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PHARMACEUTICAL INDUSTRY ADVISER

SI/AFG/82/803

AFGHANISTAN

Terminal report

Prepared for the Government of Afghanistan
by the United Nations Industrial Development Organization,
acting as executing agency for the United Nations Development Programme

Based on the work of Mr. B. E. Rao,
industrial pharmacist

United Nations Industrial Development Organization
Vienna

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Explanatory notes

References to dollars ($) are to United States dollars.

Besides the common abbreviations, symbols and terms, the following have been used in this report:

APFC	Aliabad Parenteral Fluid Centre
API	Avicenna Pharmaceutical Institute
CQCL	Central Quality Control Laboratory
EAR	estimated annual requirements
GMP	good manufacturing practices
HVP	high-volume parenterals
LVP	low-volume parenterals
ORS	oral rehydration salts
PFC	Parenteral Fluid Centre

ABSTRACT

In 1979 a feasibility study was prepared under the project SI/AFG/77/804, recommending the establishment of a pharmaceutical manufacturing centre in the public sector, with an estimated investment of about 10 million dollars. These recommendations have not been realized so far, mainly due to financial constraints, while the country's requirements of pharmaceuticals are growing steadily.

The immediate objectives of the present project "Pharmaceutical industry adviser" (SI/AFG/82/803) were (a) to update the feasibility study on the establishment of a new pharmaceutical plant and to formulate a related strategy; (b) to advise on measures for the rehabilitation and modernization of existing pharmaceutical facilities; and (c) to promote better utilization of the existing units.

The expert who was assigned to the project for a period of six months, starting on 27 December 1982, found that the existing facilities are suffering from numerous operational and productivity problems which, however, could be overcome with properly directed efforts, modest investments, and within a relatively short time.

His recommendations include the following: (a) modification or relocation of existing production facilities with the objective of re-establishing them on modern concepts with the addition of selected key equipment to improve the operation and to increase the output; (b) establishment of a facility responsible for the development of new dosage forms; (c) training of the personnel through regular on-the-job training and through fellowships; (d) preparation of an operations manual and its introduction into the operations system of all facilities; (e) regularization of the materials management with the help of a manual; (f) careful scrutinization of the existing drug-supply and distribution system and removal of identified weaknesses; (g) formulation and implementation of a comprehensive drug-control legislation.

The expert prepared detailed layouts for the modification and relocation of some units and identified six follow-up projects for the implementation of his recommendations.

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INTRODUCTION

The establishment of an efficient and effective health-delivery system requires the strengthening of related facilities supporting the health infrastructure. One of the key inputs in this direction is the creation and progressive improvement of the manufacturing and distribution systems for pharmaceuticals. The pharmaceutical industry also contributes towards the achievement of long-term health care objectives, such as improved nutrition and planned parenthood. Unfortunately, this important aspect often does not find rightful priority in developing countries, resulting in a major handicap to health delivery programmes.

The pharmaceutical industry being highly research-oriented has made rapid progress during the past 40 years and as a consequence innumerable new remedies, preventive as well as curative, have been placed at the disposal of mankind, and many processes have been evolved for economic production of otherwise expensive drugs with simultaneous availability of more refined and innovated ways of drug-delivery and administration. On the other hand, production technologies, packagings and product presentations have been constantly improving.

With the passage of time the statutory surveillance and regulatory controls on the pharmaceutical industry have been considerably strengthened in the developed economies. In developing economies, although the awareness to such controls is well realized, the degree of implementation of legislative measures is generally insufficient and varies from country to country.

In Afghanistan, the Government is following a socialized health policy and keeping in line with this approach has enforced a drug-control administration and also introduced the generic act. Although it appears that the generic act has been effectively enforced, the drug-control administration requires further reinforcement to achieve effectiveness.

In addition to some privately owned undertakings, facilities for the manufacture of pharmaceutical dosage forms, parenteral fluids and vaccines and sera have been functioning in the public sector of the economy for a considerable length of time. Inspite of all these efforts, however, the drug supply from the national sources falls extremely short of the country's requirements resulting in dependence on imports.

The package of foreign exchange consumed to import pharmaceuticals is ever rising and has reached $26 million in 1983 as against $4.3 million in the year 1973. Because of such heavy drains on the hard-earned and scarce foreign exchange, the Government is very keen to increase the local production by rehabilitation of the existing facilities and also to establish additional facilities in order to attain self-sufficiency in this important sub-sector of health care. The approach is expected to result not only in foreign exchange saving but also in a reduction of the cost of the products, the development of national capabilities and encouragement for emergence of allied industries capable of producing a variety of auxiliary raw materials and packaging supplies.

A. Project background

A feasibility study, recommending the establishment of a pharmaceutical manufacturing centre in the public sector, with an estimated investment of about 10 million dollars, was prepared in 1979 under the project SI/AFG/77/804. The recommendations were primarily aimed at enhancing the local production but

also included provisions for synthetic manufacture of certain bulk drug (pharmaceutical chemicals) and for products derived from naturally occurring medicinal plants through extraction and purification. Inspite of being well received by the Government, the recommendations have not been realized so far due to financial constraints, and even today it seems that any progress in this regard may not be possible within a foreseeable future.

During the intervening period neither any other private establishment has been set up nor has the productivity of the existing units improved, although the requirements of the country are growing steadily. On the contrary, the capacity utilization, both in the private and public sectors, has declined due to disturbed logistics, shortage of raw materials and interruptions in power supply.

Under the prevalent economic uncertainties, therefore, the rehabilitation of the existing facilities deserves high priority with less emphasis on the job of updating the feasibility study.

The existing facilities are suffering from numerous operational and productivity problems, often encountered in developing economies, although measures can be adopted to overcome them. With the facilities in Afghanistan it soon became clear that whith properly directed efforts and modest investments the required results can be obtained within a relatively short period, leading to a significant improvement both in productivity and quality. Accordingly the expert who was assigned to the project for six months, starting on 27 December 1982, concentrated on the following areas:

(a) Updating certain aspects of the feasibility study for future reference;

(b) Upgrading and expansion of the Avicenna Pharmaceutical Institute;

(c) Rehabilitation of the Aliabad Parenteral Fluids Centre;

(d) Establishment of a Product Development Laboratory;

(e) Establishment of a materials management system;

(f) Formulation of a personnel training programme;

(g) Establishment of guidelines for an operating procedures manual.

In view of the nature of the inputs, the first four of the above identified areas which covered a major part of the activities and required particular attention are described in independent sections of the report, with to-the-point analyses of the observations and specific recommendations. The last three areas are discussed briefly at the end of the main text because detailed work on these issues was beyond the scope of the present mission. Concerning the materials management system, a specimen manual is attached as annex I.

The product volumes computed under "estimated annual requirements" (EAR) in table 3 have been used as base throughout the present report in ascertaining and developing the capacity potentials during rehabilitation of the existing manufacturing facilities.

B. Development objectives

The project was to contribute to the following development objectives:

(a) To improve the country's social health sector;

(b) To create self-sufficiency in the manufacture of essential ready-made drugs commonly used in Afghanistan;

(c) To promote the development of local manpower and technical skills.

With the aim of meeting the immediate objectives, the work plan of the present mission was divided into seven activities as outlined above under the section "project background", and further broken down into subactivities which are detailed in the respective chapters of the report. The findings and observations permit to conclude that a rehabilitation of the existing facilities is viable and technically practicable as it will considerably improve the productivity and local technical capabilities. This factor in turn will be beneficial for the execution of new undertakings and the fulfilment of the development objectives.

In formulating the recommendations, a major consideration has been to evolve strategies to improve and boost up the productivity of the existing units with minimal financial investment and within the limits of capabilities available in the country.

The work of updating the feasibility studies remained confined to a revision of the plant capacities, measures to reduce the overall project cost, and considerations to stagger the investment over a longer period of time thus further reducing the initial investment.

SUMMARY OF RECOMMENDATIONS

1. The existing production facilities should be modified or relocated with the objective of re-establishing them on modern concepts with addition of selected key equipment to improve the operation and to increase the output.

2. A facility should be established which would be responsible for the development of new dosage forms essential for the national health service.

3. The personnel should be provided training in various areas of operation through regular and systematic on-the-job training and through fellowships.

4. A plant operations manual should be prepared and introduced into the operational system of all facilities.

5. The material management should be regularized with the help of the manual attached to this report as annex I.

6. The existing drug-supply and distribution system should be carefully scrutinized and identified weaknesses removed.

7. A comprehensive drug-control legislation should be formulated and implemented, incorporating rules for drugs registration, requirements for packaging, labelling, import manufacture, storage, distribution, sale and recall. It should also include authorities like inspection and quality control and their legal status.

These recommendations require considerable expert inputs for their execution, particularly in view of the complexity of the undertakings and the degree of technological capabilities and insight required. The execution, therefore, should be programmed in well-identified individual projects and activities, co-ordinated to achieve a successful realization of the objectives. Support from international sources in terms of technical expertise and training and backed by sufficient finance would be necessary to expedite the implementation.

It is not possible at this stage to determine the financial investment required for the realization of the objectives, firstly because the cost estimates for civil restructuring cannot be determined and secondly because the full details of other inputs are not known. As a reasonable rough estimate an amount of little over one million dollars, about 50 per cent of which should be in foreign hard currency, will be required for the rehabilitation of the existing facilities, the establishment of a product-development laboratory and the relocation of central quality control, but excluding the cost of international experts and training. A further increase in productivity will need additional funding of about 300,000 dollars for equipment.

The expert proposes the projects listed in table 1. for which approximate costs of major inputs have been identified as a guide for the preparation of plans to implement the recommendations.

Table 1. Estimated cost for the implementation of six projects

Project Number	Brief project title	Inputs			
		Experts (m/m)	Training (m/m)	Civil work (dollars)	Equipment (dollars)
1.	Rehabilitation of the Avicenna Pharmaceutical Institute	12	23	240 000	260 000
2.	Relocation and rehabilitation of the Aliabad Parenteral Fluid Centre (at the Vaccine Centre)	12	14	200 000	250 000
3.	Relocation of the Central Quality Control Laboratory (at the Vaccine Centre)	6	3	25 000	25 000
4.	Establishment of a products development laboratory (at API)	6	6	25 000	30 000
5.	Development of a drugs procurement and distribution system	6	3	-	-
6.	Development of a modern drug-control administration system with supporting laws, procedures and rules (Ministry of Health)	6	3	-	-

a/ About 80 per cent of the amount allocated for buildings will be in local currency while that of equipment will be almost entirely in foreign exchange.

I. FINDINGS AND CONCLUSIONS

A. Findings

The work carried out in pursuance of the project activities enables the expert to make the following general observations:

(a) The country is facing an acute shortage of essential drugs which is seriously affecting the national health-delivery programme;

(b) Prospects for the establishment of a new manufacturing facility in the near future are bleak in view of the high investment involved;

(c) The existing production facilities are unable to perform efficiently due to numerous in-built and operational weaknesses;

(d) There is an obvious dearth of technological capabilities and developmental atmosphere.

In addition, the following observations have also been made which, although they do not fit within the framework of the present mission, have all the same a strong bearing on drug-supply systems:

(a) The drug-supply management and distribution system is not properly organized;

(b) Structure as well as implementation of drug-control administration are not effective.

B. Conclusions

Due to the varied nature of the activities, the findings have been detailed in the separate chapters, while a summary of the conclusions is incorporated here for the sake of convenience:

1. The Avicenna Pharmaceutical Institute (API) can be rehabilitated in order to increase its productivity by uncorporating the desired operational concepts to meet the requirements of good manufacturing practices (GMP).

2. The Aliabad Parenteral Fluid Centre (APFC) can be relocated in an improved location to be established on the first floor of the Vaccine Centre with adequate facilities, a modernized layout and an enlarged products range.

3. The New Products Development Laboratory can be established wth the required equipment and facilities in the spare rooms at API.

4. The materials management system can be improved significantly at all existing facilities by the establishment of procedures and appropriate training of the staff.

5. The performance of the national personnel can be improved through well-designed on-the-job training and through fellowships acquainting the personnel with the working techniques of other established institutions.

6. The introduction of a plant operations manual can be a very useful means to develop discipline and systematic approaches, and to increase quality and productivity of the operations.

Adequate delivery of the above inputs is bound to effect the quality and output of the facilities, at the same time injecting the discipline and practices which are the backbone of a modern pharmaceutical plant.

II. MATERIALS MANAGEMENT

Raw materials constitute by far the largest cost component of pharmaceutical dosage forms and are the major contributor to product quality and integrity. Quality and integrity is practically impossible to be evaluated fully in the final product and therefore it must be built into its production. In order to ensure that the product meets highest quality standards, it is only logical that the components going into the pharmaceutical dosage forms must conform to the established standards individually, and that they should be identified, stored and handled in such a way that they retain the ascertained quality, identity and purity.

Additionally, in order to fulfil the obligation of safeguarding the health and well-being of the consumer and to meet the regulatory requirements on one side, and to avoid operational losses due to wastages, spoilage deterioration etc. on the other, it is imperative to develop a scientific, efficient and centralized management system for raw materials.

In this regard there is much to be desired as far as the Afghanistan pharmaceutical industries are concerned. The copy of a manual, which is being used in a well-established modern pharmaceutical plant, is included as annex I. It should be of great help in the development of a materials management system for all facilities of the pharmaceutical sector. In fact, this manual can be adopted in its existing form.

III. TRAINING OF PERSONNEL

The competence and skill of the personnel, both at managerial and operational levels, greatly contribute towards the performance and success of an organization. No matter how well the establishment has been designed, equipped and provided with procedural support, it may not operate efficiently unless the personnel have not been well groomed for their inaividual responsibilities and performance.

There is an urgent need to strengthen the capabilities of personnel and to initiate a rigorous programme for manpower development in all aspects of the pharmaceutical sector in Afghanistan. The programme designed for this purpose should incorporate both the components of training through fellowships at other established locations and courses designed for on-the-job training. Specific recommendations in this regard have been identified in table 2. The training needs have been classified in six columns which include drug control as well as commercial and distribution aspects in addition to the development of industrial capabilities, which are part and parcel of the drug delivery system. On-the-job training should be conducted in a dual way: on-the-spot briefing and instructions are supported by formal lectures on specific subjects. The schedule tabulated for this purpose includes 32 topics which cover the operational functions of a pharmaceutical plant.

The fellowship programme for managers and supervisors should be aimed at advancement of knowledge, improvement of systems and procedures, adoption of new techniques and technologies, and better management.

It is strongly recommended that all efforts be made to find resources or outside assistance to materialize the training programme which should be followed by periodic orientation and refresher courses in order to keep the technological knowlege updated.

A. On-the-job training for operational staff

On-the-job training should be conducted by managerial and senior supervisory staff. It should cover the following lectures of one hour duration, with graphical illustrations and films wherever practicable and possible.

General (all facilities)

1. Health and hygiene of the personnel.
2. Special requirements in the pharmaceutical industry.
3. Good manufacturing practices.
4. Principles of microbiology and its relation with air, water, dairy and sewage control.
5. Microbiological contamination in the pharmaceutical industry.
6. Product identification and handling of packaging materials (labels etc.).
7. Systems and system compliance and their importance.
8. Documentation and records.

9. Co-ordination with materials management, quality control and repair and maintenance.

10. Maintenance of machinery, services, installation and building.

11. Safety and housekeeping.

Production

(a) Non-parenterals (for API)

1. Manufacture of tablets.

2. Manufacture of capsules.

3. Manufacture of powders.

4. Manufacture of oral liquids.

5. Manufacture of semi-solids (ointments, creams, gells).

6. Subdivision, sealing, labelling and packaging.

(b) Parenterals (for PFC)

7. Aseptic techniques and parenteral therapy.

8. Environments and personal hygiene.

9. Origin, source and control of particulate matter.

10. Control of airborn micro-organisms and related practices.

11. Daily and weekly maintenance schedules in a sterile area.

12. Production procedures, techniques and controls, part I.

13. Production procedures, techniques and controls, part II.

14. Quality specifications for water for injection.

15. Containers and closures.

16. Washing and maintenance of equipment in sterile air.

17. Product formulation and materials handling.

18. Sterile filtration, membrane filter and aseptic filling techniques.

19. Sterilization principles and techniques (dry heat, moist heat (autoclave) filtration and irradiation).

20. Visual inspection procedure and packaging of finished products.

21. Working of air-handling unit and laminar flow systems and their maintenance.

B. Fellowships for managers and supervisory staff

The proposed fellowship programme for managers and supervisory staff is outlined in table 2.

Table 2. Fellowships for managers and supervisory staff

Area of training	Months	Number of fellowships					
		Drug control	CQCL	Pro-cure-ment	API	PFC	Product develop-ment
Drug control administration	3	1	-	-	-	-	-
Quality control administration	3	-	1	-	-	-	-
Drug procurement and distribution	3	-	-	1	-	-	-
Manufacturing:							
(a) Plant management	4	-	-		1	1	-
(b) Materials management	2	-	-	-	1	-	-
(c) Tablets, capsules, powders	3	-	-	-	1	-	-
(d) Oral liquids, ointments, creams	2	-	-	-	1	-	-
(e) Parenteral fluids	2	-	-	-	-	1	-
(f) Sterile dry fills	3	-	-	-	-	1	-
(g) Packaging	2	-	-	-	1	1	-
Quality control:							
(a) Management	2	-	-	-	1	-	-
(b) Analytical techniques	3	-	-	-	1	-	-
Products development	3	-	-	-	-	-	1
Engineering and maintenance:							
(a) Management	2	-	-	-	1	-	-
(b) Preventive maintenance	3	-	-	-	1	1	-
(c) Instruments maintenance	3	-	-	-	-	-	1

The total number of fellowships is 19, and the total man-months involved is 52.

IV. UPDATING OF THE FEASIBILITY STUDY

A. Background

As explained before, only a limited extent of work was devoted to the updating of the feasibility study. The only area where the updating was considered beneficial was the computation of the production capacities in accordance with the country's needs. In doing so it was also considered desirable to include parenteral fluids, which, although they are not scheduled for the new facility, are part of the national requirement. Another reasons for their inclusion was the fact that the present project is more directed towards the rehabilitation of existing facilities, one of which is specifically designed for parenteral fluids.

The updating of the feasibility study was oriented towards factors which would permit a reduction in initial investment and as a consequence enhance the prospects of realization of the project.

B. Estimated annual requirements (EAR)

In order to estimate the annual requirements of pharmaceuticals, the quantities considered at the time of the preparation of the feasibility study for a new plant have been updated and, in doing so, the requirements of oral liquids and ointments have been lowered, while three product groups belonging to the parenteral range have been included (see table 3). It is expected that these data, which include all major product groups, provided that they are kept up-to-date through periodical revisions, will constitute a useful reference for the planning of rehabilitation and future expansion programmes in the pharmaceutical industry subsector.

Since the establishment of a new plant within the foreseeable future is not certain, these requirement estimates have also been used as a reference during the work towards rehabilitation and upgrading of the existing facilities. Once the existing facilities are modernized and attain their optimal possible productivity, the capacities of the new plant could be more realistically determined.

C. Equipment

The equipment for the new plant has also been reviewed, bearing in mind that it could be accommodated at API and, accordingly, the selection of the size and type of equipment and its performance criteria is based on the units needed according to the EAR and considers the units already available at API. The additional equipment would be procured only to the extent that it could be accommodated at API as a consequence of restructuring and modernization.

D. Process know-how

As far as the product range to be manufactured in Afghanistan is concerned, it is apparent that the process know-how can be acquired through seeking technical assistance from UNIDO or through bilateral arrangements with an appropriate international agency or consultant firm. In the meantime the development of capabilities within the country is recommended.

In the event of a collaboration arrangement for the establishment of a new facility, this should be on the basis of a turn-key contract with inputs including plant design and construction, selection, procurement and installation of equipment, validation of the entire plant along with the provision of the necessary process know-how and a pre-agreed schedule of training of nationals, and final handing over.

Table 3. Estimated annual requirements of pharmaceuticals

Product group	Original estimates (millions)	Adjusted estimates (millions)	Difference (millions)
Tablets			
(a) Uncoated	400	400	-
(b) Coated	100	100	-
Capsules			
Hard gelatine	100	100	-
Opal liquids			
(a) 110 ml bottles	[12]	6	[-2]
(b) 250 ml bottles		2.65	
(c) 500 ml bottles		1.35	
Ointments			
(a) Jars	10	5	-5
(b) Tubes			
Parenteral fluids			
(a) High volume Infusions bottles		1.6	1.6
(b) Low volume			
(i) Vials	-	2.5	2.5
(ii) Ampoules	-	2.0	2.0

E. Buildings

The plant design, both with respect to size and layout, appears to be somewhat ambitious especially under the strained economic climate. It is suggested that the drawings should be reviewed with the particular objective of reducing the cost.

The site selected for the new plant on the Karga-Kabul road is suitable from several points of view:

(a) The site has adequate supply of water and power and sewage disposal services and is free of any kind of environmental pollution;

(b) The close vicinity of the Vaccine Centre, and the anticipated erection of the Central Quality Control Laboratory would result in the establishment of a nucleus of pharmaceutical activities with the advantage of sharing several common but expensive services such as quality control, workshop and possibly a centralized supply of steam, and deionized and distilled water. The installation of a stand-by electric generator to circumvent periodic power

failures which seriously affect performance in certain areas of the pharmaceutical industry, would also become economically justifiable.

F. Capital costs

The only reason why the proposed project for a new plant could not take off was the prohibitive amount of investment involved, the major component of which had to be in hard currency. Efforts to trim down the project investment to an acceptable amount are therefore essential if the project should be initiated in the future. Based on these very considerations the following suggestions are offered.

(a) An amount of $800,000 should be removed from the estimates as the commercial plant extraction will now be handled at the Afghan Plant Company already under construction, while the multi-purpose unit for synthesis of basic drugs should be deferred for the time being;

(b) The design and size of the building should be further scrutinized critcally in view of the high cost of construction for each cubic metre of built-up space. It is felt that such critical scrutiny and more up-to-date rates of construction would result in a substantial cut in the cost of buildings. For the time being only one of the two warehouses should be constructed and partitioned in three segments for the three different categories of warehousing;

(c) The requirements of the equipment should also be more judiciously evaluated in terms of optimization of capacities and assessed in relation to actual needs. Due consideration should also be given to the cost versus mode of performance before final selection. Generally, the evaluation should have economic hearing such as:

(i) Multiplicity of items like weighing and transportation equipment should be cut down to optimum use level;

(ii) Wherever possible a mechanical operation (such as filling, capping and labelling) should be converted to manual or semi-automatic principles on slow-speed packing lines;

(iii) The cost of packing machines such as strip packing can be eliminated by first establishing packing specifications for hospital packs, as the products are expected to be channelled mostly through public dispensaries to the patients;

(iv) Procurement of equipment should be scheduled under a periodic plan based upon the projected growth because a new plant usually takes between five to six years to reach full production levels;

(d) The allocations for vehicles and for pre-production expenditures appear to be too high and should be cut down.

V. AVICENNA PHARMACEUTICAL INSTITUTE (API)

A. Background

The manufacturing facilities at API have inherent weaknesses which render it inadequate to introduce the principles of good manufacturing practices (GMP) for the manufacture of pharmaceutical dosage forms. At the same time it is practically impossible to attain the production levels expected from a facility of this size. Some of the weaknesses are outlined below:

(a) Cross contamination and product mix-up possibilities are prevailant as segregation of varied processings is not possible;

(b) The work-flow is disorganized due to the absence of required operational stream-lining;

(c) Product integrity as well as personnel safeguards cannot be ensured in absence of adequate ventilation and dust extraction facilities;

(d) Packing operations are performed in indisciplined manner due to inappropriate layout design and absence of efficiency-inducing systems;

(e) Warehousing is inadequate and decentralized. The management is weak and devoid of organization and accordingly lacks the necessary controls which are key factors in maintaining the material accountability, quality and integrity.

In order to improve upon these weaknesses it is imperative that the facility should undergo considerable modifications. The ground floor of the Vaccine Centre should be refurnished and a substantially larger area should be allocated; otherwise relocation will not offer any advantage.

Adoption of GMP does not necessarily require high expenditure or installation of sophisticated systems. If the fundamental concepts are well understood then a reasonably satisfactory system can be evolved with modest investment. In fact, work planning, methodology, well-designed operational procedures, discipline and motivation of personnel and adoption of preventive measures can produce the desired results equally well.

In developing the proposals for redesigning of the facility, the following concepts in plant design have been taken into consideration:

(a) Allocation of floor space according to the needs of work performed;

(b) Physical arrangement of operational sequence to attain one-directional flow of work;

(c) Segregation of unit processes where cross-contamination or mix-up is likely;

(d) Provision of environmental control and dust extraction as far as possible;

(e) Exclusion of unrelated activities from the care area;

(f) Enlargement and centralization of warehouses.

B. Building

The changes in the internal layout are illustrated in figure I. They do not require any alteration in the main structure but most of the internal partitions will have to be removed. These alterations can be carried out even if the existing walls are load bearing (supporting the roof) firstly because the longitudinal walls are kept intact and secondly the proposed walls could be erected first to retain the necessary support to the roof.

The proposed layout incorporates the following features:

(a) Operations for the production of tablets, capsules and oral rehydration salts (ORS) have been streamlined to attain maximum co-ordination under the circumstances. Similar improvements have also been incorporated in the syrup and ointment operation;

(b) Material and personnel movement channels between the different functions have been arranged in order to improve performance, to ensure adequate segregation and to avoid disturbance;

(c) The packing operation for tablets, capsules and ORS has been centralized on improved principles and accommodated in a larger area. Similarly, syrup and ointment operations have been fully streamlined;

(d) Provision has been made for a quarantine in the tablets/capsules section, for a supervisor in the syrup/ointment section while a segregated area has been provided for capsulation;

(e) The dispensing service for syrup and ointments has been removed from the production care area as it is not a plant function;

(f) Uniforms distribution and change rooms have been centralized near the entrance of the care area;

(g) The warehouse has been enlarged with provision for further extension by covering the middle space (broken line on the drawing).

It is advisable that the work for modernization of API be carried out under the guidance of an expert in pharmaceutical industry who is conversant to such undertakings in developing countries.

C. Production layout

Figures II to IX illustrate individual operations in the proposed building design, and the layout of equipment for the tablets, capsules and oral-liquids sections. They show the sequence of processes and operational segregation, incorporating concepts of ease of operation and streamlining, and are subject to adjustment at the time of equipment installation. A substantial increase in the production capacities has been envisaged, as larger-capacity equipment has been included in the plans.

Figure X is an engineering illustration of a filtered-air supply system and has been included to serve as a guide for the designing of a centralized air-conditioning or clean-air supply system which can be achieved by replacing the blower by an appropriate air-handling equipment and the use of suitable filters. A dust-exhaust or dust-extraction system can also be evolved on similar lines by the installation of a centralized return-air ducting.

Figure I. API - proposal for an improved plant design

Figure II. API, tablets and capsules section - proposed layout for milling, mixing and granulation

Scale 1 : 50 (Equipment not true to scale)

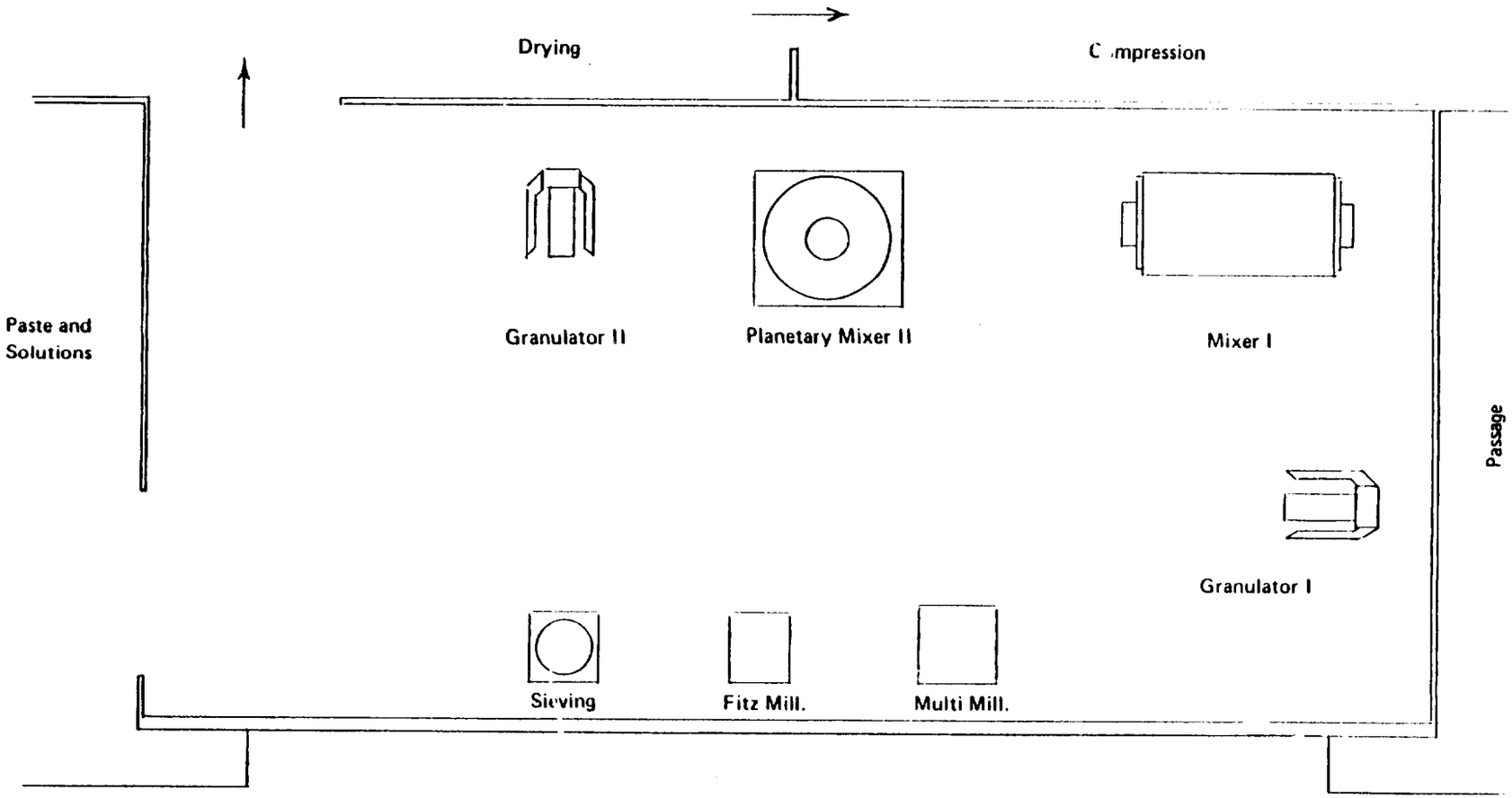


Figure III. API, tablets and capsules section - proposed layout for drying, lubrication and blending

Scale: 1 : 50 (Equipment not true to scale)

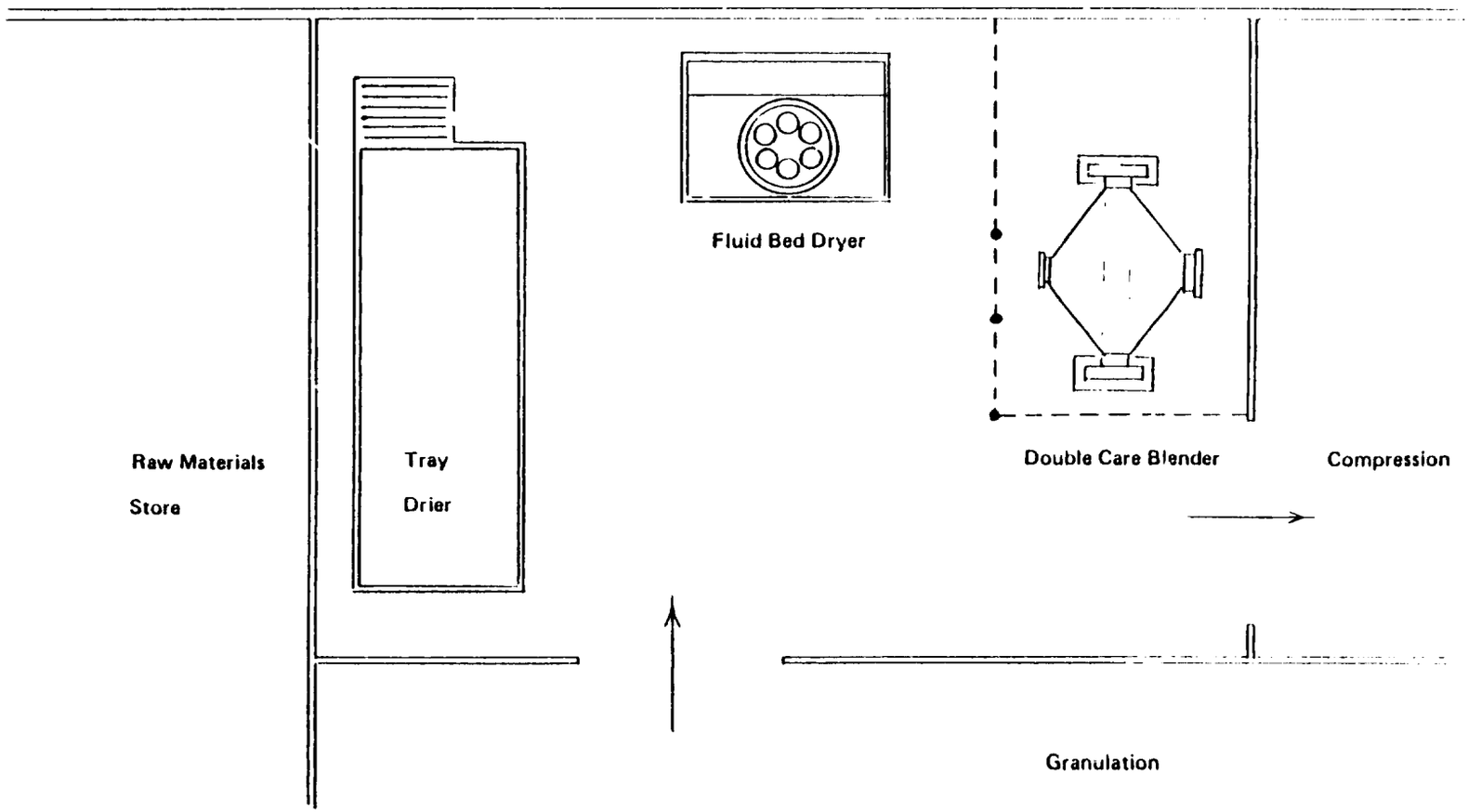


Figure IV. API, tablets and capsules section - proposed layout for compression

Scale: 1 : 50 (Equipment not true to scale)

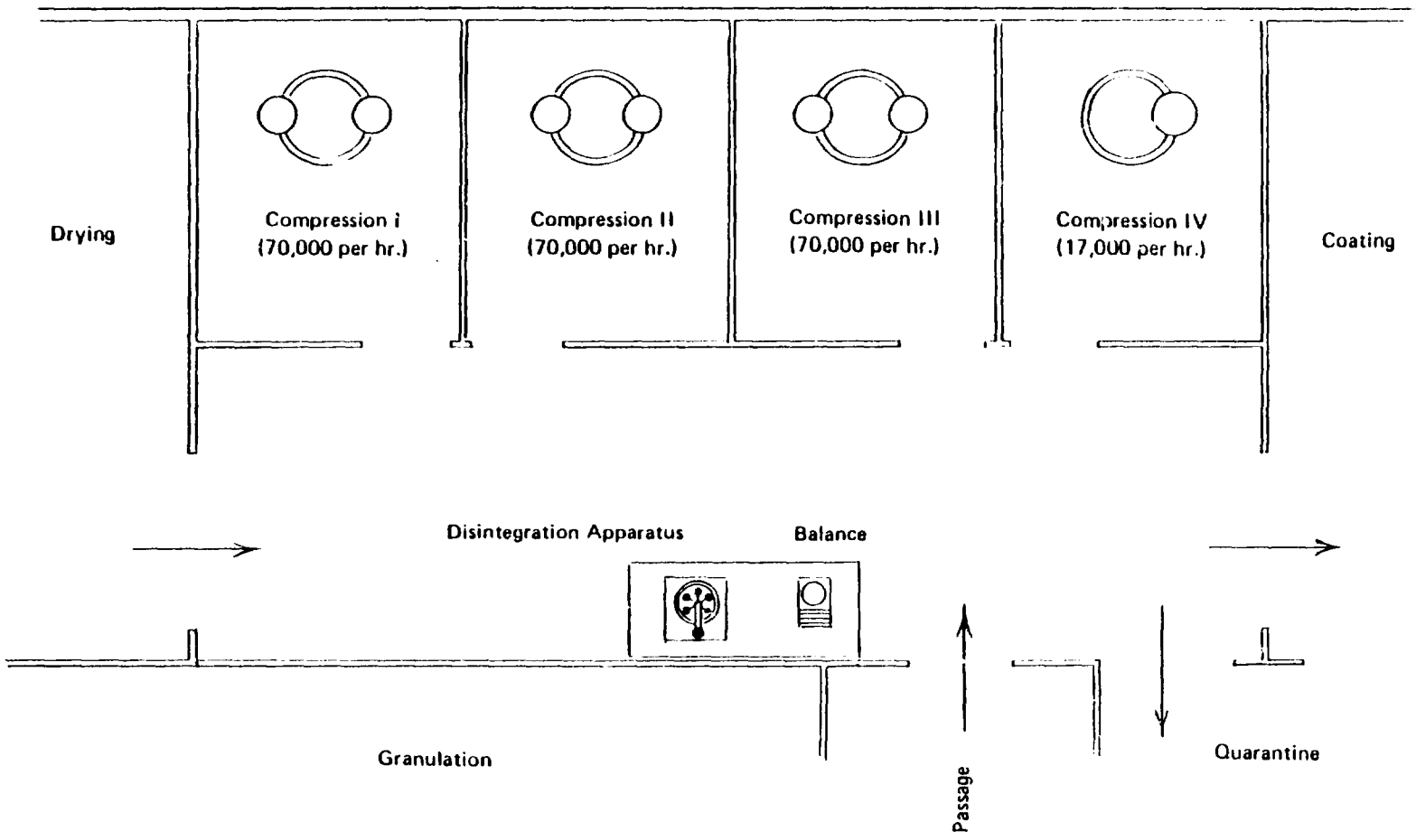


Figure V. API, tablets and capsules section - proposed layout for coating and capsulation

Scale: 1 : 50 (Equipment not true to scale)

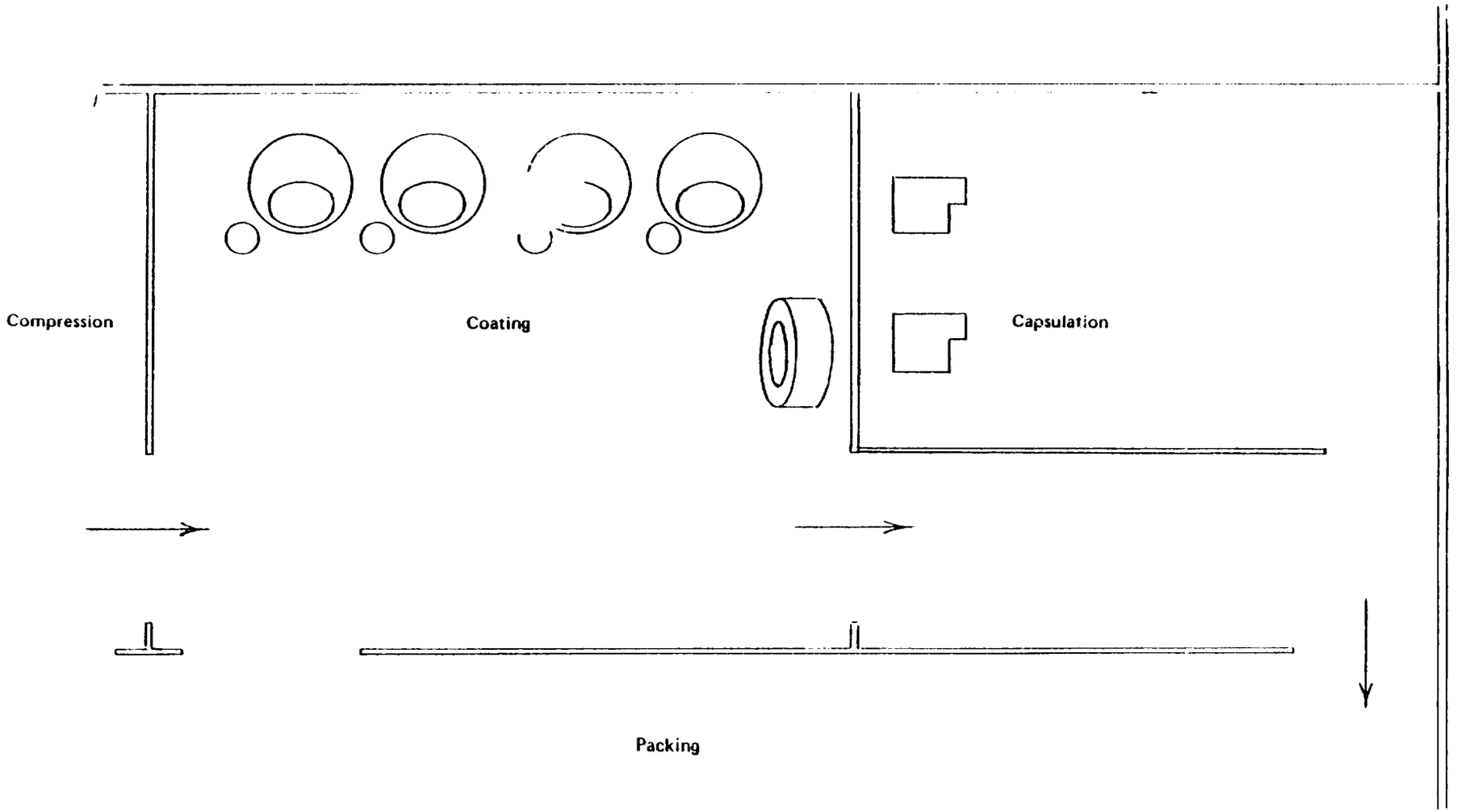


Figure VI. API, tablets and capsules section - proposed layout for packing

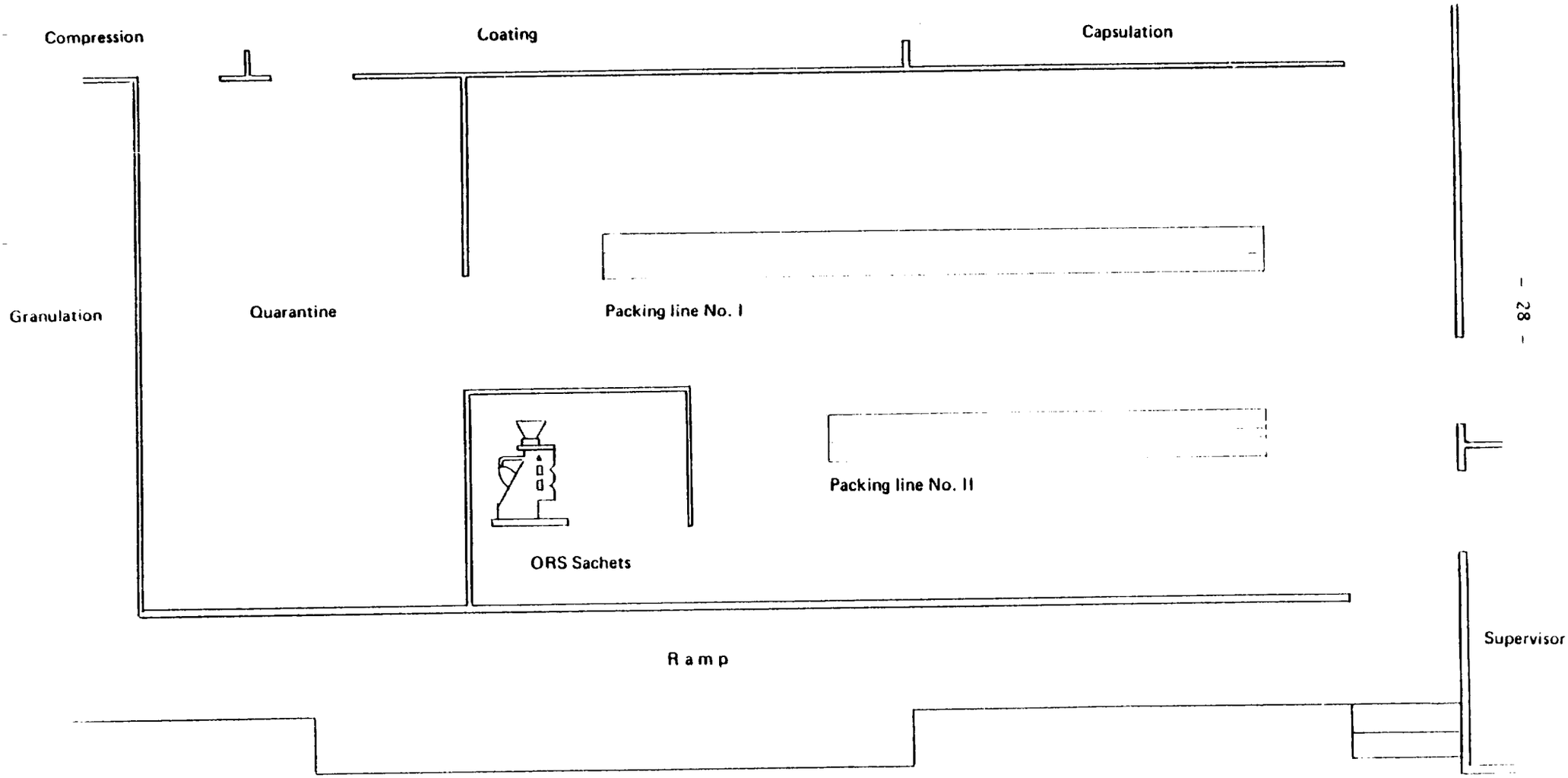


Figure VII. API, oral liquids section - proposed layout for processing and formulation

Scale 1 : 50 (Equipment not true to scale)

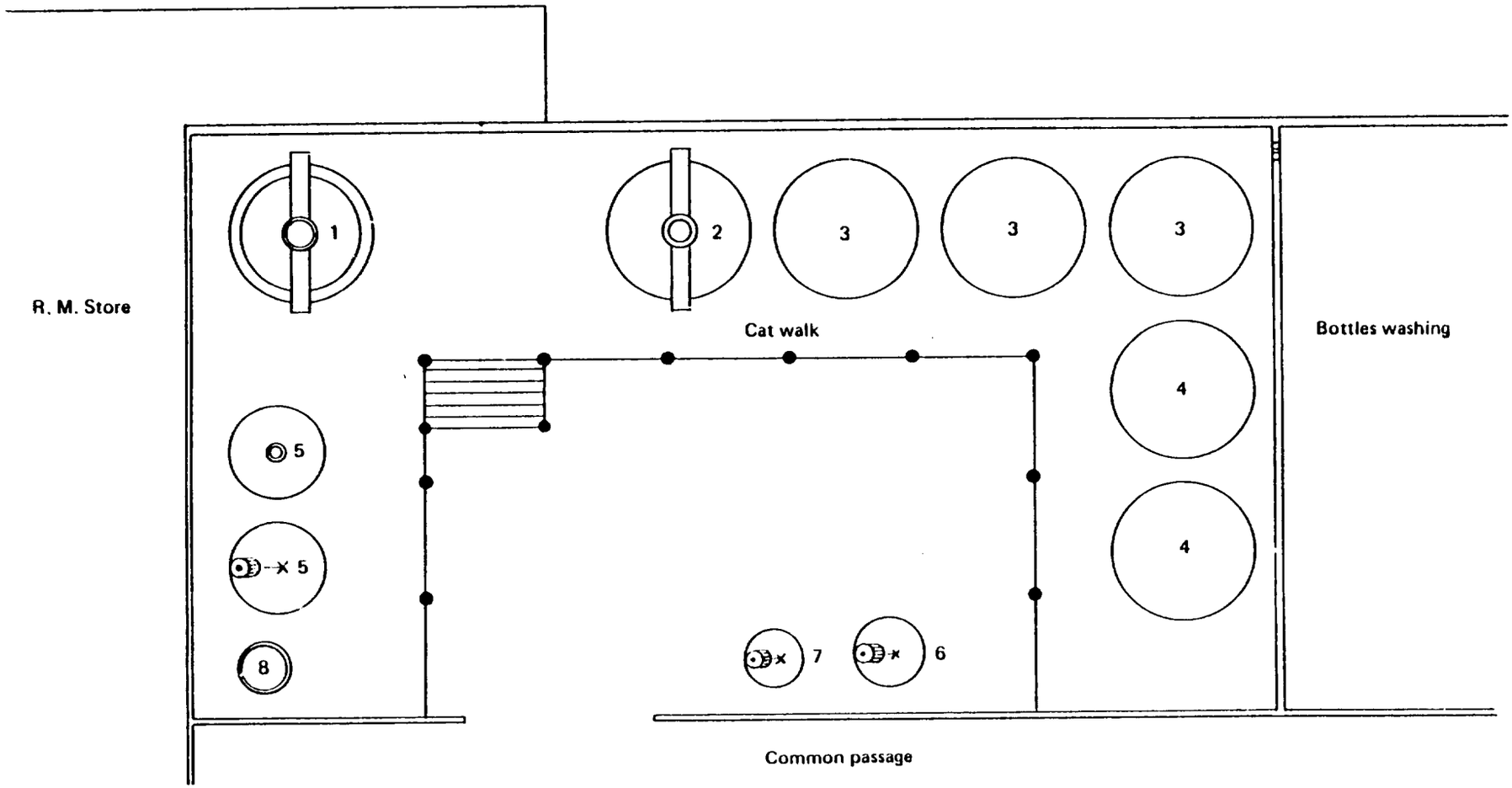


Figure VIII. API, oral liquids section - proposed layout for bottle washing

Scale 1 : 50 (Equipment not true to scale)

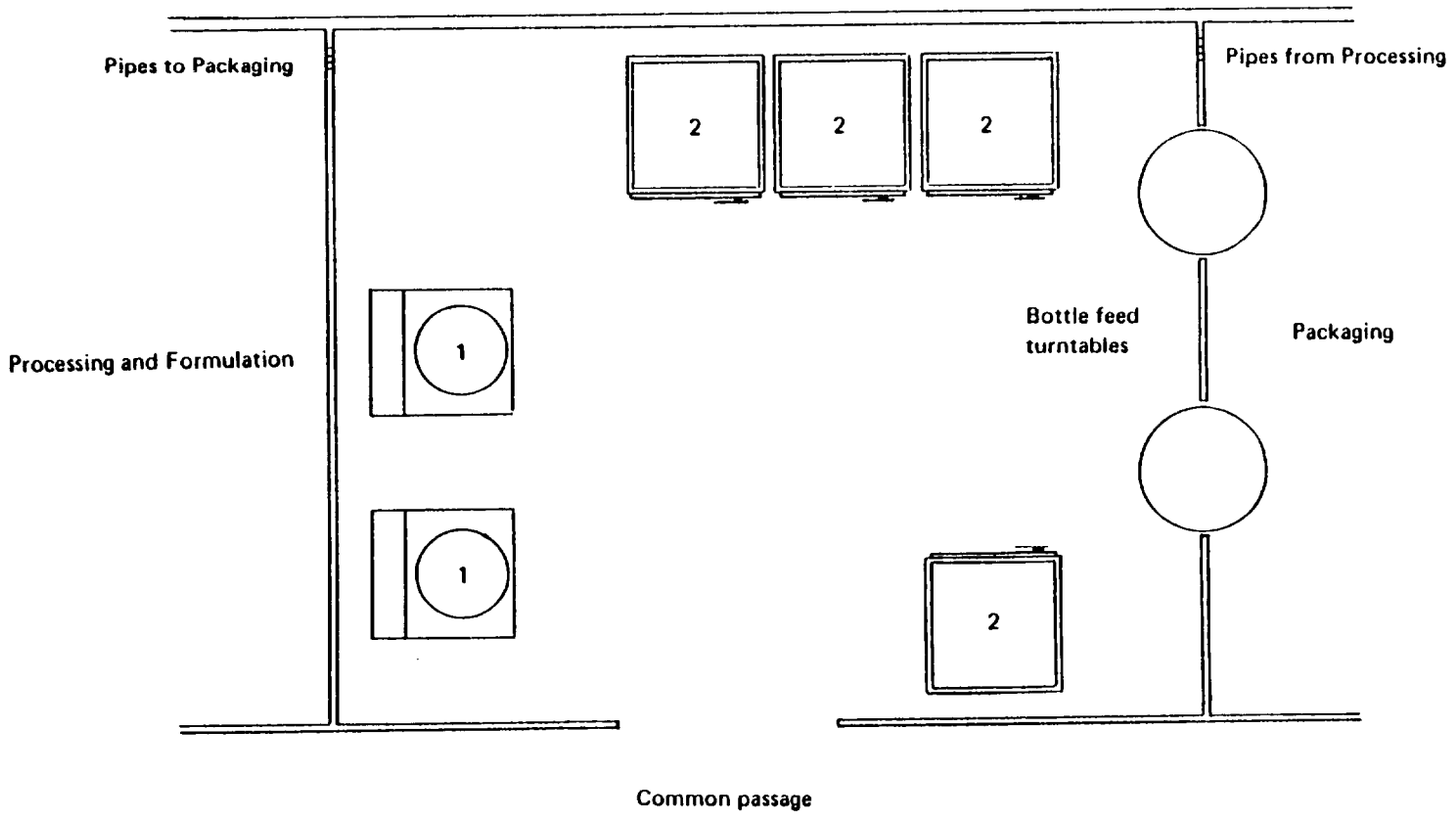


Figure IX. API, oral liquids section - proposed layout for packing

Scale 1:50 (Installations in true to scale)

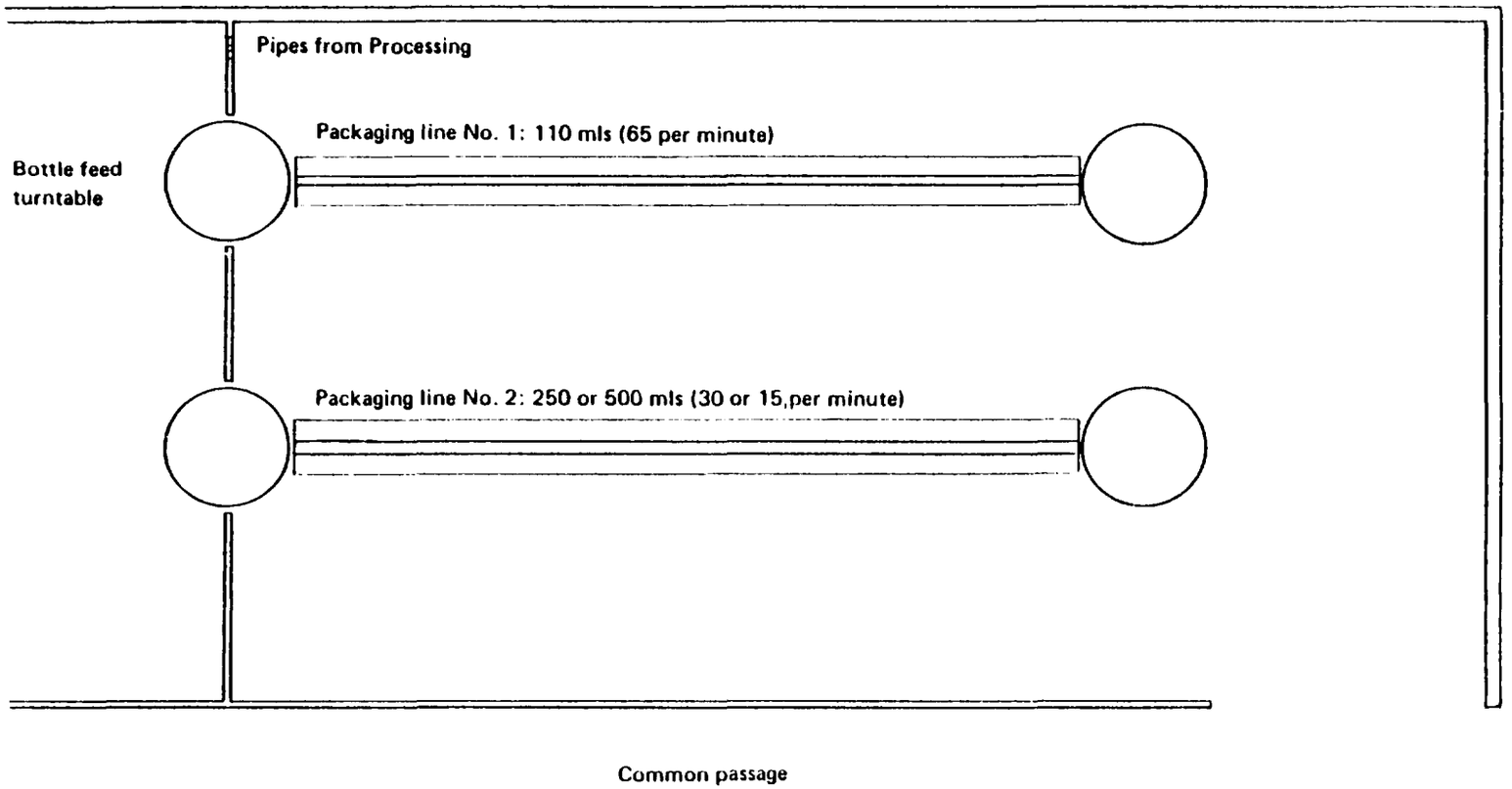
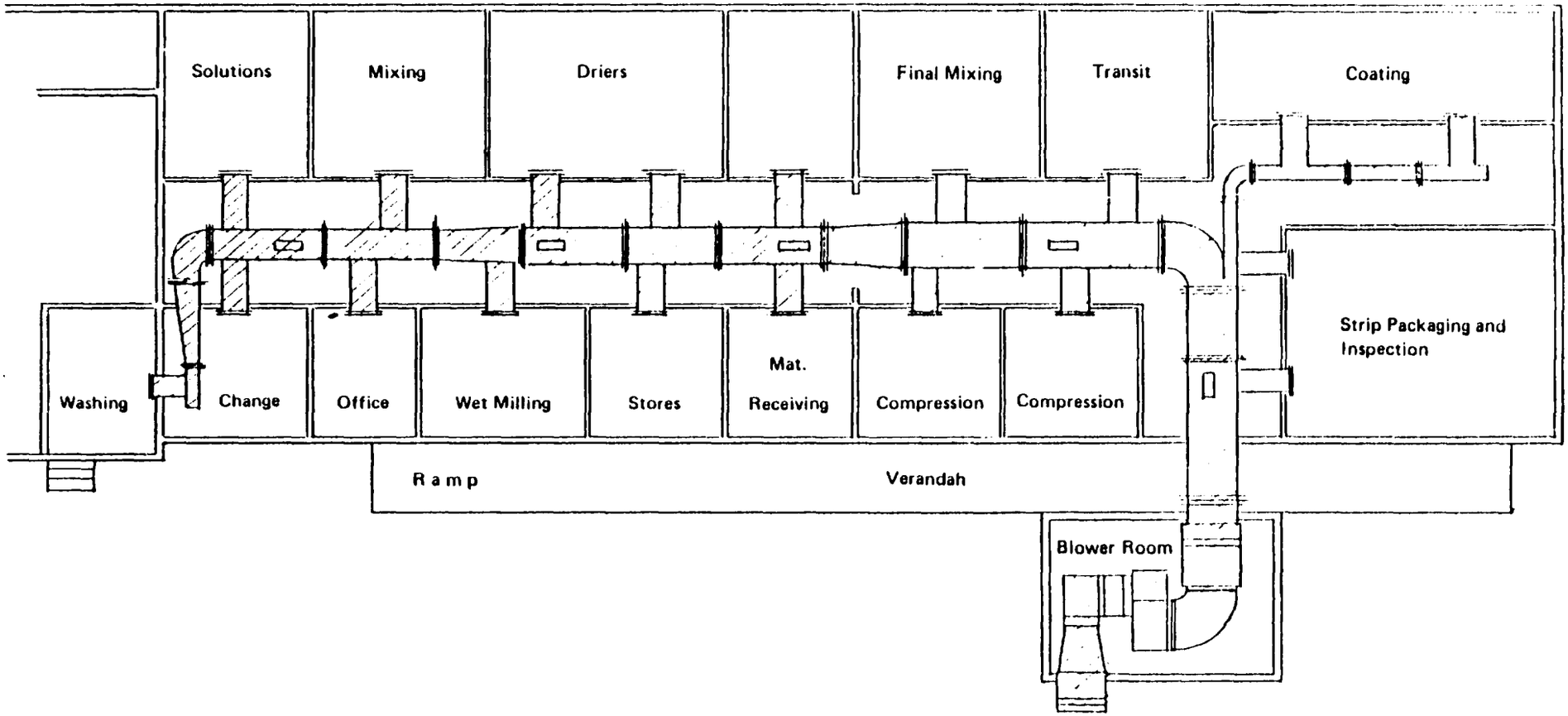


Figure X. API - example of a clean air supply system

Scale: 1 : 200



Note: Supply air duct (shaded) has multiple filters before and after the blower and terminates in each cubide again with terminal filters.

D. Plant capacities and equipment

Although it is premature to ascertain the exact production capacities of API as a result of the suggested improvements, it may be concluded that, considering the resultant layout plans and the addition of the recommended equipment, the output will possibly increase substantially. For instance, the tablets and capsules sections should be able to handle about 80 per cent of the EAR, while the syrup section should be capable of producing and packaging approximately 66 per cent.

Daily and yearly production rates for all dosage forms based on the EAR have been calculated and are shown in table 4. These also include the performance requirements at intermediary processing stages. While most of these requirements can be met after the modernization of the existing facilities of API, the warehousing facility and shelves for the intermediary stage of tablets manufacture may not be adequate. The application of process control may obviate the problem of intermediary shelving, but then additional warehouse space will have to be provided in order to permit the keeping of larger stocks of materials to circumvent uncertain import schedules and logistics.

In table 5 it has been attempted to identify the type and capacity of equipment required to reach the planned production levels, and to ascertain additional equipment. This should be helpful in determining the optimal capacities for API after modernization, and it should also serve as a meaningful reference for the planning of a new plant.

Following the establishment of the optimum production capacities a list of the required production equipment was extracted, which is reproduced in table 6. This list of equipment has been divided into three parts. The items shown in the first column (phase I) constitute immediate needs to modernize certain aspects of the production techniques, to bring about an operational balance and to moderately improve the production capacity. The approximate unit cost of that equipment is given in the second column. For a later increase of the plant capacities additional equipment, to be installed in two phases (third and fourth column), has been envisaged. The requirements of utilities and services will have to be determined for each phase separately according to production plans and will be supplemented as and when required.

The equipment for the first phase would cost approximately $260,000, including the cost of components and spares for the existing equipment listed in tables 7 and 8, while the equipment for the subsequent two phases is estimated at $250,000 at present prices.

The investment for equipment plus the cost of restructuring the building, but excluding the training component, is expected to be approximately $800,000 at the final phase.

E. Operating procedures and maintenance practices

Operations in different sections of the plant should be governed by standard procedures providing step by step guidance. This is best achieved by formulizing them and invigilating their strict implementation. In case of unusual circumstances, departure from the standard procedures should be expressly permitted by an authorized person. The development of such procedures requires long experience which enables the translation of concepts into practices within the available capabilities. A procedures manual should be consulted as a reference book by all operating personnel.

Table 4. Operation capacities for API

A. Tablets and Capsules Section

Basis: Formulation: Double shift (16 hours) per day with 250 working days per year.

Packaging: Single shift (8 hours) per day with 250 working days per year.

No.	Capacity Classification	Tablets		Capsules	Totals
		Uncoated	Coated		
1	Compression				
	i. per day	1.60 million	0.40 million	-	2.0 million
	ii. per year	400 million	100 million		500 million
2.	Capsulation				
	i. per day	-	-	0.40 million	
	ii. per year	-	-	100 million	
	AVERAGE UNIT WEIGHTS	300 mg	300 mg	500 mg	
3.	Materials Processing*				
	i. per day	480 kg	120 kg	200 kg	800 kg
	ii. per year	120,000 kg	30,000 kg	50,000 kg	200.000 kg
	*Includes				
	i. Milling (per day)	480 kg	120 kg	(200 kg)	800 kg
	ii. Wet Granulation per day)	380 kg	120 kg	-	500 kg
	iii. Drying (per day)	380 kg	120 kg	-	500 kg
	iv. Blending (per day)	480 kg	120 kg	200 kg	800 kg

continued

Table 4 (continued)

B. Liquid Orals Section

Basis: Formulation: Double shift (16 hours) per day with 250 working days per year

Packaging: Single shift (8 hours) per day with 250 working days per year

No.	Pack Sizes	Packed Units	Liquid Volumes
1.	Bottles of 110 ml		
	per day	24,000	2,64 K.Litres
	per year	6.00 million	660.00 K.litres
2.	Bottles of 250 ml		
	per day	10,720	2.68 K.litres
	per year	2.68 million	670.00 K.litres
3.	Bottles of 500 ml.		
	per day	5,360	2.68 K.litres
	per year	1.34 million	670.00 K.litres
	Total Volume of Liquid Orals		
	per day	40,000	8.00 K.litres
	per year	10.02 million	2,000.00 K.litres

Table 5. Equipment identification for API

A. Tablets and capsules section

No.	Equipment	Rated capacity/ output	Working capacity: Max. load (kg)	Working capacity: Time per load (hours)	Working capacity: Operating time per day (hours)	Working capacity: Daily output per unit (kg)	Daily requirement (kg)	Equipment status: Required	Equipment status: Available	Equipment status: Additional	Comments
	Common operations										
1.	Sifter	75 kg/h	-	-	16	1 200	800	1	nil	1	Deck type
2.	Hammer mill	125 kg/h	-	-	8	1 000		1	nil	1	
3.	Fitz mill	150 kg/h	-	-	8	1 200	800	1	1	nil	Spare set of screen
4.	Multi mill	50 kg/h	-	-	8	400		1	nil	1	Different nature granulation
5.	Jacketted pan (tilting)	63 l	50	1	8	400	(230)	1	nil	1	
6.	Mass mixer	160 l	50	1.25	8	300	500	1	1	nil	
7.	Planetary mixer	100 kg	50	1.25	8	300		1	nil	1	Spare bowl (coloured tablets)
8	Granulator (oscillating)		-	-	-		500	1	nil	1	Replacement of old unit
9.	Tray dryer	400 kg	400	24	1	400	500	1	1	nil	One reserved for ORS
10.	Fluidized-bed drier	60 kg	54	2	8	432		1	(1)*	1	*Existing one out of order
11	Blender (double cone)	250 l	150	1	8	1 200	800	1	nil	1	High capacity advantageous

continued

Table 5 (continued)

No.	Equipment	Rated capacity/ output	Working capacity: Max. load (kg)	Working capacity: Time per load (hours)	Working capacity: Operating time per day (hours)	Daily output per unit (kg)	Daily requirement (kg)	Equipment status: Required	Equipment status: Available	Equipment status: Additional	Comments
	Compression										
12.	Slugging machine		-		8			1	nil	1	Manesty RS 20
13	Tablet 6 press (16 stations)	17 500/h	-	-	8	140 000	2.0 million	1	4	nil	Manesty D3A
14.	Tablet press (27 stations)	70 000/h	-	-	8	560 000		3	nil	3	Manesty BB3B
	Coating										
15.	Coating pan	900 mm dia.	150 000	2	16	100 000	400 000	4	1	3	
16.	Polishing pan	700 mm dia.	75 000		8	600 000	400 000	1	nil	1	
17.	Dryer-air circulated		450 000	9.5	8	450 000	400 000	1	nil	1	For coated tablets
18.	Jacketted pan	63 l	50	1	8	400		1	nil	1	For shellac solution
19.	Jacketted pan	63 l	50	1	8	400		1	nil	1	For syrups for coating
	Capsulation										
20.	Capsules filler	20 000/h	-	-	8	160 000	400 000	3			Set of plates for different sizes
21.	Capsules polisher	20 000/h	-	-	8	160 000	400 000	3			
22.	Capsules checking system	30 000/h	-	-	8	240 000	400 000	2			

continued

Table 5 (continued)

B. Oral liquids section

No.	Equipment	Rated capacity/ output	Working capacity: Max. load (litres)	Working capacity: Time per load (hours)	Working capacity: Operating time per day (hours)	Daily output per unit (litres)	Daily requirement (litres)	Equipment status: Required	Equipment status: Available	Equipment status: Additional	Comments
	Processing										
1.	Tank for base preparation (steam jacketted)	3 500 l	3 000	8	16	6 000	5 000	1	nil	1	Syrup base preparation
2	Tank for final solution	3 500 l	3 000	4	16	12 000	8 000	1	nil	1	Final batch mixing
3.	Tank (quarantine hold)	3 500 l	3 000	32	8			3	nil	3	
4.	Tank (filling line)	3 500 l	3 000	4	8	6 000	8 000	2	nil	2	
5.	Tank (small batches)	1 350 l	1 000					2	nil	2	
6.	Tank (small batches)	675 l	500					1	nil	1	
7.	Tank (small batches)	350 l	250					1	nil	1	On wheels
8.	Jacketted pan (tilting)	63 l	50	1	8	400		1	nil	1	Preparation of colours

continued

Table 5 (continued)

No.	Equipment	Rated capacity/ output	Working capacity: Max. load (litres)	Working capacity: Time per load (hours)	Working capacity: Operating time per day (hours)	Daily output per unit (litres)	Daily requirement (litres)	Equipment status: Required	Equipment status: Available	Equipment status: Additional	Comments
9.	Centrifugal pump	500 l/h	-	-	8	4 000	8 000	2	nil	2	Liquid transfers
10.	Filter press (stainless steel)	500 l/h	-	-	8	4 000	4 000	2	nil	2	Filtration of syrup base

No.	Equipment	Rated capacity/ output	Working capacity: Fill size (ml)	Working capacity: Time per load (hours)	Working capacity: Operating time per day (hours)	Daily output per unit (bottles)	Daily requirement (bottles)	Equipment status: Required	Equipment status: Available	Equipment status: Additional	Comments
	Filling and packaging lines										
1.	Bottle washer	60/min	-	-	8	24 000	40 000	2	nil	2	Adaptable to all sizes
2.	Bottle dryer	2 000	-	1.5	8	10 000	40 000	4	nil	4	Preferably rotary type
3.	Liquid filler I	65/min	110	-	8	26 000	24 000	1	nil	1	Fully automatic
4.	Bottle capper (P.P.) I	65/min	110	-	8	26 000	24 000	1	nil	1	Fully automatic (28 mm ROPP)

continued

Table 5 (continued)

No.	Equipment		Rated capacity/ output	Working capacity: Fill size (ml)	Working capacity: Time per load (hours)	Working capacity: Operating time per day (hours)	Daily output per unit (bottles)	Daily requirement (bottles)	Equipment status: Required	Equipment status: Available	Equipment status: Additional	Comments
5.	Labeller	I	65/min	110	-	8	26 000	24 000	1	nil	1	Fully automatic
6.	Liquid filler	II	30/min	250	-	8	12 000	10 720	1	nil	1	Fully automatic
7.	Bottle capper (P.P.)	II	30/min	250	-	8	12 000	10 720	1	nil	1	Fully automatic (28 mm ROPP)
8.	Labeller	II	30/min	250	-	8	12 000	10 720	1	nil	1	Fully automatic
9.	Liquid filler	III	15/min	500	-	8	6 200	5 [illegible]	1	nil	1	Semi-automatic
10.	Bottle capper (P.P.)	III	15/min	500	-	8	6 200	5 360	1	nil	1	Semi-automatic (28 mm ROPP)
11.	Labeller	III	15/min	500	-	8	6 200	5 360	1	nil	1	Manually possible
12.	Label overprinter		60/min	-	-	8	24 000	40 000	2	nil	2	Fully automatic

Note: Due to high volume of production, filling and packaging will be most efficient on three separate and conveyorized packaging lines, with 63, 30 and 15 packs per minute for 110, 250 and 500 ml bottles respectively with separate filler, capper and labeller on each line. Bottle washing and drying and label overprinting machines will provide common service to all lines.

Table 6. Equipment procurement schedule for the tablets, capsules and syrup sections of API

No.	Equipment		Immediate Need (Phase I)	Approximate Unit cost	Subsequent Period	
					Phase II	Phase III
I.	TABLETS/CAPSULES SECTION					
1.	Sifter for powders		1	2,500	-	-
2.	Multi mill.		-		1	-
3.	Jacketted pan (tiltable)	63 litre	1	5,000	-	-
4.	Planetary mixer	100 kg	-			
5.	Granulator (oscilating type)		1	5,000	-	1
6.	Fluid bed dryer	60 kg	-		-	1
7.	Double cone blender	400 litre	1	10,000	-	-
8.	Slugging machine		-		-	1
9.	Tablet press (27 stations or 75,000 - 100,000 per hour)				2	1
10.	Coating pan with hot air blower	900 mm dia	1	4,000	1	1
11.	Polishing pan	00 mm dia	1	5,000	-	-
12.	Jacketted pan (tiltable)	63 litre	-			1
13.	Capsule filler (20,000 per hour, clean capsules operation)		-		1	1
14.	Capsules polisher (cube type)	50 litre	1	3,000	-	-
15.	Capsules checking table		1	2,500	-	-
16.	Tablet/capsules counter (slots)		1	20,000	-	1
17.	Bottle capper (R.O.P.P.)		1	7,000	-	1
18.	Labeller		1	8,000	-	1
19.	Unscrambler turn table	(1.0 meter dia)	2	2,500	-	2
20.	Conveyorized packing table (6.0 m and 4.0 m long)		1	4,000	-	1
21.	Polybag sealer		1	2,500	-	1

Table 6 (continued)

No.	Equipment		Immediate Need (Phase I)	Approximate Unit cost	Subsequent Period	
					Phase II	Phase III
II.	ORAL LIQUIDS SECTION					
1.	Jacketted Tank	3,500 litre (brimful)	1	12,000	-	-
2.	Tanks with slaw stirrer	3,500 litre (brimful)	1	10,000	-	-
3.	Tanks storage	3,500 litre (brimful)	2	7,000	1	2
4.	Tank with slaw stirrer	1,200 litre (brimful)	1	8,000	-	-
5.	Tank with medium speed stirrer	600 litre (brimful)	1	5,000	-	-
6.	Tank with high speed stirrer	300 litre (brimful)	1	4,000	-	-
7.	Jacketted pan tiltable	60 litre	-		-	1
8.	Pump centrifugal (St.St.)	500 litre/hour	1	3,500	-	1
9.	Filter press (St. St.)	500 litre/hour	1	5,000	-	1
10.	Homogenizer	200 litre/hour	-		1	-
11.	Bottle washer	60/minute	1	10,000	-	1
12.	Bottle dryer	2000/load	2	6,000	-	2
13.	Liquid filler	65/minute	1	8,000	1	1
14.	Bottle capper (R.O.P.P.)	65/minute	1	7,000	1	1
15.	Bottle labeller	65/minute	1	8,000	1	-
16.	Label overprinter	65/minute	1	5,000	-	1
17.	Conveyorized packing table	5.5 meter long	1	4,000	1	-
18.	Unscrambler turn table	1.0 meter dia	2	2,500	2	-
III.	SUPPLY AND SERVICE EQUIPMENT					
1.	Water deionization unit with 4,000 litre storage tank	1000 litre per hour	1	7,000	-	-
2.	Water distillation unit with 1,000 litre storage tank	100 litre per hour	1	4,000	-	-
3.	Tablets deduster		4	500	-	-
4.	Tablet disintegration unit		1	500	-	-
4.	Dust collector central for tablets		-		1	-
6.	Vacuum cleaner		1	1,000	-	-
7.	Punches polishing kit type A.K. (Manesty)		1	1,000	-	-

Table 7. Components for existing machines of API

I. Punches and Die Set for Manesty 16 Stations

No.	Punch Diameter	Shape	Products for	Quantity
1.	7 mm	Round Deep Concave	Coated Tablets	Set of 18 x 2
2.	9 mm	Round Flat bevelled	Metronidazole and Vit. B	Set of 18 x 2
3.	13 mm	Round Flat bevelled	Benzalkonium Chloride etc	Set of 18 x 2

II. Capsulation Machines

1.	Filling plates	For No. 1 Capsules	3 sets

Table 8. Spare parts for existing machines at API

SL Nr.	Name of Equipment & Address of Supplier	Spare Parts Required	Adress of Supplier
1.	Fluid bed drier	1-Air Control 2 Fan 3-Product Filter 4-Intake filter 5-Timer Switch	Manesty Machines Ltd. Speke, Liverpool L249LQ United Kingdom
2.	Tray drier	Electrical Starter	
3.	Rotorgran Oscillating Granulator	Additional Screens	Mark Liverpool L249LQ United Kingdom
4.	O.R.S. Sachets making Machine (Type S 100)	I-Iron brush II - Group 06 1-01.6.18. size 150-M6 2-01.6.17. " 130-M6 3-01.4.26. Screw-M6 III - Group 07 1-01.7.15. size 215 - M6 IV - Group 02 1-01.2.10. size 53-M6 2-sealer jaw for top-seam. V - Group 04 1-01.4.15. size 120 2-91.21.93. size 90 VI - Group 0 1-01.0.33. size 930-25	Rovema Packing Machines Fed. Rep. of Germany
5.	Fitz Mill	1-Mesh screens. size ... 100S, 120S 150S 200S 2-Dust Retainer 3-Long Vee belt from 1/2 x 55 to 1/2 x 65	Manesty Machine Ltd.

continued

Table 8 (continued)

SL Nr.	Name of Equipment & Address of Supplier	Spare Parts Required	Adress of Supplier
6.	B3B Rotary Tablet Machine	1-Motor 1.1/2 H.P-supplied with key 2-30 vee belt 3-Push button starter complete with fixing screw 4-Punch adjusting screw 5-Rear Lower guard top plate 6-Rear uper guard 7-Uper guard side piece 8-Front uper guard 9-Oil Nipples 10-Oil drop trays	Manesty Machine Ltd.
7.	Tablet Disintegration Tester	1-glass tube 12 pieces 2-Element two pieces	Manesty Machines Ltd.
8.	Strip sealing machine Type SH/VI	1-Heater holder 2-Rubber hugger roller 3-Wiper brush 4-Sealing roller 5-S1 magnet 80-1000-Tomas Schnieber 6-Switch for sealing roller 7-Switch for transformer 8-Micro switch	Demapharm Fed. Rep. of Germany
9.	Suppositoires Forming Machine Model-14 B.P.	1-Adjustment of container tensioning lever 2-B P - 4 v dosing unit	Dott Bonapace & C. Via Canova 6-12 20145 Milano, Italy
10.	Label Overprinting Machine (220 V)	1-Print cylinder 2-With different size alphabet 3-Ink roller 4-Brush	Avery Ltd. Fed. Rep. of Germany
11.	Filamatic Liquid Filling Machine	1-Valve ..... 20 ml-6No 2-Assembly .. 50 ml-2No	
12.	Mixing Tank for Syrup	1-Thermometer	Dott Bonapace & C.
13.	Disteration apperatus	1-Resistance	Dirana Czechoslovakia
14.	Pomad Filling Machine		Demapharm Fed. Rep. of Germany

Similar to the procedures manual, the engineering function should also be governed by procedurized practices which are most important for a smooth running of the plant. In addition to machines maintenance and servicing, the plant services, building and land maintenance as well as office furniture and machines should also be included in a centrally-managed system.

VI. ALIABAD PARENTERAL FLUIDS CENTRE (APFC)

A. Background

The APFC is at the moment producing approximately 400,000 transfusion bottles annually as against an estimated requirement of 1,500,000 units per year. It is therefore apparent that any plans to improve or expand the production facilities must take into account an annual growth capability of at least 25 per cent to attain the EAR level in six years and, if possible, make provision for still further expansion. The building of the production facilities at APFC was constructed about 50 years ago and, in its present physical condition and design, does not meet even the minimum requirements for the production of parenterals, with the additional problems of congestion and disorganization resulting in inherent hazards of cross-contamination and product mix-up. It is also practically impossible either to redesign the building or to revamp it so as to bring it closer to the modern concepts. Thus only two possible options are left:

(a) The construction of an entirely new building in accordance with the required capacities and incorporating the concept of good manufacturing practices;

(b) The relocation of the production facilities to some other building with adequate floor space and capable of undergoing structural modification in line with modern concepts of plant design.

The option of constructing an entirely new building incorporating the desired design criteria, however, is not possible in the near future, merely because of the high capital investment involved and accordingly the attention was focussed on the option of relocating the parenteral production facilities to the space available at the Vaccine Centre. A survey of the Centre and subsequent studies and discussions with the concerned authorities confirmed the viability of the second option based on the following aspects:

(a) Adequate space can be made available for the production of high-volume parenterals (HVP) as well as for the introduction of low-volume parenterals (LVP) in quantities attaining the EAR level. This arrangement would progressively reduce the present supply problems and will also allow further increase in production to meet longer range requirements;

(b) With the recommended modification and additions in the civil structure and an improvement of the existing ventilation system, the space can be converted into a facility which will be reasonably suitable for the production of parenterals, and this can be achieved expediently and economically;

(c) The building also has enough flexibility for the possible installation of more sophisticated systems such as "aseptic blow moulding" and the use of disposable PVC bags as product units in the future;

(d) The layout of operation can be designed to ensure streamlining and sequential steps of operation with provision of transit areas;

(e) Personnel welfare facilities are already established and still better conditions of work can be incorporated in the detailed engineering drawings.

Although the detailed engineering drawings have to be developed in consultation with architects, certain fundamental technical requirements to be incorporated in the plans are briefly discussed in the following section.

B. Building and floor plan

The structure of the building requires good quality masonary finish and robust and hard-wearing floors. In the sterile and clean-air areas it is preferable to finish the walls with tiles; otherwise a smooth and washable finish will be adequate. The fixtures and fittings should be smooth with no, or minimum, horizontal surfaces to avoid dust accumulation. External walls should have adequate glazing to maximize the use of daylight.

The first floor of the Vaccine Centre can be adequately restructured for the production of parenteral fluids. As a guideline for detailed architectural drawings, layouts have been prepared and are reproduced as figures XI to XIV.

The layouts recommended in figures XI and XII are strongly favoured with respect to process flow, streamlining and segregation of operational areas and will be possible even if the existing internal partitions are load-bearing as explained in case of proposed modifications for API. Figures XIII and XIV illustrate alternatives which are less favoured because of inherent weaknesses in process flow and streamlining, although the segregation between different operations is somewhat improved and the clean-areas concept incorporated.

In addition, a check-list of various facilities and building requirements (table 9) was prepared. These items should be incorporated in the design of the building at the time of finalizing the architectural drawings.

C. Environment

Parenteral fluids have very rigid specifications in terms of freedom from live micro-organisms and foreign particulate matter, and cross contamination with other therapeutically active materials. The living micro-organisms can be controlled at more than one stage of the operation, but foreign particulate matter and cross contamination are almost impossible to eliminate once these are present in the final product. For that reason controls ensuring the desired environments are critical during the production of parenteral fluids. Annex II contains guidelines for environmental control in sterile areas which should be helpful for the designing of air-handling systems to provide air of the following qualities:

(a) Cool air: temperature-controlled and partial humidity-controlled air (air-conditioned);

(b) Dehumidified air: humidity-reduced air;

(c) Clean air: air free of foreign particulate matter;

(d) Sterile air: air free of micro-organisms.

Avoidance of cross contamination with dust and particulate matter generated within the operational areas by normal and unavoidable activities is best achieved through air velocities, pressure gradients and flow patterns, all being measures to control the volume and flow according to pre-determined plans and thus preventing the foreign matter to enter more critical areas where the product, the final container or the stopper are exposed to the atmosphere for operational reasons.

D. Equipment

The size and capacity of the production equipment and machinery given in table 10 has been determined on the basis of the required production levels to meet the EAR while the coice of the equipment listed in table 11 is based upon efficiency of performance and degree of desirable automation to be introduced. In table 12 the approximate cost of the equipment is indicated. The required equipment for quality control, repair and maintenance and services has to be identified separately after ascertaining what is already available in the plant.

To avoid a one-time big investment, it is recommended to stagger the purchase of the equipment over a longer period of time based upon the implementation schedule of the project. Similarly it may be possible to defer the replacement of already available low-capacity equipment until the production requirement will justify such replacements.

Furthermore, the following aspects, which will entail a cost reduction should be considered:

(a) In cases where more than one unit of equipment is required, half the number of units, or even less, will meet the requirements of the initial years;

(b) Most of the parenteral liquids are simple solutions and do not require pressurized processing tanks which can be either replaced by normal tanks or be deleted for the time being;

(c) The separate vial and ampoule washers can be replaced by a washer which can be used for both, vials and ampoules;

(d) The plug dryer can be deleted and instead plugs can be dried at a lower temperature in the dryer for glass containers;

(e) Plugging and sealing machines for HVP are not required if manual plugging and sealing with a cheap hand clincher is introduced, and the filling operation can be performed by means of an inexpensive single-syringe bottle filler;

(f) The fully-automatic line for vials can be replaced by a single-syringe filler like the one for HVP, with manual plugging and hand-clinched sealing;

(g) The labelling machine can be replaced by simple gluing machines and manual application of labels;

(h) With the provision of a central clean-air handling system, several laminar flow units recommended at various operational levels can be deleted and instead air inlets can be installed directly over the operational nuclii to provide a permanent clean-air blanket.

These above suggestions would permit savings of approximatly $75,000 from the estimated total of $250,000 for the purchase of the equipment.

E. Procedures

Operating procedures for each function have to be laid down so that the personnel working in the area will become fully conversant with the methods

and techniques, practices, habits and precautions and due awareness should be created towards product sanitariness, avoidance of mix-ups and cross contamination, and personal safety.

In the early phase the production plans should be limited to products requiring terminal sterilization. The products which cannot be sterilized terminally should be included in production plans only when the personnel possesses sufficient operational capabilities. The proposed building design (figures XI and XII) permits such production to be built into it.

Annex III contains model forms used as production records in the manufacture of parenteral fluids in ampoules. With appropriate modifications certain forms can also be used for other types of parenteral products.

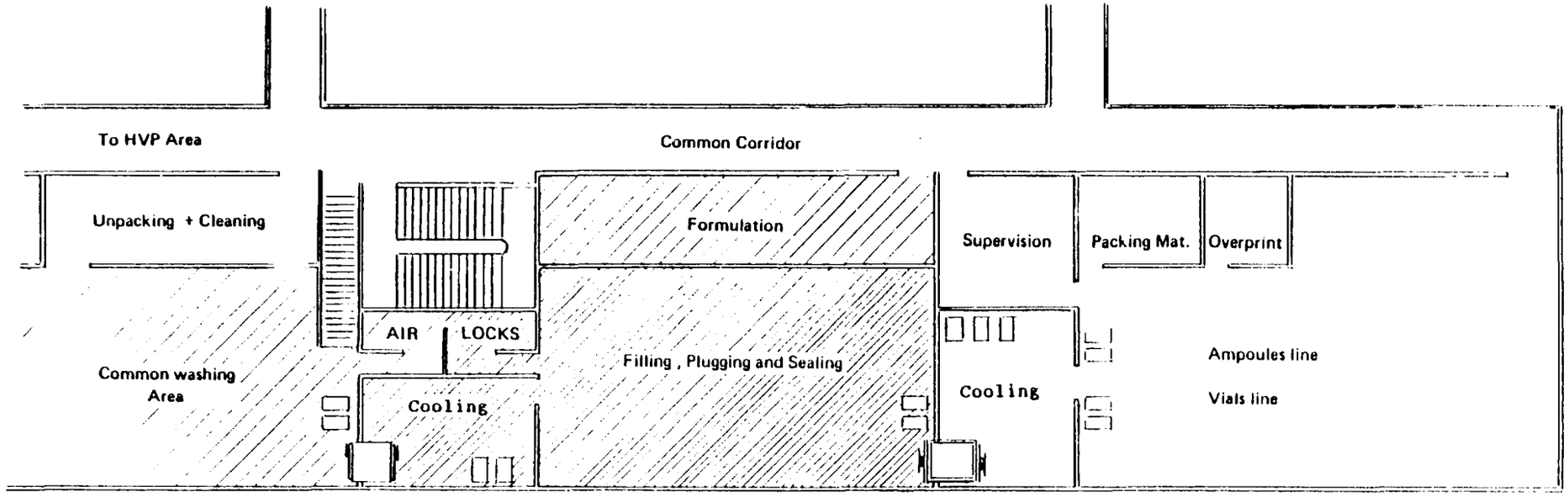
F. Maintenance

In order to ensure a proper and uninteruppted functioning of the equipment and other plant services, regular maintenance and servicing is indispensable which is best carried according to a schedule. Such schedules should be elaborated for each piece of equipment, machinery and installation, based on the literature supplied with the machine which also provides information regarding the necessary spares and components and the frequency of their replacement depending on the time or extent of usage. A conscientious maintenance system includes the keeping of stocks of all spares and components required to rectify defects expediently and to avoid breakdowns.

After a survey of the existing machinery at APFC and a verification of the stock of spares, a list of spare parts (table 13) has been compiled, including their cost and the name of the supplier. These spares should be procured immediately in order to achieve a normal performance of the equipment. The same goes for the immediate requirements of ancillary production items and certain packaging materials indicated in tables 14 and 15, which are necessary to introduce a reasonable regularity and improvement into the production performance.

Figure XI. APFC - preferred building design and layout for LVP

Scale: 1 : 200 (Approximate)

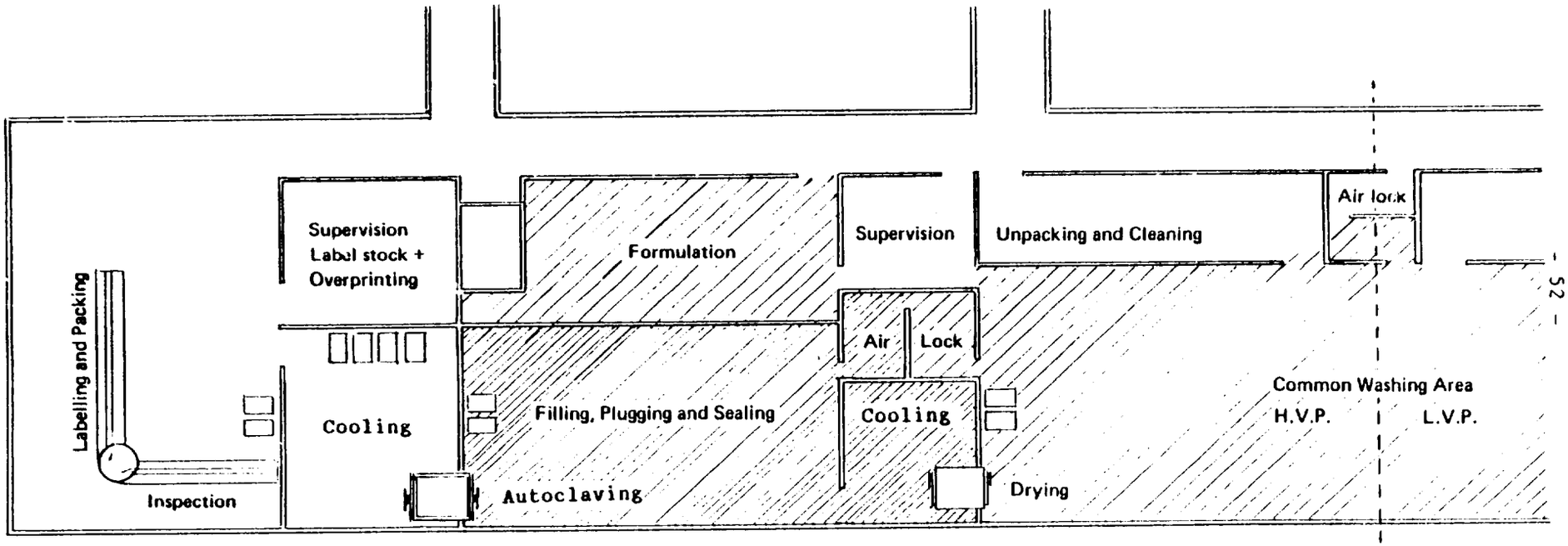


Area identification

1. Fully shaded: Sterile air
2. Half shaded: Clean (free from air born particles)
3. Unshaded: Normal air

Figure XII. APFC - preferred building design and layout for HVP

Scale 1 : 200 (Approximate)



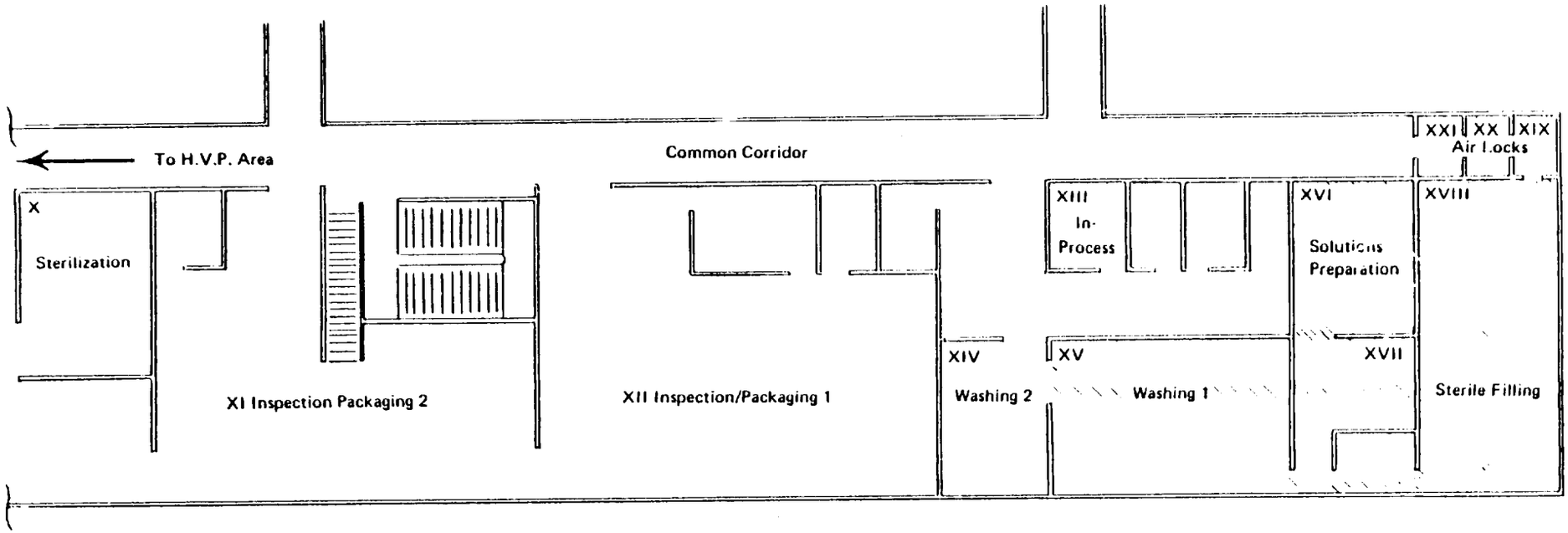
Area identification

1. Fully shaded: Sterile air
2. Half shaded: Clean (free from air born particles)
3. Unshaded: Normal air

Conceptual dividing line
between L.V.H. and H.V.P.

Figure XIII. APPC - alternate building design and layout for LVP

Scale: 1 : 200 (Approximate)

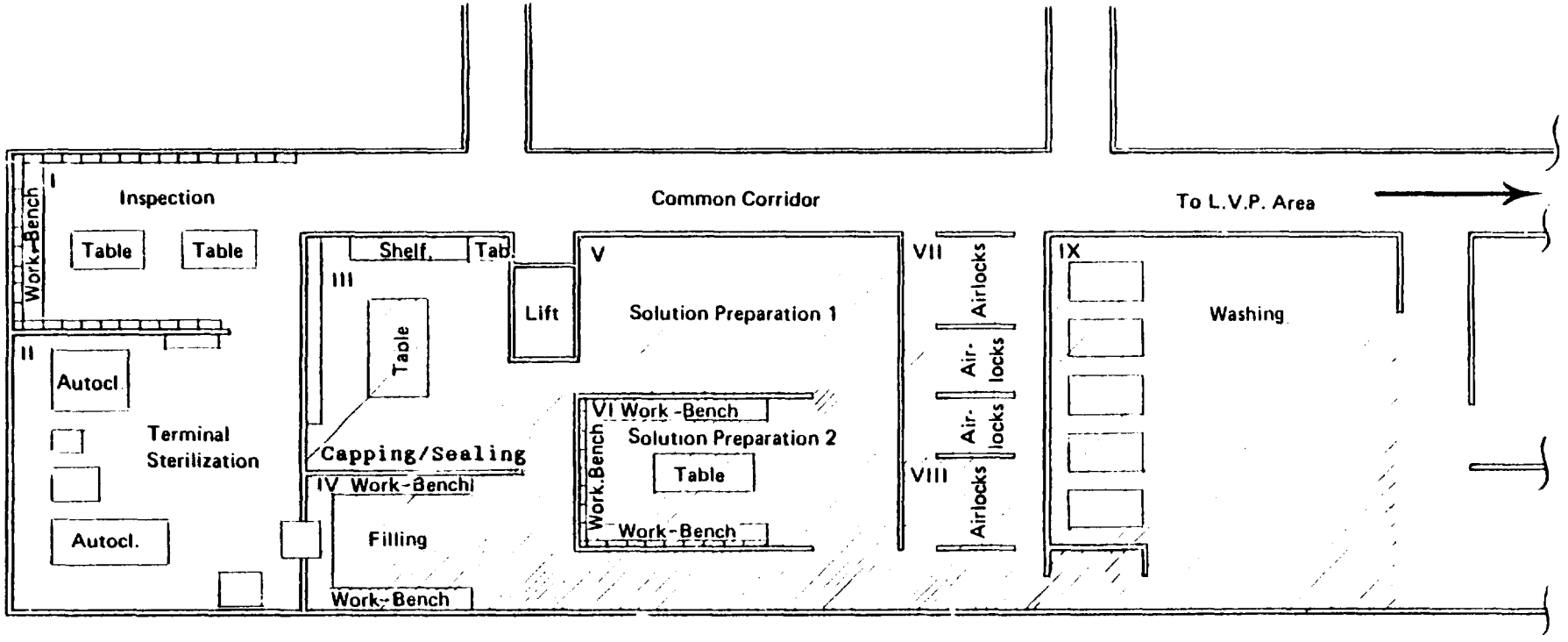


Area identification

1. Fully shaded: Sterile air
2. Half shaded: Clean (free from air born particles)
3. Unshaded: Normal air

Figure XIV. APFC - alternate building design and layout for HVP

Scale : 1 : 200 (Approximate)



Note: Rooms I, III and VI are provided with ample wall-mounted shelves to stock labels, plugs and seals and small stainless steel or polyethylene containers of formulation raw materials respectively.

Area identification

1. Fully shaded: Sterile air
2. Half shaded: Clean air (free from air born particles)
3. Unshaded: Normal air

Table 9. Check-list of facilities and building requirements to be incorporated in a new design of APFC

I. Layout

1. Storage of materials, finished products and dangerous and inflamable products
2. Sampling of materials
3. Quarantine of rejects and recalls
4. Water treatment section (deionization and distillation)
5. Unpacking, washing and drying section
6. Processing and compounding section
7. Personnel entry system (air locked)
8. Sterile operations section (filling and sealing)
9. Autoclaving and cooling section
10. Inspection, labelling and packaging section
11. Quarantine of unreleased products
12. Equipment washing section
13. Quality control and associated functions
14. Provision for expansion in future

II. Services

1. Air-conditioning and air filtration
2. Sterile-air supply system
3. Dehumidification
4. Control of air current and movement from area to area
5. Compressed-air supply
6. Pressurized-steam supply
7. Nitrogen and fuel-gas supply
8. Deionized- and distilled-water supply
9. Potable-water supply
10. Lockers for personnel

11. Showers and toilet facilities

12. Lunch room/cafeteria facilities

13. Drains and sewage

14. Disposal of wastes (incinerator)

III. Construction material

1. Walls and ceilings: long wearing, smooth finish and washable.

2. Floors: hard wearing to sustain heavy material traffic.

3. Doors and windows: hardwood, finished with hard lacquer and lined with stainless-steel sheets, plates etc. at the soilage points or places vulnerable to impacts.

IV. Illumination

As far as possible flushed with roofs and sealed in order to avoid dust deposition and subsequent dust generation in the rooms.

Table 10. Operation capacities for APFC

High Volume and Low Volume Parenterals

Basis: Water Treatments: Double shift (16 hours) per day with 250 working days per year.

Processing/Packaging: Single shift (8 hours) per day with 250 working day per year.

No.	Operation	Packed Units	Volumes
1.	Deionization		
	per day	-	3.000 K.litres
	per year	-	750.000 K.litres
2.	Distillation (Pyrogen Free)		
	per day	-	6.000 K.litres
	per year	-	1,500.000 K.litres
3.	Processing (+ 1% Process loss)		
	per day	-	3.500 K.litres
	per year	-	875.000 K.litres
4.	Filling/Plugging/Sealing and Sterilization/Labelling)		
	i. Bottles per day	6,000	3.260 K.litres
	" per year	1.5 million	815.000 K.litres
	ii. Vials per day	10,000	0.110 K.litres
	" per year	2.5 million	27.500 K.litres
5.	Filling/Sealing (Ampoules)		
	per day	8,000	0.042 K.litres
	per year	2.0 million	10.500 K.litres

Table 11. Equipment identification for APFC

No.	Equipment	Rated capacity/ output	Working capacity: Max. load (litres)	Working capacity: Time per load (hours)	Working capacity: Number of loads per day	Daily output per unit (litres)	Daily requirement (litres)	Equipment status: Required	Equipment status: Available	Equipment status: Additional	Comment
	Water treatment										
1.	Deionization unit	1 000 l/h	-	16		16 000	9 000	1			Double bed resins
2.	Water distillation unit	500 l/h	-	16		8 000	6 000	1			Pyrogen free Thermocompression system
3.	Tanks (holding water)	3 000 l	2 500	-	-	2 500	10 000	4			
	Weighing/dispensing										
1	Balance, percision		-	-	-	-	-	1			Single pan
2.	Balance, digital	up to 1 000 gm	-	-	-	-	-	1			
3.	Balance	up to 10.0 kg	-	-	-	-	-	1			
4.	Balance, platform	up to 300 kg	-	-	-	-	-	1			
	Formulation/compounding										
1.	Tank, St. St. with stirrer	1 200 l	1 000	-	-	1 000	3 600	4			H.V.P. (bottles)

continued

Table 11 (continued)

No.	Equipment	Rated capacity/ output	Working capacity: Max. load (litres)	Working capacity: Time per load (hours)	Working capacity: Number of loads per day	Daily output per unit (litres)	Daily requirement (litres)	Equipment status: Required	Equipment status: Available	Equipment status: Additional	Comment
2.	Tank, steam jacketted, with stirrer	600 l	500	-	-	-	-	-			
3.	Pressure tank, St. St.	180 l	150	-	-	150	110	1			L.V.P. (vials)
4.	Pressure tank, St. St.	60 l	50	-	-	50	42	1			L.V.P. (ampoules)
	Filtration holding										
1.	Membrane filter 293 mm	250 l/h	-	8	-	2 000 l	3 260 l	2			Teflon coated holder
2.	Membrane filter 142 mm	30 l/h	-	8	-	240 l	162 l	1			Teflon coated holder
3.	Membrane filter 47 mm	-		-	-	-	-	3			On line filtration
4.	Pump peristaltic	500 l/h	-	8	-	4 000 l	6 520 l	4			High speed for efficiency
5.	Pump vacuum	50 l/h	-	8	-	400 l	324	1			
6.	Tank St. St.	1 500 l	-	-	-	1 200 l	2 400 l	2			Filtrate holding (H.V.P.)
7.	Tank St. St.	150 l	-	-	-	120	162	2			Filtrate holding (L.V.P.)

continued

Table 11 (continued)

No.	Equipment	Rated capacity/ output	Working capacity: Max. load (litres)	Working capacity: Time per load (hours)	Working capacity: Number of loads per day	Daily output per unit (litres)	Daily requirement (litres)	Equipment status: Required	Equipment status: Available	Equipment status: Additional	Comment
	Washing and drying										
1.	Bottle washer	20/min	-	8	-	8 000	6 000	1			
2.	Vials washer	30/min	-	8	-	12 000	10 000	1			
3.	Ampoules washer	25/min	-	8	-	10 000	8 000	1			
4.	Plugs washer	10 000		2	4	40 000	16 000	1			
5.	Dryer/sterilizer (dry)	1 500 bottles or 10 000 vials and 8 000 ampoules		1.5	5	7 500 bottles or 50 000 vials and 40 000 ampoules	6 000 bottles and 10 000 vials and 8 000 ampoules	1			With two sets of trolleys High speed heating and fan blown quick cooling
6.	Dryer for plugs	10 000		2				1			

continued

Table 11 (continued)

No.	Equipment	Rated capacity/ output	Working capacity: Fill size (ml)	Working capacity: Time (hours)	Working capacity: Number of operations per day	Daily output per unit	Daily requirement	Equipment status: Required	Equipment status: Available	Equipment status: Additional	Comment
	Filling/plugging/sealing										
1.	Filter (200-600 ml bottles)	15/min	5.43	8	-	7 200	6 000	1			Semi-automatic choice
2.	Plugger for bottles	15/min	-	8	-	7 200	6 000	1			Manual choice
3.	Sealer for bottles	15/min	-	8	-	7 200	6 000	1			Semi-automatic choice
4.	Filter (10-25 ml vials)	25/min	11	8	-	12 000	10 000	1			Conveyorized
5.	Plugger for vials	25/min	-	8	-	12 000	10 000	1			Automatic line
6.	Sealer for vials	25/min	-	8	-	12 000	10 000	1			
7.	Ampoule filling and sealing machine	25/min	2-5	8	-	12 000	8 000	1			

continued

Table 11 (continued)

No.	Equipment	Rated capacity/ output	Working capacity: Fill size (ml)	Working capacity: Time (hours)	Working capacity: Number of operations per day	Daily output per unit	Daily requirement	Equipment status: Required	Equipment status: Available	Equipment status: Additional	Comment
	Sterilization										
1.	Autoclave with autoster	1 500 bottles or 10 000 vials and 8 000 ampoules		1.5	5	7 500 bottles or 50 000 vials and 40 000 ampoules	6 000 bottles and 18 000 vials and ampoules	1			Short cycle with full autocontrols
	Checking and labelling										
1.	Labeller for bottles	15/min	-	8	-	7 200	6 000	1			Manual choice
2.	Labeller for vials	25/min	-	8	-	12 000	10 000	1			On automatic packaging line under VI
3.	Labeller for ampoules	25/min	-	8	-	12 000	8 000	1			Overprinting choice

Table 12. Estimated cost of equipment for APFC

No.	EQUIPMENT	QUANTITY	ESTIMATED COST in US $		PROCUREMENT SCHEDULE		
			UNIT	TOTAL	ORDER POINT	LOAD TIME	EXPECTED DELIVERY
1	2	3	4	5	6	7	8
I	**HANDLING EQUIPMENT**						
1.	Boxes, aluminium for 100 vials each	400	15	6,000			
2.	Boxes, st. st. (with lid) for 100 amp. each	200	15	3,000			
3.	Boxes, st. st. (with lid) for 500 stoppers each	50	25	1,250			
4.	Fork lift trolley	2	1,500	3,000			
5.	Hand trolleys	10	50	500			
II	**WEIGHING AND DISPENSING**						
1.	Laminar Air Bench (Horizontal (150 x 60 cm)	1	5,000	5,000			
2.	**Balance, percision, single pan**	1	1,500	1,500			
3.	Balance, top loading, digital 1000 gms	1	500	500			
4.	Balance 10 kg	1	500	500			
5.	Balance 300 kg	1	1,000	1,000			
6.	**Accessories (scoops, spatulas etc.)**	Assorted		1,000			
	Page Total			23,250	CUMULATIVE		23,250

continued

Table 12 (continued)

No.	EQUIPMENT		QUANTITY	ESTIMATED COST in US $		PROCUREMENT SCHEDULE		
				UNIT	TOTAL	ORDER POINT	LOAD TIME	EXPECTED DELIVERY
1	2		3	4	5	6	7	8
III	**WASHING AND DRYING**							
1	Laminar air bench (Vertical 200 x 50 m)		1	5,000	5,000			
2	Vials washer		1	6,000	6,000			
3.	Ampoule washer		1	8,000	8,000			
4.	Rubber plugs washer		1	4,000	4,000			
5.	Sterilizer, dry heat (Capacity 15,000 vials)		1	15,000	15,000			
IV	**FORMULATION AND FILTRATION**							
1.	Processing tank, with stirrer, st. st.	1,500 l	1	4,000	4,000			
2.	Holding tank, st. st.	1,500 l	2	3,000	6,000			
3.	Jacketted processing tank with stirrer	150 l	1	5,000	5,000			
4.	Jacketted process tank with stirrer	50 l	1	3,000	3,000			
5.	Flasks, glass	50 l	4	100	400			
6.	Holder, membran filter (teflon coated)	293 mm	2	1,000	2,000			
7.	Holder, membrane filter (teflon coated)	142 mm	2	700	1,400			
8.	Holder, membrane filter, in-line	47 mm	3	100	300			
9.	Pump, peristaltic, vari-speed		2	150	300			
10.	Pump, vacuum, laboratory type		2	100	200			
	Page Total				60 000	CUMULATIVE		

continued

Table 12 (continued)

No.	EQUIPMENT	QUANTITY	ESTIMATED COST in US $		PROCUREMENT SCHEDULE		
			UNIT	TOTAL	ORDER POINT	LOAD TIME	EXPECTED DELIVERY
1	2	3	4	5	6	7	8
V	**FILLING AND SEALING**						
1.	Laminar air bench (Horizontal 200 x 60 cm)	2	5,000	10,000			
2.	Vials filler, rotary multiple syringe	1	10,000	10,000			
3.	Vial stoppering machine, automatic (Cozzoli)	1	6,000	6,000			
4.	Vial sealer	1	5,000	5,000			
5.	Ampoules filler and sealer, dual head	1	12,000	12,000			
VI	**STERILIZATION AND COOLING**						
1.	Autoclave with automatic controls and with compressed air and deep vacuum	1	70,000	70,000			
2.	Autoclaving boxes for 100 vials each	100	20	2,000			
3.	Autoclaving boxes for 100 ampoules each	100	15	1,500			
VII	**CHECKING AND PACKAGING**						
1.	Vials labelling machine	1	3,000	3,000			
2.	Pressure/Vacuum chamber 100 l	1	3,000	3,000			
3.	Ampoules overprinting machine	1	4,000	4,000			
4.	Labels overprinting machine	1	2,000	2,000			
	Page Total			128 500	CUMULATIVE		

continued

(e) Dirt and extraneous matter;

(f) Any other readily noticeable evidence of abnormality.

(4) Collect representative sample from each lot of raw material according to the sampling schedule given in the appendix.

(a) Powders and granular material: pass a sampling device (tubular) such as a grain sampler through the material vertically down to the bottom of the container in order to obtain a truly representative sample from the entire depth of the container;

(i) Bags: check at the walls for possible penetration of moisture, oxidation, insect infestation (a UV light is useful) rodent droppings etc.;

(ii) Wooden drums: check for wood splinters and puncture of drum liners by nails or unloading devices;

(b) Liquids: mix the contents thoroughly and sample-out liquid with a polyethylene pipette or other suitable device.

Melt and mix solidified liquids before sampling.

Note. Do not use glassware for sampling because of possible danger of breakage.

(5) Sample the material so that three (3) complete assays or examinations can be performed after a composite sample is obtained.

(6) Place the samples in clean, dry glass containers which can not be mistaken with containers used elsewhere in the plant.

(7) Label the sample container with:

(a) Nomenclature of material;

(b) Code number;

Table 12 (continued)

No.	EQUIPMENT		QUANTITY	ESTIMATED COST in US $	
				UNIT	TOTAL
1	2		3	4	5
VIII	**TESTING INSTRUMENTS**				
1.	pH meter		1	500	500
2.	Conductivity meter		1	250	250
3.	Bubble point testing unit		1	n.a.	n.a.
IX	**FURNITURE, FIXTURES AND ANCILLARIES**				
1	Conveyorized work bench		2	2,500	5,000
2.	Work tables, st. st. top	250 x 60 cm	3	500	1,500
3.	Work tables, st. st. top	150 x 60 cm	5	300	1,500
4.	Racks, st. steel	200 x 50 cm	6	2,000	12,000
5.	Cupboards, st. steel for materials	200 x 50 cm	2	500	1,000
6.	Cupboards, pigeon holes for labels	200 x 30 cm	1	500	500
7.	Cupboards for uniforms	200 x 45 cm	2	250	500
8.	Vacuum cleaners, industrial		2	250	500
9.	Chairs for offices and work stools		40	25	1,000
10.	Tables for offices		4	100	40[illegible]
11.	**Filing cabinets**		4	100	400
12.	Cupboards for offices		4	100	400
13.	Classroom materials		–	–	800
				Page Total	26 250
				Grand total	238 600

	still with single phase heating service Cat. No. 1058			
3.	Junction Box, 04218 Cat. No. 1016	2	180	360
4.	Elements for Barnstead "Vent gard" Cat. No. DS-606	2 Cartons	50	100
5.	Condenser Cat. No. Z 1064	3	990	2,970
	LEQUEX S.A., 64-RUE GAY-LUSSAC 75005 PARIS, FRANCE FOR AUTOCLAVE MODEL 18140, 1967			
6.	Contacteur Roc-63, norme ute C 63-110 Classe D usage V courant nominal thermique 63-A Puissance maximum du moteur triphase à 30 man/h au catégorie A-211 (Complete electric system)	4	50	200
		TOTAL		11,990

Carry out all quality control instructions regarding sampling when circumstances demand (e.g. physical limitations of laboratory personnel).

(9) When necessary, combine raw material samples of common lot number. This is done in the laboratory after visual examination and identification tests on each sample. In certain instances, tests such as moisture may also be determined on each sample individually.

(10) Proceed as follows for preparing a composite sample:

(a) Powders: Mix the powder and quarter it. Reject the two diagonal quarters, mix and quarter the remainder. Repeat the process until enough sample for three complete analyses remains;

(b) Liquids: Stir the individual samples and then combine them. Mix the combination and draw off the required sample. The sample should be adequate for three complete analyses.

Note: Such mixing operations must not cause any change in the sample, e.g. evaporation of any component of a mixture, sifting or settling of particles etc. In certain instances, each sample will have to be evaluated separately.

D. Quality control

1. Specifications

Quality control department

(1) Maintain up-to-date physical, chemical, bacteriological, biological, organoleptic or other specifications for each raw material (including quality of water used during processing or in the finished product). These specifications must be identical to those referred to in the product monograph.

(2) When additional specifications are needed, institute such testing as is required and notify the office. The notification should include:

(a) Reasons which necessitated additional tests;

(b) Additional tests to be performed;

Table 14. Required ancillary equipment at APFC

No.	Specifications, Catalogue Reference and Suppliers Address	No. Required	Unit Price	Total Cost
	THE MACBICK COMPANY 243 BROADWAY, CAMBRIDGE, MASSACHUSETTS USA			
1.	Flask washer-rinser, automatic (No. 6730)	2	$ 1500	3,000
2.	Flask rinser (No. 9716)	6	$ 50	300
3.	Flask drain truck (No. 1060)	4	$ 150	600
4.	Flask transfer truck (No. 1065)	2	$ 150	300
5.	Injection solution unit, Capacity 5 gal per batch, Stainless steel (No. 6126)	2	$ 400	800
6.	Solution preparation unit-A for volume/ volume bottle filling (or equivalent new system) system)	2	$ 1000	2,000
7.	Filter, fritted glass with grounded taper to fit 2-way valve 1500 ml (No. 9135)	2	$ 150	300
8.	Conductivity meter portable (No. 9717) (complete with Nos. 9717 B and 9717 C)	2	$ 220	440
	(NOTE: ALL ITEMS SAME OR LATEST TRUE EQUIVALENTS)			
	MIZUHO-IKAKOGYO CO LTD. 29-10 HONGO, 3-CHOME, BUNKYO-KU, TOKYO, JAPAN			
9.	Suction Unit, electric, portable (220 V) Model MSP-207	2	$ 100	200

continued

Table 14 (continued)

No.	Specifications, Catalogue Reference and Suppliers Address	No. Required	Unit Price	Total Cost
	KARL KOLB GmbH & Co. IM STIENGRUND 3 D-6072 DREIEICH, **Fed. Rep. of Germany**			
10.	Flask, Erlenmeyer, 5,000 ml narrow neck (No. 2121673)	15	DM 18	DM 270
	KARL KOLB 1974 D-6079 BUCHSCHLOG-FRANKFURT **Fed. Rep. of Germany**			
11.	Iron, soldering, electric, 200 W Hammer form, Max.temp 470°C, complete with 14 mm hammer type wooden handle and 1.5 m cable with plug 220 V 50/60 Hrz (No. 847-810)	4	DM 42	DM 168

Table 15. Packaging materials required at APFC

No.	Specifications, Catalogue References and Suppliers Address	No. Required	Unit Price	Total Cost
	SCHUBERT & Co. GLOSTRUP, COPENHAGEN, DENMARK			
1.	Bottles, infusion DIN-standard 500 ml brimful capacity 570 ml, type II and III	3,000	$ 1.6	$ 4,800
2.	Stopper, 3-hole, rubber, 37 mm, grey natural rubber, Cat. No. 37-83 A	150,000	$ 56 per 1000	$ 8,400
3.	Stopper, 3-hole, rubber, 42 mm for French infusion glass bottles system	30,000	$ 80 per 1000	$ 2,400
4.	Seal, Capsolut, 20 mm, tear-off centre, gold annodised aluminium with grey natural rubber disc for standard collar vials Cat. No. 2021 C-83FI	50,000	£ 6.22 per 1000	£ 311
5.	Caps, screw Capsolut, 37 mm, centre hole, clear lacquer (for bottles DIN standard 500 ml) Cat. No. 375-S.	5,000	DK 100 per 1000	DK 500

VII. PRODUCTS DEVELOPMENT LABORATORY

A. Background

The increase of the range of products is one of the key factors for the growth and expansion of a pharmaceutical manufacturing operation. The sophistication and innovative trend which has developed in the pharmaceutical sector over the years is largely due to never-ending advancements and upgrading of the techniques in search of new and improved drugs and drug delivery systems.

The Afghan pharmaceutical industry is suffering from serious operational and low-productivity problems, partly due to the erratic and inadequate supply of materials and other inputs, but also due to the absence of innovative capabilities such as a programme for the introduction of new products. In order to enhance the plant productivity one effective measure is the expansion of the range of formulations, which will also help overcome the existing shortages of essential drug in the country.

Since the development of new products involves numerous plant functions, well co-ordinated planning is extremely desirable in order to be successful. The flow chart given in figure XV illustrates these functions, with areas of responsibilities, co-ordination linkages and a time schedule for the progress of work covering three major phases in product development, namely preparation, development of the formulation and production on a commercial scale.

B. Benefits

The programme for the development of new products is expected to offer the following advantages:

(a) Savings in foreign exchange through import substitution and economic self-reliance;

(b) Reduction of the production cost by increased utilization of installed plant capacities;

(c) Creation of a nucleus for the development of local skills and capabilities leading to technological self-reliance.

The development of new dosage forms is a time-intensive undertaking, which requires careful and well-calculated conclusions at almost all fourteen steps indicated in figure XV. Additionally, factors such as the unknown extent of experimental trials before achieving a reasonably satisfactory composition and inadequate laboratory facilities can render this kind of research of rather long duration. However, considering the importance of products development, a beginning has been made.

C. Transitional arrangements

A new product development laboratory has been organized temporarily in the spare rooms made available for this purpose, as illustrated in figure XVI. Although the arrangement is modest and the availability of necessary materials and excipients is not satisfactory, a moderately workable start has been made. A list of products upon which work is progressing is given in table 16.

Figure XV. Activities involved in products development

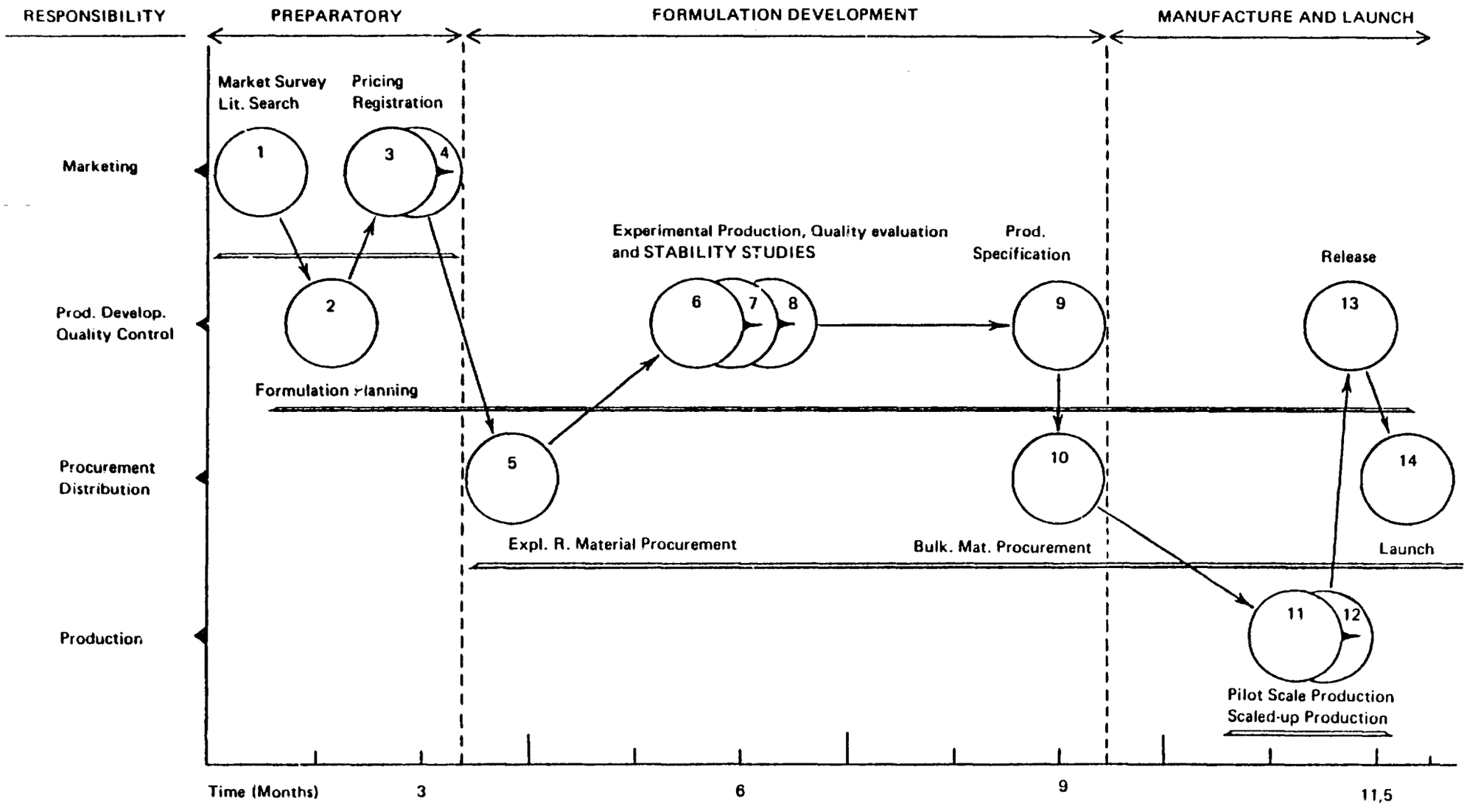


Figure XVI. Proposed layout of the products development laboratory in the existing buildings

Scale: 1 : 100

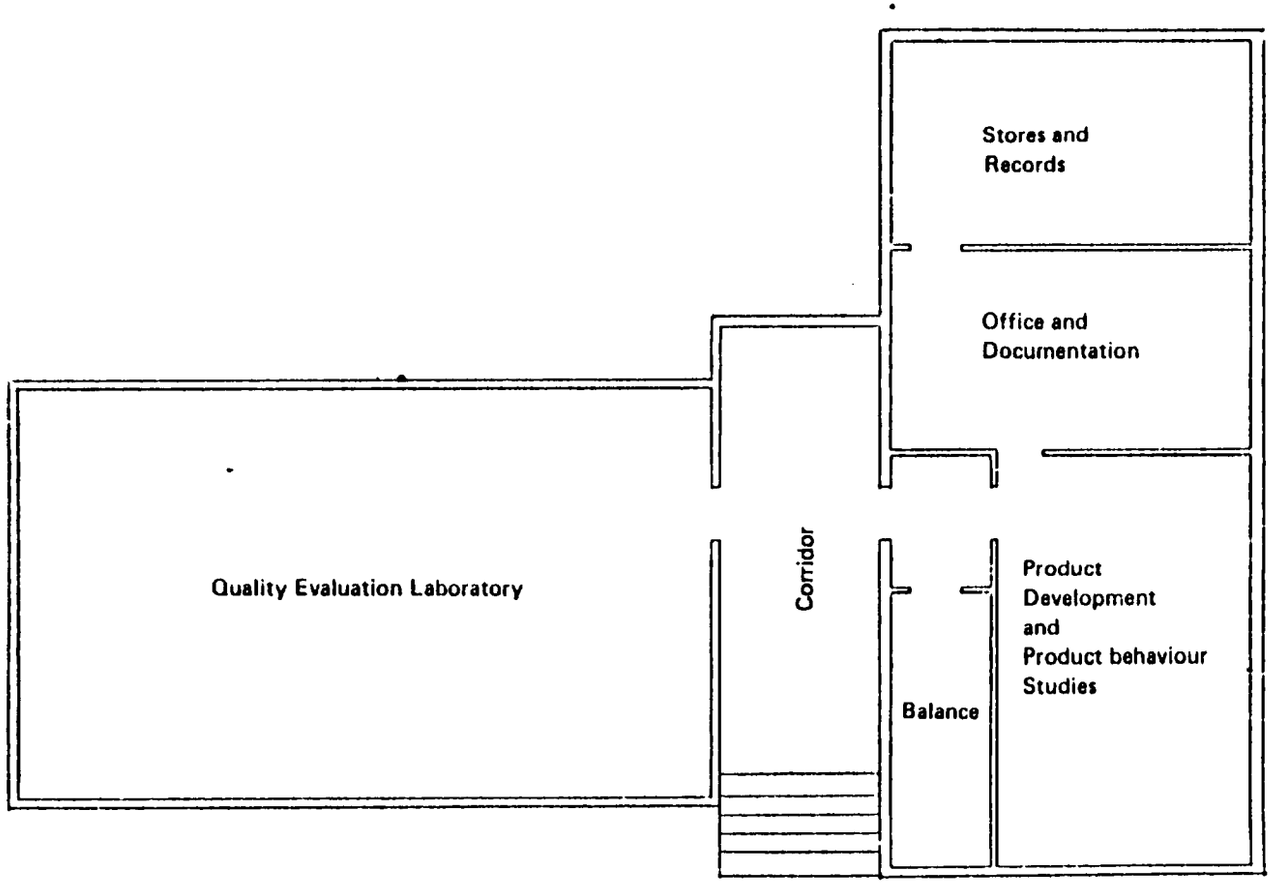


Table 16. Products being developed by the products development laboratory

1. AMPICILLIN - GRANULES FOR RECONSTITUTION
2. MULTIVITAMIN SYRUP
3. ANTISEPTIC FLUID
4. BENZYL BENZOATE EMULSION
5. ALCOHOL BASED LIQUID VITAMIN FORMULATION
6. SUSPENSION OF TRIMETHOPRIM AND SULFAMETHAZOLE
7. COUGH SYRUP FOR DRY COUGHS
8. VERMPAR ELIXIR (PIP CIT ELIXIR BPC)
9. TRICOVIN TABLETS
10. PROCHLORPERAZINE TAB BP 25 MG.
11. PARACETAMOL SYRUP
12. TETRACYCLIN SYRUP
13. TETRACYCLIN PHOSPHATE COMPLEX OR ORAL SUSPENSION
14. MALEATE ELIXIR
15. ERYTROMYCIN TABLETS
16. FILM COATING OF TABLETS
17. ORAL - CONTRACEPTIVE TABLETS
18. SUGAR - COATING OF TABLETS
19. PAEDEATRIC - DROPS OF MULTI-VITAMINE
20. IMPROVEMENT IN PRODUCTIVITY OF AMPICILLIN CAPSULES
21. SUBSTITUTION OF LACTOSE DUE TO NON-AVAILABILITY IN FORMULATIONS LIKE ASCORBIC ACID AND ACTIVATED CHARCOL TABLETS

D. New laboratory

It is considered necessary that, in the course of time and as soon as circumstances permit, an adequately equipped and properly staffed laboratory should be established as a permanent function of the plant.

In addition to the cost of the building, the design of which has to allow for all laboratory functions based on the workload and space needed for a proper flow of work, the cost of the equipment for small-scale production is expected to be approximately $30,000. The laboratory should be located in close vicinity of the quality control laboratory of the plant which would permit a joint utilization of the quality control equipment.

E. Staffing

The management of the laboratory will be under the supervision of a graduate in pharmacy, assisted by one analyst and one packaging materials development officer.

All three incumbents are required to undergo appropriate training in a well-established product-development laboratory. They will have responsibilities in the following areas:

Pre-formulation and formulation

(a) Raw materials

Evaluation of samples from suppliers

Product compatibility assessment

Cost analyses in relation to quality specifications

(b) Packaging materials

Evaluation of market samples

Development of suppliers

Package design

Container/closure suitability tests

(c) Formulation

Preparation of experimental batches

Test procedures development and initial analyses

Stability studies under pre-determined conditions

Container/closure compatibility (with product) determination

(d) Registration

Compilation of a complete set of technical documents and data in compliance with governmental regulatory requirements

Scaling-up and running-in

(a) Scaling-up

(i) Assessment of production facilities

Capacities and suitability of equipment

Blank trials

Additional equipment needs

(ii) Evaluation of process

Capability of equipment

Balancing of process at different stages of production

Adaptation of laboratory-scale production procedure for pilot-scale and ultimately commercial-scale production

Attempt to optimize economic scale of production

Introduction of in-process central measures

(b) Running-in

Auditing and materials-handling and operational procedures

Ascertainment of processing time

Optimization of procedures efficiency

Quality evaluation of pilot and commercial productions

Commercial production follow-up

(a) Extended studies

Studies in shelf-life and subsequent improvements

Process improvements

Exploration of measures for cost reduction

Improvement of packaging in line with market trends

(b) Product monitoring

Resolving operational problems

Review of consumer complaints

Evaluation of expired or damaged stocks

Annex I

MANUAL FOR RAW MATERIALS MANAGEMENT

A. Receipt

Receiving clerk

(1) Recieve all raw materials, intermediate materials and packaging materials.

Warehouse manager

(2) Maintain records of incoming materials supplies on a regular basis. These records include:

(a) Receival number (see definitions);

(b) Identification of material by:

(i) Generic name, chemical name, or established name, together with any subsidiary definitions necessary to differentiate grades;

(ii) Computer code number;

(c) Supplier's name;

(d) Supplier's lot number (see definitions);

(e) Quantity received (e.g. 5 x 100 kg);

(f) Initials of receiving clerk;

Optional records include:

(g) Type of container (e.g. fibre, wood, metal drum, glass);

(h) Apparent condition of shipment;

(i) Storage location of material;

(3) Place the material in quarantine area;

(4) Notify quality control of receipt;

Receiving clerk

(5) Affix receiving label and quarantine tag to each container, pallet, etc. of material (see definitions)

Note: Laws and policy require a strict security system for narcotics, barbiturates, other poisons and alcohol. These are discussed in the next section.

B. Storage conditions

Quality control department

(1) Provide warehouse manager with storage conditions which are required for each item:

(a) Narcotics, barbiturates, other poisons, high-value items and alcohol require a locked area with limited access;

(b) Labels and labelling require a locked area and segregation to ensure that mix-ups do not occur;

(c) Inflammables and corrosives should be stored outside in separate well-ventilated and secure locations;

(d) Flavours, perfumes, colourants, cosmetic ingredients, certain antibiotics etc. require storage in a cool place away from exposure to direct sunlight.

Head pharmacist

(2) Maintain the inventory of all narcotics, barbiturates, other poisons and alcohol

Quality control department

(3) Dispense all narcotics, barbiturates, other poisons and alcohol

Warehouse manager

(4) Affix receiving label and quarantine tag to the material

(5) See that specified storage conditions are maintained

(6) Store the material in the designated area

C. Sampling

Quality control department

(1) Instructions by the quality control department in the form of written procedures for correct sampling methods such as:

(a) Special container preparation:

(i) For aseptic sampling;

(ii) For routine sampling;

(b) Use of tape to reseal sampled bags;

(c) Plastic-coated twist wires used to close drum liners;

(d) Paper, label backings, labels;

(e) Deterioration of certain items due to exposure to light, heat, air (oxygen), moisture etc.;

(f) Hazards of cross contamination within a given lot of the same raw material, between different lots of the same raw material and between different raw materials caused by:

(i) Soiled sampling equipment;

(ii) Dirty or soiled hands or gloves;

(iii) Airborn contamination;

(iv) Opening more than one container at a time;

(g) Sample size;

(h) Sampling equipment;

(i) Safety precautions;

(j) Use of lab coats with short sleeves without cuffs;

(k) Use of hair nets and caps;

(2) Caution the quality control department to avoid hazards such as:

(a) Dusty bags and drum lids;

(b) Dirty lab coats;

(c) Loose articles, pencils, pens, glasses etc. falling into the material container;

(d) Moisture contamination from wet utensils, covers, lids, atmosphere etc.;

(e) Dirty hammers, screw drivers, pliers, scissors, knives etc.

(f) Broken desiccant bages;

(g) Improper sampling environment.

Quality control department

(3) Physically examine each lot of raw material for:

(a) Intactness of container. Segregate damaged containers and reject outright if authorized (see "rejection")

(i) If, due to stock or importation problems, this rejection is impossible, fully examine each container;

(ii) Where inner lining is undamaged, examine material for contamination/deterioration;

(iii) Where inner lining is also damaged reject the container or determine if it may be recovered by suitable treatment, advising the production department of such treatment and providing them with written procedures for recovery;

(b) Proper sealing;

(c) Appearance and odour;

(d) Particle size;

2. Analytical evaluation

Quality control department

(1) Carry out the specified physical, chemical, bacteriological, biological, organoleptic or other tests to ascertain compliance with the specifications.

(2) In cases where local control has not been established, refer the sample to the central reference laboratory with a copy of the local laboratory results for comparison purposes.

Quality control director

(3) May reduce testing to the specified minimum limits according to the reduced testing schedule described in the appendix, provided that the following conditions have been met:

(a) A sufficient number of satisfactory deliveries of the raw material, manufactured either by Associated companies or by an approved supplier, and which have been thoroughly evaluated in parent laboratories, must be logged prior to any decision for reduction in testing;

(b) The shipment has been thoroughly inspected to ensure that all containers are intact, properly sealed and free from any other damage which might affect contents;

(c) The material has been sampled according to the specified procedure;

(d) All samples have been visually examined in the laboratory;

(e) Description and identification tests have been performed;

(f) A reserve sample is retained;

(g) Protocols of analysis and/or complete analytical certificates have been received from the own manufacturing laboratories or from an approved and reputable outside supplier;

(h) A full scrutiny of past records product-by-product and plant-by-plant has been made to confirm that no problems have arisen previously with the item concerned.

(4) Carry out full testing on every sixth delivery or once per year, whichever is more frequent.

(5) Reinstate full testing whenever the situation requires.

Note: Maintain as many approved supliers as possible for each item.

Production manager

(6) Train dispensing and manufacturing staff to be alert for any deviation from the normal appearance of materials.

Production department

(7) Report any visible change in the appearance, colour, consistency etc., observed in the raw material, to the quality control department.

(8) Pass all raw materials through a sieve at the time of use and watch out for extraneous matter.

Quality control department

(9) Periodically spot-check the identity and appearance of dispensed material awaiting processing.

Quality control director

(10) Ensure that any change in the control procedure complies with all legal requirements and codes of practice and is approved by the central reference laboratory.

Note: All raw materials used in the manufacture of any product must be tested and released before use. This includes inactive ingredients, excipients, and ingredients which even do not appear in the basic raw material or the final dosage form, inlcuding items such as water, ice, alcohol, solvents, siliceous earth, charcoal, chlorine etc.

3. Release

Quality control department

(1) Release only those raw materials which meet the specifications fully.

(a) Write the Ross number in the receival book opposite the receival number (see definitions);

(b) Add the "approved" oversticker to the bottom portion of the quarantine tag;

(2) When the material does not meet one or more of the minimum requirements:

(a) Discuss the case with the production or plant manager to ascertain

(i) Whether the material can be processed so that it will comply with product specifications and whether such processing would be desirable;

(ii) Whether the finished product would be adversely affected should the non-complying material be used;

(b) Record the pertinent data on the analytical records notebook, trend card and batch record.

Quality control director

(c) Notify, the National Quality Control Authority in writing of:

(i) Complete nature of the deviation from the specifications;

(ii) Comments by the production department;

(iii) Recommendations by the quality control;

(d) Release or reject the material based on the agreement reached;

If unable to reach an agreement, notify the office, giving all details.

(e) Release or reject the material. Include all reasons for the decision on the analytical records;

Production department

(f) Use only those raw materials which have been released by quality control.

Note: Raw material inventories, the integrity of which may have become doubtful (i.e. insect infestation, moisture penetration, fire damage etc.), must be immediately quarantined and completely retested to ensure that the identity, potency and purity has not been adversely affected in any manner.

4. Rejection

Quality control director

(1) If the material does not comply with the specifications, reject it:

(a) Affix the "rejected" oversticker to the bottom portion of the quarantine tag on each container of the non-conforming lot;

(b) Attach another "rejected" tag to the entire lot;

(c) Mark all laboratory, inventory control and accounts records accordingly;

Warehouse manager

(d) Remove the materialto the section of the warehouse reserved for rejected material.

Quality control director

(2) Ensure that the material is:

(a) Returned to the supplier; or

(b) Destroyed; or

(c) Reprocessed (at the cost of the supplier) to render it acceptable.

(3) At the end of each reporting period, the supplier's name, raw material name, code number, reason for rejection and mode of disposition of each rejected supply of materials should be entered on the quality control statistics report.

E. Old stocks

Quality control director

(1) Prepare and provide a list of all items of limited life which require a "Use before (date)" or an expiration date on their labels.

(2) Advise the production and inventory control departments of such dates for each lot of such item procured.

Production department - purchasing department

(3) Maintain inventories of these items at levels which will ensure their consumption prior to that date. (Avoids costly retesting or eventual disposal.)

Quality control department

(4) If an item is approaching the expiration or is suspected of deterioration, retest the item like a new supply.

(5) Routinely retest raw materials which are six (6) months old like new supplies.

Note: Retesting of inexpensive material or of small quantities is uneconomical. In such cases the material should be destroyed.

Quality control director

(6) When the material is marginally unacceptable, follow the procedures described under "3. Release", item (2).

F. Quality control records

Quality control department

(1) Maintain records of all lots of raw materials readily accessible. These include:

(a) Identity of material by name, sub-descriptions and code number;

(b) Quantity;

(c) Supplier's lot number;

(d) Receival number;

(e) Release number (assigned after release);

(f) Report of analysis:

(i) Date analysed;

(ii) Instrumental readings, measurements, analytical data and calculations;

(iii) Initials of analyst;

(iv) Reasons for any modification of the assay procedure;

(v) All graphs, spectrograms, chromatograms etc.

(g) Expiration date or "Use before __(date)__" (if any);

(h) Disposition of material.

Quality control director

Signature or initials of quality control director authorizing release or rejection.

(2) Retain a reserve sample of the raw material which should be twice the amount required for a complete analysis for a specified period depending on the shelf life of the relevant finished dosage forms.

G. Definitions

For the purposes of this manual the following definitions apply:

Approval label

A green tag or label affixed to the bottom portion of the quarantine tag after the release of the material. It should carry the word "released" or its equivalent in the local language.

Batch

A specific quantity having specified characteristics and quality, and produced at one time in a one-unit process.

Lot

Portion of a batch which for some practical reasons has to be identified as a separate entity; e.g. a day's compression of a large batch of granules or a day's output of finished packaging.

Note: The word "lot" is frequently used to denote a "batch" but the reverse is not common.

Quarantine area

Storage area specifically reserved for those raw materials and packaging supplies which have not been released by the control.

Quarantine tag

A yellow or white tag or label which must be affixed to all drums, containers, pallets etc. of raw materials being tested.

Quarantine tagging system

Employed in situations where a quarantine area or a caged area is not available. It may also be used for large and voluminous supplies of one material.

Receiving label

A label composed of oaktag or similar weight paper containing the following information:

Name of the material
Receiving number
Date received
Quantity received (in terms of number of containers)
Weight received (gross, net and tare weights)

Name of the supplier
Supplier's lot number
Condition of shipment
Quarantine tag

This label has been utilized successfully in conjunction with the sampling information as shown in figure XVII. It should remain affixed on the raw material container until the material has been consumed.

Reject label

A red tag or label affixed to the bottom portion of the quarantine tag when the material has been finally rejected.

Rejection

Any material which does not meet established specifications. The term includes all items that are intended for destruction as well as the material that cannot be reworked or reprocessed.

Release number

A six-digit number, called Ross number, is assigned by the quality control department upon the release of the material. This number identifies a specific lot of raw material throughout the plant. Whenever the lot is used in any operation, its release number must be recorded on the appropriate documents, i.e. analytical reports, batch records, dispensing tickets, inventory records etc.

The Ross number is composed as follows:

(a) 9: Last digit of the year (1979);

(b) 02: Month of the year (February);

(c) 001: Lot released during a given month. The lots are numbered consecutively.

For example, Ross number 912569 would identify the 596th lot released during the month of December 1979. During the year 1979 the numbers for the first lot in each month would be as follows:

January 1979 - 901001
February 1979 - 902001
March 1979 - 903001
April 1979 - 904001
May 1979 - 905001
June 1979 - 906001
July 1979 - 907001
August 1979 - 908001
September 1979 - 909001
October 1979 - 910001
November 1979 - 911001
December 1979 - 912001

Similarly, in the calendar year 1980 the numbers for the second lot released each month would be:

January 1980 - 001002
February 1980 - 002002
March 1980 - 003002
April 1980 - 004002
May 1980 - 005002
June 1980 - 006002
July 1980 - 007002
August 1980 - 008002
September 1980 - 009002
October 1980 - 010002
November 1980 - 011002
December 1980 - 012002

etc.

If a total of 53 lots of material were released during the month of May 1982, the Ross number for the last lot would be 205053.

Receival number

A number which is arbitrarily assigned to each lot of raw material or packaging components which are received in the plant. This number may be the purchase order number, a warehouse reference number, or any other number, assigned to the material. (For example, RM0675 denoting the 675th raw material receival or P0342 denoting the 342nd packaging material receival.) This number is used only during the quarantine period, i.e. from the date of receipt of the material until its release (or rejection) by the Quality Control Laboratory. From then on, only the quality control release number (Ross number) assigned to a given lot of raw material should be used.

Supplier's lot number

The number which designates the supplier's batch or lot. If no lot number is furnished by the supplier, each container should be considered as a separate lot and sampled accordingly.

Figure XVII. Model of a sampling information tag

Product name:		Supplier's lot number:
Supplier:		Date received:
Receival number:		
Container number:	of (total)	Quantity received (kg):
Sampled by:	Date:	Gross weight:
Date resampled:		Tare weight:
Book number:		Net weight:
Status:		
Local release no:	Initials	Date:
Use before 1. 2. 3. 4.		

Receiving label

Appendix

PROCEDURES FOR SAMPLING OF RAW MATERIALS, APPROVAL OF SUPPLIERS AND REDUCED TESTING

A. Sampling procedure for raw materials

All receivals are subject to general inspections. The number of samples taken is based upon the number of containers received.

In the case of incoming raw materials, the square root of the number of containers plus one additional container is taken for each supplier's lot number.

In the case of packaging materials, the number of samples taken is based upon the MIL-STB 105D. The following quality assurance levels apply:

Major defects	1.0
Minor defects	2.5

Normal inspection

	Acceptance quality level			
	1.0		2.5	
Lot size	Sample	Reject	Sample	Reject
281 - 500	50	2	50	4
501 - 1 200	80	3	80	6
1 201 - 3 200	125	4	125	8
3 201 - 10 000	200	6	200	11
10 001 - 35 000	315	8	315	15
35 001 - 150 000	500	11	500	22

B. Procedure for approval of suppliers

To approve a supplier for reduced testing:

(a) Each shipment must carry specific identification batch numbers;

(b) The analytical certificates must refer to the specific batch number;

(c) Six (6) consecutive batches of the raw material must comply satisfactorily to standards in all tests.

For reduced testing the following steps have to be taken:

(a) Notify the Central Reference Laboratory of the intention to reduce testing;

(b) Supply with such notification the following information:

The material
The supplier's name
The name of the actual manufacturer
The country of origin of the material
The sets of complete analytical results of all testing

The Central Reference Laboratory will then authorize such reduced testing.

In the event that a lot fails the mandatory tests, full testing must be reinstituted and the supplier be reapproved only after six consecutive deliveries are found acceptable.

Central Reference Laboratory and the supplier should be informed whenever a supplier is removed from the list of approved suppliers.

C. Reduced testing procedure

Reduced testing is applicable only when:

(a) All containers are intact;

(b) The material has been received from an associate company or an approved supplier;

(c) The material is visually and chemically (identity) satisfactory;

(d) Complete analytical evaluation certificates have been received;

(e) Prior history (e.g. six deliveries and spot-checks) is satisfactory.

Samples must be checked for: (a) absence of foreign matter; (b) absence of dirt; and the mandatory raw-material tests must be made.

It should be pointed out that with reduced testing the hazards increase and there should be no hesitation to carry out necessary additional tests in case of even the slightest doubt.

Final product specifications, on the other hand, are framed to ensure the requirements in the finished product and the detection of possible variations during processing and, accordingly, must be fully carried out as laid down for every manufactured batch.

Annex II

GUIDELINES FOR ENVIRONMENTAL CONTROL IN A STERILE AREA

System division

The premises shall be served by a separate ventilation system. The units shall be placed in fan rooms.

Supply air unit

The unit shall be of robust construction and designed for easy service and replacement of components.

Condensate insulation in any part of the unit shall be covered to prevent entrainment of insulation material in the air stream.

The unit shall be fitted with equipment for air return, pressure rise, prefiltration, heating, cooling/dehumidification, humidification and intermediate filtration of the air.

Final filters shall be installed adjacent to the supply air outlets in individual rooms.

The supply air fan shall be sized for the required capacity at the final pressure drops over the filters. Since there is a considerable pressure drop at the time of replacement of filters the speed control of the fans is essential and fans should be fitted with devices for speed adjustment.

The operating point for the supply air fan shall be chosen within the steep portion of curves in the pressure-flow chart in order to permit maximum possible stability of the air flow.

Prefilters with collection efficiency F45 as per VVS-AMA 72.

Humidification of the ventilation air with steam.

Intermediate filters with collection efficiency F95 as per VVS-AMA 72.

Final filters with collection efficiency M99.97 as per VVS-AMA 72.

Parts of the supply air unit shall be positioned in the above-mentioned sequence. Silencers shall be installed upstream of final filters.

Exhaust air fans

The fans shall be of robust construction and located in such a way as to enable easy service.

As regards fan selection, the operating point in the pressure-flow chart shall be chosen in the same manner as for the supply air fans.

Fan rooms

The installation shall be arranged so that free floor space for easy access for care and maintenance is provided. Space shall be provided where removable components can be placed and worked on. It shall be possible to remove units without necessitating intervention in the building structure or in units connected directly to the unit being removed.

A water supply tap with hot and cold water and a floor drain shall be installed in a warm area in the fan room.

The floor surface in the fan room and the drainage plumbing shall conform to normal standard.

Filters

For the collection efficiency of different filters refer to "Supply air unit".

F45 and F95 filters shall be deeply pleated filters with large filter areas and mounted on air-tight frames. Filter replacement shall be possible without the risk of contaminating the clean side of the filter. F95 filters shall be mounted directly on the supply air duct to prevent contamination of areas downstream of the filter.

M99.97 HEPA filters shall be placed in a connecting box for installation in the ceiling. The box shall be gastight and fitted with an air-tight-sealing press device for the HEPA filter cell. It shall be possible to replace the filter from inside the room without removing the connected supply air outlet.

The connecting box shall be made of aluminium, stainless steel or internally and externally painted black sheet. Paint shall be applied to a blast-cleaned surface and shall be non-particle-repellant.

Ducting

Supply air ducts

The ducts shall be designed and fabricated as conventional ventilation ducts in accordance with VVS-AMA 72. The following special requirements shall apply to ducts downstream of F95 filters:

During fabrication, the necessary measuring holes for flow measurement and for connection of permanent measuring instruments shall be drilled. The holes shall be deburred and sealed with plastic plugs.

Sleeves for testing of filters and filter mountings shall be fitted to the duct component during fabrication.

During fabrication, all burr shall be removed, after which the ducts shall be thoroughly cleaned internally by vacuum cleaning and wet wiping with a non-particle-repellant cloth. (Provision for such cleaning must be made in connection with the design of the ductwork.) The openings of the duct components are sealed with plastic which shall not be removed until the component is installed in the system.

Air-tightness: air-tightness class B as per VVS-AMA 72 (general).

Exhaust air ducts

Conventional design as per VVS-AMA 72.

Air-tightness: air-tightness class B as per VVS-AMA 72.

Internal insulation, sound absorption

Internal insulation of ventilation ducting downstream of F95 fine filters shall be avoided.

Terminal devices

Rooms without special cleanliness requirements

Conventional supply and exhaust air terminal devices (supply air outlets and exhaust air intakes). The ventilation air shall be supplied in such a manner that the air velocity does not exceed 0.15 m/s in the occupied zone at a room temperature of +20°C.

The supply and exhaust air systems shall be designed to permit the ventilation air flow to be increased to 20 air changes per hour in the room. It shall be possible to fit the supply air outlets with HEPA filters.

Classified rooms

Special requirements on supply and exhaust air terminal devices. The ventilation air shall be supplied in such a manner that the air velocity does not exceed 0.2 m/s within the occupied zone at a room temperature of +20°C.

The supply air outlets shall be connected directly to connecting boxes for HEPA filters. In order to obtain the best possible mixing conditions and the lowest possible air velocities in the occupied zone, it may be necessary to lower the diffusers about 20 cm from the ceiling.

The supply air outlets shall be easily removable for cleaning of the outlet and the connecting sleeve between the box and the outlet and for filter replacement.

The exhaust air intakes shall be designed for easy cleaning.

Adjustment and testing

Before filters are installed in fan rooms, the rooms shall be vacuum-cleaned and wet-wiped.

Before HEPA filters are installed, the connecting box, any sleeves downstream of filters and the supply air outlet shall be cleaned with solvent and wiped dry with a non-particle-repellant cloth.

Air flows shall be adjusted by presetting of air terminal devices and dampers. Adjustment and testing shall be carried out simultaneously.

Specified pressure ratios (air flow directions) between rooms take precedence to specified air flows. But specified supply air flows must be observed as minimum limits.

With regard to pessure ratios, see later instruction.

The contractor shall keep a record of measurement results. Measurement and testing shall be carried out together with the purchaser's inspector.

Measurement of main flow and partial flow

Main flow shall be measured by means of permanent measuring instruments included in the contracted works or by means of pitot tube measurements.

Air-tightness testing

The entire duct system including air-handling units shall be tested to make sure that it is air-tight.

All HEPA filters mounted on air-supply outlets shall be tested after installation in accordance with AACC designation CS-TO (introduction of a paraffin aerosol upstream of the filter with simultaneous testing of filters and seals into the room) or equivalent.

Installation

Owing to the special nature of the system, high demands are imposed on procedures and cleaning in connection with the installation of electrical, plumbing, heating and ventilation equipment as well as ceiling, wall and floor work.

There are no special cleaning directives applicable to building work or the framework of the building.

Directives for cleaning and preparations given below apply to all areas.

Prior to the start of installation of electical, plumbing, heating and ventilation equipment, all work on the building framework shall have been completed.

In addition, the following measures shall be adopted prior to the start of the installation work:

(a) All drilling or grouting-in of holes for the installation shall have been completed;

(b) The installation areas shall be cleaned, whereby all surfaces shall be vacuum-cleaned;

(c) Dust-generating surfaces shall be treated by means of priming or the like to bind dust.

Premises on which installation work is carried out shall be vacuum-cleaned daily.

Procedural rules

All installation equipment which must meet demands on cleanliness shall be stored in separate areas and in such a manner that protective covers are not damaged. If a protective cover is damaged, the component shall be cleaned in accordance with directives prior to installation in the plant.

During installation, each contractor shall plan his work in consultation with the other contractors so that unprotected components are not soiled during the installation work. Protective covers may not be removed except for connection of components.

Protective covers on air terminal devices and on duct and pipe openings may not be removed until the last phase of final cleaning. After the protective covers have been removed, no work may be carried out by the contractor in the room unless special protective measures have been adopted. Instructions for such measures shall be supplied by the purchaser's inspector.

Each contractor shall store materials and tools at designated places in order to facilitate the work of the building contractor. The contractors shall comply with the instructions pertaining to installation and cleaning which are issued by the purchaser's inspector, who shall inspect cleaning daily during the installation period.

During the adjustment period for the ventilation equipment (approx. one week) no other work shall be performed within the concerned areas, since this would seriously disturb the work of the ventilation contractor.

Annex III

MODEL PRODUCTION RECORD FORMS

AMPOULES	Article No:	Date:
VIALS TRANSFUSION - BOTTLES	C. No:	

Instructions

Keep the washing area neat and clean.

Wash and rinse with filtered distilled water, the ampoule boxes and trays.

Check the membranes in the filter holder.

Check the filtered water for clarity.

Pre-inspect the ampoules for moulding defects.

Feeding to trays		No. of amps recieved for washing	
Washing		No. of amps rejected during washing	
Arranging in boxes		No. of amps taken for sterilisation	

Sterilisation:

Sterilise and washed amps in G.S.T. Boxes at 160°C for 1 1/2 hrs in a dry heat steriliser.

Attach the temp. chart.

Load No	Time started	Temp. Attained at	Hold	Cycle completed	operated by
Equipment					

Wash and sterilise the equipments coming in contact with the product during processing, filtration and filling as per standard operating procedure.

PROCESSING AND FILLING

Name of the item	Previous use	Cleaned by	Sterilised by	Sterilisation No. 2 date	Checked by
Processing flask					
Received flask					
Membrane filter holder					
Filling machine assembly					

The above amps and equipments used for

Product [ ] Batch No. [ ]

Signature of Chemist-in-Charge: .....

INSPECTION

Product:
Batch No.:

Article No. ..... Date
Batch size: .....

Instructions: Remove all irrelevant material from the inspection area

Inspect each vial/ampoule against black and white illuminated background

Inspect for particulate matter in solution, container and closure defects

sl no.	Particular	Name of person	Total	Remarks
1.	Fibres			
2.	White particles			
3.	Black particles			
4.	Glass particles			
5.	Glass flakes			
6.	Volume less			
7.	Volume more			
8.	Broken			
9.	Container defects			

(continued)

sl no.	Particular	Name of person	Total	Remarks
10.	Sealing defects			
11.	Charring at the tip			
12.	Rubber stopper defects			

Total rejected .....

No of units recieved for inspection .....

Quality control samples .....

No of units rejected .....

No of units passed .....

Information given to

Signature of Chemist-in-Charge

STORES INDENT - Packing Materials

PRODUCT:				ARTICLE NO.		
Batch No.				Batch size:		
S. No.	Item	Article No.	C.No.	Qty.	Issued by	Remarks
A.	Primary packing materials					
	2 ml amber amps					
B.	Secondary packing Materials					
1.	Labels					
2.	25's box labels					
3.	100's labels					
4.	S'S cartons					
5.	25's box					
6.	100's box					
			Issued by ..... Received by			

PACKAGING

Product:	Article No.	Sales/samples:	Date:
Batch No.:	Batch size:	Batch size in: units	
Date of Mfg:	Date of exp.:		

Instructions: Remove all irrelevant material from the packing area.

Check for the product, pack and approval for packing and attach.

Inspect and certify first final packed unit.

Attach stores indent for sec. packing materials

Operation	Performed by
Label over printing	)
Carton overprinting	)
Carton folding	)
Labelling	)
Dust capping	)
Packing	)
Closing	
Final packing	
Checked by	

(continued)

No. of units approved for packing

No. of labels received

No. of units packed

No. of labels used

No. of units rejected

No. of labels rejected

Reasons

No. of units for ref. sample

No. of excess labels destroyed

No. of units transferred to F.P. stores

Q.C. Inspector	Production Chemist

Q.C. Inspector	Production Chemist

Signature of Chemist-in-Charge: .....