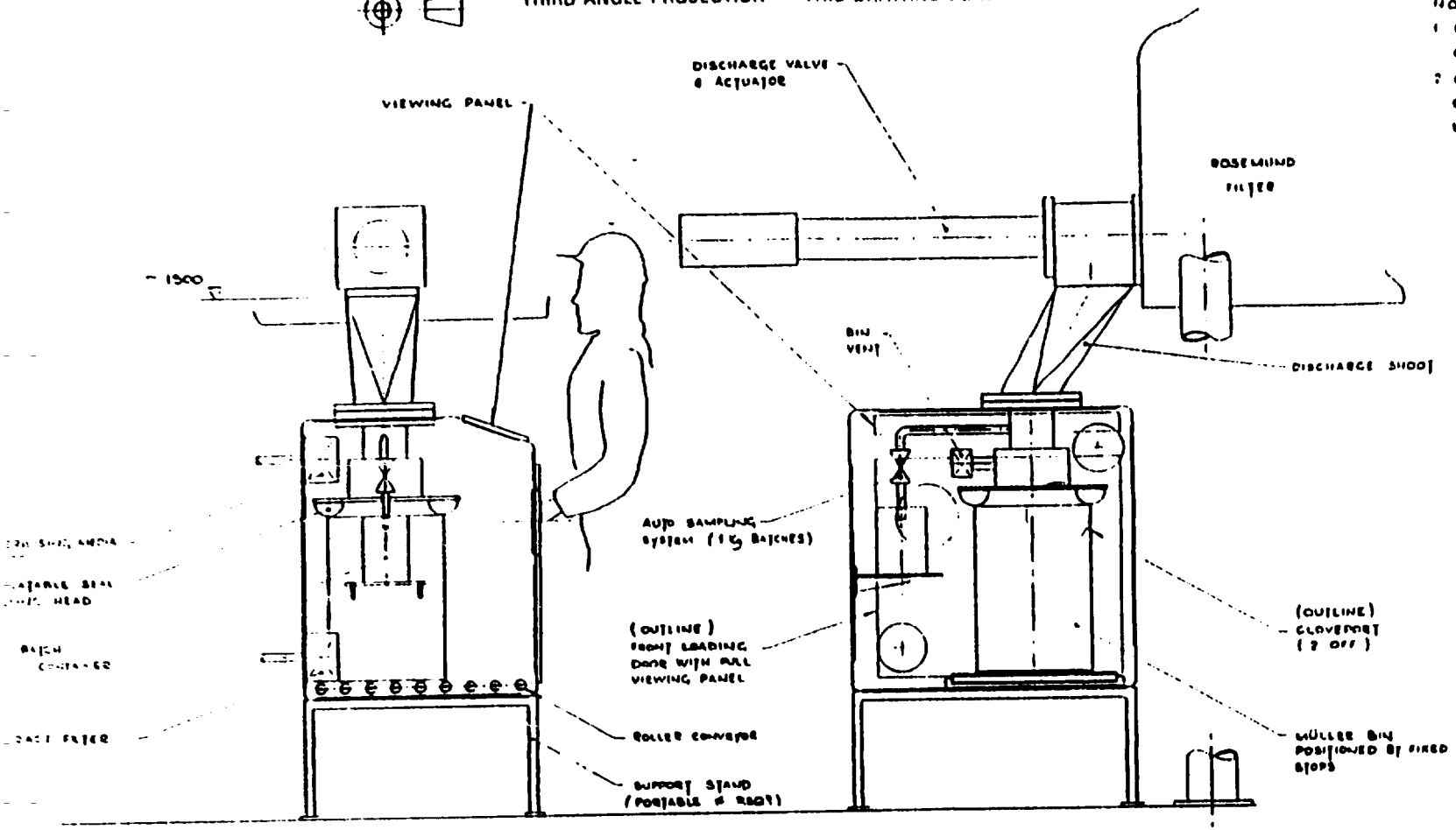
# OFFLOAD CONTAINMENT FOR BOLZ DRIER




TECHNOLOGY FOR THE PHARMACEUTICAL INDUSTRY AEA TECHNOLOGY

THIRD ANGLE PROJECTION · THIS DRAWING CONFORMS TO BS 308 · IF IN DOUBT ASK

NOTES
1 LOCATION OF OPERATING FACE TO SUIT POSITION OF FILTER SUPPORT LEGS
2 CONTROL OF INFLATABLE SEAL & STERILISATION CYCLE TO BE MADE FROM CONTROL PANEL LOCAL TO ISOLATOR




END ELEVATION
(SECTION ON END FACE)

FRONT ELEVATION
(SECTION ON FRONT FACE)

ARRANGEMENT - FILTER/DRYER OFFLOADING, ISOLATOR

### 3.4.5 Visit 5 - Evans Medical Ltd

Gaskill Road
Speke
Liverpool
L24 9GR

Evans Medical Ltd are a wholly owned subsidiary of the Medeva Group plc, a recently formed pharmaceutical group with production facilities in the UK, Europe and the USA. The Medeva Group has grown principally by acquisition, basing its growth initially on the manufacture and sale of human vaccines although the company is now involved in a much broader range of production. Evans Medical was established in the late 1920's developing a wide range of ethical products but eventually concentrating on the manufacture of a range of freeze dried products and vaccines. For a period Evans Medical became part of the Glaxo Group which incidentally still retains a site adjacent to the Evans site at Speke.

In 1991 Medeva completed the purchase of the Wellcome Biotechnology human vaccines business and decided, after investigation of a number of alternatives, to expand its operations at the Speke site which included the consolidation of its vaccine manufacturing capacity in one location. GRC Consultants were commissioned to design and project manage the new facility and the restructuring of the site.

The site development included new manufacturing areas, the expansion of existing vaccines manufacturing capacity, refurbishment of vaccine production units, new quality control laboratories, a new animal cell culture facility and a development pilot plant. The overall programme took approximately 2 years to complete but was finished in stages with various elements of the plant being handed over between 12 months to 18 months after commencement of the project.

The facility is considered to be one of the most advanced vaccine manufacturing facilities in the world and has been approved both by the Medicine Control Agency and the Food & Drug Administration for the manufacture of vaccines.

Note: It was agreed that the Evans Medical project should be the subject of one of the workshops carried out during the period of intensive training in Budapest.

A tour of the manufacturing facilities took place which included a review of the following areas:

(a) Freeze dried products unit which included freeze drying, ampoule filling and sealing, all undertaken in low relative humidity conditions.

(b) A multi purpose viral vaccine manufacturing unit in which robots were being installed for polio antigen manufacture.

(c) Multi purpose bacterial vaccine manufacturing unit.

(d) Typhoid vaccine manufacturing unit.

(e) A general support area in which vessels and glassware were washed and prepared for sterilisation.

(f) Media department in which all of the media used in the vaccines manufacturing processes were prepared and then distributed to the various specific production units.

(g) A central vaccine blending unit where all vaccines both viral and bacterial were blended into final formulations. It was noted that the blending area had two separate parallel production areas for viral and bacterial vaccines.

(h) Vaccine filling unit which included a new syringe filling line, all of which was incorporated in an isolator system. This facility is regarded as being one of the most advanced in the world and demonstrates how isolator systems can enable the standards within the production rooms to be lowered on the basis that very high quality conditions are maintained within the isolator itself.

(i) A review of the research and development pilot plant area which included two clinical trials production units plus general fermentation, microbiological and laboratory areas.

One other novel feature of the facility visited was the fact that the development and clinical trials units, typhoid unit and the multi purpose bacterial vaccines area had adopted a novel material containment system which enabled the production areas to operate under positive pressure whilst still maintaining a containment barrier around the facility.

### 3.4.6 BWI Manesty Ltd

Evans Road

Speke

Liverpool

L24 9LQ

BWI Manesty Ltd are a specialist manufacturer of pharmaceutical tabletting and tablet coating equipment. The company had been established in Liverpool for over half a century. The Manesty tablet presses have been used all over the world by a very wide variety of pharmaceutical companies. It was noted that there are a number of units currently in operation in Hungary.

The visit to the factory was in three parts. Initially a presentation of Manesty was given and the range of products which it manufactures, this was followed by a visit to the product development area where an opportunity was provided to inspect the latest tablet coating and computer controlled tabletting equipment.

A visit to the manufacturing facility was undertaken giving an opportunity to see all aspects of both tabletting and tablet coating machinery being constructed. Particular note was taken during the visit of the need for material traceability and the manufacturing validation undertaken. The factory operates a total quality procedure and can produce all necessary documentation to enable its equipment to be validated in accordance with European and US regulatory requirements.

The visit ended with a question and answer session and the provision of a full set of documents on BWI Manesty's product range.

### 3.4.7 Glaxo Group Research Ltd

Gunnels Wood Road
Stevenage
Herts
SG1 2NY

Glaxo Group Research Ltd is the company within the Glaxo Group responsible for the discovery and development of new pharmaceutical entities. During the last 10 years Glaxo has been one of the fastest growing pharmaceutical companies in the world and has moved from being an important British based company to a major multinational operating in many countries.

Glaxo is committed to research and as a result have invested heavily in new research and development facility in the USA and more recently in the UK. The site being visited is Glaxo's new corporate research and development site which has a planned capital investment of between £800-1000 million. The site, which includes research laboratories, a biological pilot plant and a full infrastructure to support the research programme, is due for completion in 1994.

The facility being visited by the Vegyterv team is the Chemical Development Pilot Plant which is regarded as one of the most advanced facilities of its type in the world. The capital cost of the facility of approximately £100 million and it provides an extremely flexible and comprehensive facility in which most types of process chemistry can be carried out.

The facility has been developed with the following principles in mind:-

(a) There should be a series of independent high serviced process units consisting of feedstock handling systems, header vessels, reactors, receivers and primary product recovery units.

(b) The control should be from outside the process modules and should be validatable.

(c) The plant should be designed to ensure zero exposure of hazardous chemicals to the research staff and to the environment.

(d) The temperature of the chemical reactions should be controlled using a central heat/cool/chill system and should include the facility to neutralise run away reaction.

The Vegyterv team were able to visit the facility as a whole and to review in full detail a typical module. A lecture was also given on the principle of the plant's design and specifically on the depth of validation employed. A paper on the principles of validating development units was handed over for information.

### 3.4.8 Baker-APV Ltd

Manor Drive
Paston Parkway
Peterborough
PE4 7AP

Baker-APV Ltd is a company formed from the Baker Perkins and APV companies. Both companies are regarded as major manufacturers of equipment and process systems for the food industry. The primary market sectors in which the company works are Baking and Confectionery, Dairy Products and the Chemical industries. In addition, APV also manufacture equipment for the pharmaceutical and biotechnology industries including fermentation, separation and purification equipment.

The factory at Peterborough is generally regarded as one of the most advanced of its kind in the UK and in which very high quality equipment and components are manufactured. The developed and test area is also considered to be of very high quality and one in which new products are developed for clients in the food industry.

A presentation of Baker-APV was given noting that the company has a significant capability in Eastern Europe with an operating company, APV Ungaro, which is based in Budapest.

A tour of the following areas then took place:-

1. Design offices in which advanced CAD/CAM systems were in operation.

2. Manufacturing facilities where examples of advanced computer and numerical controlled machinery was seen.

3. A review of the development area where a new food product was being tested for a client.

### 3.4.9 British Biotechnology Ltd

Watling Road

Cowley

Oxford

OX4 5LY

British Biotechnology is one of the UK's leading companies dedicated to the development of new biochemical and chemical entities. The company is typical of the new breed of biotechnology companies funded by speculative investment and dependent on their capacity to convert research into realistic products.

British Biotechnology established a research laboratory in Oxford in the mid 1980s and on the basis of research into Virus Like Particles (VLPs) funded a new pilot plant which incorporated a contained facility, advanced fermentation plant, various forms of downstream processing plant and also a product purification and filling area.

It was fortunate that during the visit to the facility, no processing of hazardous organisms was taking place and therefore the Vegyterv team had full access to the fermentation and primary separation areas.

Examples of the following types of equipment were reviewed in detail:-

(a) Multi purpose fermentation plant manufactured by Chemap AG of Switzerland
(b) Contained homogeniser
(c) Sterilisable centrifuge
(d) Ultrafiltration equipment
(e) Clean-in-Place (CIP) system

In addition the plant is installed in a clean room facility which is built to operate under contained conditions which meet Cl. 10,000 (US Fed Std 209D).

In general terms the British Biotechnology facility is an example of a modern biotechnology plant which meets USA and European standards on safety and cGMP.

## 3.5 CONCLUSIONS

The Study Tour provided the Vegyterv team with examples of a very broad range of plant and equipment currently used in the target industries. Throughout the tour, the need for quality control at all stages of design, procurement and construction was emphasised.

The team was also introduced to the practice of validation particularly for pharmaceutical production and clinical trials facilities. This aspect of the study tour was probably the most important in terms of Vegyterv's long term development.

# 4 TRAINING IN HUNGARY

## 4.1 INTRODUCTION

The purpose of the training in Hungary was to enhance the groundwork established by the UK study tour team and to provide the maximum amount of information to a core team of Vegyterv engineers and managers. This was undertaken by means of a series of seminars, discussion groups and workshops in which a broad range of subjects relating to Good Manufacturing Practice and the design of pharmaceutical plants were discussed.

The seminar took place from 20th November to 25th November including 4 full days of lectures followed at the end of the training period by a series of review meetings.

At the suggestion of Vegyterv it had been agreed that a seminar should be developed to present key subjects of interest to the pharmaceutical industry. This seminar was arranged with the intention of providing Vegyterv with two key benefits, firstly the transfer of know-how to key personnel in pharmaceutical manufacturing companies in Hungary, and secondly to help re-establish Vegyterv's position as a leading designer and constructor of pharmaceutical plant in Hungary. This seminar was attended by all of the leading pharmaceutical companies and was considered to be of enormous value to those attending.

In addition, the seminar was considered to be of sufficient importance for the Deputy Director of the National Institute of Pharmacy (OGI) to attend and to provide a paper.

## 4.2 INTENSIVE TRAINING PROGRAMME

The intensive training programme in Hungary was planned as a series of lectures, workshops and discussions on a range of key subjects relating to modern pharmaceutical design and construction. The training took place at a hotel conference centre in Budapest and was attended by engineers from Vegyterv.

The training was supervised by two partners from GRC Consultants, and took place between 22nd to 26th November 1993.

Training Programme

**Monday a.m.**

The GRC Consultants and Vegyterv teams assembled at a hotel conference centre in which the general lectures were to be held. The centre enabled the team to divide into small groups in which the study of specific subjects could take place. The following programme was undertaken:-

(a) Introduction by Mr Szicksay (General Manager) on the purpose and background of the UNIDO programme.
(b) Introduction to the overall programme for the remainder of the week.
(c) General background on the contracting industry in Western Europe, USA and international.

**Monday p.m.**

(a) Introduction to Good Manufacturing Practice (cGMP)
(b) Regulatory Authorities
(c) Standards and Codes of Practice

**Tuesday a.m.**

(a) Workshop - Comparison between facilities constructed in the UK and Hungary

**Tuesday p.m.**

(a) Plant Layout
(b) Materials and personnel flow diagrams
(c) Product Segregation
(d) Cross Contamination

**Wednesday a.m.**

GROUP 1

Hygienic Standards

(a) Sterile Pipework

(b) CIP & SIP

(c) Environmental Standards and Building Finishes

GROUP 2

(a) Company Organisation

(b) Project Teams and Task Force Organisation

(c) Contract Conditions

**Wednesday p.m.**

GROUP 1

(a) Construction of Pharmaceutical, Fine Chemical and Biochemical Plant

GROUP 2

Specialist Utility Services Generation and Distribution

(a) Specialist Waters

(b) Clean Steam

(c) Gases

**Thursday a.m.**

(a) Quality Control and Validation

**Thursday p.m.**

(a) Tendering

(b) Marketing

(c) Cost analysis and estimating

**Friday a.m.**

Review Session

Questions and Answers

Closing Statements

### 4.2.1 Good Manufacturing Practice and Regulatory Matters

Throughout the lectures, visits and discussion groups great emphasis was placed upon the importance of current Good Manufacturing Practice (cGMP) and the impact of regulatory requirements. It is recognised that the Hungarian Guide to Good Manufacturing Practice (see Appendix 6) is not as extensive as the current codes of practice issued by the European Community and by the United States FDA. It should be noted, however, that Hungary is a signatory to the Pharmaceutical Inspections Convention and that the code of practice adopted is very similar in format, content and in detail to the EC standards.

It is also noted that many of the inspectors in the Hungarian National Inspection Authorities have been trained by the Medicines Control Agency of the United Kingdom and maintain close connections with the Agency. This factor was further emphasised during the paper given by the Deputy Director of OGI who clearly had a similar approach to standards and inspection requirements as would be expected by a UK inspector. It perhaps should be emphasised that the role of the inspection agencies were to an extent subsidiary to the interests of the State during the period of Communist control. This situation has clearly changed and companies operating in the pharmaceutical industry in Hungary must now expect to have to meet far higher standards than was the case in the past and that the inspections will be far more aggressive leading to the issue of closure notices if the inspection agency's requirements are not met.

It was emphasised that none of the codes of practice, standards or regulations which applied to pharmaceutical manufacture instruct the designer or the operator how to achieve Good Manufacturing Practice. It is the responsibility of experienced engineers, pharmacists and chemists operating within the design and manufacturing field to interpret the guidelines. Furthermore, although the inspection agencies should be consulted at key stages in project development, it would be unrealistic to expect them to provide detailed guidance on design

solutions or standards that are to apply to any specific product or production unit. During the presentation to the Hungarian pharmaceutical companies held during the period of intensive training, it became very clear that many Hungarian pharmaceutical companies do not understand fully the relationship between the regulatory authorities and themselves. There was clearly an expectation that the inspectors would assist in the design procedure and some dismay when the inspection agencies when respond by informing the pharmaceutical companies that the question of standards and design is their responsibility.

In conclusion, it was emphasised that there is no substitute for experience in the interpretation of regulatory matters and that if the expertise does not exist within the pharmaceutical company then the use of external consultants is essential.

During the lectures on regulatory matters introductions were given to the general requirements of the US Federal Standard 209E, the European Guide to Good Manufacturing Practice.

### 4.2.2 Standards and Codes of Practice

There are a wide variety of standards and codes of practice which apply to modern pharmaceutical plant design. A wide range of these were discussed in detail. In particular, comparison was made between Hungarian regulations for the production hygiene in the manufacture of pharmaceuticals, the Pharmaceutical Inspection Convention (Guide to Good Manufacturing Practice for Pharmaceutical Products), the World Health Organisation Good Practices in the Manufacture of Quality Control of Drugs (WHO No. 226, 1975 Annex 12) and the latest European Commission Standards for the Guide of Good Manufacturing Practice of Pharmaceutical Products. It is clear that Hungary tends to adopt the PIC standard which is most closely aligned to the European Commission standard and therefore theoretically standards applied in Hungary should be equivalent to those in Europe.

In addition to the above regulatory standards, a number of standards and codes of practice were reviewed. The most important of these was the British Standard BS5295 which relates to the environmental cleanliness in enclosed spaces and is used very widely for the design of clean rooms.

Undoubtedly one of the most important standards to be reviewed was the US Federal Standard FED-STD209E which relates to the airborne particulate cleanliness classes in clean rooms and clean zones. This standard is one of the most widely used throughout the world and although alternative standards are now becoming available, these bear a very close relationship to the Federal Standards.

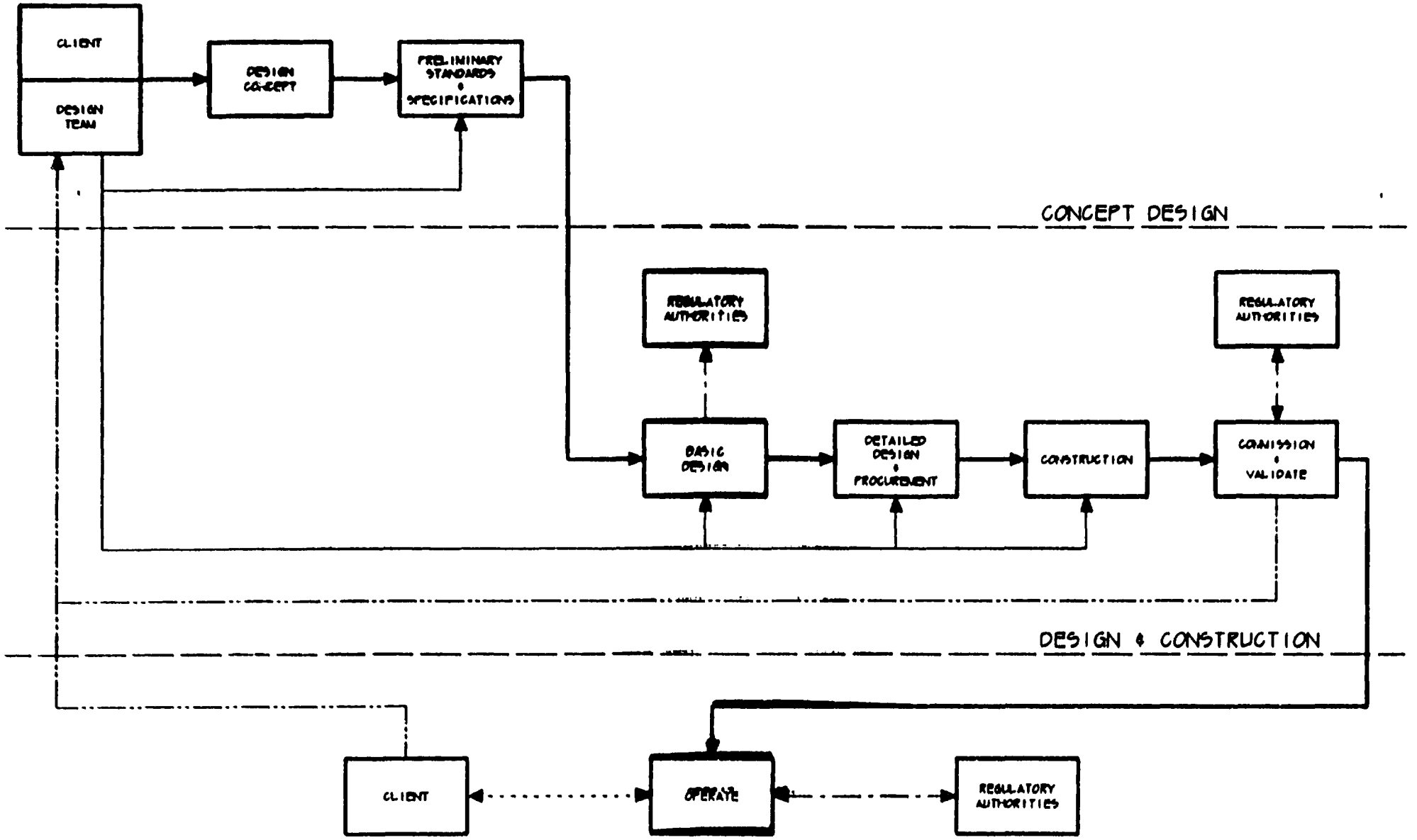
The importance of these standards was emphasised but more importantly how these standards should be applied when developing a pharmaceutical facility. A number of important points were made, in particular the need to set appropriate standards. This is clearly an area in which both operators and contractors in Hungary find some difficulty simply because there is a relatively limited track record of companies having to meet fully regulatory standards and to accept that they must be validated once the specifications are set.

It was noted that although high standards mean higher costs of design, construction and validation, the application of low standards may mean failure in the future. It was noted that during the presentation given by the Medicines Inspector during the intensive training programme in Hungary, it was stated that two major projects in Hungary have not received an operating licence because they do not meet GMP satisfactorily. This situation will clearly have a major effect on the operators in the pharmaceutical industry and may force them to apply the necessary financial input to achieving standards which are now normal in Western Europe.

In addition to discussing the well established codes of practice in the pharmaceutical industry, a brief presentation on the relevant ISO standard, particularly on aseptic processing of healthcare products and also the two standards ISO/DIS11135.2 which relates to performance qualification and ISO11134 which covers all aspects of validation.

All of the above standards were put into context by showing their impact on the design process. It was emphasised that the early approach to the regulatory authorities once the design concepts and preliminary standards have been set is absolutely essential. In spite of this, it must be understood that the regulatory authorities will not provide free consultancy on the design of a plant. It is therefore of absolute importance that engineers and designers who are fully knowledgeable in the codes of practice and their application are employed to design manufacturing facilities which are to apply to GMP standards and the relevant codes of practice which are currently in operation in the pharmaceutical industry.

# IMPACT OF GMP ON DESIGN PROCESS



### 4.2.3 Workshop on Comparison of Parenteral Plant Design

It was of some interest and considerable value that Vegyterv were designing and constructing a parenteral facility (details confidential) which was similar to a unit being constructed by GRC Consultants more or less at the same time. The workshop commenced with presentations from both parties during which the overall concepts of design, processes and methods of contract execution were discussed.

The introductory presentations were then followed by a series of technical discussions covering the following broad topics:

- General arrangement of the facility
- Outline process definitions
- Material and personnel flow patterns
- High quality utility services generation and distribution
- Internal production area environmental containment of hazardous organisms
- Quality control in construction
- Piped Utility System Design

The immediate difference noted between the two facilities was the difference in cost of the finally constructed facility and, as identified by Vegyterv, the difference in general standards and quality of the facility.

The view was clearly of considerable value to the participants as it helped to identify a number of clear differences in standards which had been applied in the United Kingdom and Hungary.

### 4.2.4 Plant Layout

The efficient and effective arrangement of buildings and plant to meet Good Manufacturing Practice in the pharmaceutical industry is dictated by a number of the factors which have been described elsewhere in this report. The key factors which affect layout are as follows:

(a) Material flow
(b) Personnel flow

(c) Product segregation
(d) Process requirements
(e) Safety
(f) Statutory requirements
(g) Space available on the site and within the appropriate buildings
(h) Budgetary considerations

There are no easy formula available to the designer when laying out a facility. Much depends on the experience and knowledge of the processes which take place but importantly a full understanding of the considerations which affect Good Manufacturing Practice. In particular the material flow, personnel flow and segregation considerations are key factors which are usually carefully reviewed in detail by the regulatory authorities.

Considerable discussion took place both during lectures and the workshops on the above factors and numerous examples of layouts for a variety of facilities were discussed.

Of particular value were the presentations made on manufacturing facilities which had been designed and constructed by GRC Consultants and Vegyterv. It is clear from the discussions that many of the principles used in Western Europe are familiar to the Vegyterv team. However, client and budgetary constraints have often conspired to force the company to adopt design principles which they know to be unacceptable in the light of modern GMP requirements.

The impact of the type of equipment and processes used must also be carefully considered particularly if there is a danger of the release of hazardous material. In particular the use of isolators can have a significant effect on layout allowing much greater flexibility in the arrangement of rooms and adjacent areas which is not the case when full scale containment is required.

### 4.2.5 Clean Room Design

In view of the generally poor standard of clean rooms installed in many of the pharmaceutical facilities in Hungary and other Eastern European countries it was considered necessary to review in considerable detail the design features of modern clean rooms. Considerable attention was given to this aspect of the intensive training programme.

As some pharmaceutical products require preparation in high quality environments, solutions may need to be filtered free of bacteria and dispensed into vials, ampoules or syringes which are sterile. They are then either capped or closed immediately but are still at risk if the environments in which they are handled are not reliably of high quality.

Many regulatory authorities consider these products require aseptic conditions similar to those of aqueous products. Pharmaceutical clean rooms are also used for the dispensing of powders into suitably sterilised containers when the containers are then closed within the clean zone. Providing the area operates under controlled humidity conditions it is quite usual for regulatory authorities to require these operations to be carried out in an aseptic environment particularly if terminal sterilisation is not possible.

The filling of such powders usually requires low humidity conditions and carefully consideration must be given to containment and control of powder particles which might contaminate personnel and equipment. These processes are often carried out in separate facilities which are isolated from adjacent areas.

Topical and oral products are usually produced in lower grade environmental conditions typically between Class 10,000 and Class 100,000 to US Federal Standard 209D, but some products particularly solutions to be used in the eye or implants may still require part of the process to be carried out under aseptic conditions.

Particular care must be employed to reduce the chances of cross contamination between different products or products and people especially where powders are concerned.

Preservatives are often used as part of the compound of oral products and do not usually require such close environmental control within the clean room.

Within the pharmaceutical industry standards are continually becoming more stringent. It is therefore prudent to involve the regulatory authorities at an early stage in the design process to assure full compliance with GMP which should ultimately lead to the granting of the necessary product and facilities licences.

The following are the most important basic requirements of almost all pharmaceutical clean rooms and must be thoroughly reviewed at all stages of the design:-

(i) Material and Personnel Flow
(ii) Personnel entry and changing
(iii) Material or product entry
(iv) Component entry
(v) Solution preparations
(vi) Equipment/component preparations
(vii) Equipment/component sterilisation
(viii) Sterilised equipment/component receiving
(ix) Solution transfer to filling area
(x) Clean or aseptic filling area
(xi) Product terminal sterilisation and exit
(xii) Product exit airlock system
(xiii) Various transfer hatches between different grades of area
(xiv) Waste removal from the controlled area

Most clean room suites have areas of differing grades of cleanliness and are usually arranged so they can be separated by different air pressures which ensure that air transfers between these areas around or through doorways, hatches, and any other points of interface are in a direction which will not compromise the required environmental standards in the most critical parts of the suite. There are numerous specialised methods of achieving this where the HVAC system design, layout and control play a vital part in continuously maintaining this separation.

In addition, for aseptic filling there is a complete demarcation between the preparation areas which have their own clean changing entries and aseptic filling areas which have a separate and more rigorous changing and entry procedure.

## TYPES OF PHARMACEUTICAL CLEAN ROOMS

### Clean

Can include cleanliness levels between Class 6.5 and 3.5 to United States Federal Standard (US Fed Std) 209E (EC - GMP Guide A-D) and often achieved by turbulent airflow except Class 3.5 which is usually unidirectional flow. These facilities do not normally require facilities for gas or vapour fumigation. For lower standard areas adequate conditions are achieving by using specialised non-shedding partitions and ceiling system which are not necessarily a continuous membrane type. Two stage changing facilities are usually required. Water supplies, sinks and drainage often present although generally of a sealed hygienic design.

### Aseptic

Normally includes cleanliness levels of Class 4.5 to 3.5 to US Fed Std 209E (EC - GMP Guide A&B) and even up to Class 2.5 with very much higher standards of finish and sealing throughout the facility. Smooth, sealed, non-reacting materials and non shedding surface finishes are required. Often large areas of unidirectional air flow and higher rates of air change are employed. Very careful integration of equipment and services is required. Three stage changing is often required. No open water services or drains are to be installed. Much stricter clean room garment regimes are required with very strict changing protocols. There are often facilities for gas or vapour fumigation and degassing integrated with the HVAC systems.

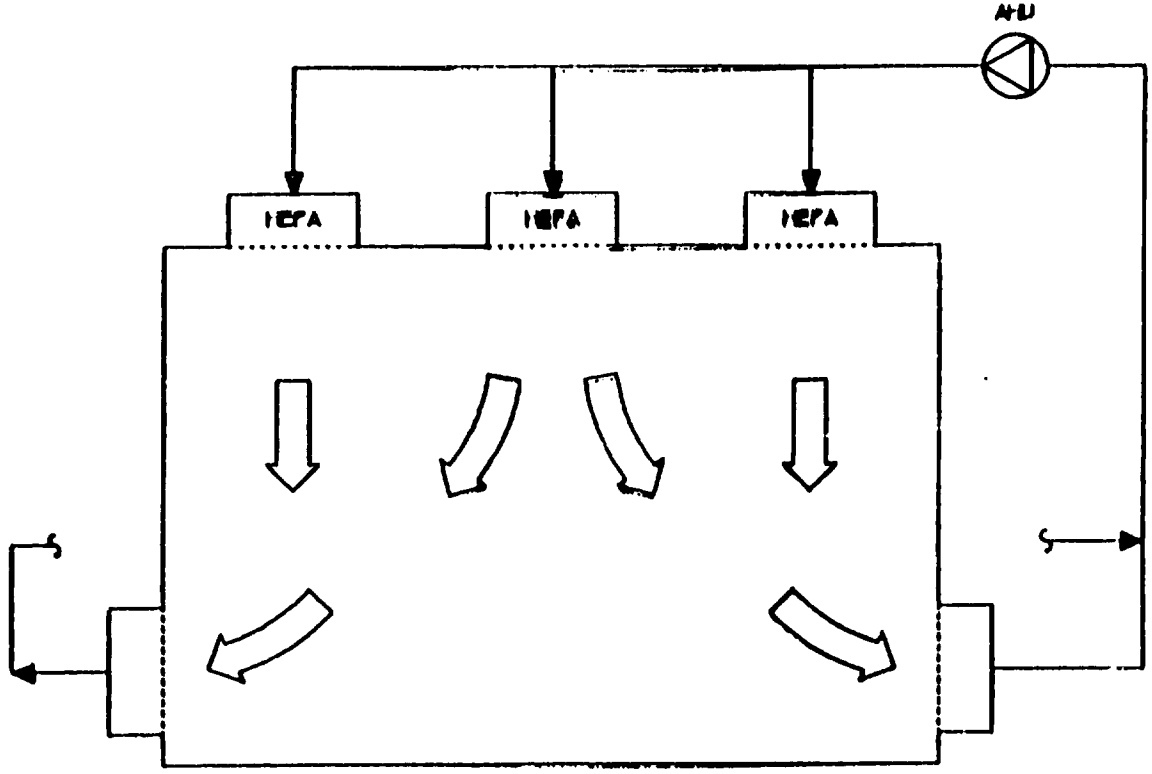
### Standard Contained

The units are usually of similar construction to aseptic areas but generally operate at negative pressures to prevent escape of powders or live organisms and exhaust air is usually HEPA filtered to retain any contamination that may become airborne. Cleanliness usually Class 5.5 or 6.5 US Fed Std 209E (EC GMP C-D). The HVAC systems are often designed for gas fumigation to kill hazardous organisms that may be present in the facility or on filters.

### Clean Contained

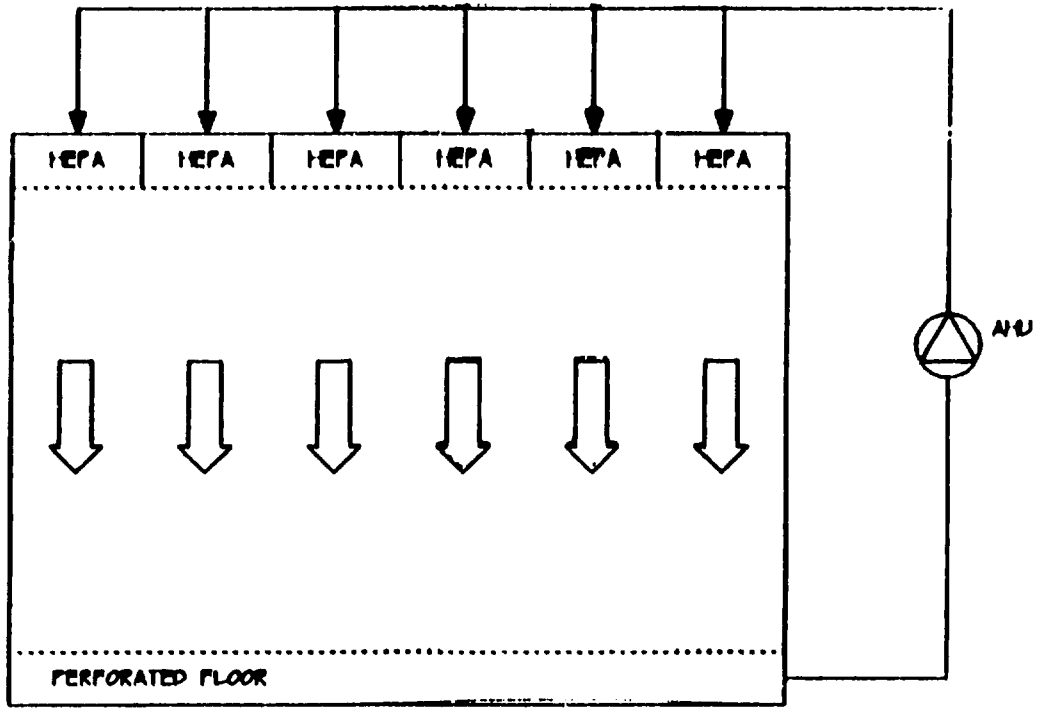
A new development providing similar facilities and conditions to be contained but at much higher cleanliness levels, similar to aseptic. These systems employ a patented structure airway system built into the wall and ceilings of the clean room which operates at strongly negative pressure thus preventing the escape of contaminants within the room and prevents the ingress of external contamination into the clean room. This system is currently being

# MIXED FLOW CLEAN ROOM

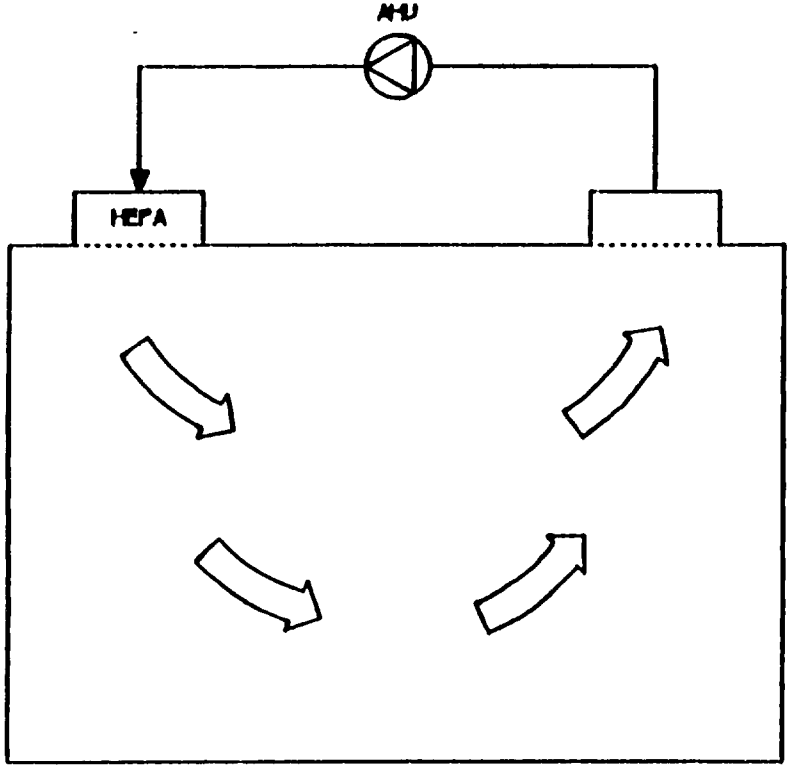



ALSO KNOWN AS 'HIGH IN - LOW OUT'

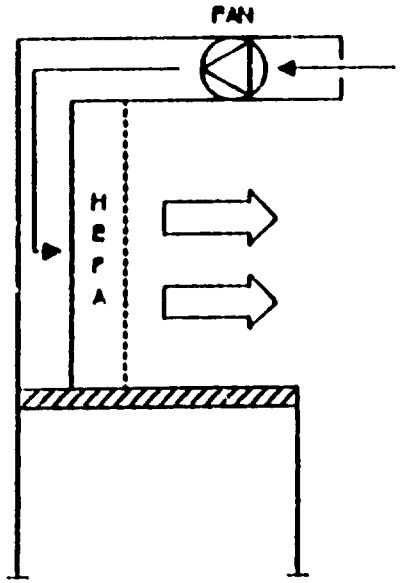
# LAMINAR FLOW CLEAN ROOM



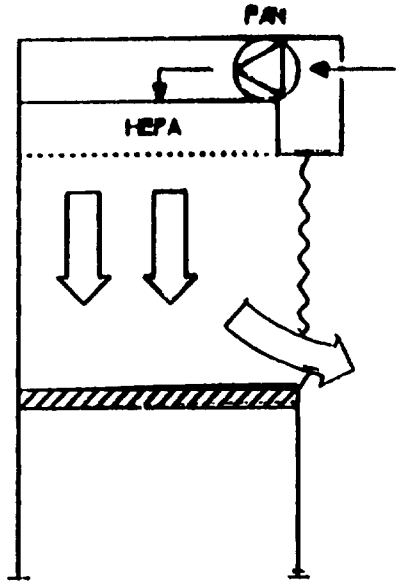
# RANDOM FLOW CLEAN ROOM



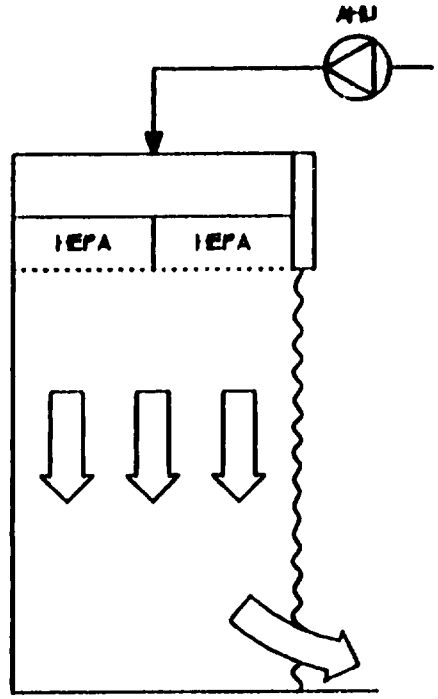
# LAMINAR FLOW WORKSTATIONS




HORIZONTAL BENCH

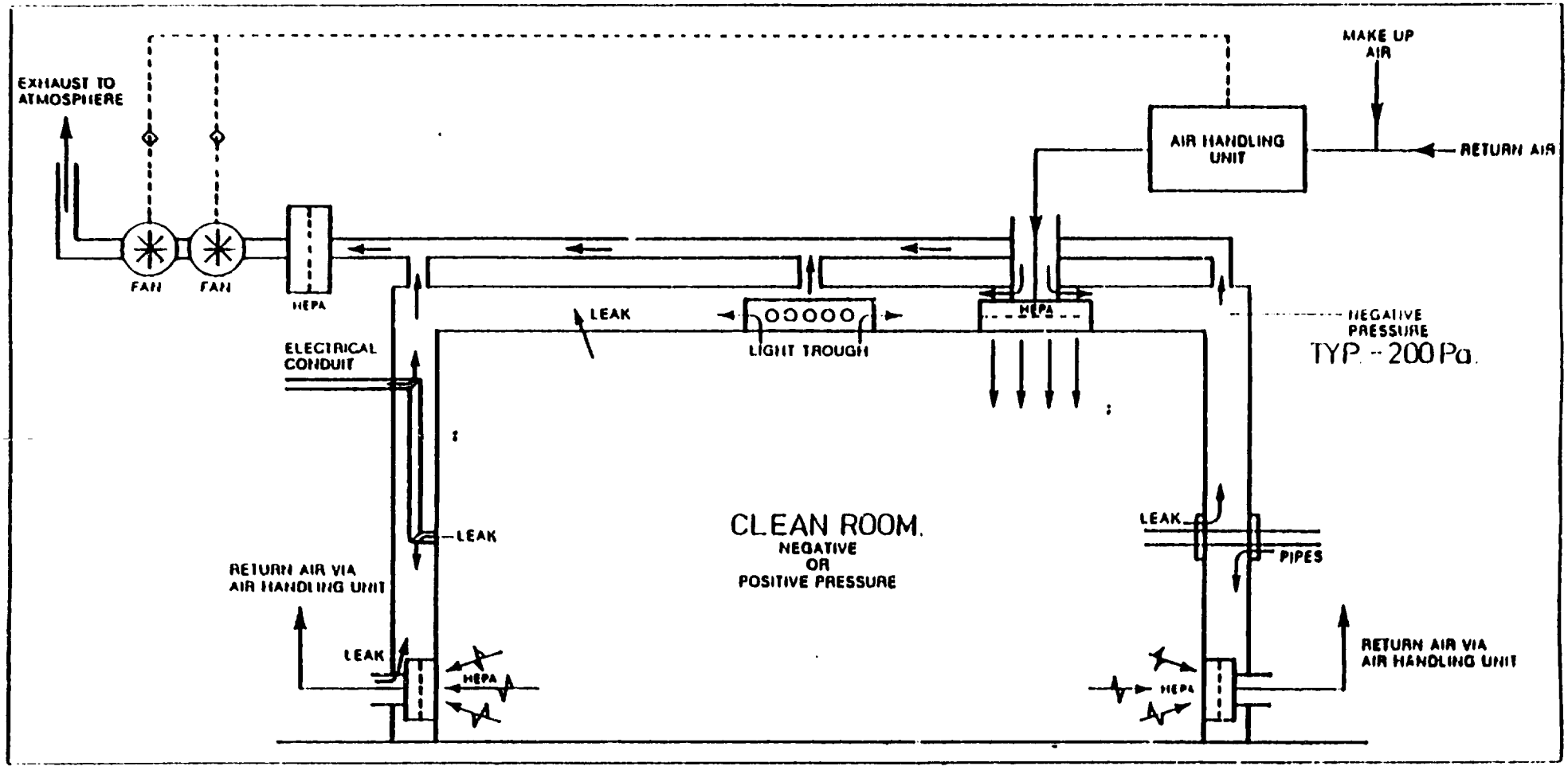



VERTICAL BENCH

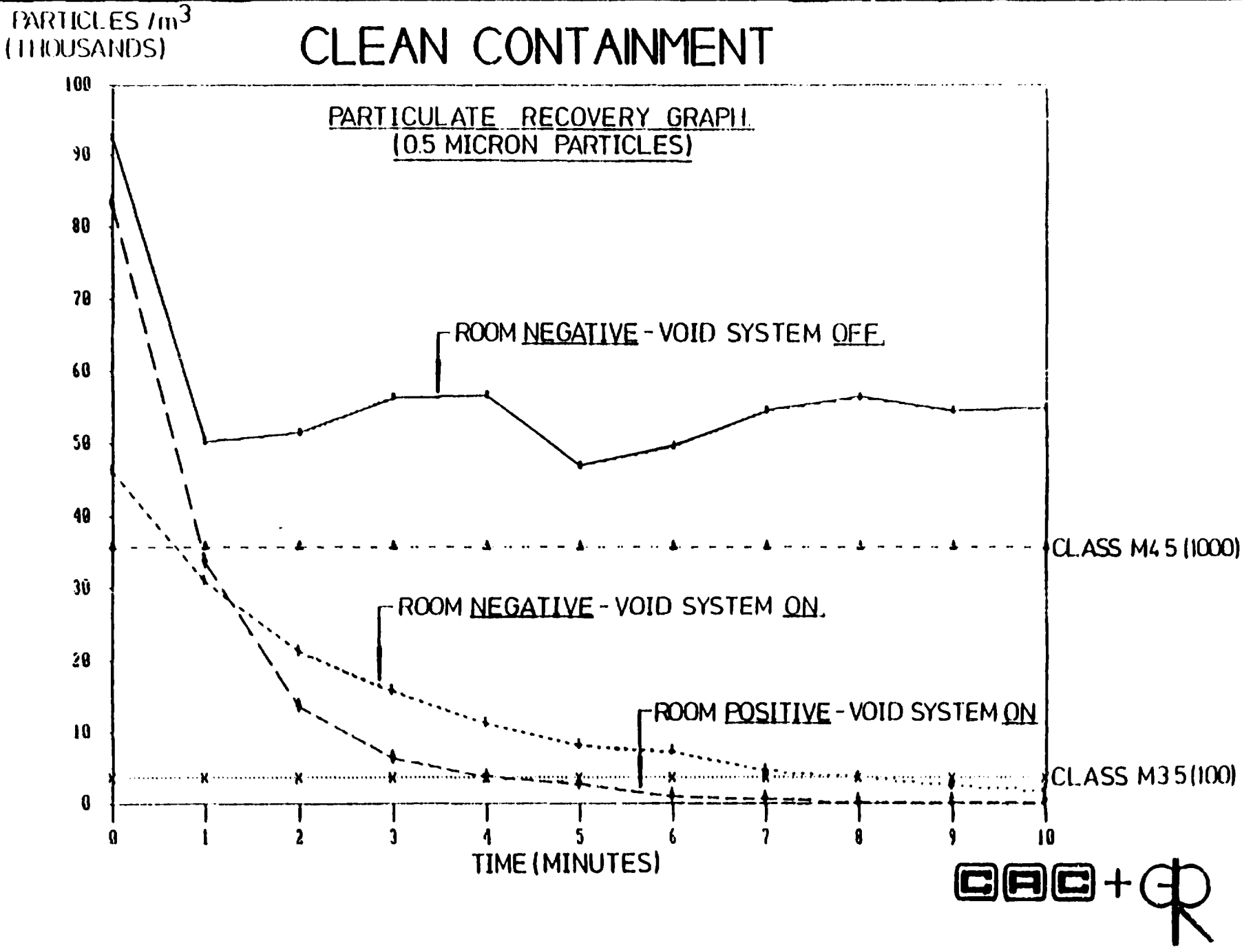



VERTICAL INTEGRATED BOOTH

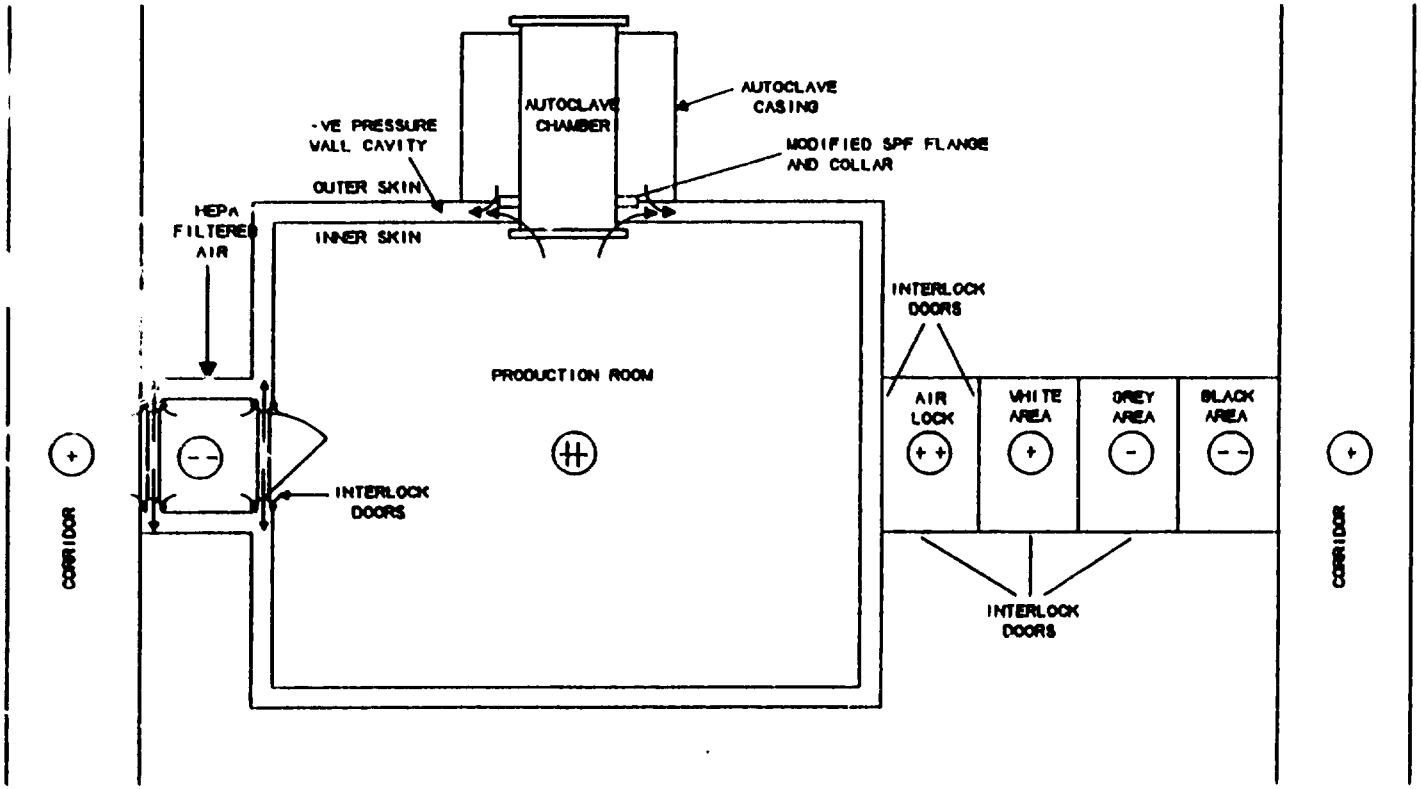
# CLEAN CONTAINMENT



# CLEAN CONTAINMENT



# CRC CONTAINMENT SYSTEMS



developed by a collaborative agreement between GRC Consultants and Clean Room Construction (London) Ltd.

## ENVIRONMENTAL CONDITIONS

The main environmental parameters which must be designed in and controlled are:-

- Environmental cleanliness and pressures
- Temperature
- Humidity
- Illumination
- Noise level
- Lighting levels

### Environmental Cleanliness and Pressures

In general supply air is introduced to the clean rooms through HEPA filters which take the form of filter cells located at the entry point to the clean room. Air introduction can be turbulent in the lower grade of clean area or unidirectional flow in the highest grades of clean room. The primary objective of introducing the clean supply is to maintain the environmental cleanliness but consideration also has to be given to operator comfort and the acceptability of high air movement at some places in the facility.

The HEPA filtered supply air must protect the most critical zones within the clean rooms and the location and type of air supply terminal selected is critically important as part of the design process.

The filtered supply air must be designed to remove contamination products that are generated within the space.

The primary role of the supply air into the room is the displacement, dilution and sweeping of contamination out of the critical zones. This is most often achieved by location of supply points close to or immediately above critical areas and then arranging exhaust points at low level to induce appropriate flow patterns.

## TABLE I

## AIRBORNE PARTICULATE CLEANLINESS CLASSES

Class limits are given for each class name. The limits designate specific concentrations (particles per unit volume) of airborne particles with sizes equal to and larger than the particle sizes shown.

| Class Name | | Class limits | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 0.1 μm | | 0.2 μm | | 0.3 μm | | 0.5 μm | | 5 μm | |
| | | Volume units | | Volume units | | Volume units | | Volume units | | Volume units | |
| SI | English | ($m^3$) | ($ft^3$) | ($m^3$) | ($ft^3$) | ($m^3$) | ($ft^3$) | ($m^3$) | ($ft^3$) | ($m^3$) | ($ft^3$) |
| M 1 | | 350 | 9.91 | 75.7 | 2.14 | 30.9 | 0.875 | 10.0 | 0.283 | -- | -- |
| M 1.5 | 1 | 1 240 | 35.0 | 265 | 7.50 | 106 | 3.00 | 35.3 | 1.00 | -- | -- |
| M 2 | | 3 500 | 99.1 | 757 | 21.4 | 309 | 8.75 | 100 | 2.83 | -- | -- |
| M 2.5 | 10 | 12 400 | 350 | 2 650 | 75.0 | 1 060 | 30.0 | 353 | 10.0 | -- | -- |
| M 3 | | 35 000 | 991 | 7 570 | 214 | 3 090 | 87.5 | 1 000 | 28.3 | -- | -- |
| M 3.5 | 100 | -- | -- | 26 500 | 750 | 10 600 | 300 | 3 530 | 100 | -- | -- |
| M 4 | | -- | -- | 75 700 | 2140 | 30 900 | 875 | 10 000 | 283 | -- | -- |
| M 4.5 | 1 000 | -- | -- | -- | -- | -- | -- | 35 300 | 1 000 | 247 | 7.00 |
| M 5 | | -- | -- | -- | -- | -- | -- | 100 000 | 2 830 | 618 | 17.5 |
| M 5.5 | 10 000 | -- | -- | -- | -- | -- | -- | 353 000 | 10 000 | 2 470 | 70.0 |
| M 6 | | -- | -- | -- | -- | -- | -- | 1 000 000 | 28 300 | 6 180 | 175 |
| M6.5 | 100 000 | -- | -- | -- | -- | -- | -- | 3 530 000 | 100 000 | 24 700 | 700 |

# CONTROLLED ENVIRONMENT TC
# BS 5295: PART 1: 1989

| BS Class | Approx Old Class | MAX. PARTICLES/M³ ≥ STATED SIZE: 0.3um | 0.5um | 5um | 10um | 25um | 4 | 5 | 6 |
|---|---|---|---|---|---|---|---|---|---|
| C | | 100 | 35 | 0 | NS | NS | M1.5 (1) | 10 | D |
| D | | 1000 | 350 | 0 | NS | NS | M2.5(10) | 10 | D |
| E | (1) | 10.000 | 3500 | 0 | NS | NS | M3.5(100) | 10 | W |
| F | (1) | NS | 3500 | 0 | NS | NS | M3.5(100) | 25 | W |
| G | | 100.000 | 35.000 | 200 | 0 | NS | M4.5(1K) | 25 | M |
| H | | NS | 35.000 | 200 | 0 | NS | M4.5(1K) | 25 | M |
| J | (2) | NS | 350.000 | 2000 | 450 | 0 | M5.5(10K) | 25 | M |
| K | (3) | NS | 3.500.000 | 20.000 | 4500 | 500 | M6.5(100K) | 50 | Q |
| L | (4) | NS | NS | 200.000 | 45.000 | 5000 | | 50 | Q |
| M | | NS | NS | NS | 450.000 | 50.000 | | 50 | Q |

1. ALWAYS REFER TO COMPLETE STANDARD FOR FULL DETAILS
2. ALL FIGS. ROUNDED DOWN EXCEPT CLASS C/0.5um.
3. NS–NO SPECIFIED LIMIT
4. APPX. FED. STD. 209E AT 0.5um SIZE (NOT PRECISE COMPARISON)
5. MAX. AREA PER SAMPLING POSITION ($M^2$)
6. PARTICLE SAMPLING FREQUENCY - DAILY/ WEEKLY/MONTHLY/QUARTERLY.
7. $1M^3 \triangleq 35.71FT^3$

# CONTROLLED ENVIRONMENT TO U.S. FEDERAL STANDARD 209E

(95% UPPER CONFIDENCE LIMIT AS SECTION 5.4)

| F.S. CLASS | | MAX. PARTICLES/M³ ≥ STATED SIZE | | | | | APPROX. ** B.S. 5295 |
|---|---|---|---|---|---|---|---|
| S.I. | ENGLISH | 0.1um | 0.2um | 0.3um | 0.5um | 5um | 1989 CLASS |
| M1 | | 350 | 75.7 | 30.9 | 10 | – | |
| M1.5 | 1 | 1.240 | 265 | 106 | 35.3 | – | C |
| M2 | | 3.500 | 757 | 309 | 100 | – | |
| M2.5 | 10 | 12.400 | 2.650 | 1.060 | 353 | – | D |
| M3 | | 35.000 | 7.570 | 3.090 | 1.000 | – | |
| M3.5 | 100 | – | 26.500 | 10.600 | 3.530 | – | E (F) |
| M4 | | – | 75.700 | 30.900 | 10.000 | – | |
| M4.5 | 1.000 | – | – | – | 35.300 | 247 | H (G) |
| M5 | | – | – | – | 100.000 | 618 | |
| M5.5 | 10.000 | – | – | – | 353.000 | 2.470 | J |
| M6 | | – | – | – | 1.000.000 | 6.180 | |
| M6.5 | 100.000 | – | – | – | 3.530.000 | 24.700 | K |
| M7 | | – | – | – | 10.000.000 | 61.800 | |

1. ALWAYS REFER TO COMPLETE STANDARD FOR FULL DETAILS.
2. ALL CLASSES - OPTION TO SPECIFY ONE OR MORE PARTICLE SIZES.
3. IT IS IMPORTANT TO APPLY STATISTICAL ANALYSIS AS DESCRIBED IN SECTION 5.4 OF THE F.S. WHEN DETERMINING RESULTS.
4. PARTICLES/FT³ ARE NOT SHOWN ABOVE BUT ARE SHOWN IN THE COMPLETE STANDARD.
5. ALTERNATIVE PARTICLE SIZES AND CLASSES MAY BE BE DEFINED WITHIN CERTAIN LIMITS - SEE COMPLETE STANDARD.
6. * S.I. CLASSES AND UNITS ARE PREFERRED.
7. ** NOT A PRECISE COMPARISON.
8. $1M^3 \simeq 35.71\ FT^3$

Where adjacent zones within a facility have different levels of cleanliness, they are segregated by differential pressure regimes with the cleanest areas operating at the highest pressures. Pressure regimes and their maintenance are critical to achievement of higher cleanliness levels and the HVAC plant, controls, airlocks and interlocking of doors, together with sealing of interfacing equipment are all essential considerations as part of the design development process.

It is normal to use pressure cascades where large volumes of air transfer from the cleanest zones into areas of lower cleanliness by virtue of the general air flow from higher pressure zones to the lowest pressure areas. The continuous flow of air through any aperture normally ensures the cleanliness of each space.

Careful consideration must be given to all of the above aspects in order that the facility will operate consistently within the design parameters and can be validated at the outset and monitored on a regular basis thereafter.

Temperature

Control of temperature always dictates the use of mechanical heating and cooling in pharmaceutical clean room facilities. It is normal to design for an air temperature between 18-22°C $\pm$ 2° with the lower temperatures providing operator comfort where they are fully garmented and air movement immediately adjacent to the skin is severely restricted.

High air change rates in clean rooms often mean that a bypass system of condition is utilised which also helps to give good temperature control. The design of the heating and cooling equipment must take account of all heat gains within the space from people, equipment, lights, fans and also from the replacement air drawn into the system to off-set that lost by pressurisation.

Humidity

It is usual to incorporate humidification and dehumidification into the HVAC plant in pharmaceutical clean rooms. Normally design room humidities are in the range of 40-45% RH $\pm$ 5% RH which assist in the comfort of the operators, particularly as they are

usually fully garmented. For areas handling powder the relative humidity may be greatly reduced.

Lower humidities are often necessary for moisture sensitive materials and where materials are exposed after freeze drying down to perhaps 15% RH. In addition, areas in which hygroscopic products are stored can be as low as 5% RH. At this level the HVAC plant must incorporate absorbent chemical dehumidifiers with careful integration into the HVAC system design. With low humidities additional care is necessary in the selection and maintenance of relative area pressures to prevent transfer of moist air into dry spaces and care in the selection and detail of finishes, sealing, doorways and hatches, etc. is vital.

## Illumination

It is relatively unusual for pharmaceutical clean rooms to be illuminated by natural daylight, since they are often deep within the core of the production facilities. Permanent artificial lighting is therefore provided, especially at the critical clean locations and often has to be incorporated into or around the air terminal housings which are necessarily located at the same point.

In general illumination levels of 500-750 lux are normally required, however in the USA these are sometimes specified as high as 1000 lux in inspection areas. Care is necessary in the design and selection of lighting to avoid glare which is often found with many of the clean room surfaces being light or even white in colour.

Consideration has to be given to the cleanliness of the lighting fittings, their sealing into the room finish and accessibility for maintenance and lamp changing.

It is usual to provide emergency battery maintained facilities to enable safe egress of personnel from facilities in the case of emergencies.

## Noise Level

Pharmaceutical filling equipment often produces quite high noise levels and it is uneconomic to over silence the HVAC system where noisy equipment is operating. The HVAC system

in a pharmaceutical clean room is often handling high air volumes and over attenuation of this would be an unnecessary cost burden. It is normal to design in the range 50-60 dBA, but this may be lower in areas with no production machinery. Since clean rooms contain no soft surfaces they are acoustically very live and additional care is necessary in the acoustic design to take account of the long reverberation times. More recently a slightly lower noise rating figure of NR45 has tended to be specified.

## HVAC SYSTEMS

Pharmaceutical clean rooms, especially where large areas of unidirectional flow are required, have very high air flow rates sometimes between 80-100 air changes per hour. In many pharmaceutical clean rooms the wall and ceiling structure acts as part of the air circulation network particularly since return air from the clean room has to be taken in most cases from low level.

A number of alternative solutions to this aspect of design are available. The physical presence of the air supply and return points in the boundary of the clean room fabric requires great care in detailing installation and sealing to ensure that GMP is not compromised.

Fittings are generally fabricated from plastic, aluminium or stainless steel and are designed to provide minimum crevices, cracks and recesses and must be smooth and non-shedding. Smoothness is important in many features of the clean room to prevent snagging of gloves or swabs when cleaning of the room is in progress.

Standard HVAC supply and extract terminal fittings are often unsuitable and must be reviewed in considerable detail before being accepted for installation.

Almost all aseptic pharmaceutical clean rooms require that the HVAC system is designed to permit routine gas fumigation of the space and of the duct system. Design of the air moving system fans and controls must take account of the need to seal the room for the static gassing phase and then of degassing the room, paying attention to the hazards presented by sterilising gases such as formaldehyde. Experienced clean room design companies take these requirements into account during the design development of the facility.

## CONSTRUCTION

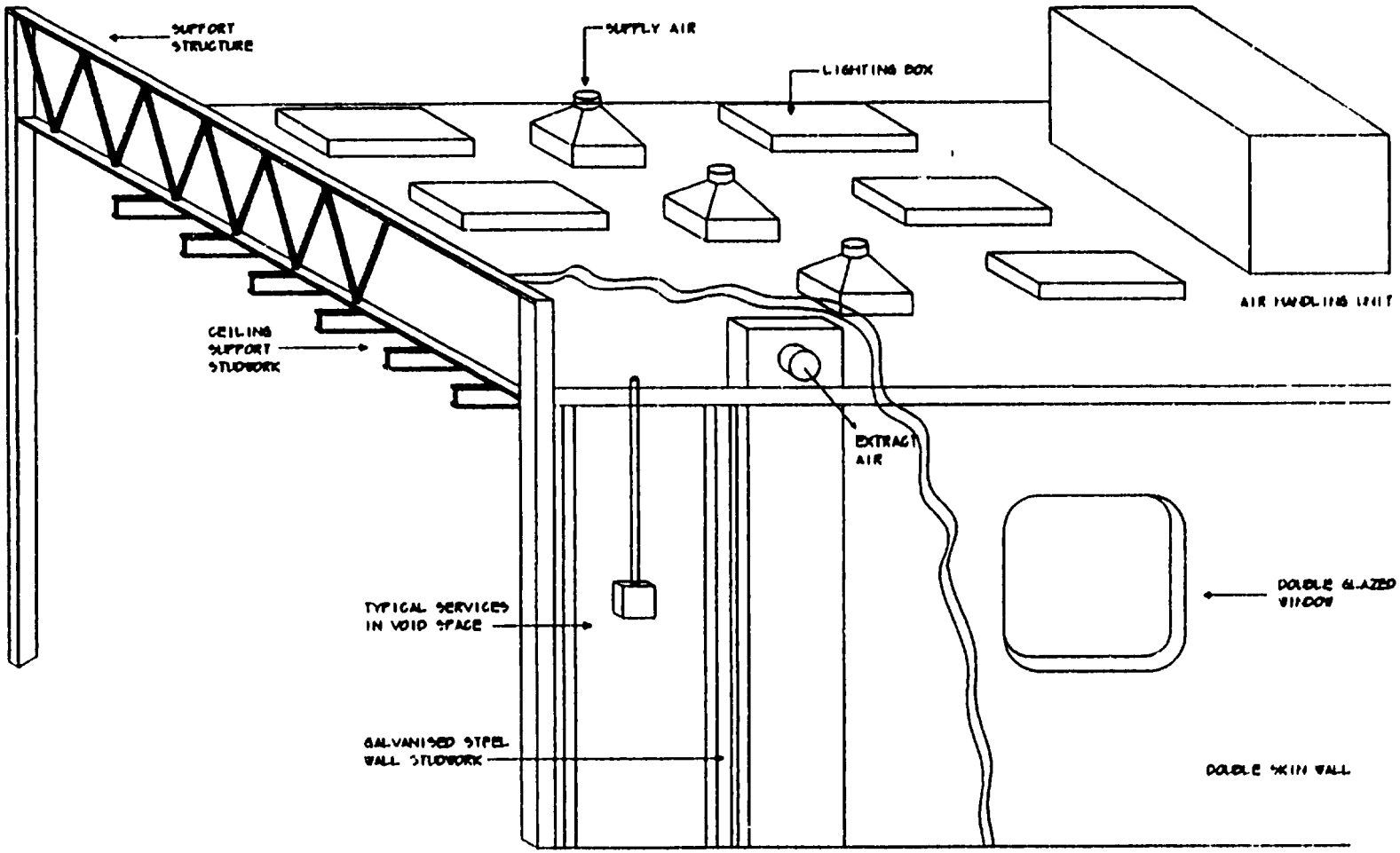
The construction aspect of pharmaceutical clean rooms, in the pursuit of a facility which supports GMP, involves the provision of a basic structure which can use traditional dry construction techniques or purpose designed prefabricated modular systems. Construction design solutions have evolved which provide an effective compromise in terms of cost and timescale for construction yet provide a reasonable degree of flexibility and for the facility to incorporate the necessary air moving, mechanical and electrical services within the structure.

Additionally there is often requirement for the air moving plant and air conditioning equipment to be located above the clean room facility and this is often supported on purpose made steelwork or on structural systems which support the clean room ceiling.

Great care must be taken in the detailed design of clean rooms, particularly the basic structures which form the surfaces on which the final clean room finishes are laid. Close inspection of all stages of the construction is required to ensure that the clean room will meet the standards required.

For most pharmaceutical clean rooms the floor at ground level or on an intermediate floor is laid on concrete with a smooth power floated or sand/cement finish. A number of alternative final finishes can be applied including epoxy, granolithic or PVC sheet flooring systems. Careful consideration needs to be given to the incorporation of any underfloor drainage during the design development phase of the project together with the existence of any expansion or bay joints in the floor the movement of which might compromise the final clean room floor finish.

The achievement of the required standards in conjunction with the facilities described above dictates the need for site construction technicians who are experienced and aware of the demanding requirements of a clean room structure. The use of unsupervised, inexperienced and unskilled construction labour can carry heavy penalties in terms of facilities that do not provide a well constructed basis for the achievement of GMP.




# TYPICAL CLEAN ROOM CONSTRUCTION

GPC CONSULTANTS

## FINISHES

The finishes of all surfaces within pharmaceutical clean rooms that come into contact with the air within the rooms themselves are critically important in the achievement and maintenance of GMP.

The surface finishes must be sealed, non-shedding, non-reactive to a range of disinfectants and cleaners and must be capable of ongoing maintenance and repair should damage occur.

The ideal surface finish would be entirely joint free and some finishes that this company use come very close to this.

Sheet PVC of approximately 2mm thickness with fully welded joints is perhaps the most universally used material and features in nearly all pharmaceutical clean room floors. For the highest grade aseptic areas the same material is also used on walls and ceilings with all corners and junctions being fully coved to avoid uncleanable recesses. Particular attention is required to the three way joints at corners and solutions have been developed to address this particular area. Once all joints have been welded this finish system provides a complete unbroken membrane on all surfaces of the clean room. This greatly assists the achievement of GMP.

However considerable skill, care and attention to detail is necessary, particularly at the connection point of the surface finishes to all construction features such as doors, windows, return air outlets and items of equipment. Surface finishes which are trapped beneath border flanges and then sealed using a suitable elastomer, often silicone rubber which is applied as a gel but sets to a solid, are necessary to maintain the cleanable yet unbroken barrier.

Sheet PVC is entirely suitable for areas which operate at positive pressures but where negative pressures are involved, typically in containment zones, there is a tendency for this material to be disconnected from the wall by the reverse pressure. In this situation a site applied glass reinforced plastic finished system can be used which has been found to be entirely resistant to continuous negative pressures yet provides a completely joint free, smooth, cleanable and resistant surface and has been effectively evaluated in aseptic filling areas up to and including one operating at Class 2.5 (US Fed Std 209E).

## ROOM FINISHES

Pharmaceutical clean rooms often require many combinations of electrical and mechanical service outlets for bench mounted or in built user equipment.

As a general rule no services should be run on the surface of the clean room wall but must be concealed within the clean room fabric with the neatest and cleanest detail where the service emerges into the clean zones. The avoidance of unnecessary ledges and uncleanable recesses is the paramount aim. Careful design and integration of the chosen surface finish or construction system with installation by skilled clean room technicians will provide details which do not violate GMP.

Where items of equipment are sited centrally within the clean rooms, they are often served by services pendant protruding down from the ceiling carrying the necessary mechanical and electrical service outlets and connections but these are still carefully integrated in terms of finished sealing and cleanability.

Where piped services penetrate the clean room finish these must be carefully designed with closing plates and sealed using an elastomer such that allowance is made for any expansion or contraction whilst maintaining an unbroken seal. Exposed pipework within pharmaceutical clean rooms, where unavoidable, is normally all routed in stainless steel. Typical applications include hot and cold water for injection where a recirculating loop has to be brought close to the point of outlet.

Intercommunication between clean zones can be provided by diaphragm type speak through panels located in clear glass windows or by flush mounted, electrical intercom systems providing hands free operation.

Particular care is necessary to ensure that air leakage and connection with uncleaned areas does not occur in electrical distribution systems and where conduit systems are employed these are normally sealed close to the point of room outlet using a silicone elastomer.

## QUALIFICATION AND VALIDATION FOR GMP

To ensure compliance with the required quality considerations within the various guides to GMP, it is essential to validate clean rooms if they have been classified to determine what environmental conditions exist in the room at rest. As it is practically difficult to obtain repeatable measurements when a room or area is in production the measurement of room quality at rest gives a predictive analysis of how the room will operate during actual production. The determination of these conditions will then be used during subsequent retesting during production such that the quality of the environment can be measured particularly if there are failures or problems in production.

Trial batches of product may also be produced during the validation which can then be tested to ensure that the required conditions for GMP are being attained.

Prior to the validation being carried out all air moving and service systems must be 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.

- Room temperature tests
- Room humidity tests
- Calibration of all monitoring equipment on parameters such as flow rates, pressure and temperature
- HEPA filter integrity tests
- Airborne particulate counts which may be carried out in the as built, at rest or operational conditions
- Pressure differential tests throughout all zones
- Air visualisation tests with doors closed and open
- Air pattern visualisation within individual rooms usually recorded using a video camera
- Room recovery to indicate the "clean up rate" within individual rooms

All of the above 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.

In addition, in aseptic areas settle plates and contact plates will be used to determine the level of biological organisms that are present within the room air during operator occupation and normal use.

### 4.2.6 Material and Personnel Flows

Material and personnel flow patterns are one of the essential stages in the design process for any pharmaceutical manufacturing unit. It is not possible to even attempt to describe how to approach this subject other than to give outline principles which should always where possible be adopted. It is essential when developing flow patterns for a new facility to consider the overall site as well as the main manufacturing areas because poor site traffic patterns can seriously affect the flow patterns within the manufacturing unit. The following key factors were discussed during the training programme.

(a) Unless practically impossible, all flow patterns should be linear.

(b) Where possible, process materials and personnel flow should be parallel and if possible segregated.

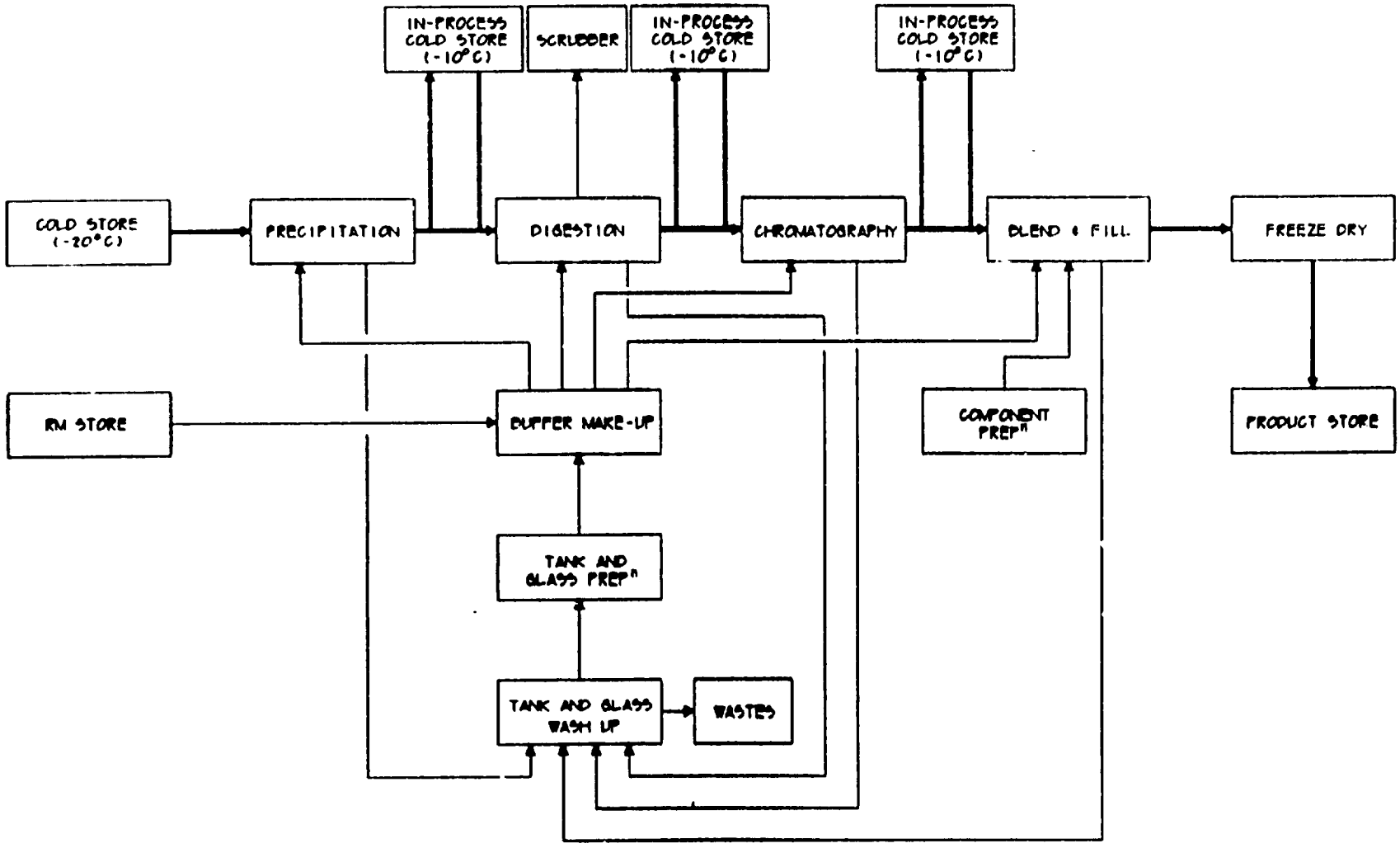
(c) The crossover of clean and dirty equipment should be avoided and if this is not possible then it should be controlled with a suitable operating procedure.

(d) Adequate space should be provided to prevent cross contamination when personnel and materials are being moved throughout a facility.

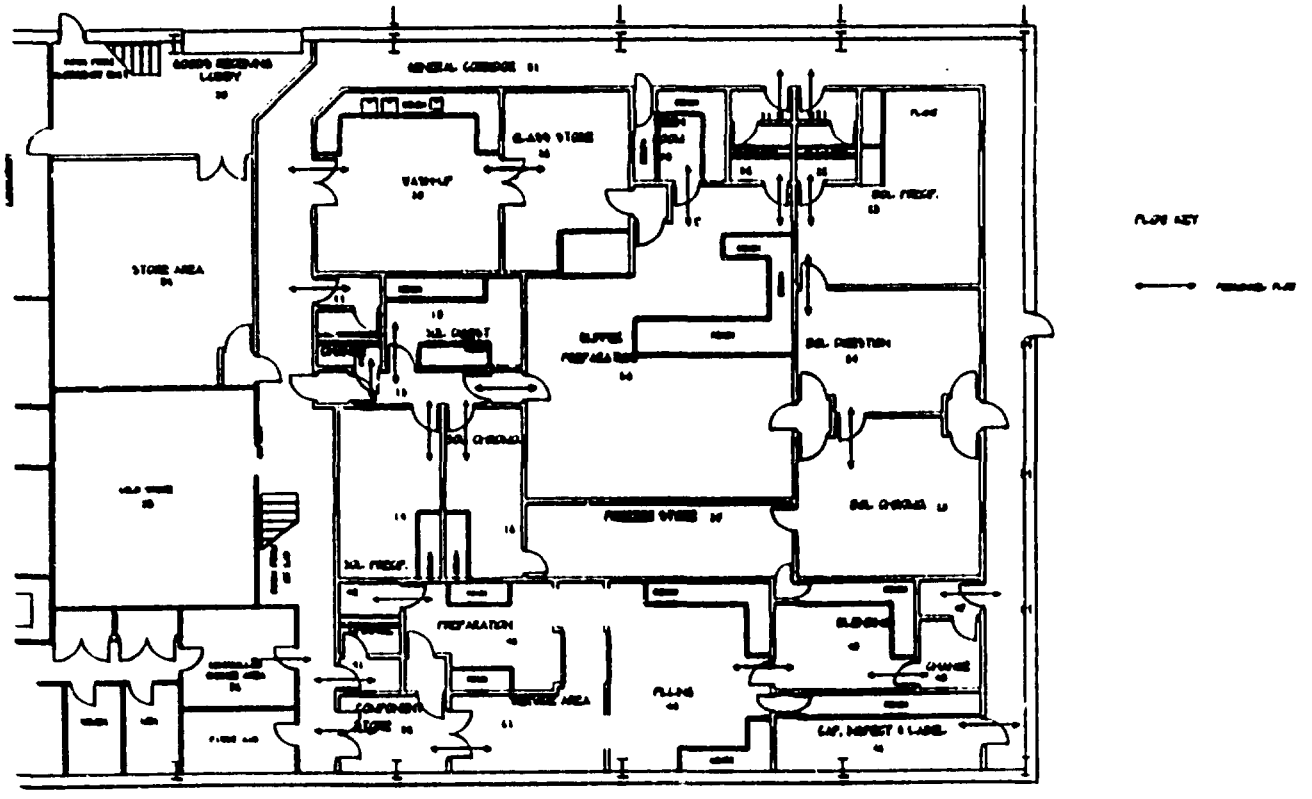
(e) Personnel working in areas of different classification must firstly be subject to a different and separate changing procedure for clothing but must also be segregated from each other.

(f) Where product and material are to be moved into and out of classified areas there must be a physical barrier usually an airlock or pass through hatch through which such items must be passed.

The above principles were demonstrated by using typical plans of facilities which had been approved by both the Medicines Control Agency (United Kingdom) and also the Food &

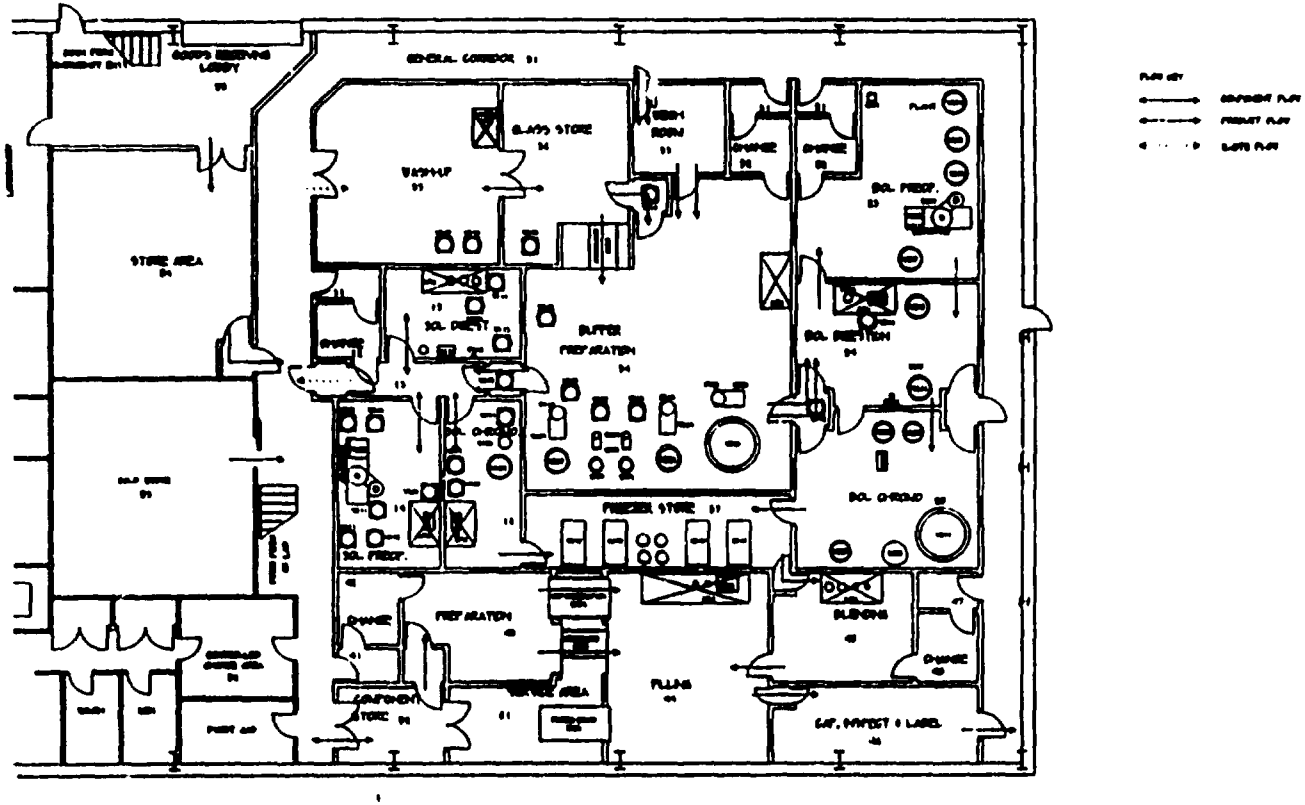



# PROCESS MATERIALS FLOWS



# PERSONNEL FLOW PATTERNS

GRC CONSULTANTS



## MATERIAL FLOW PATTERNS

Drug Administration (USA). The key aspect of the above review of material and personnel flow was to emphasise the need for the segregation of products, waste and the different levels of room or area classification.

### 4.2.7 Hygienic Standards

All of the GMP guidelines indicate that facilities designed to manufacture pharmaceuticals must be of an appropriate standard. This may mean that the hygienic standards required can range from the cleanable by standard manual washing to aseptic class 2.5 (Fed Std 209E). There are a number of factors to take into account when designing a pharmaceutical facility to ensure that the appropriate standards are achieved. These are as follows:

**Changing Protocols**

The manner in which people enter or leave a pharmaceutical facility can be critical to its satisfactorily maintaining the classification to which it has been specified. Most modern pharmaceutical companies have very detailed changing procedures for its production staff which include a description of the clothing to be worn, the sequence in which it is to be put on, the numbers of times each item can be used, and the method of storing such clothing in preparation for use and also for disposal.

**Personnel Hygiene**

Some pharmaceutical companies have a very rigorous cleaning procedure for its production staff ranging from simply washing hands to a full shower and the use of sterilising sprays. It should be noted that showering before entering a sterile facility is not entirely in favour in Western companies because it has been found that people who have recently showered tend to shed far more skin particles than those that merely prepare themselves by washing their hands and then spraying them with a sterilant. The procedures to be adopted for personnel entering classified environments depends on a number of factors including the hygienic standards prevalent in the homes of the operators, the standards of production required and whether there are any particular local problems of airborne contamination which could affect production quality.

For particularly critical production areas it may be considered appropriate to undertake regular monitoring of the environment and the staff to ensure that the classification is being met. Particularly in sterile filling areas, personnel monitoring is particularly important if there is a tendency for unpredictable contaminations to occur.

**Equipment Cleaning**

It is imperative that all equipment used in the production of pharmaceuticals is regularly cleaned either between batches or campaigns depending on the sensitivity of the material. It is essential that close attention is paid to the detailed design of all equipment to ensure that it can be cleaned easily either by manual means or by cleaning in place methods and if sterile equipment is to be used then it can be adequately sterilised. In most pharmaceutical companies the cleaning and general decontamination procedures are controlled by standard operating procedures (SOPs) and are often validated in a most vigorous manner.

**Cleaning of Production Areas**

A similar approach must also be adopted to the cleaning of production areas which again means that close attention has to be paid to the detailed design of all finishes to ensure that there are no ledges, hidden voids, holes, cracks or any other discontinuity in the surfaces of rooms which would allow the build up of contaminants. Most pharmaceutical companies have procedures which define how often the plant is to be cleaned down, what cleaning materials are to be used and the method of carrying out the cleaning down procedure.

The effectiveness of the cleaning must be monitored and in principle there are two aspects this, firstly the revalidation of any classified area to check that from a particulate point of view it is within the specified limits. Secondly, swabs may be taken from various parts of the room including walls, ceilings, floors and architectural features such as windows and doors and these will be checked for microbiological contamination. Once again all of these procedures are normally validated and controlled by standard operating procedures.

**Choice of Materials**

It is essential when specifying materials for pharmaceutical plant that close attention is paid to the cleanability of each element. It should also be noted that the European and USA GMP codes of practice, whilst not calling for specific standards, that all materials will be of a hygienic nature and will not react to any of the cleaning processes and furthermore will not leach specific components into the product.

## 4.2.8 Construction of Pharmaceutical, Fine Chemical and Biochemical Plant

One of the crucial aspects of the successful construction of pharmaceutical, fine chemical and biochemical plant is the recognition that in spite of how well design documents are produced, without constant supervision during manufacture and construction the standards of the final plant being built may not be adequate. The concept of developing a design for the facility without involvement in its subsequent construction is foreign to most international contractors simply because without an involvement in the construction phase of any project they have no control over the final quality of the plant that is built yet still have liability for design faults.

It was strongly recommended to Vegyterv that they must, at every opportunity, take responsibility for the installation of plant and be in a position to adequately control the sub-contractors or the main construction contractors to prevent them from moving away from the basic design concepts.

Considerable discussion took place about the type of organisation required to ensure that facilities were built to an adequate standard and an example of the site construction management teams most regularly used is given in this section.

It was also emphasised that for pharmaceutical plants validation takes place throughout the construction period with constant checking of material quality, conformance to design and as the job is mechanically complete, by testing equipment to ensure it operates in accordance with the specifications.

What must be emphasised is the responsibility of the managing contractor not to accept inadequate quality or performance by the construction contractors or sub-contractors. This is

particularly important in Hungary and indeed in other Eastern European states where often the responsibilities for design and construction are completely separate and often lead to one company blaming the other for any problems which occur in the quality or capacity of the production unit. Much of the responsibility for this problem lies with the client companies in not paying sufficient attention to the method of specifying the plant and then contracting for the services to design and build it.

### 4.2.9 Specialist Utility Services

There are a wide range of specialist services used within the pharmaceutical industry particularly where parenteral products are concerned. It is of the utmost importance that services such as specialist waters and gases are adequately specified and meet the appropriate pharmacopoeia standards. The following services and their applications were reviewed in depth:

- Water for Injection
- Reverse Osmosis water
- Demineralised water
- Compressed air
- Medical gases
- Clean steam

**Water for Injection (WFI)**

Particular attention was paid to the production and distribution of Water for Injection (WFI) because it is one of the primary process fluids used in great quantities not only as part of the production cycle but also in the cleaning of plant and equipment. Vegyterv are clearly familiar with the design and application of high quality stills manufactured by companies such as Finn-Aqua. However, the area which needed considerable discussion was the distribution of WFI, validation and the inspection protocols required during construction.

Regarding the distribution of WFI, GRC Consultants explained a number of alternative methods which can be adopted, particularly the use of hot and cold distribution systems. This was of particular interest as it is normal in Hungary to distribute WFI at high

temperature in order to reduce the risk of contamination. Many of the problems associated with WFI systems in Hungary relate principally to the quality of the pipework system, in particular the welding and quality of components used. The practical approaches used firstly to qualify contractors and suppliers then to inspect the quality of materials used and work carried out were explained in considerable depth. It is recognised that in many cases the standards applied in Western Europe are beyond the reach of many of the Hungarian pharmaceutical companies at this time, particularly from a cost point of view. It was also explained that there is very limited capability within Hungary to carry out high quality pipework fabrication and welding and that if facilities are to meet modern GMP either there must be an improvement in local contractor capability or specialist contractors will have to be imported to carry out the work.

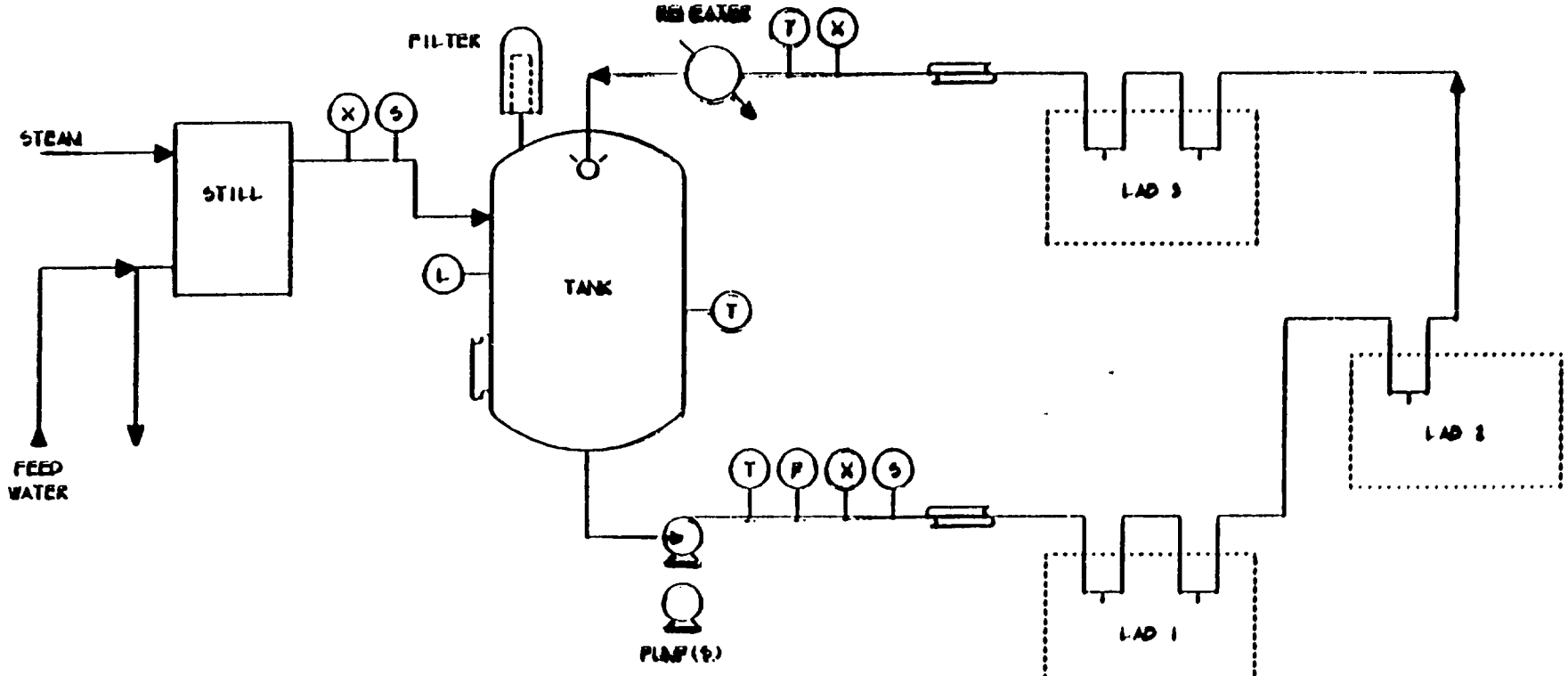
**Compressed Air Systems**

It was emphasised from the outset that the basic standard for compressed air used in pharmaceutical plants is oil free and filtered. The use of lubricated compressors is generally considered unacceptable, particularly as it is extremely difficult to remove oil to a sufficient degree that would enable validation of air particularly for sterile applications.

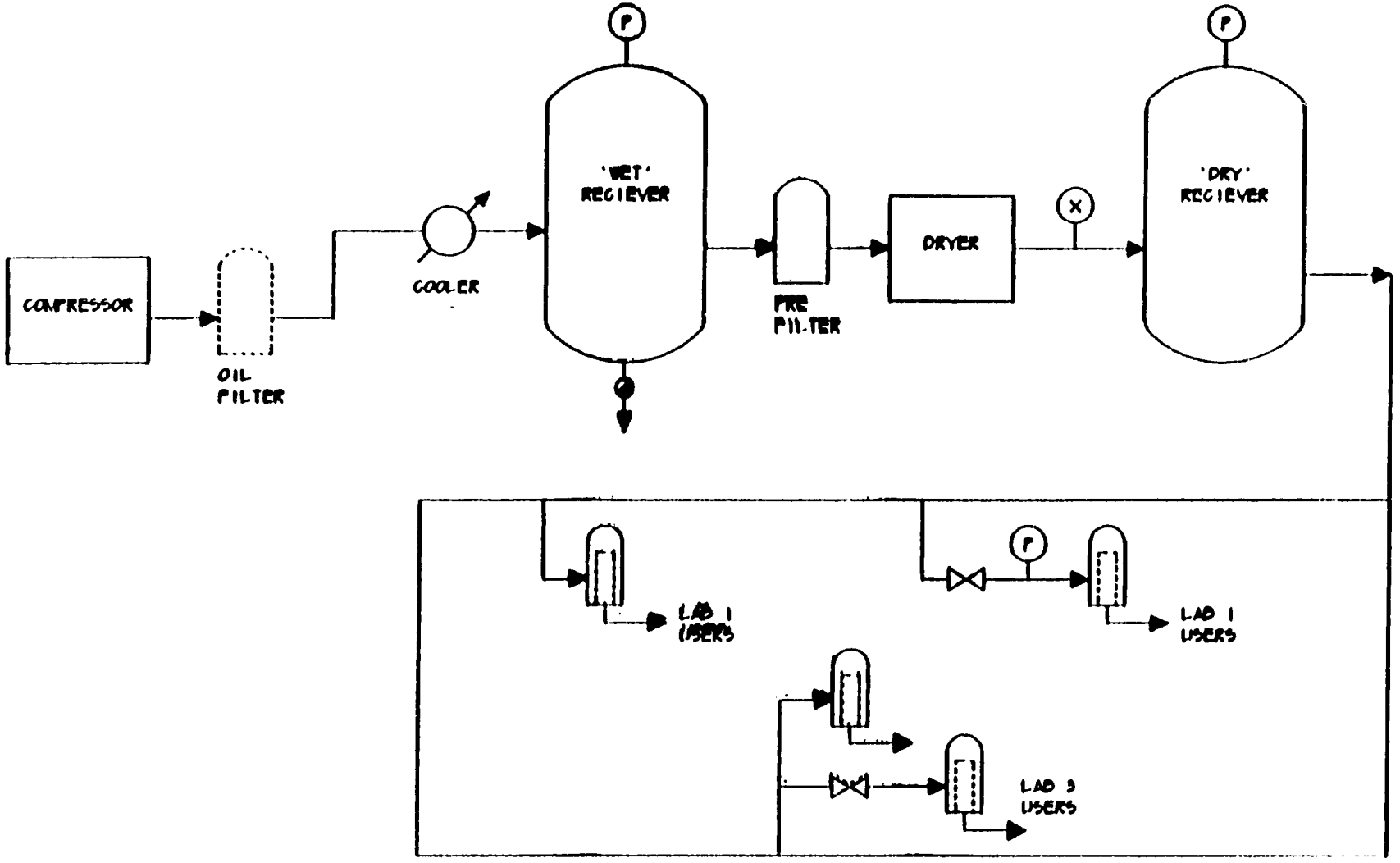
The types of compressors most regularly used are either screw or lobed compressors and as some of the major manufacturers have distributors in Hungary, it is not considered a problem to purchase units of adequate quality for the pharmaceutical industry.

Regarding the distribution pipework, discussions took place on the specification of materials and type of pipework fittings to be used and again there appears to be little difference in specification between that used in Hungary and elsewhere in Western Europe. It was noted, however, that for sterile air applications suitable filter systems must be installed. Where this is the case appropriate filter integrity testing and validation must be undertaken to ensure that the quality of air remains within specification. It was also noted there are some sophisticated methods of sampling the air not only for particulates but also for the presence of microorganisms. In the latter case, it is most important that air is thoroughly dried to reduce the potential for microorganism growth in the pipework systems. It was pointed that desiccant air driers tend to be used in preference to refrigerant systems as their control and reliability is far higher.

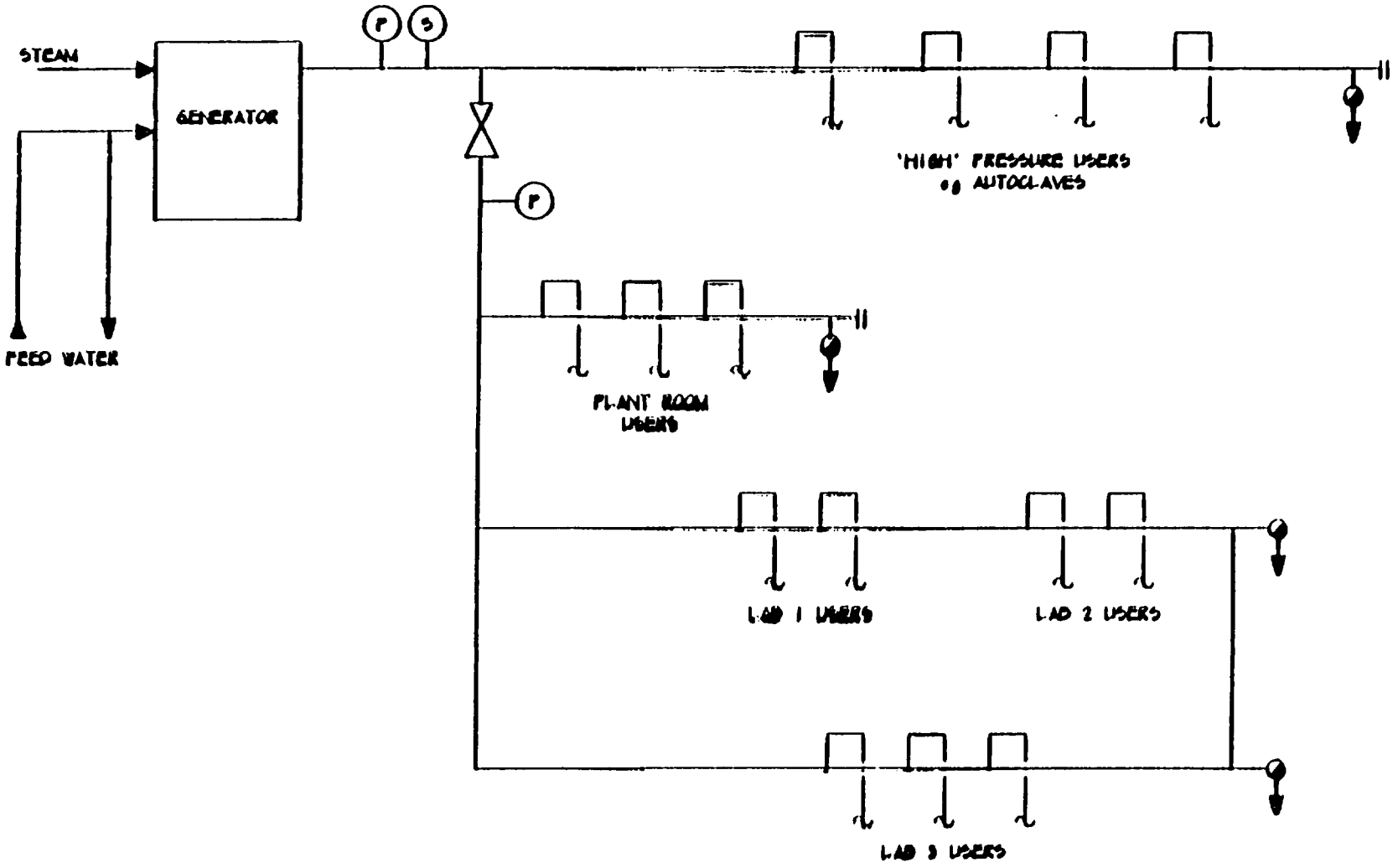
# TYPICAL WFI SYSTEM



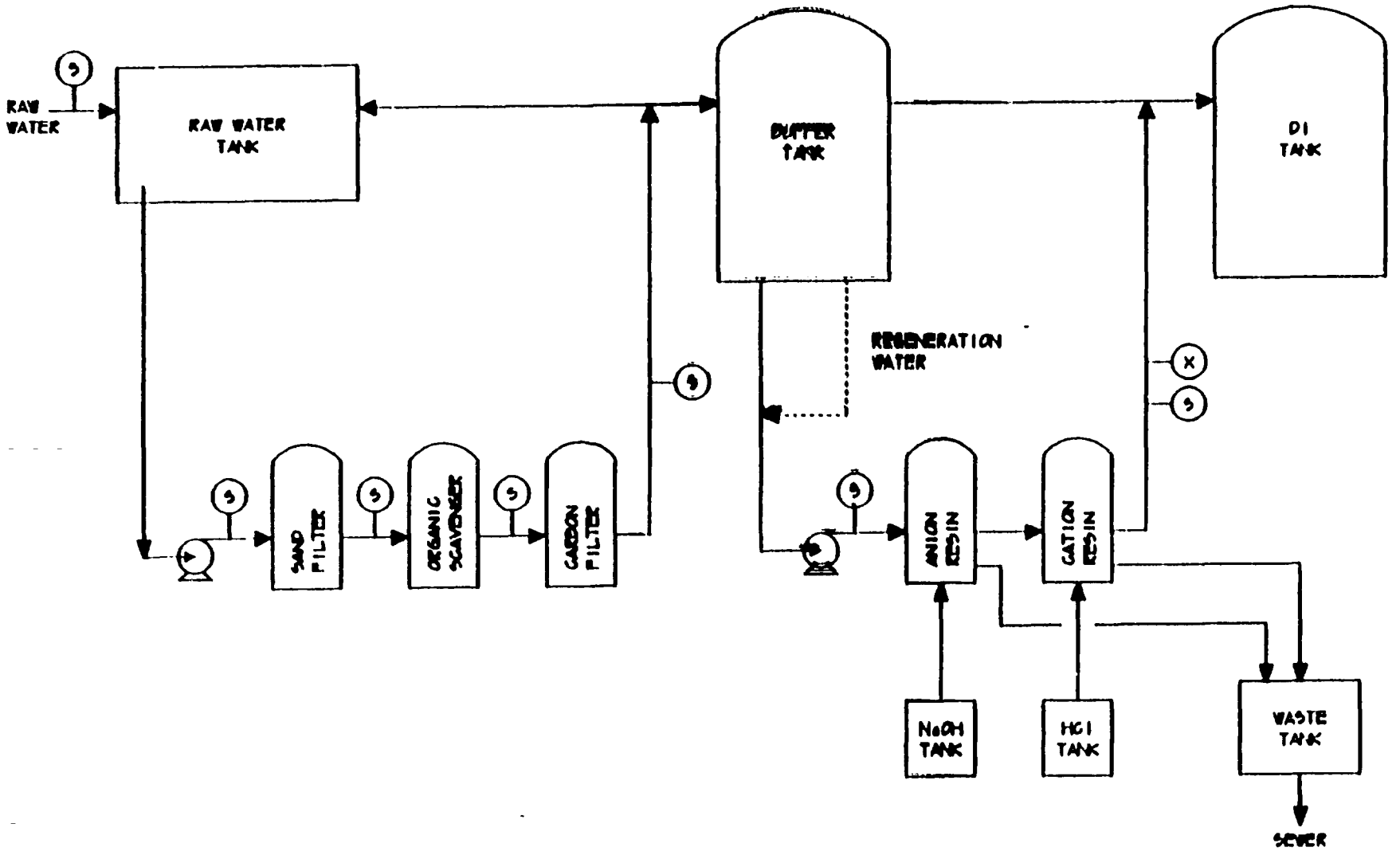
# TYPICAL COMPRESSED AIR SYSTEM



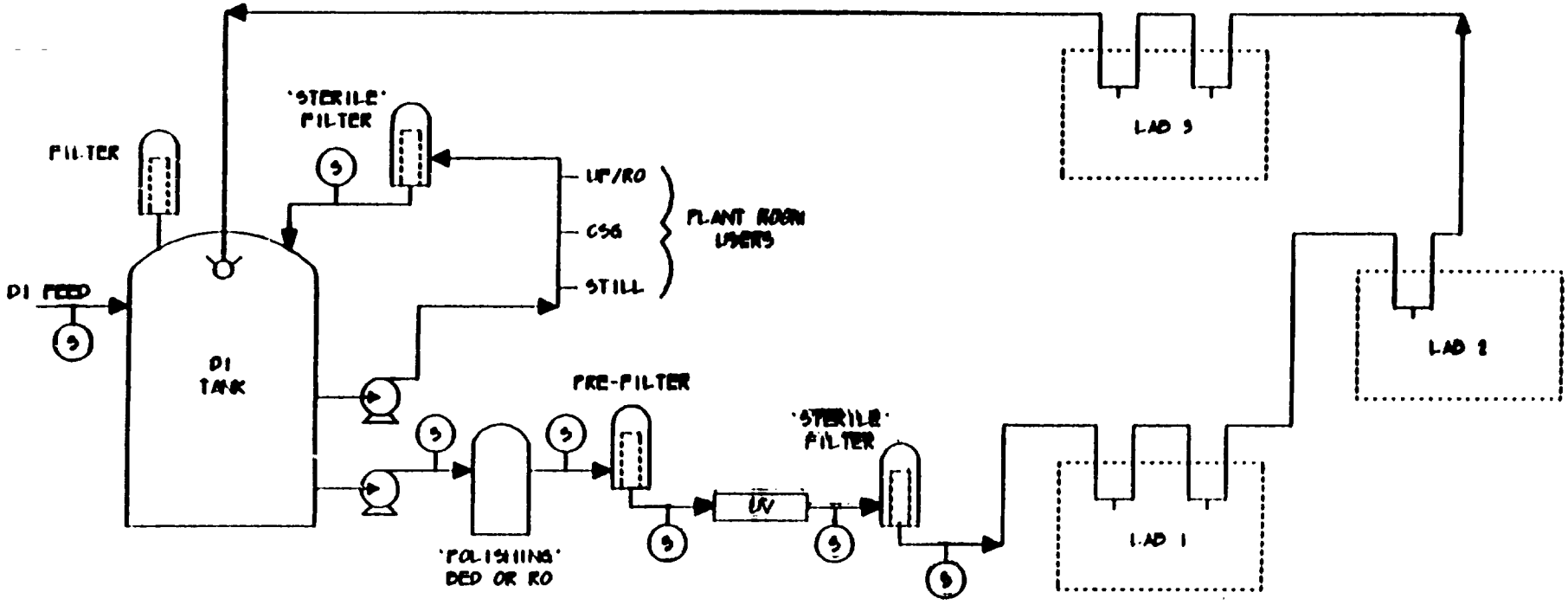
# TYPICAL CLEAN STEAM SYSTEM



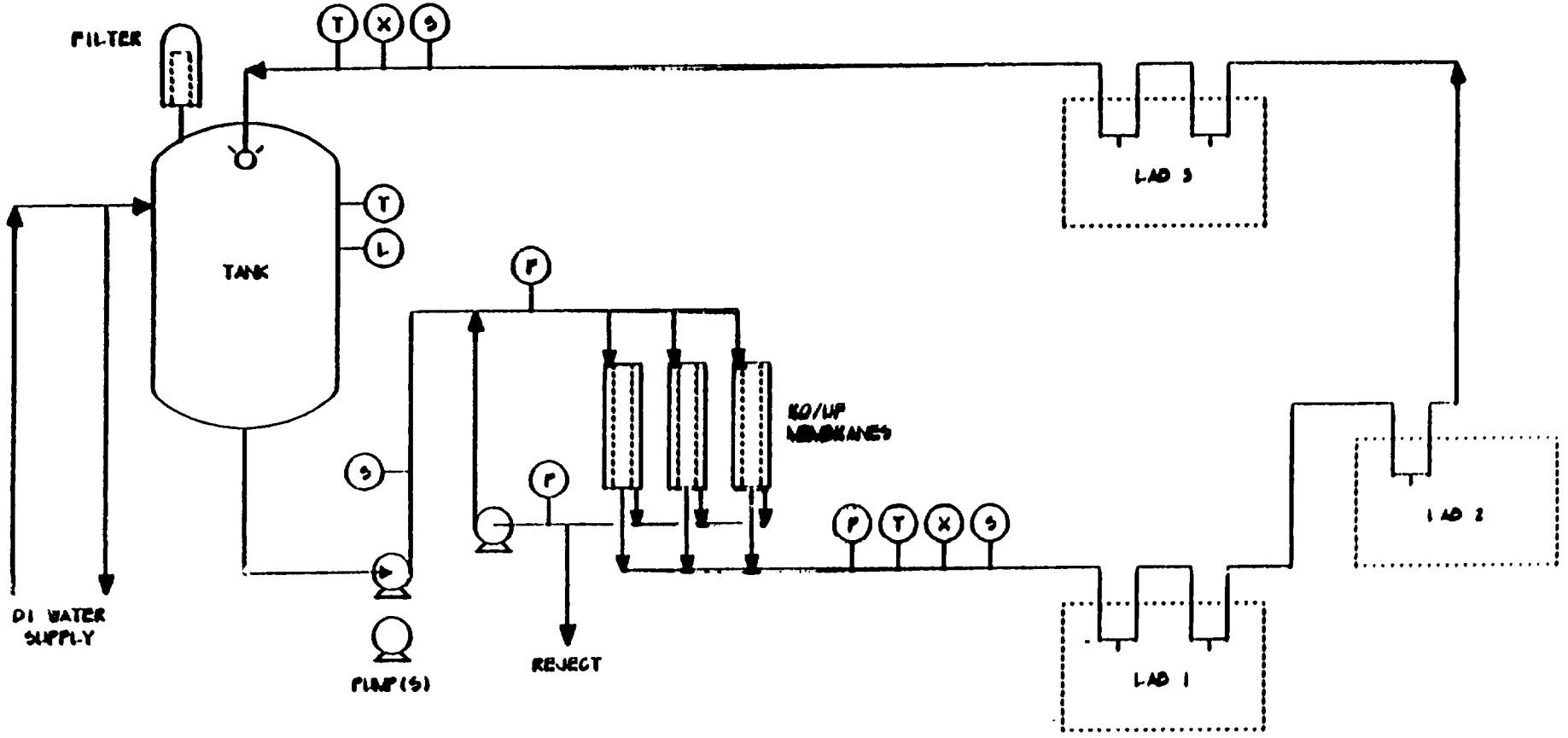
# TYPICAL DI SYSTEM



# TYPICAL PURIFIED WATER SYSTEM



# TYPICAL MEMBRANE SYSTEM



**Medical Gases**

The supply and distribution of medical gases can also be critical in some process applications. In particular, biological processes use a wide variety of medical gases and it is of extreme importance that the distribution systems are of high quality, prevent leakage particularly of hazardous gases. It is considered important from a safety point of view that both oxygen depletion and oxygen detection systems are installed in buildings where high volumes of medical gases are used as a prevention for the outbreak of fire and also to safeguard operators from suffocation.

**Clean Steam**

The use of clean steam is critical when sterilising plant for production purposes. In particular, the use of clean steam with autoclaves is essential if autoclaves are to operate to the various international standards applied. During discussions on clean steam systems it was noted that the usual practice in Hungary in many instances has been the filtering of boiler steam. GRC indicated that this approach is not normally tolerated in Western pharmaceutical companies unless the filter is capable of producing sterile steam (through a 0.2 micron filter). In most cases clean steam is produced from a clean steam generator using WFI or as a minimum high purity deionised water as a feedstock.

### 4.2.10 Clean in Place Systems

At several occasions throughout the project, the need for validated cleaning procedures had been emphasised. Although in many instances manual cleaning of equipment both fixed and mobile is used in Western Europe, the USA and in particular in Hungary, there is a move towards the use of fixed cleaning in place systems which can be validated more readily than manual activities. The reason for the ease of validation is quite simply that once a cleaning cycle has been proven to clean, the cleaning in place control systems will be set to repeat the operation without variance and therefore give repeatable results. Manual cleaning of equipment is notoriously unpredictable and can lead to serious contamination if the cleaning standard operating procedure is not carried out carefully.

CIP systems generally take two forms and are often used in combination. These are as follows:

(i) A central CIP unit consisting of a control package, circulation pumps, scavenging pumps, storage tanks for detergent, acid and alkali (if required) and buffer tanks, all generally mounted on a skid unit. These central units are generally built to very high standards either in food grade plastics or in 316L stainless steel. Such systems are then connected by a series of pipe lines to the equipment, pipework and vessels which are to be subjected to the cleaning process. The piping systems usually consist of a flow and return header with connections to each of the items to be cleaned. Control of the flowrates and sequence of cleaning materials is usually by automatic feedback valves located close to the item being cleaned.

Cleaning is effected in two ways which are as follows. Within the apparatus either permanently fixed or temporary spray nozzles, heads or rotating sprayheads are installed which provide a high pressure and varying spray pattern which is designed to penetrate all areas of the equipment being cleaned.

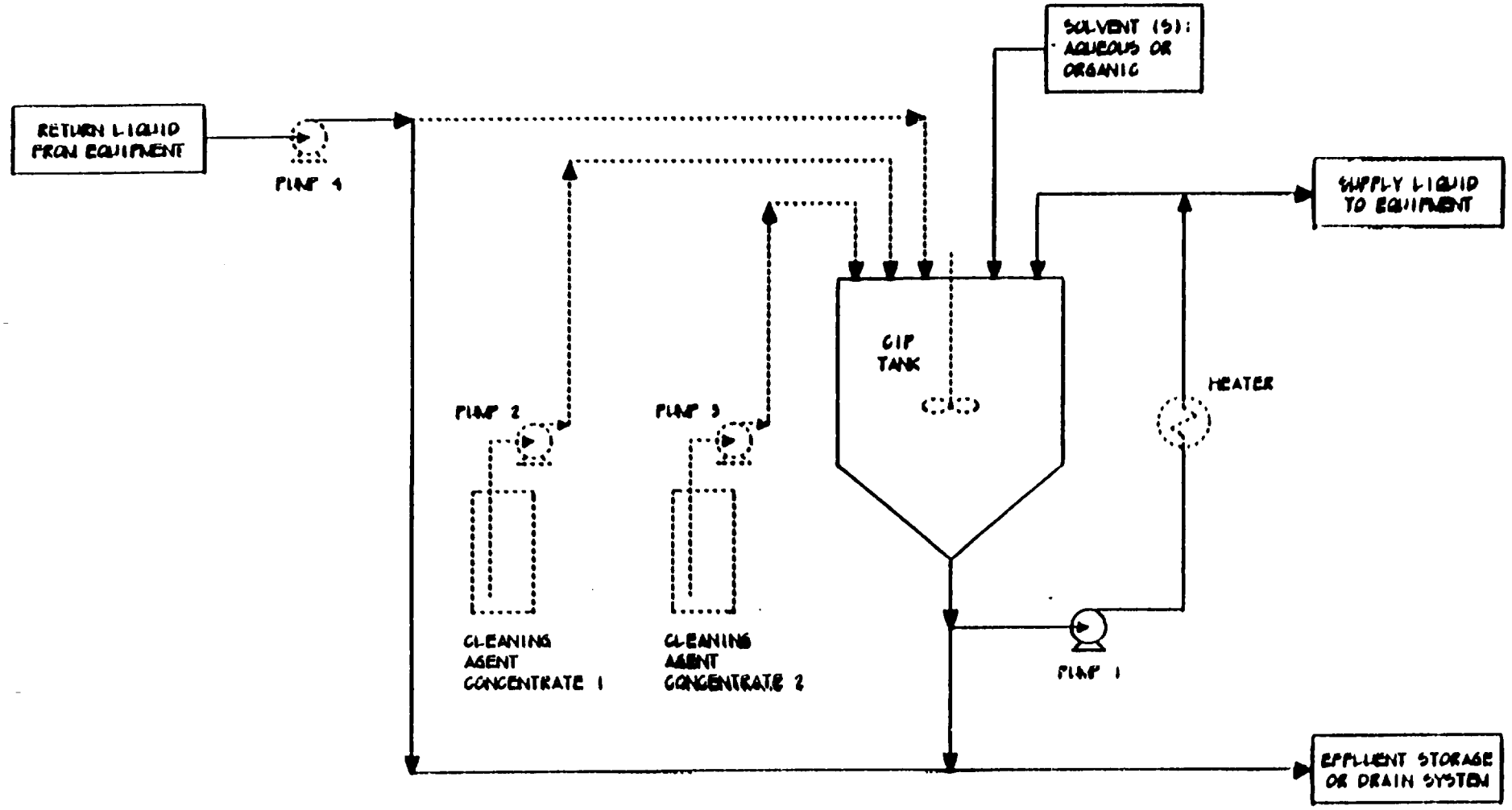
The cleaning of pipework is generally achieved by introducing the CIP fluids at strategic points in the piping system and passing the CIP fluid at high velocities thus providing a scavenging effect. Great care must be taken on the locations at which the CIP fluids are introduced to the piping system, particularly with a view to cleaning all sections of pipe and to ensure that the pipework system is self drainable.

The normal sequence of cleaning is as follows:

Pre-rinse - The pre-rinse stage is to wet the areas to be cleaned using the final stage rinse water from the previous wash carried out. This approach is adopted because most final rinse water used is of high quality and therefore too expensive to dump to drain on completion of a wash.

Cleaning stages - The cleaning stages consist of a combination of cleaning fluids both hot and cold and are dependent upon the type of product which has been used in the system. Cleaning fluids range from proprietary detergents, acid and alkali mixtures and the exact combination of washing materials can only be determined by experimentation.

# SCHEMATIC OF SIMPLE CIP SYSTEM



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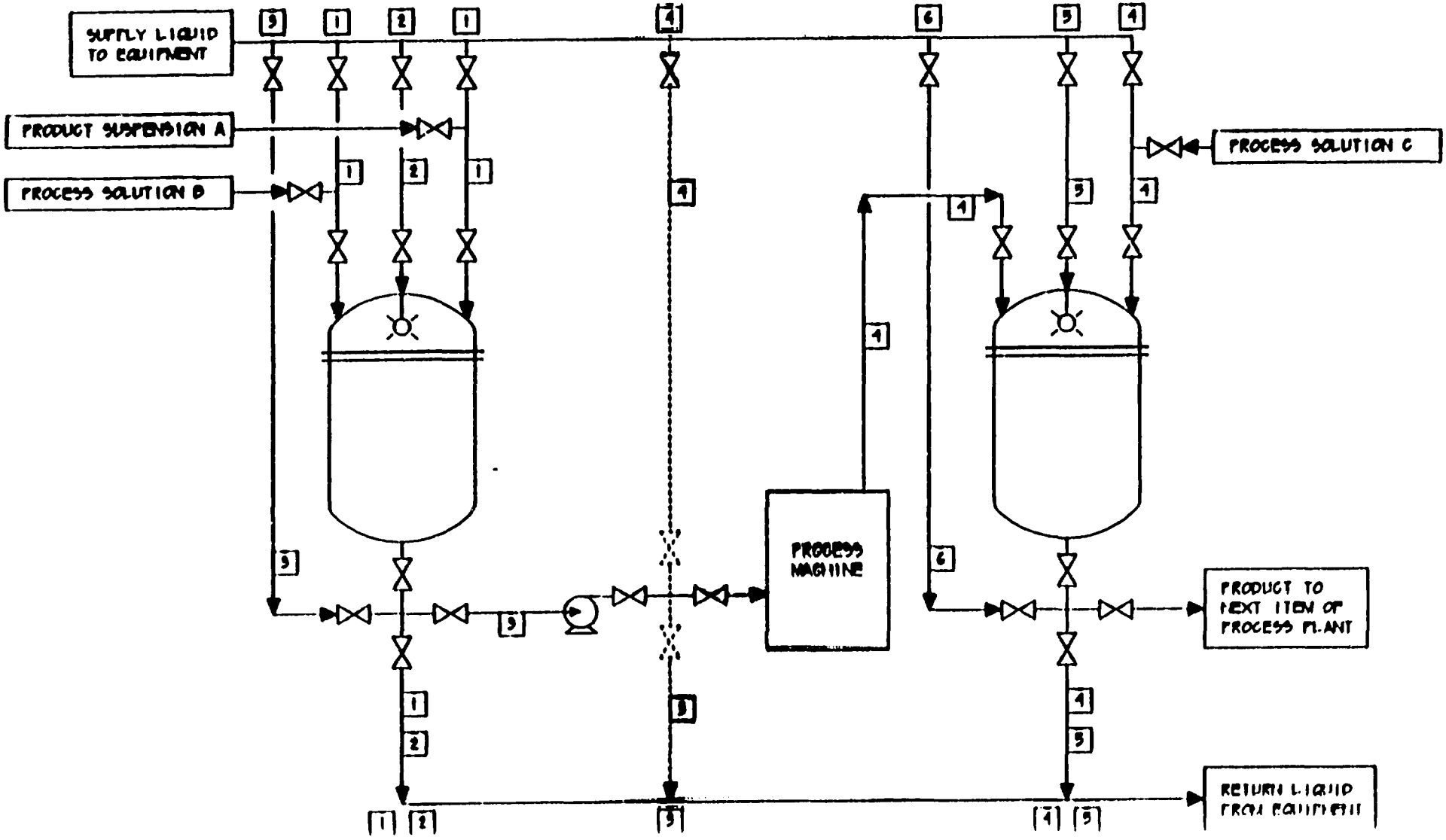
# SCHEMATIC OF SEQUENCE OF CIP OPERATIONS



Rinse cycles - Depending on the cleaning cycle there may be a number of intermediate rinse cycles to remove traces of acid or alkali from the system prior to introducing other cleaning materials and of course there is a final rinse using either demineralised water, reverse osmosis (RO) water or water for injection (WFI) depending on the standard of production being carried out.

(ii) In addition to cleaning the fixed equipment, it is often necessary to clean a range of mobile vessels, tanks, also plastic and glassware. The approach to be adopted depends generally on the size of the items to be washed. For items up to approximately 20l particularly glassware and plastic containers, these are usually cleaned in proprietary washing machines which are capable of validation. For larger items it is normal either to build a wash cabinet in which the units can be placed or to connect mobile vessels to a CIP system using temporary sprayballs. In both of the above instances a central skid mounted package similar to that used for cleaning static equipment is adopted.

### 4.2.11 Sterilising in Place

Although the principles of sterilising in place are well known to Vegyterv, it had become apparent to GRC Consultants that many of the key features of this practice are not adequately carried out in Hungary and other Eastern European states. Discussions and presentations took place on the methods currently used for sterilising in place in most advanced pharmaceutical facilities. It was emphasised that great care must be taken to ensure that the following factors in design are observed:

(a) The quality of all pipework is such that the internal surfaces are smooth and have no excessive weld metal protruding into the internal bore.

(b) The pipework is laid out to be self draining and adequate steam trapping is provided.

(c) There are no high points in the piping system which will enable the entrapment of air.

(d) Adequate insulation must be applied to ensure that there are no cold spots.

(e) Sufficient points at which sterilising steam can be injected into the system must be provided.

(f) Validation of the system is essential to test that there are no cold spots and that the temperature is always in excess of 121°C.

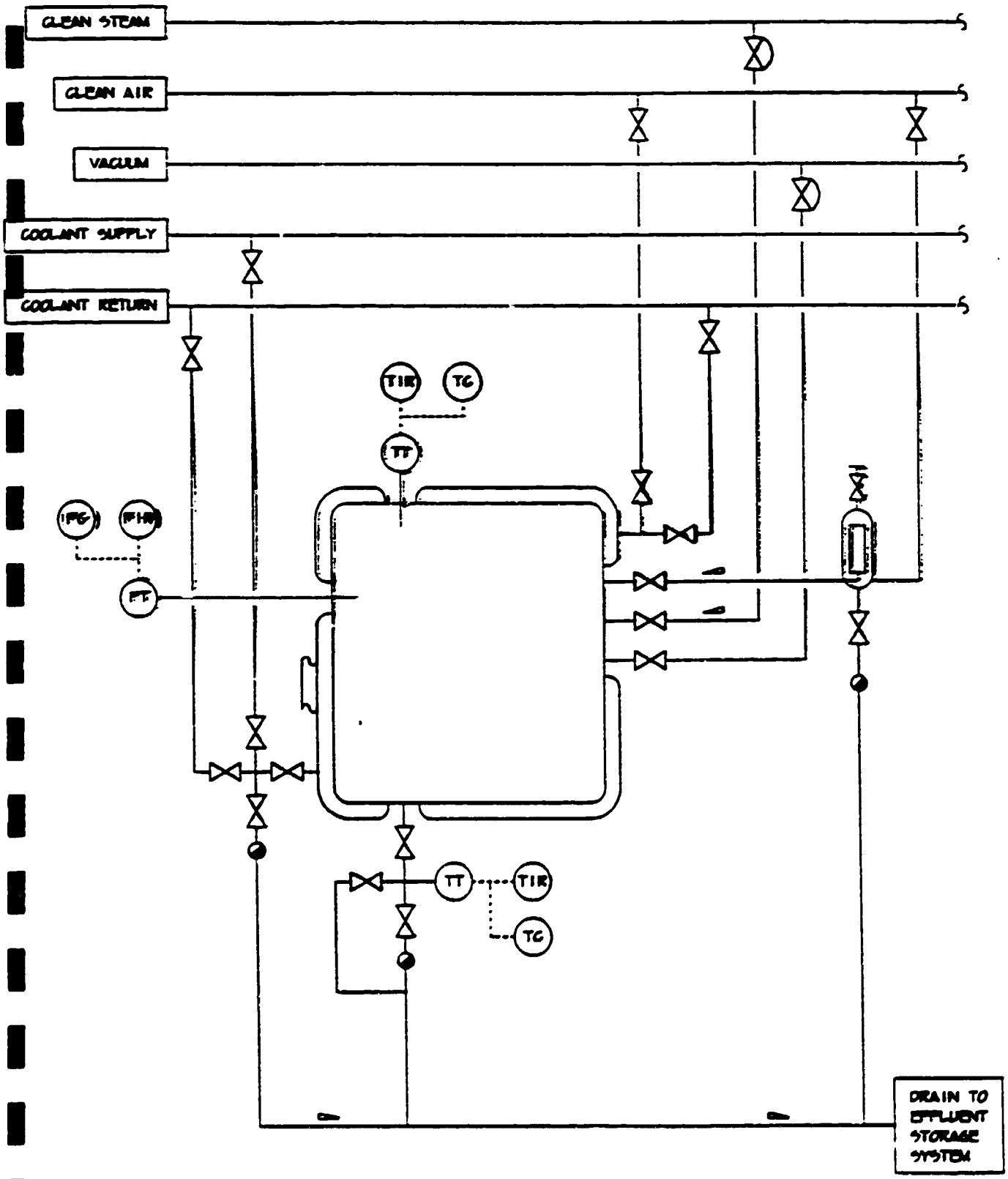
(g) Prior to undertaking the sterilisation a pressure test is carried out to ensure that the system is sound both before and after the sterile test. thus preventing the pulling in of any contamination as the system cools.

(h) Clean steam must be used for this process. generally produced in a high quality clean steam generator.

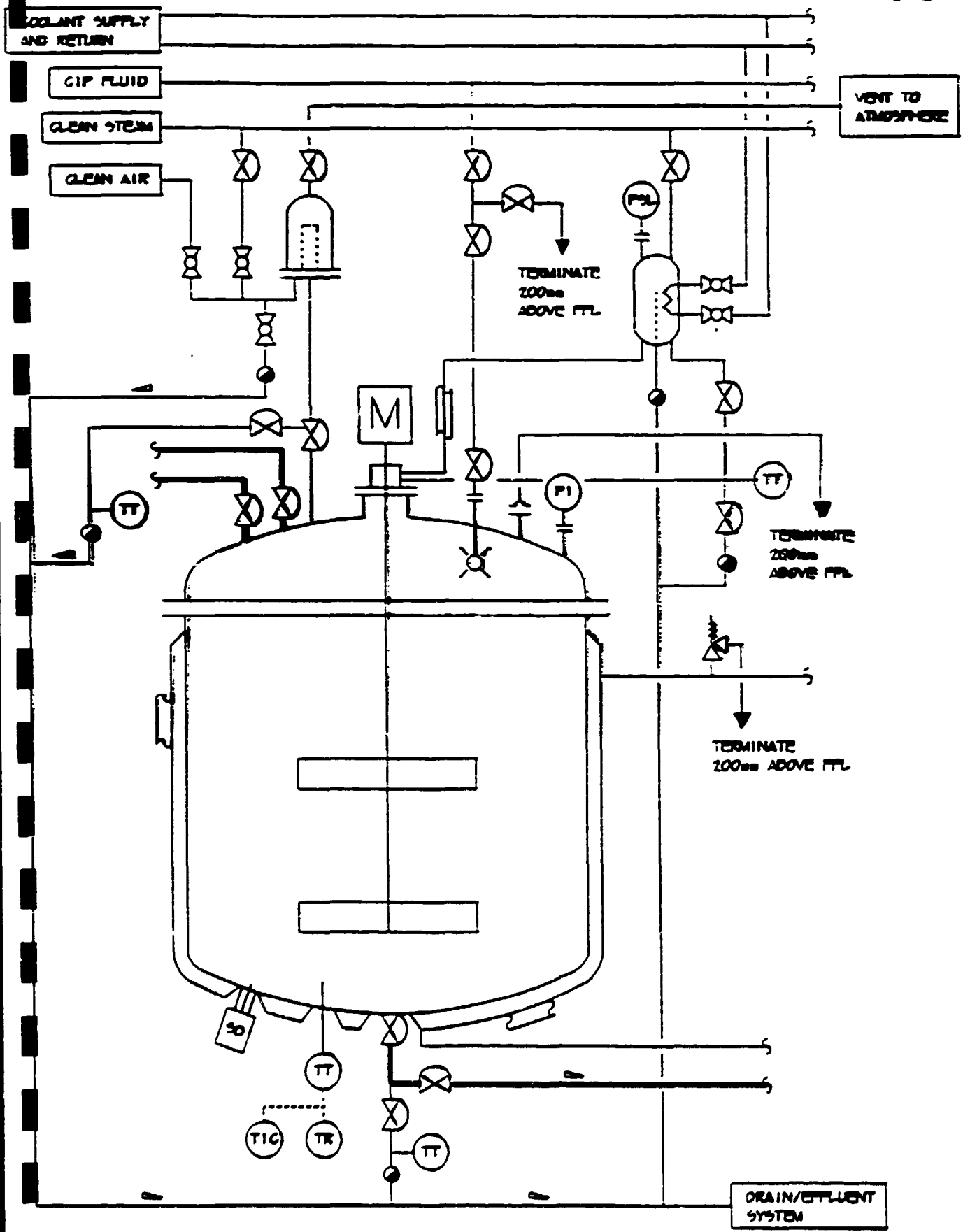
Finally, examples of typical systems including the sterilisation of vessels. autoclaves and filters was discussed in detail. Typical examples of such systems are included at the end of this section.

It was emphasised that considerable attention must be paid to the validation of such systems to ensure that temperature is reached at all points in a piece of equipment. pipework system and this is carried out by using a variety of protocols including temperature measurement. temperature indicators and for proving a system when it is operating under decontamination mode (kill in place), the use of biological sensors such as spore strips or spore bags are often used. Great care must be taken in setting up the validation equipment to ensure that no false readings are given and that there are reference instruments or materials used in order to assist with the overall calibration.

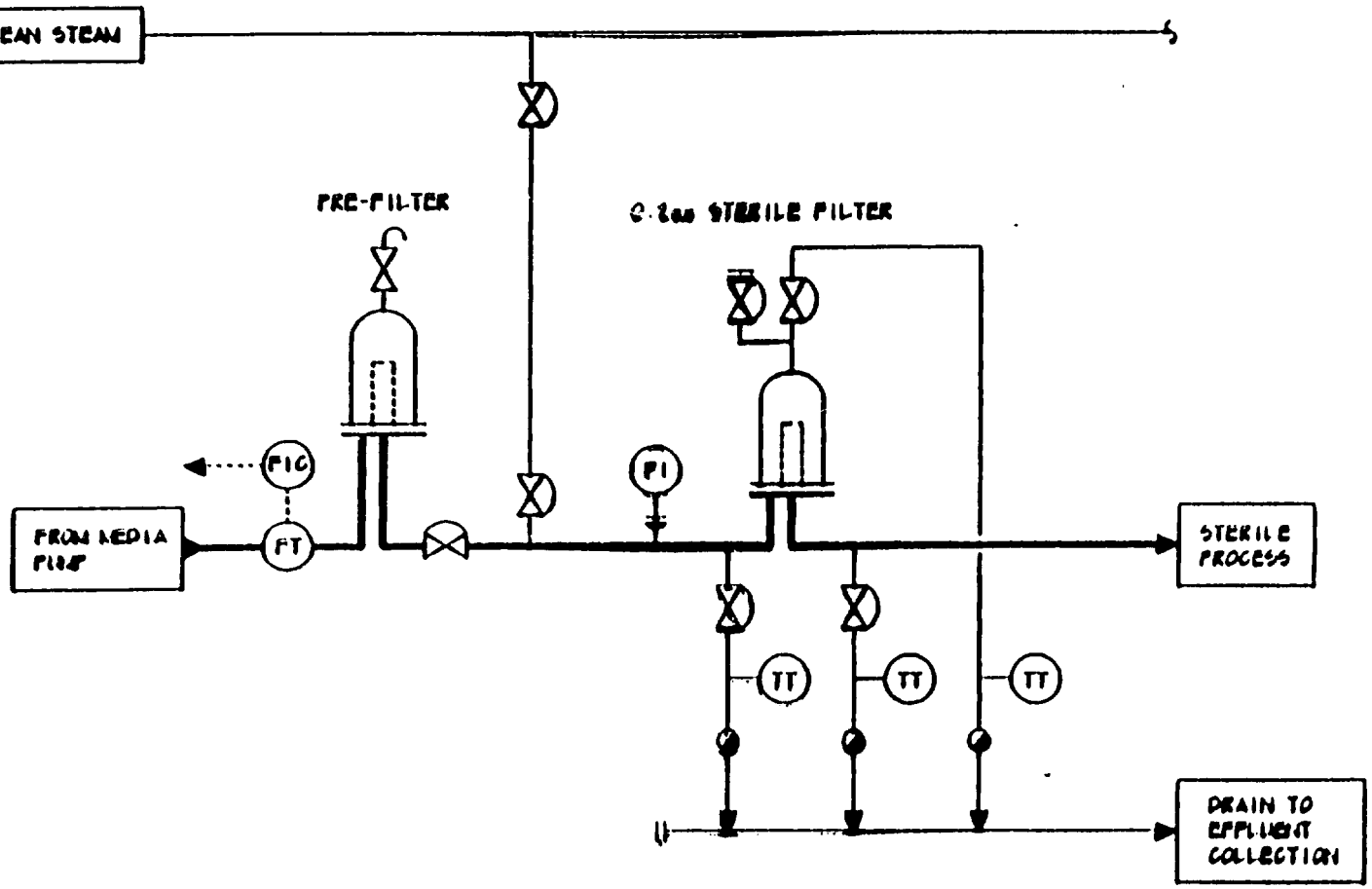
# AUTOCLAVE


CLEAN STEAM
CLEAN AIR
VACUUM
COOLANT SUPPLY
COOLANT RETURN
TIR
TC
TT
PG
PIR
PT
TT
TIR
TC
DRAIN TO EFFLUENT STORAGE SYSTEM

# STERILE VESSEL AND ANCILLARIES



# STERILE FILTRATION OF MEDIA SOLUTIONS



## 4.3 QUALITY CONTROL AND VALIDATION

As stated elsewhere in the report, validation is becoming increasingly important in the pharmaceutical industry. Although validation has been practised for up to 10-15 years, it is only in the last 5-10 years that it has become commonplace for all new pharmaceutical factories. This factor is an important consideration for Vegyterv because many Eastern European countries are unfamiliar with the detailed application of validation. In general terms the majority of pharmaceutical companies in Hungary are familiar with the theory of validation but have little experience in its practical application.

Validation affects every aspect of pharmaceutical plant operation and is applied not only to the production areas but also to the transport of materials, movement of materials and personnel around the site, quality control practices particularly in laboratories, and the storage of materials. The interrelationship between Good Manufacturing Practice, validation and quality control procedures such as the ISO standards is best described on the chart shown in this section. In general terms, validation is part of overall quality control and interfaces with each of the other three disciplines. Until the formulation of the ISO quality standards, validation linked with Good Manufacturing Practice was considered to be adequate in the pharmaceutical industry. In general terms it is unclear at present how much effect the application of ISO standards will have on the manufacture of pharmaceuticals. In some quarters the feeling is that they will eventually replace many of the existing guides to Good Manufacturing Practice and associated standards, others believe that they will exist in parallel with the existing methods operated by most pharmaceutical companies.

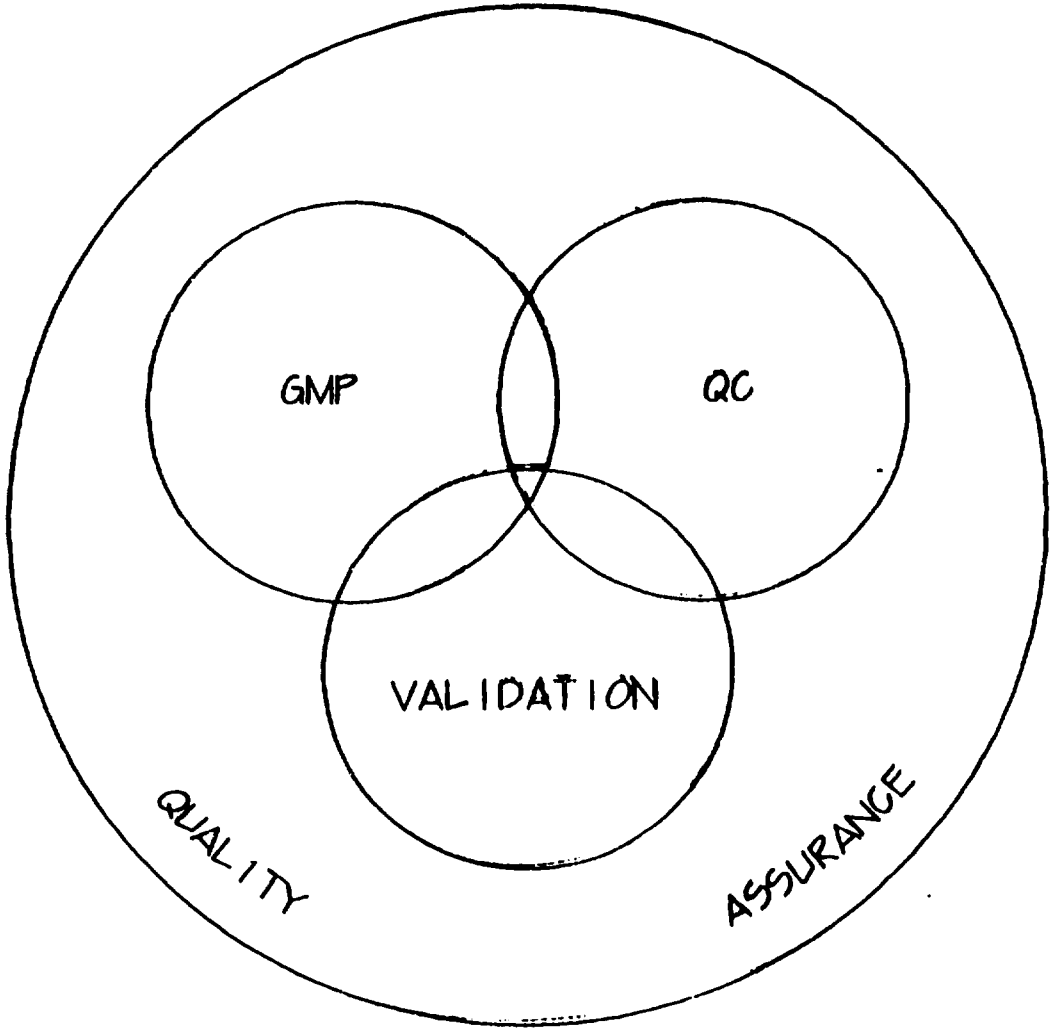
The key aspects of validation are as follows:

(a) That a facility should be constructed and operate in accordance with the specifications and procedures laid down in the design and specification.

(b) That there should be full and adequate documentation to prove that the plant operates not only to the specification but consistently and within established parameters on every occasion that it is manufacturing a product.

The latter point is extremely important in so far that it is not sufficient to validate a facility and accept or expect that it will adequately validated for all products. It is necessary to revalidate a facility on each and every occasion that there is a change in the product being

# VALIDATION AS PART OF QUALITY ASSURANCE



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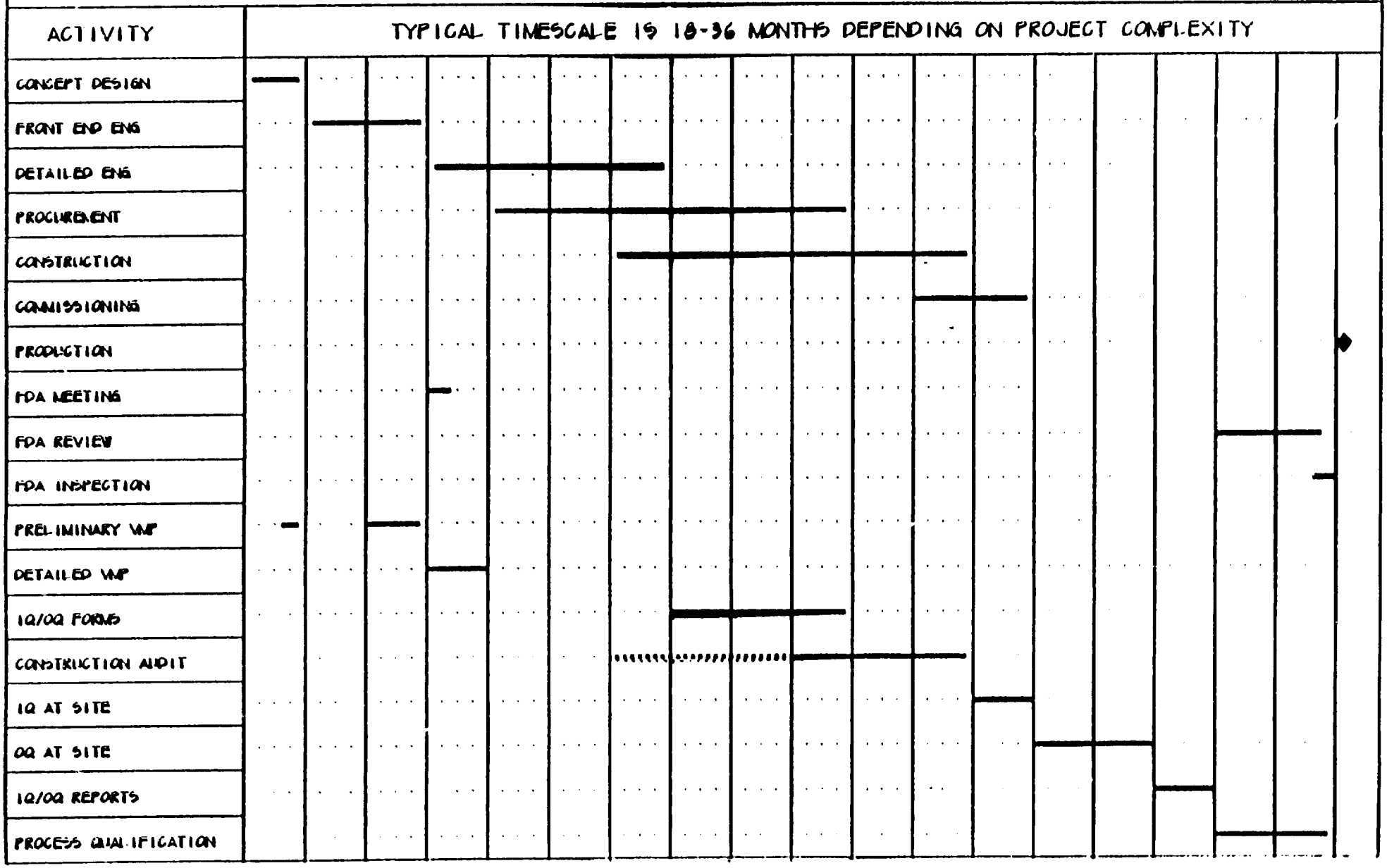
# VALIDATION SCHEDULE



manufactured. Furthermore, if the facility is a multi purpose or multi product unit where different products are manufactured in campaigns, it will be essential to revalidate certain aspects of the facility on each change of campaign. This form of validation is normally carried out by client companies as part of their overall quality control procedures.

Another aspect of validation, particularly during the design and construction, is associated with firstly the proven quality of the materials used in the plant and secondly the control of any design or construction changes taking place up to the point of completion of the plant. This type of validation is unknown in Hungary and will be necessary particularly if the country adopts EC standards or intends to export to regions governed by the FDA.

The lectures and discussions which took place with Vegyterv on the subject of validation were centred around a number of standard documents used in validation which were all put into context of overall project timeframes. Some typical examples of project programmes and the documentation discussed are included in Appendix 2.

Attention is drawn to the bibliography where a number of the standard codes of practice, standards and regulations are listed. These documents were discussed in some detail and copies were handed to Vegyterv for their reference and use.

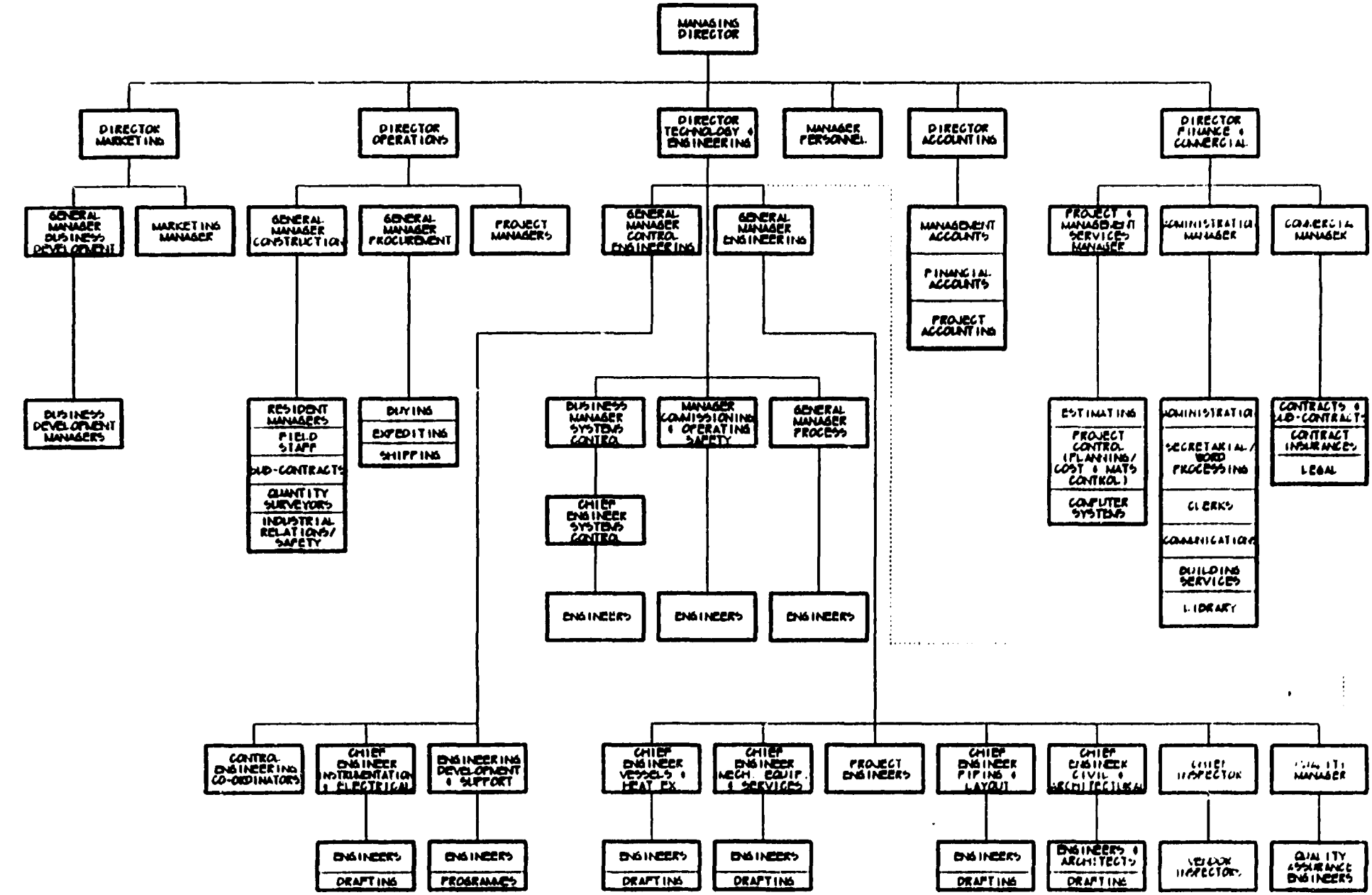
## 4.4 PROJECT TEAMS AND TASKFORCE ORGANISATION

Considerable discussion took place with the senior management of Vegyterv regarding the structures of teams required to execute projects in the pharmaceutical industry. As was stated in Section 2, the size and complexity of projects currently being considered in Hungary are such that relatively small teams are required to design, manage and construct such facilities. In spite of this, it was felt appropriate to present a range of typical organisations which are used for projects of differing sizes. Detailed analysis of large scale multi million dollar projects was undertaken and compared with the organisation of much smaller teams for the scales of projects currently being handled in Hungary.

Typical examples of the organisation charts discussed are attached to this section.

The use of project taskforces was also discussed, particularly when clients require strict confidentiality to be observed. Vegyterv confirmed that they had in the past operated such

# TYPICAL MAJOR CONTRACTOR'S COMPANY ORGANISATION

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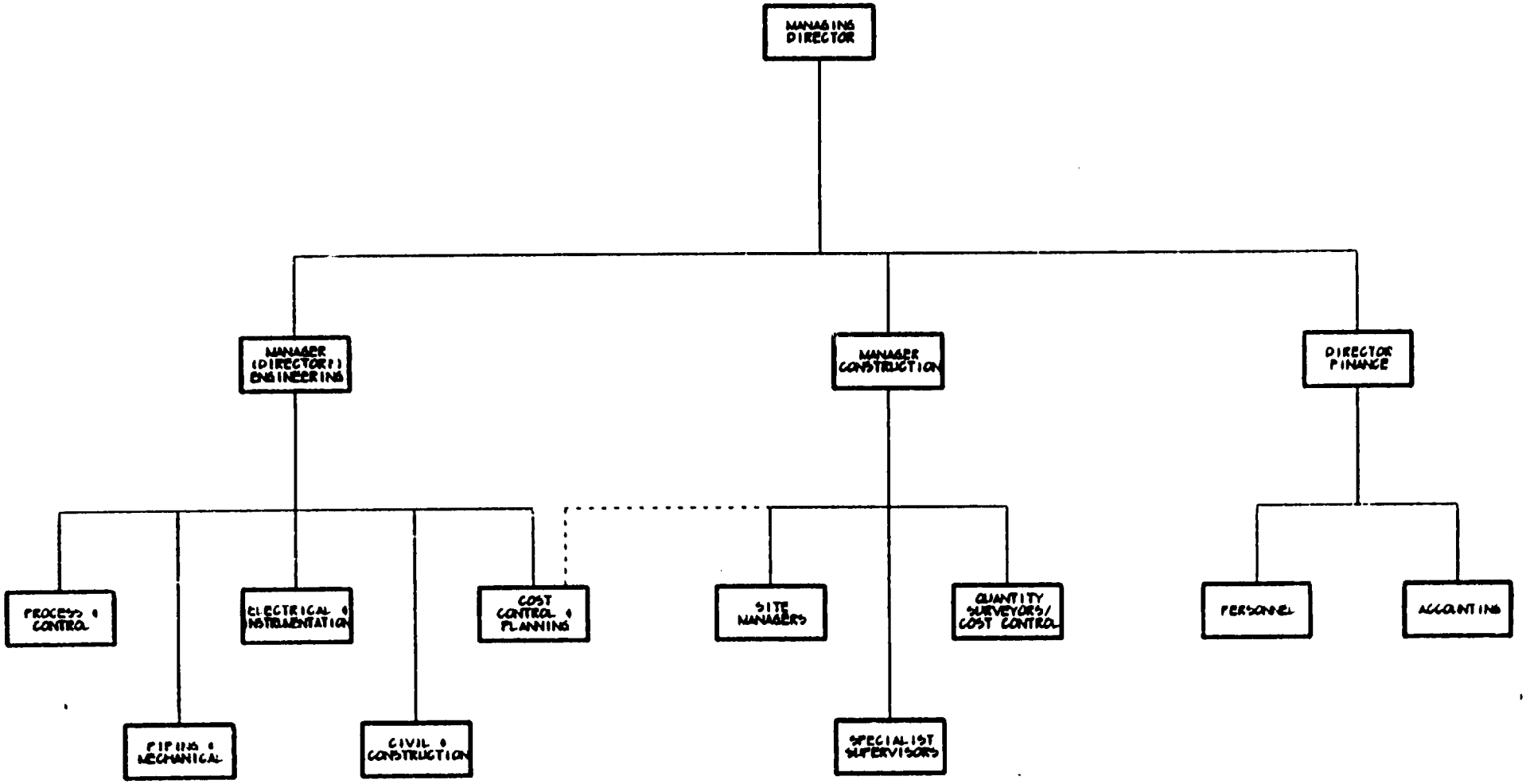
TYPICAL SMALL/MEDIUM CONTRACTOR ORGANISATION

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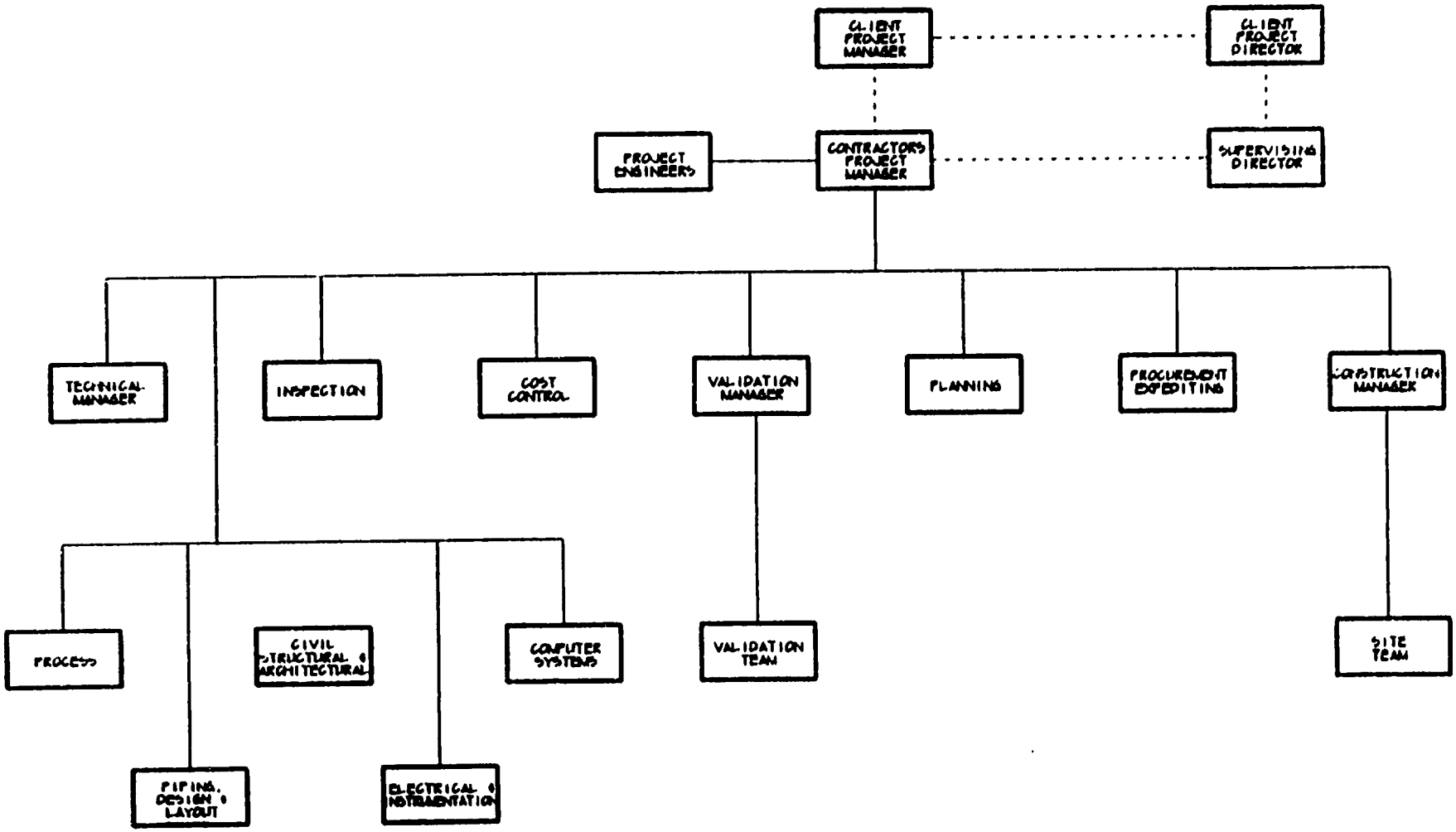
PROJECT TEAMS AND TASK FORCE ORGANISATIONS

## CLASSIC PROJECT TEAM - MAJOR PROJECT

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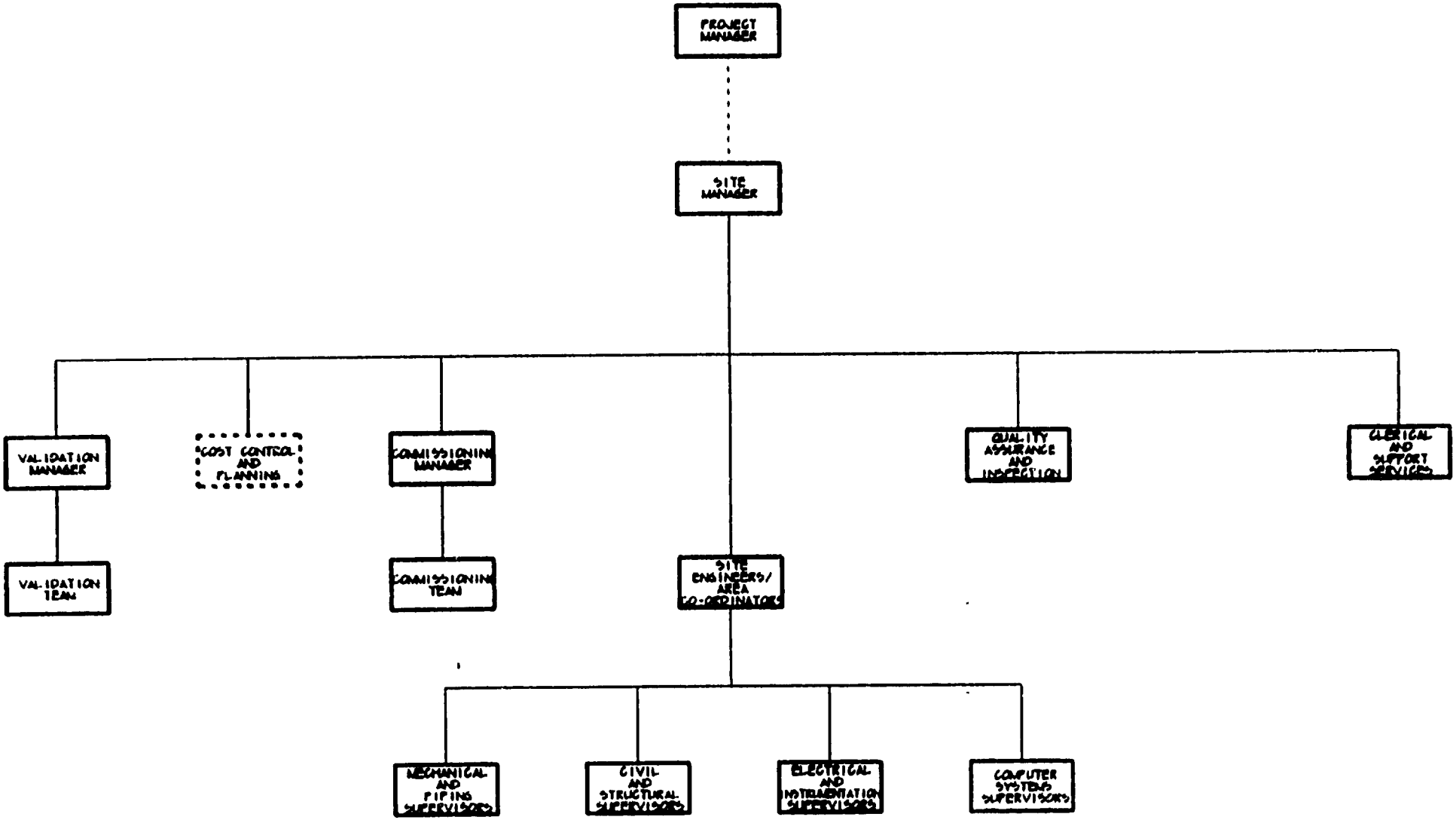
TYPICAL CONSTRUCTION SITE MANAGEMENT

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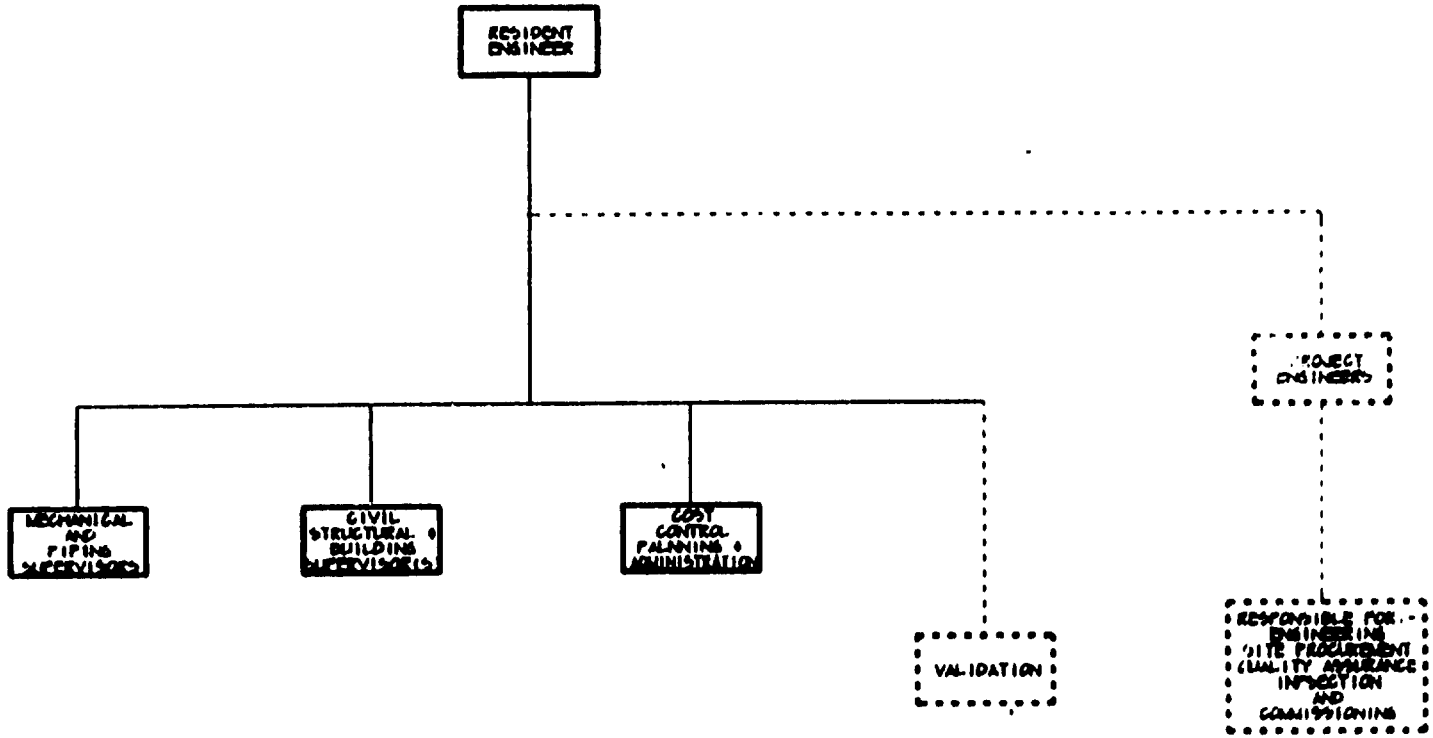
TYPICAL SMALL CONSTRUCTION SITE

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teams but considered that currently the workload was not sufficiently large to enable such practices to be carried out.

## 4.5 MARKETING

In common with many of the State owned industries in Eastern Europe, Vegyterv have limited experience of marketing and sales activities. Currently the company has practically no organisation capable of carrying out marketing and sales activities normally associated with the contracting industry. This situation has arisen principally because until 1990 the company gained projects either through direction by central government or by non-competitive negotiation with the production companies that used their services. It should also be noted that Vegyterv in practical terms had no competition in their home market and were able, with support from the Hungarian Government and those of the other East European states, to have a completely protected market. It was against this background that the company grew in size, turnover and capability, particularly during the boom periods of the 1960's, 1970's and early 1980's.

During GRC Consultants first review meetings with Vegyterv in 1989 and 1990, it was apparent at the time that the company would be faced with competition not only from companies that were being formed in the new liberalisation but could also face competition from foreign companies.

In view of the necessity to build a credible sales and marketing capability Vegyterv need to develop the following key areas if they are to compete for and win what work is available within their sphere of activity.

### Marketing and Sales Organisation

Due to the manner in which projects were assigned to Vegyterv in the past, the company had no marketing organisation or experience of marketing its services and products. This is recognised by the management of Vegyterv as being a serious deficiency and within this context the company is seeking to establish a department which can firstly secure work in Hungary and that subsequently seek projects in other target regions.

At present Vegyterv are attempting to secure projects with practically no marketing organisation in place. The company had allocated a senior project manager to develop marketing activities but as this position is now vacant due to the person leaving the company there is no active marketing department at present. In any event, this position was only created during the last 6 months and as the experience of the personnel involved is very limited, little headway has been made in organising the department, securing work for the company or in publicising or promoting the company's reputation.

In addition to the identified post of Sales and Marketing Manager, the company still has a number of established contacts with its previous and existing clients at the engineering level and there are signs that these contacts are at least maintaining a steady flow of small but important projects in the target industries.

The senior management recognise the importance of effective marketing and sales and are making efforts at high level to attract work. Due to the general lack of experience in this field of activity guidance and advice is needed on how best to set about successfully securing work.

## Market Analysis

There appears to be little understanding within Vegyterv of the need to determine the likely investment patterns of their prospective clients and against such information to evaluate the likelihood of success in winning contracts and thereby establishing an effective plan regarding fee income, turnover and profits.

Because the company has no short term, intermediate or long term plan for overall development, it is practically impossible to establish overheads and thereby determine what their selling rates and margins should be. Due to the importance of these factors a separate section in this report is devoted to the basis of sales planning and costing.

The other key management exercise which Vegyterv have in hand is the evaluation of what is an appropriate size for the company to be effective and survive in the current market climate. It is clear at present that although Vegyterv have a number of very competent and experienced personnel, it is also believed that there are a number of people working within the organisation who do not comprehend the requirements of a modern competitive

contracting environment. An evaluation of this aspect of the company's organisation needs to be undertaken on an urgent basis but only once the strategy for marketing and sales is established.

### Sales and Marketing Documents

Currently the company has two printed brochures, one which covers Vegyterv's general capability and experience, the other being a listing of projects executed between 1975 - 1989 (a copy of this document is included in Appendix 1). The experience list is well laid out and perfectly satisfactory for its purpose and requires updating to indicate the current experience. In other aspects there would appear to be little need to change this document.

The general brochure needs replacement as soon as possible with a high quality concise and accurate statement of the company's capability, its target markets and its organisation.

In addition to the general brochure it is recommended that Vegyterv develop market sector and technology brochures or information sheets which can be added to the main brochure so that when presenting the company to a prospective client a structured document which is relevant to the clients business is available. In this regard Vegyterv need to develop a series of support brochures not only for the pharmaceutical, fine chemical and biochemical industries, but also for their other areas of business such as heavy and inorganic chemicals, polymers and petrochemicals.

## 4.6 TENDERING

### Introduction

In general there is little experience in Vegyterv of the basic methods of competitive tendering. This is, to an extent, due to the same reasons as stated previously, that the company had worked in a protected environment and therefore was not used to the rigours of competitive bidding.

## Key Factors

There are a number of key factors which Vegyterv must take into account when tendering, these are as follows:-

(a) Always respond to the clients enquiry preferably in the format requested.

(b) Establish by good marketing and sales intelligence the important factors which will decide the choice of contractor. Typically, is the client looking for a keen price or a plant that will validate to a particular standard, or is there some other factor which will secure the project.

(c) Who are the competing companies and what will their sales strategy be?

(d) What pricing policy to adopt including profit level.

(e) Is the client looking for a particular team of engineers, if so which of Vegyterv's staff are most appropriate to be nominated for the project.

(f) Include as appropriate, sufficient information to indicate clearly to the client that Vegyterv can carry out the project successfully.

(g) Maintain close contact with the client throughout the bid period.

(h) Evaluate carefully the contract terms and ensure there is sufficient protection to prevent Vegyterv taking responsibilities which could prove costly during the project.

(i) Develop a clear project execution strategy particularly for handling client changes, lack of information or any other factor that could cause a change to Vegyterv's scope of work.

(j) Try if possible to establish good personal relationships between the client's team and the nominated Vegyterv project team.

## Selling Price

Vegyterv have no clear policy at present regarding the establishment of a selling price for a particular scope of work. In common with most contractors, they will evaluate the content of work in any project, particularly from a management and design point of view, which leads to a manhour content for any particular job. Thereafter no policy exists regarding the overhead and profit which will be applied to project costing.

The first area of concern is that the actual level of overhead for the company has not been established and evaluation of this particular area must take place on an urgent basis. The concept of profit is of course now well known in Hungary but the discipline of evaluating projects from a financial point of view is not practised at present and the establishment of profit levels which are acceptable or a maximum achievable with any particular client should be carefully reviewed.

At present the setting of a daily or hourly manhour selling rate appears to be arbitrary and given the availability of projects in Hungary at present, engineering companies in general are happy to secure project on any practical basis available. Nevertheless, it is considered essential that the establishment of baseline selling rates which exclude profit should at least be established for all grades of productive personnel.

The following are suggested as typical grades which might be established as part of a manhour selling rate schedule:-

Project Manager
Head of Department
Senior Engineer
Engineer
Junior Engineer
Designer
Draughtsman
Procurement Specialist
Inspector
Construction Manager
Construction Supervisor
Commissioning Engineer

It is recognised at present that Vegyterv do not have specialists in all of the above categories but this should not prevent the establishment of appropriate selling rates for each of the grades as a basis for pricing projects.

## Overhead Construction

Vegyterv have a serious problem in hand regarding the level of overhead which they appear to carry within the company. It must be recognised that the salaries of personnel are very low by European standards and that it is necessary to retain staff to provide reasonable social amenities and services within the company. This situation should be closely reviewed to determine whether it is better to pay higher wages and therefore place the responsibility for their own welfare on to the staff or whether the existing level of social support should be maintained.

The retention of smaller numbers of more highly paid and motivated staff would give Vegyterv far greater flexibility in employment and remove a major feature of cost which would appear to be a constant and high overhead at present.

The content of overhead had been reviewed with senior staff at Vegyterv and it was agreed that the content would incorporate the following:

Payroll burden, which is an established element based on salary and is of the order of 0.4-0.5 x salary for each staff member.

Overhead - this would include all aspects of operating Vegyterv which would be as follows:

- heating
- electricity
- office equipment
- cleaning, maintenance of building
- subsidised meals
- medical welfare
- secretarial and support staff
- building management *
- non productive management (non fee earning)

- vehicles, including staff cars
- financing costs, if any
- travel (non reimbursable)
- marketing and sales costs
- holidays

* It should be noted that at the time of the report Vegyterv administer the building in which they are located and currently earn rents from a major tenant. In this regard there are overhead costs which to some extent can be offset by the rents paid by the tenant.

It is clear from the above that Vegyterv must evaluate carefully some of the elements of overhead, particularly those that could be offset by an increase in salary. Those elements of the overhead considered worthy of this evaluation would be as follows: medical services, subsidised meals. It is noted that Vegyterv support external caterers who are supplying meals not only to Vegyterv staff but also to external personnel in the building. The price of the meals is extremely low and consideration should be given to increasing the costs of meals to make the operation profitable rather than a drain on overhead.

Overhead applied to selling rates is dependent on the numbers of manhours it is anticipated that Vegyterv will sell in any one financial year. The concept of forward planning with the establishment of targets for the marketing and sales department have not been used in Vegyterv before. From this point of view the marketing department must attempt to establish a realistic manhour intake for each year in order that firstly staffing levels can be established, and secondly an overhead agreed for the office.

## 4.7 THE INTERNATIONAL CONTRACTING INDUSTRY

A presentation was given on the contracting industry and in particular the potential competitors that Vegyterv may meet in the course of its activities. It was emphasised that the contracting industry in the West has been suffering, albeit to a lesser extent, with the same downturn in the activity as experienced by Vegyterv in Eastern Europe.

Many major contracting organisations have now recognised that the pharmaceutical, fine chemical and food industries are rather more stable in their investment programmes than the oil, gas and petrochemical industries and as a result many of these companies are either

seeking to develop specialist groups to undertake work or are currently developing such groups. In spite of this potential competition on the world market, most of these companies will not be able to operate cost effectively in Hungary unless they are constructing projects for international pharmaceutical firms who are used to expending considerable sums on capital investment. Provided Vegyterv can secure its position in the Hungarian and Eastern European markets, there should be an assured future for the company as its engineering costs are generally much lower than those of Western European contractors.

Typical organisation charts were shown for Western European contractors with particular emphasis on a number of key departments which are not familiar to Vegyterv. Quality control and validation organisations within contractors was noted as indeed was the structure adopted for construction activities. It is reasonable to say that Vegyterv is organised in its design office similar to most medium sized Western contractors but that it lacks the construction organisation and has practically no validation capability at this time. It is noted, however, that Vegyterv intend to develop that capability and the head of the process department has been assigned to develop validation know-how inside the Vegyterv organisation.

The other serious difference between Vegyterv and the major international contractors is the point raised on a number of other occasions in this report which is the lack of experience on the commercial aspects of contracts. Most international contractors have a commercial department which handles contracts, estimating and the absolutely important discipline of marketing and sales. These subjects were discussed in separate sections in this report and Vegyterv have clearly recognised the need to develop a sales organisation and to employ an experienced sales and marketing manager.

The other aspect which was noted specifically regarding the major Western contractors is that many have overseas offices or joint venture companies in order to secure work in foreign locations. It is notable that many of the major companies have established offices in locations where the pharmaceutical companies are also operating, typically in the following areas:

- United Kingdom
- USA
- Mexico
- Germany

- France
- Italy
- Spain
- Singapore
- Taiwan
- Ireland
- Puerto Rico

The location of offices tends to be related directly to whether the contractor has long term contracts with a specific client but nevertheless in certain areas where there has been a considerable amount of government investment or there are special financial incentives, contractors have set up speculative offices to win work as it arises in the area. Typically, Ireland, Puerto Rica, Singapore are typical of such areas.

## 4.8 CONTRACT ARRANGEMENTS

One aspect of the early discussions with Vegyterv was the review of the contracts which are used regularly in Hungary. It is clear that at present there are no standard forms of contract used which is in complete contradiction to the general practice in Western Europe and the USA. It was explained during the various presentations that in the United Kingdom in particular the development of standard contracts for the chemical industry, civil and structural industry, mechanical and electrical engineering industry, and for consultancy work have a very advanced state of development. A variety of standard contracts are available and in particular the two forms were reviewed in detail. Federation Internationale des Ingineurs-Conseils Client/Consultant Model Services Agreement, and the Institution of Chemical Engineers Conditions of Contract for Process Plant - Fixed Lump Sum Contracts.

It was explained by Vegyterv that considerable difficulty would be experienced in persuading many of their clients to adopt such a rigorous client/contractor relationship. It was pointed out that without such rigorous arrangements between both parties executing complex projects, considerable difficulty would arise if appropriate contractual arrangements had not been established between them.

The importance of adequately defining the project in the form of specification, drawings and general descriptions was strongly emphasised. It was pointed out that although the basic

general conditions of contract may be very well defined. if the technical appendices to the contract are inadequate both parties will still find themselves meeting difficulties from a contractual point of view due to inaccuracies. inconsistencies and misunderstandings.

As part of these discussions on contract. it was recognised that there appear to be few organisations in Hungary which have the standing of the engineering institutions in the United Kingdom. France and Germany and therefore the value of engineers in Hungary has. to an extent. been eroded during the last few years. This position is unlikely to change for the foreseeable future until the importance of the role that engineers play in developing design. managing construction and achieving the execution of projects in the pharmaceutical industry to the standards which the regulatory authorities require has been recognised by the operating companies.

## 4.9 PRESENTATION MATERIAL

Throughout the training programme. both in the UK and Hungary, a considerable amount of presentation material was generated in order to help explain the very wide variety of technical and commercial information which was to be transferred to Vegyterv. As stated earlier. this information is not included in the report document as it would be rather excessive in volume. however. full sets of the documents were handed over to Vegyterv prior to the training programme.

Copies of these documents including company brochures and other technical information which was generated for this project would be available on request.

## 4.10 CONCLUSIONS

The basic capability of the Vegyterv staff is very high and many of the engineering staff would easily be absorbed into an international contracting organisation.

The primary problem as far as Vegyterv is concerned. is that in spite of the quality of their engineering people the general development of the engineering and construction industry in Eastern Europe was never exposed to the wide variety of contract execution methodologies

used in the West and therefore the general quality of design has not evolved at the same speed.

Because the Vegyterv had a basic understanding of the requirements for pharmaceutical plant design, it was a relatively easy impart information on the latest standards being applied in the USA and Western Europe. It must be noted, however, that although some aspects of design had been clearly demonstrated during the study tour in the United Kingdom, there was still a fair amount of scepticism as to whether the Hungarian pharmaceutical industry would ultimately be willing to pay the increased prices necessary to achieve the higher standards required by the international regulatory authorities.

It is reasonable to suppose that if Hungary joins the European Community and if its inspection authority are allowed the freedom to apply its undoubted skills in the application of regulatory standards, then pharmaceutical companies in Hungary will be forced to adopt these higher standards. Provided Vegyterv continue to invest time in the training of its staff by attending courses, obtaining up to date information and extracts on regulatory matters and generally reviewing publications which specialise on the pharmaceutical and associated industries. Vegyterv will be in a good position to the requirements of the improved standards in the pharmaceutical industry in Hungary provided it can weather the current poor market situation and adapt its organisation to the requirements now prevailing in Hungary.

It is also considered necessary that considerable effort should be made to improve the following areas within the company:

- Marketing - it is clearly an area that needs to be developed and the employment of a suitably qualified marketing manager will be essential to Vegyterv's future ability to gain work.
- Further adjustment to the organisation will be required if Vegyterv are to provide cost effective and yet specialised capability in the pharmaceutical industry.
- It is essential that Vegyterv take advantage of the training programme developed and expand the knowledge base developed during the study programme.
- There is no doubt that Hungary needs a substantial process engineering contractor capable of handling a broad range of projects not only in the pharmaceutical industry but in other fields and therefore it is essential that the company is given every opportunity to build on the substantial track record that it has already and to put into practice many of the aspects of GMP which were the subject of the project.

## BIBLIOGRAPHY

Federation Internationale des Ingineurs-Conseils - Client/Consultant Model Services Agreement

Joint IMechE/IEE Committee on Model Forms of Conditions of Contract

Institution of Chemical Engineers:
Conditions of Contract for Process Plant
(i) Fixed Lump Sum
(ii) Reimbursable
(iii) Sub-contracts

American Society of Heating, Refrigeration and Air Conditioning Engineers Inc - Guidelines for Commissioning of HVAC Systems

British Standards Institute - BS5295: Part 1: 1989
Environmental Cleanliness in Enclosed Spaces

US Federal Standard - FED-STD-209E
Airborne Particulate Cleanliness Classes in Cleanrooms and Clean Zones

IES Standard - IES-RP-CC-006-84T
Recommended Practice for Testing Clean Rooms

EC

Hungarian - Regulations for Production Hygiene in the Manufacture of Pharmaceuticals

Pharmaceutical Inspection Convention
Guide to Good Manufacturing Practice for Pharmaceutical Products (PIC-GMP)

Guidelines for the Manufacture of Active Pharmaceutical Ingredients

World Health Organisation
Good Practices in the Manufacture and Quality Control of Drugs (WHO No. 226, 1975 Annex 12)

# APPENDIX 1

## PLANTS DESIGNED AND BUILT IN THE TARGET INDUSTRIES

## BETWEEN 1975 - 1992

A PHARMACEUTICAL INDUSTRY

| Plant | Capacity | Investor | Site | Process | Commissioned |
|---|---|---|---|---|---|
| Penicillin | 250 t/yr | Biogal Pharmaceutical Factory | Debrecen | Biogal | 1981 |
| | 50 t/yr | Makinaimport | Tirana (Albania) | Biogal | 1985 |
| Penicillin intermediate plant | | Biogal Pharmaceutical Factory | Debrecen | Biogal | 1986 |
| Cyanidol-3 | 40 t/yr | Biogal-Zyma SA | Debrecen | Zyma SA | 1982 |
| Cyrethindine | 20 t/yr | G Richter Pharmaceutical Factory | Dorog | G Richter | 1982 |
| Medicine Conditioning plants | | G Richter Pharmaceutical Factory | Budapest | G Richter | 1982 |
| tablets | $5x10^9$ pill/yr | | | | |
| syrups | $3x10^6$ bottle/yr | | | | |
| ointments | $3x10^6$ bottle/yr | | | | |
| Pyretinroid confectioning plant | | Chinion Pharmaceutical Factory | Bp Nagyteteny | Chinion | 1987 |
| Pharmacology | | G Richter Pharmaceutical Factory | Budapest | G Richter | 1982 |
| Blood plasm fractioning plant | 12.000 lit | Human Oltoanyagtermelo es Kutato Intezet | Godollo | Vegyterv-Human | 1985 |
| Semi-synthetical antibiotics plant | | Chinion Pharmaceutical Factory | Budapest | Chinion | 1987 |

| Plant | Capacity | Investor | Site | Process | Commissioned |
|---|---|---|---|---|---|
| Erythromicin | | Biogal Pharmaceutical Factory | Debrecen | Biogal | 1988 |
| Fermentation plant | | Phylaxia VEGYEPSZER | Budapest | Phylaxia VEGY-TERV | 1991 |
| Tablet making plant | 2000000 tablets/year | Alkaloida | Tiszavasvari | VEGY-TERV | Under way |
| Synthetic plant | | Biogal | Debrecen | Biogal | 1989 |
| Adbesive - plaster plant | | Biogal | Debrecen | Biogal | 1989 |
| Hydrogenate plant | | Chinion | Budapest | Chinion | 1989 |
| Ipriflavon plant | | Chinion | Budapest | Chinion | 1989 |
| "Half" - synthetical plant | | Chinion | Budapest | Chinion | 1989 |
| KIK II | | Chinion | Budapest | Chinion | 1989 |
| Vaccine plant | | Human Oltoanyagtermelo es Kutato Intezet | Godollo | Human | 1991 |
| Pharmaceutical Waste plant | 20000 t/year | Gyogyszeripari Egetomu Kozos Vallalat | Dorog | W & E | 1990 |

B ORGANIC SYNTHESES. INTERMEDIATES

| Plant | Capacity | Investor | Site | Process | Commissioned |
|---|---|---|---|---|---|
| Sorbital | 5000 t/year | Vitamen-es Gyogyszergyar | Joskar-Ola (SU) | Peti Nitro-genmivek | 1978 |
| Fine Chemical Plant | 290 t/year | Reanal | Budapest | Reanal | 1984 |
| Diagnostic Chemical Plant | 20 $m^3$/year 3 t/year | Reanal | Budapest | Reneal | 1987 |

C PESTICIDES

| Plant | Capacity | Investor | Site | Process | Commissioned |
|---|---|---|---|---|---|
| Dithocarbam-ates | 1,244 t/year | Peremartoni Vegyipari Vallalat | Peremarton | NEVIKI-PVV | 1980 |
| Pesticide | | Agrokemia Szov | Sellye | Vegyterv | 1980 |
| Pesticide manufacturing and forming plant | | Peremartoni Vegyipari Vallalat | Peremarton | PPV-NEVIKI | 1981 |
| Pesticide manufacturing and forming plant complete | 1 t/shift | Chemiekombinat Bitterfold | Bitterfield (GDR) | CKB Bitterfield - Vegyterv | |
| Pesticide Plant | 1,360 t/year Difenamide | G Richter Pharmaceutical Factory | Dorog | G Richter | 1981 |

| Plant | Capacity | Investor | Site | Process | Commissioned |
|---|---|---|---|---|---|
| Alirox weed killer | 8.100 t/year | Eszakmagyarorszagi Vegyimuvek | Sajobabony | EMV | 1985 |
| Fundazol 50 WP | 2.600 t/year | Chinion Pharmaceutical Factory | Budapest | Chinion | 1985 |
| Powder forming plant | 500 kg/h | G Richter Pharmaceutical Factory | Dorog | Micropul | 1985 |
| Insecticide plant, complete | | VEB Fettchemie Karl-Marx-Stadt | Mohsdorf (GDR) | VEB Fettchemie | * |

* Date of establishment unknown

D COMESTICS INDUSTRY

| Plant | Capacity | Investor | Site | Process | Commissioned |
|---|---|---|---|---|---|
| Miscellaneous cosmetics plant | | Caola | Budapest | KHV-Vegyterv | 1975 |
| Aerosol plant<br>Active agent<br>LPG | <br>2.000 t/year<br>4-500 t/year | Caola | Budapest | GFR-Caola | 1983 |

E OTHER PLANT

| Plant | Capacity | Investor | Site | Process | Commissioned |
|---|---|---|---|---|---|
| Drum filling station | 8-position stn 1300 drum/shift | AFOR | Budapest | Vegyterv | 1978 |
| Industrial waste water treatment plant | 7,500 $m^3$/year | Mezogep-Kecskemet | Kecskemet | Vegyterv | 1983 |
| Industrial waster water treatment plant | 325 $m^3$/year | Tatabanyai Szenbanyak Fogep | Tolcsva | Fogep | 1983 |
| TABTA waste water treatment plant | 550 $m^3$/day | TIFO | Nyirbogdany | Vegyterv | 1983 |
| Corn sugar plant and alcohol distillery | 200 t/day | Szabadegyhazi Szeszipan Vallalat Aszari Kemenyitogyara | Szabadegyhazi | Door-Oliver DDS-Kroyer Vogelbusch | 1981 |
| Chikory Bakehouse | 17 t/h 30000 t/annual campaign | Gyori Keksz es Ostyagyar | | Barth-Vegyterv | 1983 |
| Waste incinerator at Dorog | 25000 t/year | G Richter Pharmaceutical Factory | Dorog | W + E | 1989 |
| Complete demineralization plant | 120 $m^3$/h water | Raba | Gyor | Vegyterv | 1980 |
| Air-conditioning refrigerator plant | 37.7 GJ/h | Magyar Viscosagyar | Nyergesujfalu | Vegyterv | 1976 |

| Plant | Capacity | Investor | Site | Process | Commissioned |
|---|---|---|---|---|---|
| Air conditioning centre. with absorption-type cooling agregate | 2 x2267 kW | G Richter Pharmaceutical Factory | Budapest | Vegyterv | 1980 |

# APPENDIX 2

## Equipment, Systems and Procedures to be Validated

| Equip. # | Description | IQ | OQ | PQ | Computerized |
|---|---|---|---|---|---|
| aaa-aaa | Vial Washer | X | X | X | X |
| bbb-bbb | Depyrogenation Tunnel | X | X | X | X |
| ccc-ccc | Accumulation Table | X | X | | X |
| ddd-ddd | Vial Filler/Stoppering | X | X | X | X |
| eee-eee | Vial Capper | X | X | X | X |
| fff-fff | Vial Inspection | X | X | X | X |
| ggg-ggg | Ink Jet Printer / Tray Loader | X | X | X | X |
| hhh-hhh | Labeler/Label Verification | X | X | X | X |
| iii-iii | Ball Bancer | X | X | | X |
| jjj-jjj | Vial Accumulator | X | X | | X |
| kkk-kkk | Tray Maker | X | X | | X |
| lll-lll | Overwrapper | X | X | | X |
| mmm-mmm | Palletizer | X | X | | X |
| nnn-nnn | Case Packer | X | X | | X |
| ooo-ooo | Stopper Processor | X | X | X | X |
| ppp-ppp | Steam Sterilizer | X | X | X | X |
| qqq-qqq | Parts Cabinet Washer | X | X | X | X |
| | Ultrasonic Parts Washer | X | X | X | X |
| | Autoclave Bag Sealers | X | X | X | |
| | Calibration Equipment | X | X | | |
| | Filter Integrity Apparatus | X | X | | X |
| | Sanitization Equipment | X | X | | |
| | HEPA Vacuum Cleaners | X | X | | |
| rrr-rrr | Clean Steam System | X | X | X | X |
| sss-sss | WFI System | X | X | X | X |
| ttt-ttt | Deionized Water System | X | X | X | |

IRC Consultants

# INSTALLATION QUALIFICATION

Client: Date: 30/6/93

Project: IQ No: Revision: 00

Equipment: Sterile Fill Vessels Item No: R103/1,2,3,4

Inventory No: Page 2 of 3

| Attributes | Comments | | | Acceptance |
|---|---|---|---|---|
| DESIGN & CONSTRUCTION | R103/1 | R103/2 | R103/3 | R103/4 |
| Construction materials are: | | | | |
| - 316L and 316 stainless steel | ..... | ..... | ..... | ..... |
| - glass sightglass | ..... | ..... | ..... | ..... |
| - PTFE or silicone gaskets | ..... | ..... | ..... | ..... |
| | R103/1 | R103/2 | R103/3 | R103/4 |
| Check internal and external surfaces can be wiped down and that there are no crevices | ..... | ..... | ..... | ..... |
| | R103/1 | R103/2 | R103/3 | R103/4 |
| Check unit is fully constructed and assembled as per drawings/parts list | ..... | ..... | ..... | ..... |
| Vessel Drg No | ..... | ..... | ..... | ..... |
| Parts List | ..... | ..... | ..... | ..... |
| | R103/1 | R103/2 | R103/3 | R103/4 |
| Check that all nozzles have seals fitted | ..... | ..... | ..... | ..... |

Approvals: Production: Engineering: QA:

CLIENT: PROJECT: REV: APPROVED

# CONSTRUCTION VALIDATION PROGRAMME
# VERIFICATION OF SLOPE IN PIPE-RUNS

PIPEWORK SYSTEM:

| PIPE SECTION MEASURED | RECORDED SLOPE | MEASUREMENT METHOD | PERFORMED BY DATE |
|---|---|---|---|
| | | | |
| | | | |
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| | | | |

SIGNED:..... DATE:..... SIGNED:..... DATE:.....

Contractor Consultant

GRC Consultants

# COMMISSIONING LOG - STEAM STERILISATION

Client: .....  Sheet ... of ...

Project: .....  Project No: .....

Equipment/pipework steam sterilised:

.....

.....

Sketch of system showing temperature measurement points (or attach a marked up flowsheet)

RESULTS

| Temp measurement point | Temp °C | Time | Temp °C | Time |
|---|---|---|---|---|
| ..... | ..... | ..... | ..... | ..... |
| ..... | ..... | ..... | ..... | ..... |
| ..... | ..... | ..... | ..... | ..... |
| ..... | ..... | ..... | ..... | ..... |
| ..... | ..... | ..... | ..... | ..... |
| ..... | ..... | ..... | ..... | ..... |
| ..... | ..... | ..... | ..... | ..... |
| ..... | ..... | ..... | ..... | ..... |

Remarks: .....

.....

Commissioning performed by .....  Company .....  Date .....

Commissioning witnessed by .....  GRC Consultants  Date .....

GRC Consultants

# OPERATIONAL QUALIFICATION

Client: Date: 30/6/93

Project: OQ No: Revision: 00

Equipment: Sterile Fill Vessels Item No: R103/1,2,3,4

Inventory No: 

---

ACTIVITY:

Vessel can withstand internal pressure without leaking

REQUIREMENT:

To hold 0.15 bar g internal pressure (for filling) without leaking

TEST METHOD:

Hydrostatically pressure test each vessel with all the associated valves fitted at 1.0 bar g for at least 1 hour.

ACCEPTANCE CRITERIA:
Check that the pressure is held in the vessel and that there are no leaks.

RESULTS:

| | | | |
|---|---|---|---|
| R103/1 | Pressure at start | ..... | time ..... |
| | Pressure at finish | ..... | time ..... |
| R103/2 | Pressure at start | ..... | time ..... |
| | Pressure at finish | ..... | time ..... |
| R103/3 | Pressure at start | ..... | time ..... |
| | Pressure at finish | ..... | time ..... |
| R103/4 | Pressure at start | ..... | time ..... |
| | Pressure at finish | ..... | time ..... |

COMMENTS

Tested by: Date:

---

Approvals: Production: Engineering: QA: B Smith

GRC Consultants

# OPERATIONAL QUALIFICATION

Client: Date: 30/6/93

Project: OQ No: Revision: 00

Equipment: Sterile Fill Vessels Item No: R103/1.2.1.4

Inventory No: Page 1 of 7

---

Serial/Model No: Location: Mobile

IQ complete: Yes/No IQ ref:

Critical Operating Features:

Confirmation that the vessels are capable of functioning as designed is required. The critical operating features are:

- Standard Operating Procedures have been identified
- vessel can withstand internal pressure without leaking
- vessel is self draining with no pockets
- function of the bursting disc alarm
- vessel bottom skirt fits onto the DPTE port on the Filling Isolator and maintains the integrity of the isolator when the DPTE lid is removed for filling

Qualification Approved: Date:

Additional Requirements

---

Approvals: Production: Engineering: QA:

# APPENDIX 3

# APPENDIX 4

# STAFF NUMBERS

## APPENDIX 4

## STAFF NUMBERS

| | 1990 | 1992 |
|---|---|---|
| Full time | 583 | 240 |
| Part time | 27 | 7 |
| Total | 610 | 247 |
| | | |
| Engineers and technicians | 424 | 154 |
| Commercial, financial, etc. staff | 58 | 25 |
| Office workers, secretaries, etc | 49 | 22 |
| Others * | 79 | 46 |
| | 610 | 247 |

(* Computer service staff, legal department, archives, library, printing office, door keepers, maintenance staff, drivers telephone exchange, canteen staff)

Breakdown of technical staff

| | | |
|---|---|---|
| Mechanical engineers and technicians | 184 | 80 |
| Chemical engineers and technicians | 42 | 15 |
| Civil engineers and technicians | 100 | 28 |
| Electrical engineers and technicians | 54 | 13 |
| Other engineers and technicians | 44 | 28 |
| | 424 | 154 |

Breakdown by Departments

| | | |
|---|---|---|
| Inorganic Process Department | 52 | |
| Petrochemical and Organic Process Department | 83 | |
| Process Department | | 14 |
| Electric Department | 39 | |
| Mechanical Department | 57 | 50 |
| Civil Engineering Department | 90 | 44 |
| Miskolc Branch Office | 69 | |
| Other | 220 | 139 |
| | 610 | 247 |

# APPENDIX 5

# ANNUAL TURNOVER

# INCOME

Value HUF 1.000.000

| | 1987 | 1988 | 1989 | 1990 | 1991 | 1992 |
|---|---|---|---|---|---|---|
| Total sales income | 547.6 | 525.5 | 597.7 | 544.0 | 360.1 | 340.0 |
| Sub-Contractors | 68.1 | 139.6 | 219.4 | 193.0 | 85.5 | 65.0 |
| Total sales income of own | 479.5 | 385.9 | 378.3 | 351.0 | 274.4 | 275.0 |
| From this: | | | | | | |
| - planning, contracting, research, studies | 421.1 | 321.9 | 275.7 | 278.1 | 115.9 | 152.0 |
| - rent | - | 11.8 | 22.0 | 42.0 | 0.1 | 2.0 |
| - sundry income | 58.4 | 52.2 | 80.6 | 30.9 | 158.7 (1) | 121.0 (1) |

(1) Rent income from building included in sundry income

## COSTS

Value: HUF 1.000.000

| | 1987 | 1988 | 1989 | 1990 | 1991 |
|---|---|---|---|---|---|
| Wages costs | | | 144.9 | 123.0 | 88.5 |
| Social insurance costs | | | 62.1 | 52.7 | 40.2 |
| Costs of material | | | 34.8 | 25.6 | 18.2 |
| Depreciation charge | | | 22.3 | 19.0 | 17.0 |
| Other costs of material | | | 45.8 | 34.5 | 46.0 |
| Other wages costs | | | 15.8 | 13.0 | 17.4 |
| Other services | | | 21.0 | 13.7 | 16.0 |
| Bank costs | | | 15.2 | 11.0 | 4.7 |
| Other costs | | | 21.4 | 16.5 | 1.0 |
| Total costs | | | 383.3 | 309.0 | 249.2 |

## PROFIT AND LOSSS ACCOUNT

Value: HUF 1.000.000

| | 1987 | 1988 | 1989 | 1990 | 1991 |
|---|---|---|---|---|---|
| Total sales income of own | | | 378.3 | 351.0 | 274.7 |
| Work in progress | | | - 5.2 | 0 | - 0.4 |
| Total costs | | | 383.3 | 309.0 | 281.5 |
| Others | | | - | 9.0 | - |
| Profit | | | 0.2 | 33.0 | - 7.2 |