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ESTABLISHMENT OF A DEVELOPMENT PLAN
FOR THE PHARMACEUTICAL INDUSTRY

UC/ALG/85/062

ALGERIA

Technical Report: Transfer of Technology
for the Production of Pharmaceutical Chemicals
in a Multi-Purpose Plant*,

Prepared for the Government of the Democratic
and People's Republic of Algeria by the
United Nations Industrial Development Organization

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SUMMARY

1. The pharmaceutical industry in Algeria is confined to the production of pharmaceuticals in dosage form. The local production meets around 8 percent of the country's requirement in value and the balance is met through imports.
2. At present all the bulk drugs and most of the excipients required by the local pharmaceutical industry are imported. A large modern complex for the production of antibiotics is at an advanced stage of establishment at Médéa. This will enable the country to achieve self-reliance with respect to antibiotics in bulk.
3. As regards synthetic drugs, with the exception of Aspirin, Vitamin C and Sorbitol, the individual requirements are rather small even when projected to the year 2000. In view of the limited domestic market, the establishment of a single line production in the case of each pharmaceutical chemical will not be economically viable. In such cases, the establishment of a multi-purpose plant is the logical choice and is, therefore, recommended. Such a plant is ideally suited to produce a number of pharmaceutical chemicals in small quantities, which suits the situation in Algeria. Such a plant has flexibility, can be used for training, adaptation of technology and research and development. The investment in this case is also comparatively low.
4. The proposed multi-purpose plant is designed to produce 17 pharmaceutical chemicals considered essential for the country. The plant is divided into two sections. In Section I, fourteen pharmaceutical chemicals of small volume are produced. In Section II three pharmaceutical chemicals of relatively large volume are produced. The production level in each case is the anticipated demand in the year 1990.
5. The technology for the production of all the 17 pharmaceutical chemicals is such that there are no complicated reactions involved, no high sophisticated equipment required and patents have expired in most of the cases. The processes start at an early stage and the raw materials required are widely available and not bound to any source or country.
6. An important feature of the multi-purpose plant is that it has adequate facilities for research and development. This will facilitate adaptation of the acquired technology to suit local conditions and raw materials. This will also enable the country to have a sound base for the development of new drugs and products to meet its specific requirements.

7. The selection of equipment is such that the equipments are available from several sources and are not bound to any country or source.
8. Training is an important feature of the multi-purpose plant. Algerian engineers and technicians will be trained right from the stage of design of the plant, through construction, installation and operation. Key persons are also trained abroad.
9. Details of investment have been worked out. The proposed multi-purpose plant including the laboratory for chemical technologies will entail an investment of US\$ 11.06 million out of which the cost of equipment amounts to US\$ 5.12 million, that of civil construction to US\$ 5.00 million and the balance being the cost technical know-how and engineering design.
10. The multi-purpose plant project can be implemented in the course of three years.

1.0 INTRODUCTION

The Pharmaceutical Industry in Algeria is confined to the production of pharmaceuticals in dosage form. The local production meets around 8 percent of the country's requirement, in value which amount to US\$ 144.1 million in 1988 and the balance is met through imports in the finished form. The production is carried in three units: El Harrach, Pharmal and Biotic and comprises tablets, capsules, creams and suppositories except for two injectables produced by Biotic. The above three units have conventional machinery, some of which is automated and in some cases rather old. Out of the three units, Pharmal plant is the most modern and automated. These three units together produce 56 products with 69 pharmaceutical forms. The plants operate in one shift only.

Each unit has its own quality control laboratory but no Research and Development facilities. These laboratories are reasonably well equipped. They also have well trained staff. The analytical facilities in general are satisfactory. The objective of SAIDAL is to substantially increase the production within the country and gradually decrease the dependence on imports.

The control laboratory is under the Ministry of Health and is situated in the premises of the Biotic plant. This laboratory has a staff of about 30 and has conventional equipment for analysis of formulations. The size of the laboratory is much too small and the equipment rather inadequate to carry out all the studies. The laboratory for Development and Research (LDR) is the only development laboratory of SAIDAL and was established in 1975 for the development of formulations and for providing technical assistance to production units. It has a staff of 40.

As regards production of bulk drugs, a large modern complex for the production of antibiotics is under establishment at Médéa. The plant with a capital investment of approximately \$220 million has nine fermentors each of 130 m³ capacity and is expected to be completed in 1987. When in full operation, the plant is expected to produce Penicillin G 135 t, Penicillin V 29 t, Tetracycline 49 t, Oxytetracycline 15.4 t, Streptomycin 33 t, Semisynthetic Penicillin 61 t and their formulations.

At present all the bulk drugs and most of the excipients required by the local pharmaceutical industry are imported.

The quantities of pharmaceutical chemicals consumed in 1982 and the projected requirements in 1990, 1996 and 2000 are indicated in Annex 1.

2.0 STRATEGY FOR LOCAL PRODUCTION OF PHARMACEUTICAL CHEMICALS THROUGH SYNTHESIS

As already indicated above, a large complex for the production of antibiotics in bulk is at the final stages of establishment at Nédéa. As can be seen from Annex 1, a large number of pharmaceutical chemicals is being imported at present to feed the local pharmaceutical industry. In view of this, the feasibility of undertaking the local production of some of these pharmaceutical chemicals needs to be examined. This aspect has been dealt with in several UNIDO documents some of which have been presented to the second consultation on the Pharmaceutical Industry.¹

The economic feasibility of local production of pharmaceutical chemicals on an industrial scale depends primarily on:

- Adequate size of domestic market
- Required level of technology which is appropriate
- Availability of skilled manpower and infrastructure, etc.

Based on the above factors, the production of a single pharmaceutical chemical would be feasible if the market demand justifies and production becomes economically feasible given the appropriate technology. However an examination of Annex 1 reveals that with the exception of a few pharmaceutical chemicals, the individual requirements are rather small even when projected to the year 2000. In such cases the idea of multi-purpose plant for the production of essential pharmaceuticals has been recommended.

2.1 CONCEPT OF MULTIPURPOSE PLANT FOR PRODUCTION OF PHARMACEUTICAL CHEMICALS

Depending on the similarity of the production technologies of different synthetic drugs relating to unit processes and unit operations involved, facilities for production of a group of pharmaceutical chemicals can be designed and equipped. Such a facility is termed "Multi-purpose plant" since several synthetic drugs can be manufactured in this plant either sequentially or to some extent simultaneously using a single series of equipment.

1. Second Consultation on the Pharmaceutical Industry ID/311/1983
Multi-purpose plant for production of UNIDO essential drugs based on raw materials and intermediates ID/WG.393/18

The main advantages of a multi-purpose plant for the production of pharmaceutical chemicals are as follows :

- It is ideally suited to produce a number of different pharmaceutical chemicals and in small quantities.
- Relatively small investment is needed
- At a later date, new products can be introduced with minimum investment
- The production of any particular pharmaceutical chemical can be increased to a certain extent with marginal investment to cope with an increase in the demand

3.0 MULTI-PURPOSE PLANT FOR THE PRODUCTION OF PHARMACEUTICAL CHEMICALS IN ALGERIA

Taking into consideration the market demand and prospects as can be seen from Annex 1, infrastructure facilities and skilled manpower available based on the assessment made recently, the establishment in Algeria of a multi-purpose plant for the production of a group of 17 pharmaceutical chemicals is recommended. The pharmaceutical chemicals and the production level proposed in each case are indicated in Annex 2. As can be seen from the latter annex, the pharmaceutical chemical production is grouped in two sections. Section I contains 14 pharmaceutical chemicals of relatively small quantities with a combined quantity of 53.5 tons. The equipments required for this section are also of relatively smaller size. Section II contains 3 pharmaceutical chemicals with a combined quantity of 500 tons. All these three chemicals are of relatively larger quantities. In fact Sorbitol is also an intermediate for the production of Vitamin C.

3.1 BASIS FOR SELECTION OF PHARMACEUTICAL CHEMICALS

In Annex 1, the demand forecast for the years 1990 and 2000 is given. The production level in the case of each pharmaceutical chemical is the anticipated demand in the year 1990. By the time the multi-purpose plant is established, it is expected that the entire output of the plant will be consumed. As regards the selection of the pharmaceutical chemicals, this is based on their essential nature as well as the fact that these drugs are widely used all over the world, have no known adverse reactions and are not expected to become obsolete in the foreseeable future.

3.2 TECHNOLOGY

Technology is perhaps the key element in the production of pharmaceutical chemicals. The type of technology, the appropriateness, efficiencies at each step, starting materials their price and availability, patent situation and

finally the availability of technology itself and price are important factors to be taken into account while acquiring technology. The technology for the production of pharmaceutical formulations is relatively simple and is well diffused. However the technology for the production of pharmaceutical chemicals is more sophisticated and is held by few sources. It is, therefore, necessary to acquire such a technology which can be adapted to local conditions. The pharmaceutical chemicals indicated in Annex 2 are such that there are no complicated reaction steps involved, no sophisticated equipment required and the patents have expired in most of the cases. So the acquisition of technology and its adaptation should not present problems.

3.3 STARTING MATERIALS

An important consideration in the selection of technology is the starting materials. It is important to start the reaction from as early a stage as possible so that the starting materials are available widely. This will also provide an opportunity to the Algerian technicians to master different unit processes and operations. If the technology is based on late intermediate chemicals, for which there is monopoly, this will restrict the viability of the multi-purpose plant since such intermediates may not be available from a number of sources and their cost may be higher than the finished product itself. Taking into consideration all these factors, the starting materials in the case of each pharmaceutical chemical have been selected and these are indicated in Annex 3.

3.4 REACTION SCHEMES FOR THE PRODUCTION OF PHARMACEUTICAL CHEMICALS

The reaction schemes for the production of pharmaceutical chemicals are given in Annex 4.

3.5 RESEARCH AND DEVELOPMENT

It is important to establish research and development facilities within the multi-purpose plant complex for various reasons. First, it is necessary to adapt the acquired technology to suit local conditions and raw materials. Second, it is also necessary to improve the economics of production. Finally Algeria should be in a position to develop new pharmaceutical chemicals or new products to meet its specific requirements. As already indicated, at present no adequate facilities are available for research and development. In view of this, an area of 868 m² has been provided for this purpose along with necessary equipment, sophisticated instrumentation and other facilities.

3.6 SELECTION OF EQUIPMENT

The proposed multi-purpose plant has been designed to have flexibility, ease of operation and facilities for research and development. It has a combined reactor capacity of 37 m³, and has scale up facilities. The laboratory equipment is designed to facilitate routine in-process control, quality control of raw materials and finished products as well as up-to-date facilities for research and development. The equipment details are indicated in Annex 5.

3.7 TRAINING

Training assumes great importance while planning the establishment of basic manufacture of pharmaceutical chemicals. In view of this, training is an integral part of the multi-purpose plant starting right from the design stage, continuing through the stages of construction, installation of equipment, testing and commissioning and operation and research and development. The personnel requirements are shown in Annex 6. 81 skilled workers, technicians, engineers and scientists are provided. All these personnel are trained at site and 20 out of these are also trained abroad as shown in Annex 7.

3.8 INVESTMENT PARAMETERS

The cost of civil construction is indicated in Annex 8. The cost of installed equipment is shown in Annex 9. The estimated cost of the project is given in Annex 10. As can be seen from the latter annex, the project is estimated to cost US\$ 11,060 million out of which 46 percent is the cost of equipment and 45 percent is that of civil construction. This is due to high cost of building.

Market demand of pharmaceutical chemicals

| Pharmaceutical Chemicals | Quality | Quantity (in tonnes) | | |
|-----------------------------|---------|----------------------|-------|-------|
| | | 1982 | 1990 | 2000 |
| <u>Presently supported</u> | | | | |
| Sorbitol | | 60.0 | 109 | 200.0 |
| Vitamin C | | 100.0 | 183 | 360.0 |
| Acetylsalicylic acid | | 102.0 | 185 | 370.0 |
| Tri-acetyl oleandomycin | | 7.0 | 12.8 | 25.0 |
| <u>To be manufactured</u> | | | | |
| Dexchlorpheniramine maleate | | 0.021 | 0.038 | 0.075 |
| Sulfamethoxazole | | 6.5 | 11.8 | 23.0 |
| Trimethoprim | | 1.3 | 2.3 | 4.5 |
| Codeine | | 0.2 | 0.36 | 0.7 |
| Codethyline | | 0.2 | 0.36 | 0.7 |
| Cetrimonium bromide | | 0.2 | 0.36 | 0.7 |
| Ibuprofen | | 2.4 | 4.4 | 8.7 |
| Haloperidol | | 0.02 | 0.03 | 0.06 |
| Amitriptyline | | 1.0 | 1.83 | 3.5 |
| Mebeverine | | 0.6 | 1.1 | 2.0 |
| Furosemide | | 0.4 | 0.7 | 1.4 |
| Paracetamol | | 8.0 | 14.6 | 28.0 |
| Fluphenazine | | 0.005 | 0.010 | 0.020 |
| Diclofenac | | 0.6 | 1.1 | 2.0 |
| Glafenine | | 10.0 | 18.3 | 36.0 |
| Allopurinol | | 1.5 | 2.7 | 5.3 |
| Niflumic acid | | 3.0 | 5.5 | 10.0 |
| Piroxicam | | 0.06 | 0.1 | 0.2 |
| Alimemazine | | 0.25 | 0.45 | 0.90 |
| Mebhydrolin | | 0.2 | 0.36 | 0.7 |
| Napadisylate | | | | |
| Carbamazepine | | 2.0 | 3.6 | 7.1 |
| Phenobarbitone | | 0.75 | 1.3 | 2.5 |
| Phenytoin | | 0.5 | 0.9 | 1.7 |
| Thiobendazole | | 0.75 | 1.3 | 2.5 |
| Pyrantel pamoate | | 0.4 | 0.7 | 1.4 |
| Doxycycline | | 2.0 | 3.6 | 7.1 |
| Nifuroxazide | | 1.5 | 2.7 | 5.4 |
| Tiliquinol | | 2.0 | 3.6 | 7.1 |
| Tibroquinol | | 0.5 | 0.9 | 1.8 |
| Pyrimethamine | | 0.025 | 0.045 | 0.09 |

| | Quantity(in tons) | | |
|--------------------------------|-------------------|-------|-------|
| | 1982 | 1990 | 2000 |
| <u>Pharmaceutical chemical</u> | | | |
| Sulphadoxine | 0.5 | 0.9 | 1.8 |
| Nalidixic acid | 4.0 | 7.3 | 14.0 |
| Cephalexine | 1.2 | 2.2 | 4.0 |
| Metronidazole | 1.0 | 1.8 | 3.5 |
| Dihydroergotamine | 0.036 | 0.06 | 0.12 |
| Cyclophosphamide | 0.125 | 0.22 | 0.4 |
| Trihexyphenidyl | 0.040 | 0.07 | 0.13 |
| Levodopa | 1.5 | 2.7 | 5.2 |
| Benzetazide | 0.4 | 0.7 | 1.3 |
| Acenocumazole | 0.025 | 0.045 | 0.09 |
| Aminocaproic acid | 12.0 | 22.0 | 41.0 |
| Methyldopa | 5.2 | 9.5 | 18.0 |
| Dipyridamol | 0.7 | 1.2 | 2.1 |
| Ethyl biscoumacetate | 1.2 | 2.2 | 4.0 |
| Nicotamide | 0.4 | 0.7 | 1.3 |
| Acebutolol | 2.4 | 4.3 | 8.0 |
| Quinine phenethylbarbitone | 2.0 | 3.6 | 7.1 |
| Cinnarizine | 0.6 | 1.0 | 2.0 |
| Diltiazem | 0.6 | 1.0 | 2.0 |
| Digoxin | 0.004 | 0.007 | 0.013 |
| Isosorbide | 0.060 | 0.1 | 0.2 |
| Phenylindanedione | 0.3 | 0.5 | 1.0 |
| Ethamsylate | 2.5 | 4.5 | 8.9 |
| Propranolol | 0.6 | 1.0 | 2.0 |
| Clonidine | 0.3 | 0.5 | 1.0 |
| Hexachlorocyclohexane | 1.5 | 2.7 | 5.3 |
| Betamethasone | 0.005 | 0.009 | 0.018 |
| Miconazole | 1.0 | 1.8 | 3.5 |
| Dexamethasone | 0.006 | 0.01 | 0.02 |
| Spiroglactone | 0.100 | 0.18 | 0.35 |
| Althiazide | 0.06 | 0.1 | 0.2 |
| Cimetidine | 3.0 | 5.0 | 10.0 |
| Phloroglucinol | 8.0 | 14.6 | 28.0 |
| Levonorgestrel | 0.2 | 0.18 | 0.35 |
| Ethylloestrenol | 0.002 | 0.003 | 0.007 |

| | Quantity (in tons) | | |
|-------------------------------|--------------------|--------|-------|
| | 1982 | 1990 | 2000 |
| Dydrogesterone | 0.020 | 0.0036 | 0.07 |
| Triamcinolone acetonide | 0.050 | 0.09 | 0.17 |
| Nandrolone | 0.050 | 0.09 | 0.17 |
| Saccharine | 0.5 | 0.9 | 1.7 |
| Dienoestrol | 0.005 | 0.009 | 0.017 |
| Prednisolone | 0.030 | 0.05 | 0.1 |
| Glybenclamide | 0.030 | 0.05 | 0.1 |
| Baclofene | 0.150 | 0.27 | 0.5 |
| Chlormezanone | 1.6 | 2.9 | 5.7 |
| Hydrocortisone acetate | 0.075 | 0.13 | 0.25 |
| Lorazepam | 0.025 | 0.04 | 0.08 |
| Calcium bromogalactogluconate | 180.0 | 329 | 600.0 |
| Salbutamol | 0.016 | 0.03 | 0.05 |
| Terbutaline | 0.040 | 0.07 | 0.14 |
| Thiamine | 0.125 | 0.228 | 0.400 |
| Riboflavin | 0.125 | 0.228 | 0.400 |
| Calcium pantothenate | 0.125 | 0.228 | 0.400 |
| Nicotinamide | 0.625 | 1.14 | 2.2 |
| Calcium gluconolactate | 30.0 | 55.0 | 100.0 |
| Aluminium hydroxide | 5.0 | 9.0 | 17.0 |
| Magnesium hydroxide | 5.0 | 9.0 | 17.0 |
| Aluminium phosphate | 220.0 | 400.0 | 750.0 |
| Indomethacin | 0.2 | 0.5 | |
| Isoniazid | 0.1 | 0.2 | |
| Lidocaine hydrochloride | 0.01 | 0.05 | |
| Diazepam | 0.035 | 0.10 | |

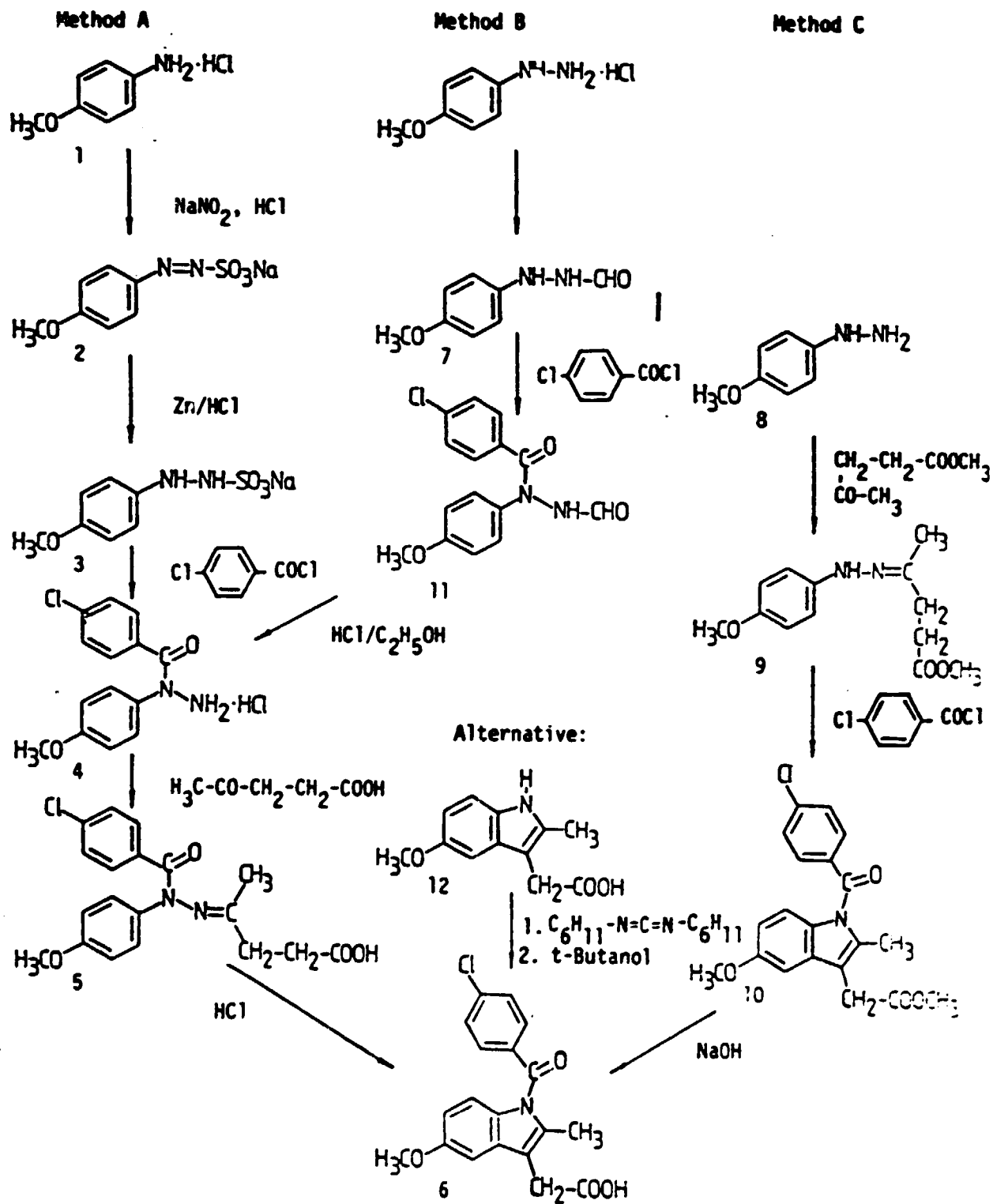
PROPOSED PRODUCTION LEVEL FOR DIFFERENT
PHARMACEUTICAL CHEMICALS

| | <u>Serial No.</u> | <u>Pharmaceutical Chemical</u> | <u>Quality Standard</u> | <u>Proposed Annual Production (in tons)</u> |
|------------|-------------------|--------------------------------|-------------------------|---|
| SECTION I | 1 | Carbamazepine | F.P. | 4.0 |
| | 2 | Clonidine | F.P. | 0.5 |
| | 3 | Diclofenac | F.P. | 1.0 |
| | 4 | Ibuprofen | F.P. | 4.5 |
| | 5 | Indomethacin | F.P./U.S.P./ B.P. | 0.5 |
| | 6 | Metronidazole | F.P./U.S.P./ B.P. | 2.0 |
| | 7 | Nalidixic Acid | F.P./U.S.P./ B.P. | 7.5 |
| | 8 | Nicotinamide | F.P./U.S.P./ B.P. | 1.0 |
| | 9 | Nikethamide | F.P./B.P. | 1.0 |
| | 10 | Paracetamol | F.P./B.P. | 15.0 |
| | 11 | Phenytoin | F.P./U.S.P. | 1.0 |
| | 12 | Propranolol | F.P./U.S.P./ B.P. | 1.0 |
| | 13 | Sulphamethoxazole | F.P./U.S.P. | 12.0 |
| | 14 | Trimethoprim | F.P./U.S.P. | 2.5 |
| | | | <u>53.5</u> | |
| SECTION II | 1 | Sorbitol | | 110 |
| | 2 | Vitamin C | F.P./U.S.P. | 200 |
| | 3 | Acetyl Salicylic Acid | F.P./U.S.P. | 190 |
| | | | <u>500</u> | |

STARTING MATERIALS FOR PHARMACEUTICALCHEMICALS

| <u>Serial No.</u> | <u>Pharmaceutical Chemical</u> | <u>Starting Material/Intermediate</u> |
|-------------------|--------------------------------|---------------------------------------|
| SECTION I | | |
| 1 | Carbamazepine | Iminostilbene |
| 2 | Clonidine | Dichloroformanilide |
| 3 | Diclofenac | Dichloroaniline |
| 4 | Ibuprofen | Isobutylbenzene |
| 5 | Indomethacin | P-Anisidine |
| 6 | Metronidazole | 2-Methyl-5-Nitro-imidazole |
| 7 | Nalidixic Acid | 6-Amino-2-Picoline |
| 8 | Nicotinamide | 3-Cyanopyridine |
| 9 | Nikethamide | Nicotinic acid |
| 10 | Paracetamol | P-Aminophenol |
| 11 | Phenytoin | Benzil |
| 12 | Proprianolol | Alpha-naphthol |
| 13 | Sulphamethoxazole | 3-Amino-5-Methyl-isoxazole |
| 14 | Trimethoprim | 3,4,5-Trimethoxy-benzaldehyde |
| SECTION II | | |
| 1 | Sorbitol | D-glucose |
| 2 | Vitamin C | D-glucose |
| 3 | Acetyl Salicylic Acid | Salicylic Acid |

INDOMETACIN



* Please note that only a few reaction schemes and brief process description as illustration.

METRONIDAZOLE

Chemical Name : 2-methyl-5-nitroimidazole-1-ethanol

Uses : Antiprotozoal

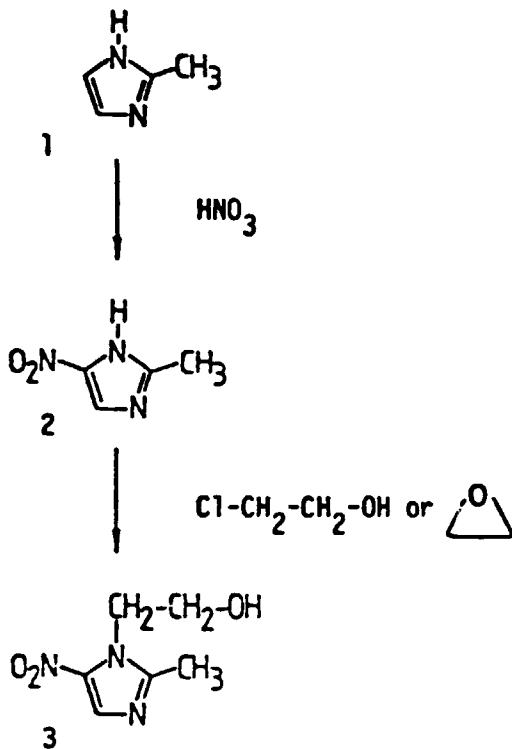
Brief Description of Process

2-Methyl-5-nitroimidazole is heated with an excess of ethylene chlorohydrin for several hours at 130°C. The excess ethylene chlorohydrin is then distilled over under reduced pressure. The residue is slurried in water and filtered. The filtrate is made alkaline by addition of sodium hydroxide solution and extracted with organic solvent. The organic extract is concentrated under reduced pressure and the residue recrystallised from ethyl acetate to give metronidazole.

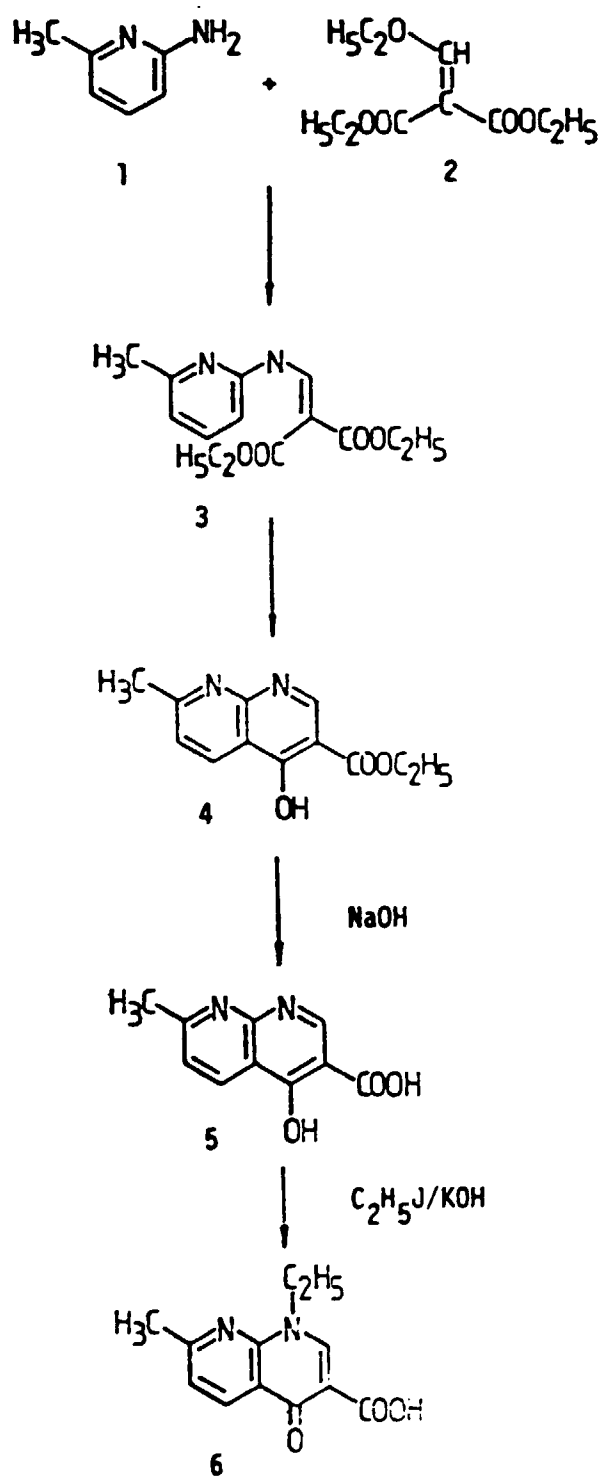
Intermediates : 1. 2-methyl-5-nitroimidazole
2. Ethylene chlorohydrin (or ethylene oxide)

Notes : Handling of ethylene chlorohydrin or ethylene oxide is hazardous and involves carefully designed storage and manufacturing equipment.

METRONIDAZOLE



NALIDIXIC ACID



NICOTINAMIDE

Chemical Name : Nicotinamide

Use : Enzyme co-factor vitamin

Brief Description of Process :

1. 3 Cyano pyridine is heated with aq. sulphuric acid for 12 to 15 hours to give nicotinamide. Alternately reaction of 3-Cyanopyridine with aq. ammonia at 200°C to 260°C also gives nicotinamide.

Intermediates : 1. 3-Cyano pyridine

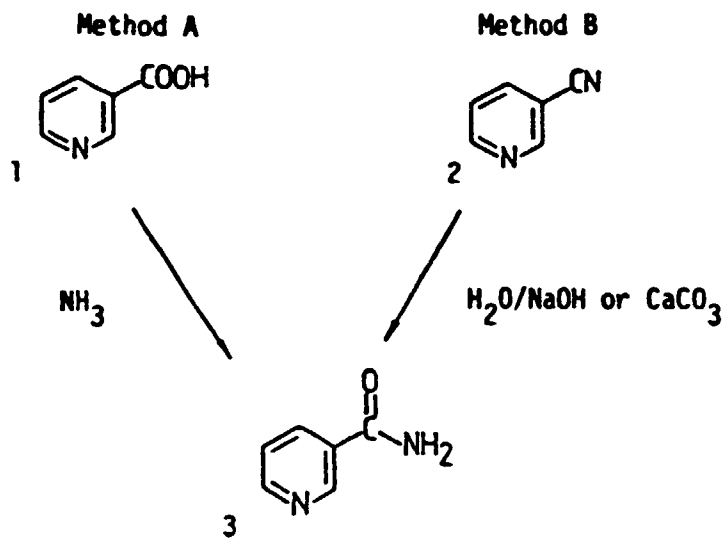
2. Nicotinic acid

Notes

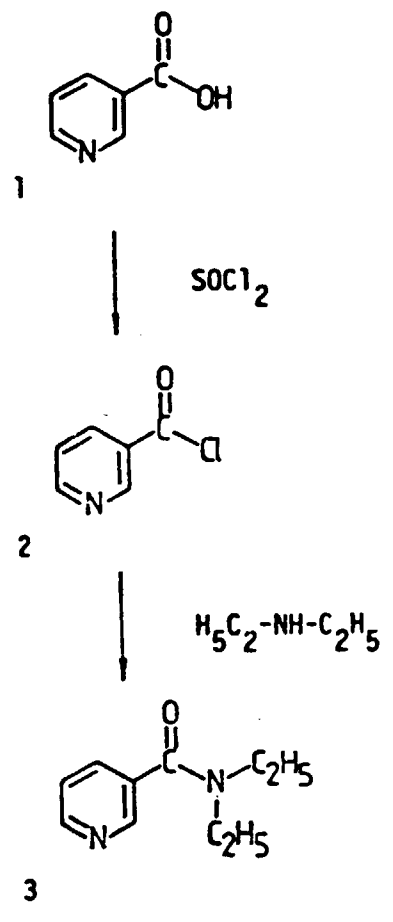
: 1. Involves handling of ammonia under high pressure and temperature.

2. Involves handling of concentrate sulphuric acid at high temperatures.

NICOTINAMIDE



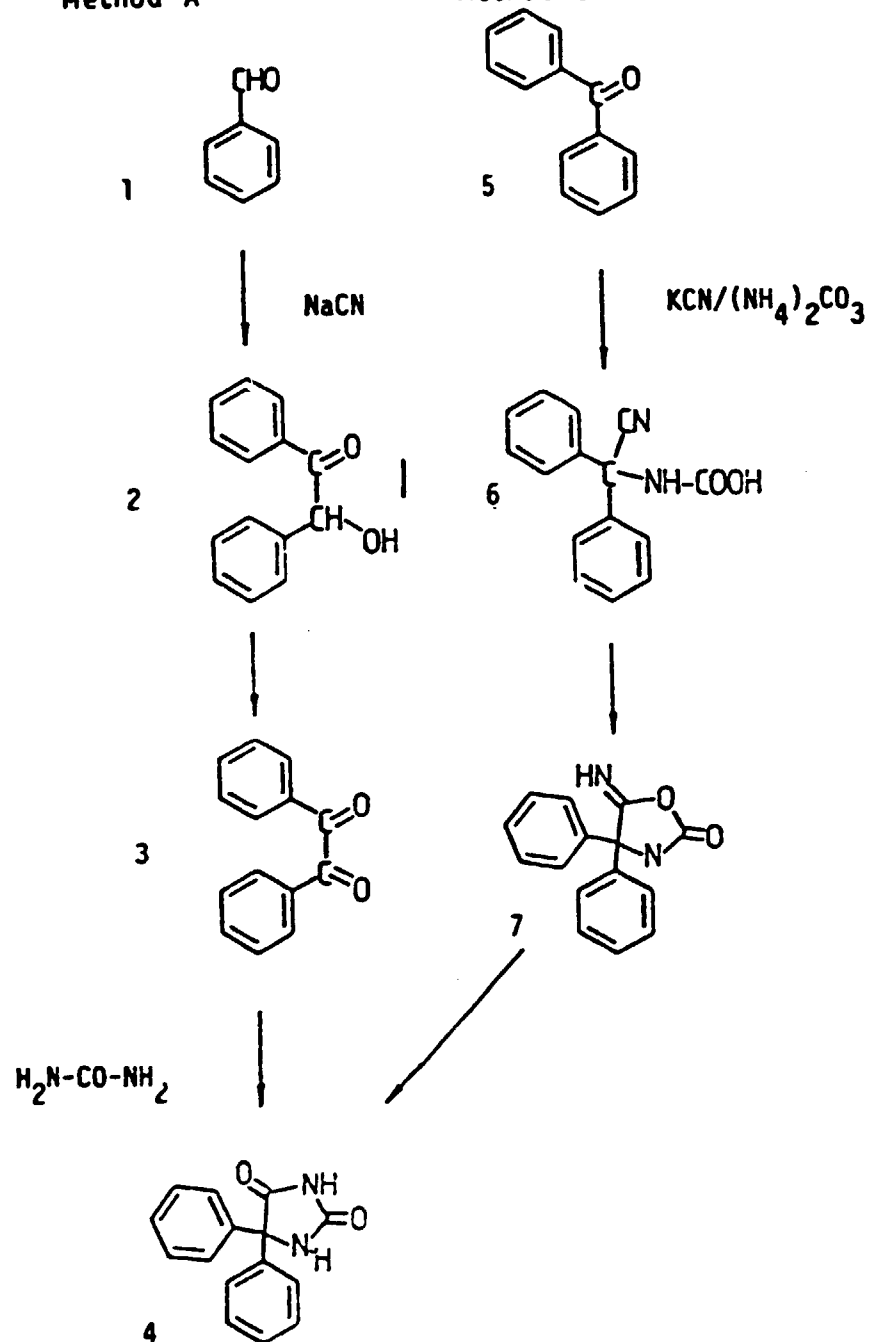
NIKETHAMIDE



DIPHENYLHYDANTOIN
(PHENYTOINE)

Method A

Method B



PARACETAMOL (ACETAMINOPHEN)

Chemical Name : N-(4-Hydroxyphenyl) acetamide
Uses : Analgesic, Antipyretic

Brief description of process:

p-Aminophenol is acetylated with acetic anhydride in presence of anhydrous sodium acetate and trace of sodium hydrosulfite or sodium sulfite. The reaction mixture is then chilled to 8° to 10°C with stirring to crystallise out paracetamol.

Intermediates : 1) p-Aminophenol

PARACETAMOL



1



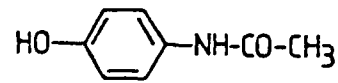
H₂/Raney-Ni



2

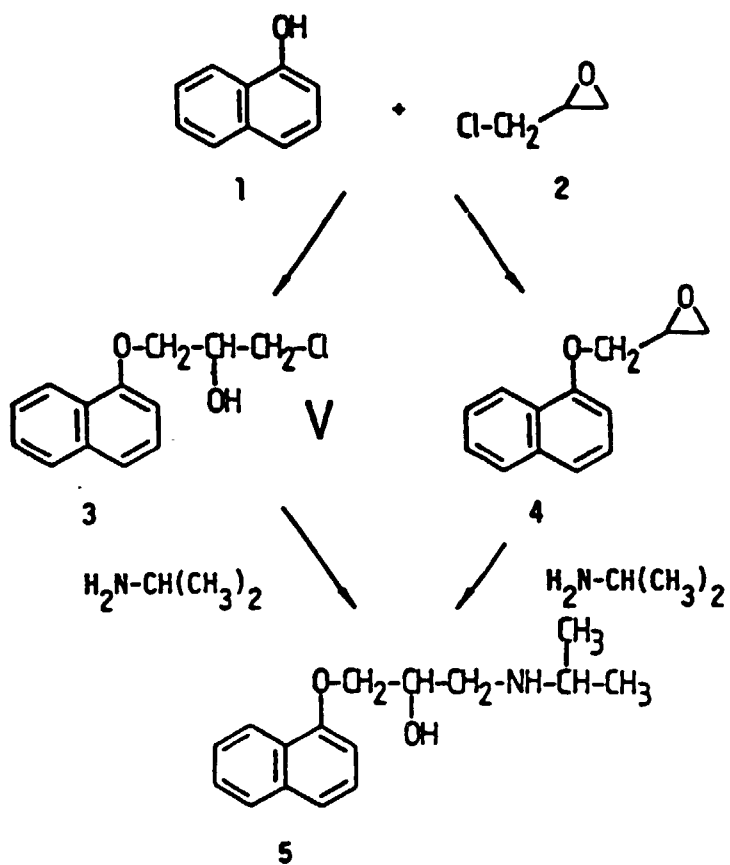


(H₃C-CO)₂O



3

PROPRANOLOL



SULPHAMETHOXAZOLE

Chemical Name : 4-Amino-N-(5-methyl-3-isoxazolyl) benzene-sulfonamide

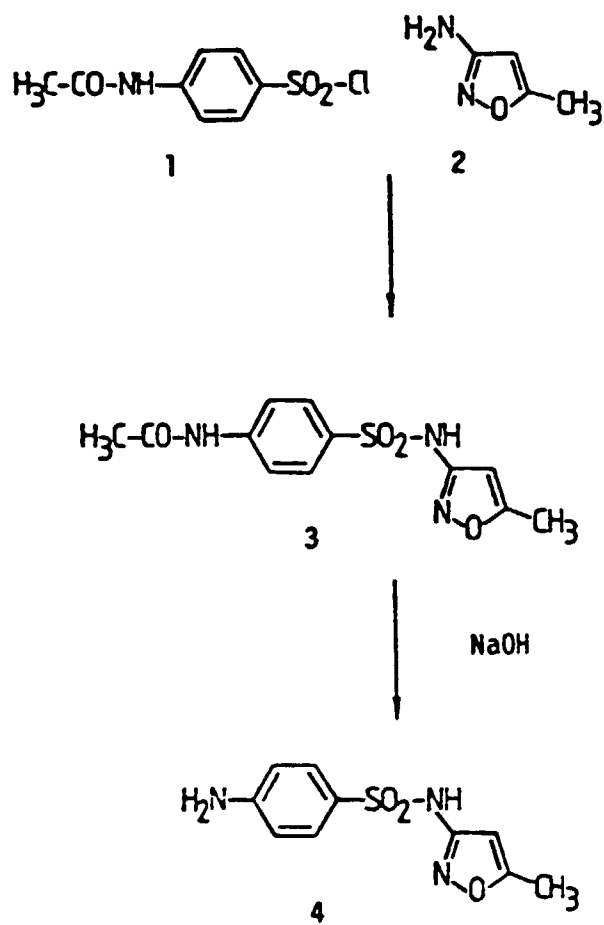
Use : Antibacterial

Brief description of process :

3-Amino-5-methylisoxazole solution in pyridine is reacted with acetyl sulphanil chloride. After the exothermic reaction is over water is gradually added to the reaction mixture to precipitate 3-Acetylsulfanilamido-5-methylisoxazole. The crude product is recrystallised from alcohol. The pure 3-acetylsulfanilamido-5-methylisoxazole is heated with aq. sodium hydroxide solution for an hour and then the reaction mixture is acidified by addition of acetic acid. The precipitate is filtered and recrystallised from dilute alcohol to give sulphamethoxazole.

Intermediates : 1) 3-Amino-5-methylisoxazole
2) Acetyl sulphanil chloride

SULFAMETHOXAZOLE



TRIMETHOPRIM

Chemical Name : 5-[(3,4,5-trimethoxyphenyl) methyl]-2,4-pyrimidine diamine

Use : Antibacterial

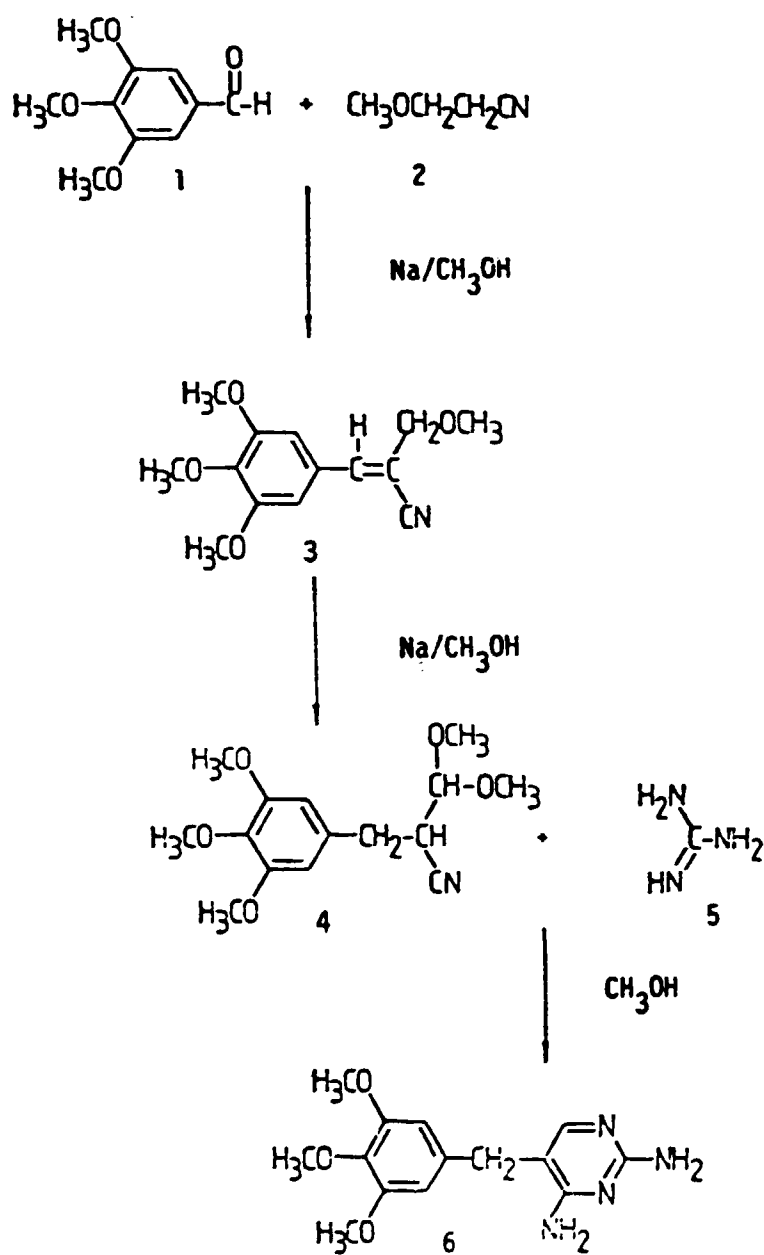
Brief description of process:

3,4,5 trimethoxybenzaldehyde is reacted with B-methoxy propionitrile in presence of sodium methoxide in methanol. After refluxing for 4 hours, the reaction is chilled and water is carefully added. The crude product is filtered and recrystallised from methanol to give 3,4,5 trimethoxy-2-methoxy methylcinnamionitrile. This is reduced by sodium in methanol to give 3,4,5 trimethoxy-2'-cyano-dihydrocinnamaldehyde dimethyl acetal. The recrystallised product is refluxed with a solution of guanidine base in methanol for two hours, the excess methanol removed by distillation and the crude product isolated after chilling the reaction mixture.

The crude product is purified by dissolving in aq.acid, charcoaling the solution and basifying the clear filtered solution to give pure trimethoprim.

Intermediates : 1) 3,4,5-Trimethoxy benzaldehyde
2) B-Methoxypropionitrile
3) Sodium / Sodium methoxide
4) Guanidine base.

TRIMETHOPRIM



ASPIRIN

Chemical Name : 2-(Acetoxy) benzoic acid

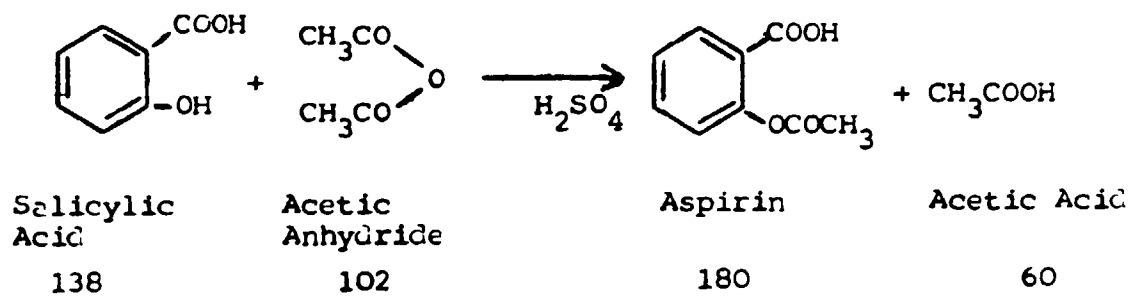
Use : Analgesic, antipyretic, anti-inflammatory

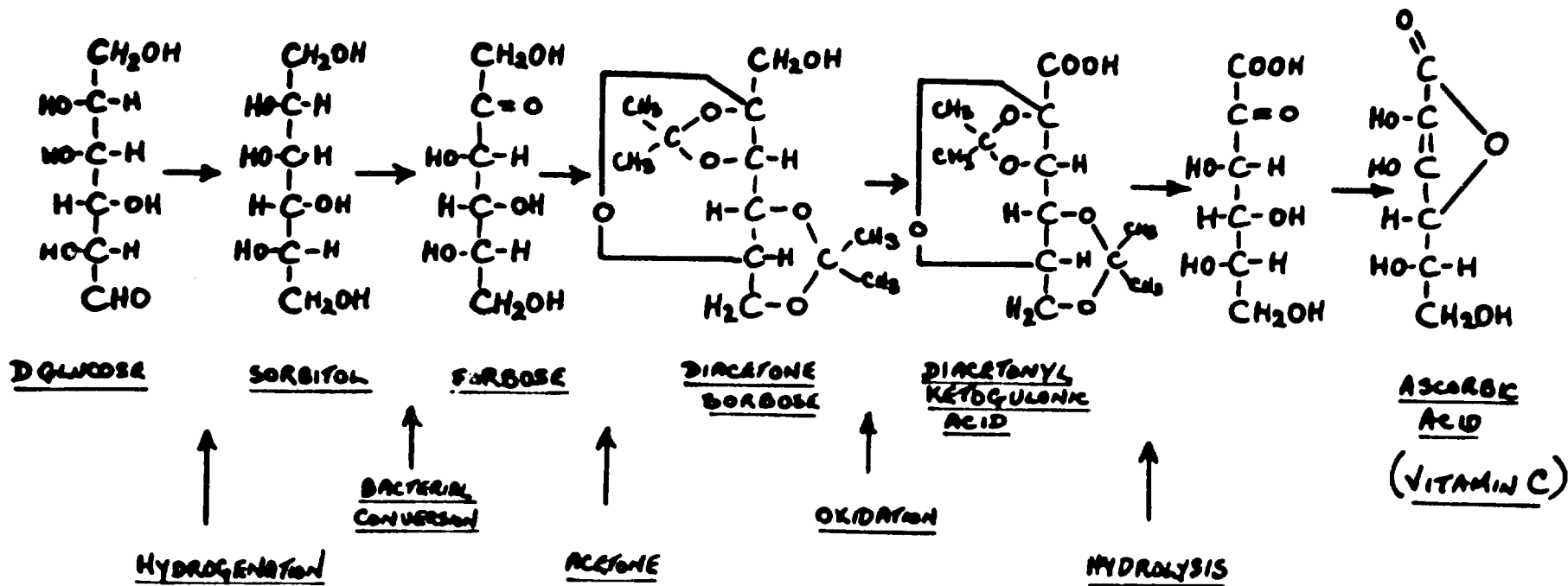
Brief description of process:

Salicylic acid is heated to 90°C with excess of acetic anhydride in toluene medium. After several hours of heating the reaction mixture is allowed to cool and the crystallised product is centrifuged and washed with water until the product is free from acetic acid to give the pure product.

Intermediates : Salicylic acid

ACETYL SALICYLIC ACID





VITAMIN C PROCESS.

PROPOSED LIST OF EQUIPMENT - PROCESS EQUIPMENT

| Serial No. | Equipment | Capacity | Quantity | Material of Construction |
|------------|---------------------------------------|----------------------|----------|-----------------------------|
| 1 | 2 | 3 | 4 | 5 |
| 1 | Jacketed reactor with agitator | 1600 l | 2 | Enamelled |
| 2 | Condenser | 8 m ² | 3 | Glass lined |
| 3 | Charging tank | 250 l | 1 | Polyester with glass fibres |
| 4 | Receiver tank | 500 l | 4 | Glass lined |
| 5 | Balance | 500 kg | 1 | Steel |
| 6 | Balance electronic | 250 kg | 2 | Steel |
| 7 | Pump | 10 m ³ /h | 3 | Teflon coated |
| 8 | Centrifuge with under-evacuation | ∅ 1250 m/m | 2 | Coated with Halar |
| 9 | Collecting tank for centrifuge liquid | 630 l | 6 | Coated with Halar |
| 10 | Collecting tank | 630 l | 2 | Rubber coated |
| 11 | Pump | 10 m ³ /h | 6 | PP |
| 12 | Gas suction injector | H = 60m | 1 | PP |
| 13 | Jacketed tank with cooling | 1000 l | 1 | Glass lined |
| 14 | Jacketed reactor with agitator | 3000 l | 3 | Enamelled steel |
| 15 | Condenser | 12,5 m ² | 2 | Glass lined |

| 1 | 2 | 3 | 4 | 5 |
|----|---------------------------------------|----------------------|----|-----------------|
| 16 | Feeding tank | 250 l | 1 | Stainless steel |
| 17 | Balance electronic | 500 kg | 2 | Steel |
| 18 | Jacketed reactor with agitator | 3000 l | 2 | Glass lined |
| 19 | Condenser | 12,5 m ² | 1 | Glass lined |
| 20 | Bag filter | 0,5 m ² | 2 | Enamelled steel |
| 21 | Condenser | 12,5 m ² | 1 | Glass lined |
| 22 | Charging tank | 250 l | 1 | Stainless steel |
| 23 | Receiver tank with cooling | 1000 l | 2 | Stainless steel |
| 24 | Water ring vacuum pump | 60 m ³ /h | 2 | Steel |
| 25 | Pump | 10 m ³ /h | 5 | Stainless steel |
| 26 | Centrifuge with under-evacuation | Ø 1000 m/m | 3 | Stainless steel |
| 27 | Collecting tank for centrifuge liquid | 630 l | 10 | Stainless steel |
| 28 | Collecting tank | 500 l | 1 | Stainless steel |
| 29 | Pump | 6 m ³ /h | 2 | Stainless steel |
| 30 | Jacketed reactor with agitator | 500 l | 2 | Glass lined |
| 31 | Condenser | 8 m ² | 1 | Glass lined |

| 1 | 2 | 3 | 4 | 5 |
|----|--------------------------------|-----------------------|---|-----------------|
| 32 | Receiving tank/cooled | 8 m ² | 2 | Stainless steel |
| 33 | Cooled tank | 1000 l | 1 | Steel |
| 34 | Absorption injector | | 1 | PP |
| 35 | Tank | 6300 l | 1 | Enamelled steel |
| 36 | Vacuum-Puffer tank | 250 l | 1 | Steel |
| 37 | Water ring vacuum pump | 250 m ³ /h | 2 | Steel |
| 38 | Pump/mud | 10 m ³ /h | 2 | Stainless steel |
| 39 | Tank with cooling | 250 l | 1 | Stainless steel |
| 40 | Fluid dryer | 250 kg/h | 1 | Stainless steel |
| 41 | Balance electronic | 50 kg | 2 | Steel |
| 42 | Turmix sieve | | 1 | Stainless steel |
| 43 | Homogenizer | 1000 l | 1 | Stainless steel |
| 44 | Jacketed reactor with agitator | 1600 l | 1 | Glass lined |
| 45 | Condenser | 8 m ² | 2 | Glass lined |
| 46 | Feeder tank | 250 l | 1 | Stainless steel |
| 47 | Balance electronic | 500 kg | 3 | Steel |
| 48 | Balance electronic | 250 kg | 2 | Steel |
| 49 | Bag filter | 0,5 m ² | 2 | Enamelled steel |
| 50 | Tank | 6300 l | 3 | Glass lined |

| 1 | 2 | 3 | 4 | 5 |
|----|----------------------------|----------------------|---|-----------------------------|
| 51 | Dryer with 40 trays | | 1 | Stainless steel |
| 52 | Condenser | 8 m ² | 2 | Glass lined |
| 53 | Receiving tank/cooled | 500 l | 4 | Enamelled steel |
| 54 | Receiving tank/cooled | 1000 l | 3 | Enamelled steel |
| 55 | Water ring vacuum pump | 60 m ³ /h | 2 | Steel |
| 56 | Gas-absorption injector | | 2 | PP |
| 57 | Cooled tank | 1000 l | 2 | Glass lined |
| 58 | Condenser | 12,5 m ² | 2 | Glass lined |
| 59 | Feeding tank | 250 l | 1 | Polyester with glass fibres |
| 60 | Condenser | 12,5 m ² | 2 | Glass lined |
| 61 | Feeding tank | 250 l | 1 | Stainless steel |
| 62 | Receiving tank/cooled | 1000 l | 4 | Stainless steel |
| 63 | Bag filter | 0,5 m ² | 2 | Glass lined |
| 64 | Condenser | 8 m ² | 2 | Glass lined |
| 65 | Feeder tank | 250 l | 1 | Stainless steel |
| 66 | Receiver tank with cooling | 500 l | 4 | Stainless steel |
| 67 | Water ring vacuum pump | 60 m ³ /h | 2 | Steel |
| 68 | Collecting tank | 500 l | 2 | Stainless steel! |

| 1 | 2 | 3 | 4 | 5 |
|----|------------------------------------|----------------------------|---|-----------------|
| 69 | Hot water boiler | 2000 l | 1 | Stainless steel |
| 70 | Dryer with 40 trays | | 1 | Stainless steel |
| 71 | Vacuum distillations unit complete | p = 0,5 Hgm/m t = 200°C | 1 | Stainless steel |
| 72 | Condenser | 4 m ² | 2 | Glass lined |
| 73 | Receiver tank with cooling | 100 l | 2 | Stainless steel |
| 74 | High-vacuum pump/oil | | 2 | Steel |
| 75 | Water ring vacuum pump | 60 m ³ /h | 2 | Steel |
| 76 | Jacketed reactor with agitator | 1250 l | 2 | Glass lined |
| 77 | Condenser | 4 m ² | 2 | Glass lined |
| 78 | Feeder tank | 100 l | 1 | Stainless steel |
| 79 | Balance electronic | 100 kg | 1 | Steel |
| 80 | Filter press | 2 m ² | 2 | Stainless steel |
| 81 | Jacketed reactor with agitator | 1250 l | 1 | Enamelled steel |
| 82 | Condenser | 4 m ² | 2 | Glass lined |
| 83 | Feeder tank | 100 l | 2 | PP |
| 84 | Receiver with cooling | 250 l | 4 | Glass lined |
| 85 | Water ring vacuum pump | 60 m ³ /h | 2 | Steel |

| 1 | 2 | 3 | 4 | 5 |
|----|---|--------------------|---|-----------------|
| 86 | Gas absorption injector | | 1 | PP |
| 87 | Tank with cooling | 500 l | 1 | Enamelled Steel |
| 88 | Receiver tank | 500 l | 2 | Stainless steel |
| 89 | Tank with cooling | 250 l | 2 | Stainless steel |
| 90 | Filter press | 0,5 m ² | 2 | Glass lined |
| 91 | Vacuum dryer unit with agitator | 0,5 m ³ | 1 | Stainless steel |
| 92 | Balance Electronic | 100 kg | 1 | Steel |
| 93 | Turmix sieve | | 1 | Stainless steel |
| 94 | Pulveriser | | 1 | Stainless steel |
| 95 | Homogenizer unit with 200 l barrels | | 1 | Stainless steel |
| 96 | High pressure hydrogenator for Sorbitol | | 1 | Stainless steel |

TANK FARM EQUIPMENT

| Serial No. | Equipment | Capacity | Quantity | Material of Construction |
|------------|---|-------------------|----------|----------------------------|
| 1 | 2 | 3 | 4 | 5 |
| 1 | Tank for HCL | 10 m ³ | 1 | Polyester with glass fibre |
| 2 | Tank for mother liquor acidified with HCL | 10 m ³ | 1 | Polyester with glass fibre |
| 3 | Tank for sulfuric acid | 10 m ³ | 1 | Steel |
| 4 | Tank for sodium hydroxide | 10 m ³ | 1 | Steel |
| 5 | Tank for ammonium hydroxide | 10 m ³ | 1 | Steel |
| 6 | Tank for ion free water with electrical heating | 10 m ³ | 2 | PP |
| 7 | Tank for softened water with electrical heating | 10 m ³ | 2 | PP |
| 8 | Underground tank for ethanol | 10 m ³ | 1 | Steel |
| 9 | Underground tank for regenerating ethanol | 10 m ³ | 1 | Steel |
| 10 | Underground tank for benzene | 10 m ³ | 1 | Steel |
| 11 | Underground tank for regenerating benzene | 10 m ³ | 1 | Steel |
| 12 | Underground tank for methanol | 10 m ³ | 1 | Steel |

| 1 | 2 | 3 | 4 | 5 |
|----|--|-------------------|---|-----------------|
| 13 | Underground tank for mixture of ethanol-methanol | 10 m ³ | 1 | Steel |
| 14 | Underground tank for toluene | 10 m ³ | 1 | Steel |
| 15 | Underground tank for regenerating toluene | 10 m ³ | 1 | Steel |
| 16 | Underground tank for regenerating acetone | 10 m ³ | 1 | Steel |
| 17 | Underground tank for regenerating acetone | 10 m ³ | 1 | Steel |
| 18 | Underground tank for iso-propanol | 10 m ³ | 1 | Steel |
| 19 | Underground tank for regenerating iso-propanol | 10 m ³ | 1 | Steel |
| 20 | Underground tank for ethylacetate | 10 m ³ | 1 | Steel |
| 21 | Underground tank for regenerating ethylacetate | 10 m ³ | 1 | Steel |
| 22 | Underground tank for ethylenechloride | 10 m ³ | 1 | Stainless steel |
| 23 | Underground tank for regenerating ethylenechloride | 10 m ³ | 1 | Stainless steel |
| 24 | Tank for acetic acid, heated | 10 m ³ | 1 | Aluminium |

| 1 | 2 | 3 | 4 | 5 |
|----|-----------------------------------|---------------------|----|-----------|
| 25 | Tank for regenerating acetic acid | 10 m ³ | 1 | Aluminium |
| 26 | Tank for Diesel-oil | 10 m ³ | 2 | Steel |
| 27 | Pump for several solvents | 5 m ³ /h | 14 | Steel |
| 28 | Pump for several solvents | 6 m ³ /h | 4 | Steel |
| 29 | Pump for acids | 6 m ³ /h | 2 | PP |
| 30 | Pump for sulfuric acid | 6 m ³ /h | 1 | Steel |
| 31 | Pump for alkali | 6 m ³ /h | 2 | Steel |
| 32 | Pump for Diesel-oil | 6 m ³ /h | 1 | Steel |
| 33 | Pump for demineralized water | 3 m ³ /h | 2 | PP |

EQUIPMENT FOR UTILITIES

Boiler Plant

4,5 t/h steam capacity, maximum pressure 12.0 bar gauge, 1 piece of 2 HD type, oil fired boiler, with a degasification feed tank of 5 m³ volume, with feed pumps and feed-water preheater.

Fuel Oil Supply

Unloading station, discharge and storage facilities with 2 pieces of 40 m³ volume storage tanks.

Demineralized Water Supply

Peak requirement 9.0 m³/h demineralized water for the boiler plant, for the cooling water make up and for the process water. Water softener, type DH-1000 HOH with quick strainer type KSz-IV.

3 pieces of 15 m³, type V-56-11 cylindrical storage tank for raw, filtered and demineralized water.

2 pieces of 10 m³ storage tank for chemicals.

Pumps for the demineralizing equipment.

Refrigeration Unit

Capacity : 2 x 290 KW, for the cooling of water solution with 40% propylene glycol.

2 pieces type KWS 560-2 h refrigeration aggregate .

2 pieces 50 m³/V-56-11 type/vertical cylindrical tank.

1 piece 15 m³/V-56-11 type/vertical cylindrical tank.

Circulation and feed pumps, fittings.

Mini-cooling Tower

For the cooling of maximum 400 m³/h cooling water, 2 pieces, type 4 x H40 with pumps and underground lines.

Solid Waste Incinerator

Capacity 400-500 kg/h solid waste to be burned.

Pipeline Network

Mounted on piperacks on steel structure for the distribution and collection of steam, condensate, basic materials and fuel oil. The loading of the pipe-rack is about 1.0 t/running meter.

POWER SUPPLY

In normal operation, No. 1 transformer of 1.000 KVA capacity, voltage reduction 10/0,4 KV, serves for the power supply. In case of failure from the mains, the generator of a 400 KVA Diesel-electrical unit starts automatically and is connected to the common busbar of 0,4 KV voltage.

The aluminium-wound dry transformer/insulated with synthetic resin/ is located in a container Mod. ICC, meeting the ISO standard as per dimensions, lifting and fixing facilities. The same container houses also the 0,4 KV switching equipment of the transformer station.

Several shop distributors serve to supply power to the consumer units in the plant hall. These distributors are located in separate cabins built aside the hall. A distributor unit located on level \pm 0.00 m of the service wing of the building supplies power to the consumers within the service building and to the external consumers. The said distributors will be fed from the transformer station in the container.

The Diesel-electrical reserve power source will be located - also incorporated in a container - in vicinity of the transformer station.

An electric lifting-truck charging station should also be installed on the plant area, suitable to charge simultaneously accumulators of two trucks. Charging will be done outside the building, under a rain-shield cover whereas the charging units themselves will be located within the building/on level \pm 0.00 mm of the service wing.

Laboratory Equipment

| I. | For Pilot Plant Laboratory: | <u>No.</u> |
|----|---|------------|
| | 1. Stainless Steel (SS) Reactor 50 Lit. | 1 |
| | 2. S.S. Reactor 100 lit. | 1 |
| | 3. Glass lined Reactor 50 ltr. | 1 |
| | 4. Glass lined Reactor 100 Lit. | 1 |
| | 5. Fluid Bed Drier 50 Kg. | 1 |
| | 6. S.S. Centrifuge 24" | 1 |
| | 7. All Glass Reactors-cum-distillation Unit 10 lit. | 2 |
| | 8. All Glass Reactors-cum-distillation Unit 25 Lit. | 2 |
| | 9. All Glass Reactors-cum-Distillation Unit 50 lit. | 1 |
| | 10. Vacuum pumps industrial | 4 |
| | 11. High pressure autoclaves - 1 lit & 10 lit. | |
| | 12. Solvent Recovery Unit | 1 |
| | 13. Filter: Nutsche | 1 |
| | Sparkler | 1 |
| | Rotavacuum | 1 |
| | 14. Centrifuge - Basket type | 1 |
| | Sparkler | 1 |
| | 15. Crystallisers - 250 lit. | 2 |
| | 16. Soxhlet Extraction with distillation unit 250 lit | 1 |
| | 17. Climbing film cyclon evaporator | 1 |

| | <u>No.</u> |
|---|------------|
| II. For Chemical Technology Laboratory: | |
| 1. Heating mantles for 100 ml to 1000 ml Flasks | 12 |
| 2. Mechanical stirrers | 6 |
| 3. Magnetic stirrers | 6 |
| 4. Melting point apparatus | 2 |
| 5. Water Baths | 12 |
| 6. Balances, semimicro and analytical | 4 |
| 7. Flash Evaporators | 4 |
| 8. TLC Unit | 1 |
| 9. Flash Chromatography apparatus | 1 |
| 10. Laboratory Centrifuge | 1 |
| 11. Glass distillation unit | 2 |
| 12. Hydrogenation pressure-Low pressure | 1 |
| 13. High Pressure hydrogenation pressure on lit. capacity | 1 |
| 14. High pressure steel bombs 100 & 250 ml | 2 |
| 15. Ovens | 2 |
| 16. Vacuum pumps | 4 |
| 17. Laboratory Glassware - miscellaneous | |
| III. For Pharmacology Laboratory: | |
| 1. 4 Channel Polygraph with preamplifiers and transducers | 1 |
| 2. Electronic stimulators | 2 |
| 3. 2-Unit Isolated Organ Bath | 1 |
| 4. Respiration Pump | 1 |
| 5. Columbus activity monitor | 1 |
| 6. Rota Rod | 1 |
| 7. Electroconvulsometer | 1 |
| 8. Analgesiometer | 1 |
| 9. Paw Plethysmography | 1 |

| | | |
|-----|--|--------|
| 10. | Operation table Shadowless lamp and other related equipment | 1 |
| 11. | PH meter, Flame Photometer, Spectrophotometer, etc. | 1 each |
| 12. | Electronic thermometer with thermistor Probes | 1 |
| 13. | Binocular microscope | 1 |
| 14. | E.K.G. Machine | 1 |
| 15. | Desktop Computer | 1 |
| 16. | Dissolution simulator and Absorption simulator with artificial gastric and intestinal barrier Kits for Bioavailability studies | 1 |
| 17. | Pipette centrifuge "Analysette" - 21 for particle size analysis (0.01-5 μ m) | 1 |

IV. Instruments for Central Laboratory for Instrumentation

| | <u>No.</u> |
|---|------------|
| 1. High Resolution Mass Spectrometer with Chemical Ionisation, Field Desorption capability. | 1 |
| 2. 100 & 220 Mz NMR Spectrometer with Liquid Helium liquification and liquid nitrogen plants. Artianalyser for (C,H,N,O) | 2 |
| 3. Elemental Autoanalyser for (C,H,N,O) | 2 |
| 4. High performance liquid chromatographs (analytical and preparative) | 2 |
| 5. Gas liquid Chromatograph | 1 |
| 6. Fourier IR Spectrophotometer | 1 |
| 7. Infra Cord | 1 |
| 8. Recording UV Spectrophotometer | 2 |
| 9. ORD/CD Spectrometer | 1 |
| 10. Spectropolarimeter | 1 |
| 11. Spectrophotoflorimeter | 1 |

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JOURNALS:

| SR.NO. | NAME OF THE JOURNAL | PUBLISHED BY |
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| 1. | Abstracts of World Medicine | British Medical Asson Tavistock Square London WC1H 9 JR, England. |
| 2. | Accounts of Chemical Research | American Chemical Society, 1155 Sixteenth Street, N.W. Washington DC.20036 U.S.A. |
| 3. | American Jr. of Hospital Pharmacy | american Society for Hospital Pharmacists 4630 Montgomery Avenue Washington DC 20014, U.S.A. |
| 4. | American Jr. of Clinical Nutrition | American Society for Clinical Nutrition Inc., 9650 Rockville Pike Bathesda, Maryland 20014 U.S.A. |
| 5. | American Jr. of Medical Sciences | American Jr. of Medicine 666 Fifth Avenue New York, N.Y. 10019, U.S.A. |
| 6. | American Jr. of Medicine | American Jr. of Medicine 666 Fifth Avenue New York, N.Y. 10019, U.S.A. |
| 7. | Analytical Abstracts | The Chemical Society Distribution Centre Blackhouse Road Latchwarth, Herth SO6 1 HN London, U.K. |

| S.R. | NAME OF THE JOURNAL | PUBLISHED BY |
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| 8. | Analytical Biochemistry | Academic Press Inc., 111, Fifth Avenue New York, NY 10005, U.S.A. |
| 9. | Analytical Chemistry | American Chemical Society, 1155 Sixteenth Street N.W. Washington DC20036 U.S.A. |
| 10. | Angewante Chemie (English Edition) | Verlag Chemie Intl. 175 Fifth Avenue New York, N.Y. 10010, U.S.A. |
| 11. | Annals of New York Academy of Sciences | The New York Academy of Sciences, 2 East Sixty-three Street New York, NY 10021, U.S.A. |
| 12. | Annals of Nutrition & Metabolism | Watt Publishing & Co., Sandest Buildings Mount Morris Illinois 81054, U.S.A. |
| 13. | Annual Drug Data Report | JR Prous, J.A. Provenza, 385 -387 Barcelona 25 SPAIN |
| 14. | Antibiotics & Chemotherapy | Antibiotics & Chemotherapy, Hermes Press, Inc., 82 Morningside Drive, New York, NY 10027, U.S.A. |
| 15. | Antibiotics Medicine | MD Publications, Inc., 30 E, 60th Street New York, NY., U.S.A. |

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| 16. | Antibiotics Medicine & Clinical Therapy | MD Publications, Inc., 30 E, 60th Street New York, NY., U.S.A. |
| 17. | Arthritis and Rheumatism | The Arthritis Foundation 3400 Peachtree Road N.E. Atlanta, Georgia U.S.A. |
| 18. | Arzneimittel Forschung | Editio Cantor KG D - 7960 Auldendorf Postfach, P.O. Box: 1310 West Germany |
| 19. | Bacteriological Reviews | American Soc. for Microbiology, 1912, 1st Street, N.W. Washington DC 2006 U.S.A. |
| 20. | Biochemical Pharmacology | The Fulfillment Manager Pergamon Press Limited Headington Hill Hall Oxford OX3 OBW, England |
| 21. | British Jr. of Clinical Pharmacology | Macmillan Journal Ltd. Brunel Road, Basignstoke, Hants RG21 2ZS, U.K. |
| 22. | British Journal of Dermatology | Blackwell Scientific Pub Osney Mead, Oxford OX2 OEL England, U.K. |
| 23. | British Jr. of Pharmacology | Macmillan Jr. of Ltd. Brunel Road Basignstoke Hants RG 21 2XS, U.K. |
| 24. | Canadian Jr. of Chemistry | Canadian Jr. of Chemistry National Research Council of Canada, Ottawa Ontario, Canada K1A OR6 |

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|--------|---|---|
| 25. | Canadian Jr. of Pharmaceutical Sciences | Canadian Pharmaceutical Association 175 College Street Toronto, ONT M5T 1P5 CANADA |
| 26. | Central Patent Index (B - Farm doc) | Derwent Publications Ltd., Rochelle House 128 Theobalds Road London WC 1X 8RP England, UK. |
| 27. | Chemical Abstracts | Chemical Abstracts Services, The Ohio State University Post Box No. 3012 Columbus, OHIO 43210, U.S.A. |
| 28. | Chemical Engineering News | American Chemical Society, 1155 Sixteenth Street N.W. Washington DC20036, U.S.A. |
| 29. | Chemist & Druggist | Chemist & Druggist Benn Publications Ltd. 25 New Street - 89 London EC4A 3JA, England, |
| 30. | Chemistry & Industry | The Chemical Society Distribution Centre Blackhouse Road Latchwarth, Hert 506 1 HN. |
| 31. | Clinical Pharmacokinetics | ADIS Press Intl. Ltd. 18/F, Tung Sun Commercial Centre 194-200 Lockhart Road Wanchai, Hong Kong. |

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| 32. | Clinical Pharmacology & Therapeutics | The C V Mosby Co 11930 Westline Industrial Drive Saint Louis Missouri 63141, U.S.A. |
| 33. | Drug Intelligence Clinical Pharmacy | Drug & Intelligence & Clinical Pharmacy 1247 Broadway Hamilton Illinois 62341, U.S.A. |
| 34. | Drug Metabolism Reviews | Marcel Dekker Inc., 95 Madison Avenue New York, N.Y. 10429, U.S.A. |
| 35. | Drugs of the Future | Drugs of the Future Apartado de Correos 1179 Barcelona, Spain |
| 36. | Drugs Under Experimental Research | Drugs under Experimental & Clinical Research Bioscience Ediprint 8 Rue Winkelried, rue Winke, 8, 1211 Geneva 1 Switzerland. |
| 37. | General Pharmacology | IPC Science & Technology Press Limited IPC House 32 High Street, Guild Ford England, U.K. |
| 38. | Helvetica Chimica Acta | Verlag Helvetica Chimica Acta P.O. Box: 273 4002 Basel Switzerland |
| 39. | Heterocycles an Intl. Journal | Sendai Inst. of Heterocyclic Chemistry Sendai Pakusokan Kayaku Kenkysho, Japan |

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|---------|---|---|
| 40. | Indian Jr. of Chemistry | Indian Journal of Chest Diseases Vallabhbai Patel Chest Institute P.O. Box No. 2102 Delhi - 110 057. |
| 41. | Japan Pharmaceutical Abstracts | Drug Business Research Co., Ltd. Tokyo, Japan. |
| 42. | International Pharmaceutical Abstracts | American Society of Hospital Pharmacists 4630 Montgomery Avenue Washington DC 20014, U.S.A. |
| 43. | Japan Jr. of Medicine | Nandkodo Co., Ltd. 42- 6, Hongo, 3-Chome Bunkeyo-KU, Tokyo-113 Japan |
| 44. | Journal of American Medical Asson | American Medical Asson 535 North Dearbon Street, Chicago, 111 60610, U.S.A. |
| 45. | Journal of Pharmaceutical Asson | American Pharmaceutical Asson 2215 Constitution Avenue N.W. Washington DC20037 U.S.A. |
| 46. | Journal of Antimicrobial Chemotherapy | Academic Press Ltd., 24-28, Ouar Road, London NW 17 DK, UK. |
| 47. | Journal Chemical Education | Jr. of Chemical Education 20 th Northampton Streets Easton Pennsylvania - 180042, U.S.A. |
| 48. | Journal of Chemical Society | American Chemical Society 1155 Sixteenth Street N.W. Washington DC. 20036 U.S.A. |

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|---------|------------------------------------|--|
| 49. | Journal of Heterocyclic Chemistry | Journal of Heterocyclic Chemistry University Station Box No.: 7524 Provo Utah 84601, U.S.A. |
| 50. | Journal of Medicinal Chemistry | American Chemical Society, 1155 Sixteenth Street N.W. Washington DC 20036, U.S.A. |
| 51. | Journal of Organic Chemistry | American Chemical Society 1155 Sixteenth Street N.W. Washington DC 20036, U.S.A. |
| 52. | Journal of Parasitology | American Society of Parasitologists 1041 New Hampshire P.O. Box - 368, Lawrence, Kanas 66044, U.S.A. |
| 53. | Journal of Pharmaceutical Sciences | American Pharmaceutical Asson 2215 Constitution Avenue N.W. Washington DC 20036, U.S.A. |
| 54. | Journal of Pharmacy & Pharmacology | The Pharmaceutical Press High Street Lembeth London SE1 7JN. England, UK. |
| 55. | Lancet | The Lancet Ltd. 7 Adam Street London WC2 6AD, U.K. |

| SR. NO. | NAME OF THE JOURNAL | PUBLISHED BY |
|---------|-------------------------|---|
| 56. | Microbiology Reviews | American Society for Microbiology 1912, 1st Street, N.W. Washington DC 20006, U.S.A. |
| 57. | Nature | Macmillan Journal Ltd Brueel Road Basingstoke Hants RG21 2XS, U.K. |
| 58. | Package Engineering | Package Engg. 270 St. Paul St., Denver, Colorado 80206 U.S.A. |
| 59. | Packaging | Morgan-Grampian Ltd., 30 Calderwood Street London WC1X 8RP, U.K. |
| 60. | Packaging Review | IPC Industrial Press Ltd. 33-39 Bowling Green Lane London EC1, England |
| 61. | Pharmacological Reviews | The Williams and Wilkins Co., P.O. Box: 64025 Baltimore MD. 21264, U.S.A. |
| 62. | Science | American Asson for the Advancement of Science 1515 Massachusetts Ave. N.W. Washington DC 20005 U.S.A. |
| 63. | Synthesis | George Thieme Publishers Postfach No. 732 D-700, Stuttgart - 1 Harweg, West Germany |
| 64. | Tetrahedron | Pergamon Press Limited Headington Hill Hall Oxford OX3 08W, England |

| SR. NO. | NAME OF THE JOURNAL | PUBLISHED BY |
|---------|---------------------|--|
| 65. | Toxicology | Haymarket Pub. Ltd., Regent House, Regent Street, London W1A 4Y, U.K. |
| 66. | Unlisted Drugs | Unlisted Drugs Box No. 401 Chatham N.J. 07928, U.S.A. |

BOOKS:

| SR. NO. | TITLE | AUTHOR |
|---------|--|--|
| 1. | Standard methods for the Examination of water and wastewater | American Public Health Association |
| 2. | Methods of biochemical analysis | Click, David (ed.) |
| 3. | Advances in organic Chemistry | Taylor, E.C. and Wynberg H. (eds.) |
| 4. | Organic reactions | Adams, Roger, etal |
| 5. | Compendium of organic synthetic methods | Harrison, Ian T. and Harrison, Shugen |
| 6. | Lange's handbook of Chemistry | Lange |
| 7. | Rodd's chemistry of carbon compounds | Rodd |
| 8. | Organic functional group preparations | Sandler, Stanley R. and Karo, Wolf. |
| 9. | Synthetic methods of organic chemistry | Theilheimer, W. (ed.) |
| 10. | A textbook of practical organic chemistry | Vogel, Arthur I |
| 11. | Heterocyclic systems with bridge-head nitrogen systems. | Weissberger, ARnold (ed.) |
| 12. | Organic synthesis | Buchi, G.H. (ed) |
| 13. | Organic synthesis | Brown, Herbert C. |
| 14. | Physical properties of chemical compounds-II | American Chemical Society |
| 15. | Laboratory instruction in biochemistry | Kleiner, Israel S. and Dotti, Louis B. |

| SR. NO. | TITLE | AUTHOR |
|---------|--|--|
| 16. | Survey of organic synthesis | Buehler, Calvin A. and Pearson Donald E. |
| 17. | Reactive intermediates in organic chemistry | Isaacs, N.S. |
| 18. | Annual reports in organic synthesis | McMurry, John and Miller R. Bryan (eds.) |
| 19. | Handbook of catalyst manufacture | Sitting, Marshall |
| 20. | Modern classics in analytical chemistry | Beilby, Alvin L. (ed.) |
| 21. | NMR data tables for organic compounds | Bovay, Frank A |
| 22. | Isolation and identification of drugs in pharmaceuticals body fluids and postmortem materials | Clarke, E.G.C. (ed.) |
| 23. | Treatise on analytical chemistry | Kolthoff, I.M. (ed.) |
| 24. | Reagents for organic synthesis | Fieser, Mary and Fieser, Louis |
| 25. | Infrared and ultraviolet spectra of some compounds of pharmaceutical interest | Association of official Analytical chemists |
| 26. | Infrared absorption spectroscopy | Solomon, H. Philip |
| 27. | Advances in heterocyclic chemistry | Katritzky, A.R. |
| 28. | Encyclopedia of antibiotics, | Glasby, John S. |

| SR.NO. | TITLE | AUTHOR |
|--------|--|--|
| 29. | Textbook of microbiology | Burrow |
| 30. | Principles of microbiology and immunology | Davis, Bernard D. et-al. |
| 31. | Difco manual of dehydrated culture media and reagents for microbiological and clinical laboratory procedures | Difco Laboratories |
| 32. | Methods in microbiology | Norris, J.R. (ed.) |
| 33. | Essays in microbiology | Norris, J.R. and Richmond, M.G. (eds.) |
| 34. | Advances in applied microbiology | Perlman, D. (ed.) |
| 35. | Quality control in microbiology | Prier, James E. et-al. |
| 36. | Microbiology | Schlessinger, David (ed.) |
| 37. | Microbiology | Davis, D.B. et-al |
| 38. | Microbiology | Pelcsar, Michael Jr. |
| 39. | Actinomycetes the boundary micro-organisms | Aral, T. (ed.) |
| 40. | Teratology-principles and techniques | Wilson, James G. and Josef, Warkang |
| 41. | Chamber's dictionary of science and technology | Chamber |
| 42. | Recent advances in medicine | Baron, D.N. (ed.) |
| 43. | Stedman's medical dictionary | Stedman |
| 44. | Clinical pharmacological evaluation in drug control | World Health Organisation |

| SR. NO. | TITLE | AUTHOR |
|---------|--|---|
| 45. | Second symposium on the clinical pharmacological evaluation in drug control | World Health Organisation |
| 46. | Third symposium on clinical pharmacological evaluation in drug control | World Health Organisation |
| 47. | Chemical sterilization | Borick, Paul, M. (ed.) |
| 48. | Lectures in sterilization | Brewer, John H. (ed.) |
| 49. | Sterilization of medical products | Gaughran, Eugene, R.L. and Kereluk, Kari |
| 50. | Industrial sterilization | Phillips, G. Briggs and Miller, William S. (eds.) |
| 51. | Introduction of industrial sterilization | Richards, J.W. |
| 52. | How to remove pollutants and toxic materials from air and water, 1977. | Sitting, Marshall |
| 53. | Environmental pollution and human health-proceedings of the International symposium on industrial toxicology | Zaidi, S.H. (ed.) |
| 54. | Water and water pollution handbook | Ciaccio, Leonard L. |
| 55. | World directory of pharmaceutical manufacturers | IMS World Publications |
| 56. | The Merck Index | Merck & Co. |
| 57. | Drug design | Ariens, E.J. (ed.) |
| 58. | British pharmacopeia | Her Majesty's Stationery Office |

| SR. NO. | TITLE | AUTHOR |
|---------|---|--|
| 59. | British National formulary | (The) Pharmaceutical Press |
| 60. | European pharmacopeia | Maisonneuve, S.A. |
| 61. | The extra pharmacopeia | Martindale |
| 62. | Formulation and preparation of dosage forms | Polderman |
| 63. | Annual reports in medicinal Chemistry | Cain, Cornelius K. |
| 64. | Bentley and Driver's textbook of pharmaceutical chemistry | Bentley and Driver |
| 65. | Medicinal Chemistry | Burger, Alfred |
| 66. | Microencapsulation | Nixon, J.R. (ed.) |
| 67. | Design of biopharmaceutical properties through pro drugs and analogs | Roche, Edward B. |
| 68. | Textbook of organic medicinal and pharmaceutical chemistry | Wilson, Charles O. (ed.) |
| 69. | Chemistry in medicine | American Chemical Society |
| 70. | Synthetic antidiarrheal drugs synthesis-preclinical and clinical pharmacology | Bever, Wllem Van and Lal. Harbans (eds.) |
| 71. | Antibiotics-mechanism of action of antimicrobial and antitumour agents | Corcoran, John W. and Hahn, Fred (eds.) |
| 72. | Topics in antibiotic chemistry | Sammers, P.G. (ed.) |
| 73. | Bentley's textbook of pharmaceuticals, | Bentley |
| 74. | Unit processes in pharmacy | Ganderton, David |
| 75. | The theory and practice of industrial pharmacy | Lachman, Leon, et-al (ed.) |

| SR. NO. | TITLE | AUTHOR |
|---------|--|--|
| 76. | Remington's pharmaceutical Sciences | Remington |
| 77. | Principles of drug action the basis of pharmacology | Goldstein, Avram, et-al. |
| 78. | Drug interactions | Grahame-Smith, D.G. |
| 79. | Progress in drug research | Jucker, Ernst (ed.) |
| 80. | Laboratory manual of biopharmaceutics and pharmacokinetics | Ritschel, W.A. |
| 81. | Cardiovascular drugs-B-Adrenoceptor blocking drugs | Avery, Graeme S |
| 82. | Cardiovascular drugs-B-Adrenoceptor blocking drugs, Antiarrhythmic, antihypertensive and lipid lowering drugs. | Avery, Graeme S. |
| 83. | Advances in drug research | Harper, NJ, and Simmonds, L.B. (eds.) |
| 84. | Manual of clinical microbiology | Lennette, Edwin H. (ed.) |
| 85. | Benzodiazepines in clinical practice | Grennblatt, David J. and Shader, Richard I. |
| 86. | Textbook of adverse drug reactions | Davies, D.M. (ed.) |
| 87. | Analytical profiles of drug substances | Florey, Klaus (ed.) |
| 88. | Clinical trials protocol | Maxwell, Cyril |
| 89. | Dermato-toxicology and pharmacology | Marzulli, Francis N. & Maibach, Howard I. (eds.) |
| 90. | Advances in parasitology | Dawes, Ben (ed.) |

| SR. NO. | TITLE | AUTHOR |
|---------|---|---|
| 91. | The corrosion and oxidation of metals | Evans, Ulick R. |
| 92. | Gas encyclopedia | Liquide, L'air |
| 93. | Antifungal compounds | Siegel, Malcolm R. and Sisler, Hugh D. (eds.) |
| 94. | Environmental pollution by pesticides | Edwards, C.A. (ed.) |
| 95. | Pesticides process encyclopedia | Sitting, Marshall |
| 96. | Analytical methods for pesticides and plant growth regulators | Zweig, Gunter and Sherma JOseph (eds) |
| 97. | Farm chemicals handbook | Meister Publishing Co. |
| 98. | British Pharmacopoeia (veterinary) | Her Majesty's Stationary Office |
| 99. | Optimization techniques for chemical engineers, | Husain, Asghar and Gangian, Kota. |
| 100. | Encyclopedia of chemical technology | Kirk and Othmer |
| 101. | Encyclopedia of chemical processing and design | Mc Ketta, John J. (ed.) |
| 102. | Process plant and equipment cost estimation | Kharbanda, O.P. |
| 103. | Industrial chemicals | Faith |
| 104. | British Pharmaceutical Codex | Pharmaceutical Soc. of G.B. |
| 105. | U.S. Pharmacopoeia with supplements | U.S. Pharmacopoeial Convention |
| 106. | Dictionary of Organic compounds | Heilbron (Chapman & Hall) |
| 107. | Synthetic methods of organic chemistry | Theilheimer |
| 108. | Cephalosporins & penicillins (Chemistry & Biology) | Flynn, Edwin, H. (ed.) |

- 65 -

Personnel Requirement for the Multi-Purpose Plant

| | <u>Produc-</u> <u>tion</u> | <u>Labora-</u> <u>tory</u> | <u>Mainte-</u> <u>nance</u> | <u>Adminis-</u> <u>tration</u> | <u>Pur-</u> <u>chase</u> | <u>Finance</u> | <u>Services</u> |
|--|-------------------------------|-------------------------------|--------------------------------|-----------------------------------|-----------------------------|----------------|-----------------|
| Plant Manager, Chemist and high-level personnel | 10 | 6 | 2 | 1 | 1 | 1 | - |
| Operators Technicians, Clerk | 8 | 6 | 3 | 3 | 2 | 3 | 1 |
| Skilled Workers | 12 | 12 | 6 | 1 | 1 | 1 | 1 |
| Unskilled Workers | 20 | 15 | 3 | - | - | - | 6 |
| Total | 50 | 39 | 14 | 5 | 4 | 5 | 8 |

Total need: 125

The personnel requirement of pilot multi-purpose plant and laboratory of chemical technology is 65 and 60, respectively. The maintenance personnel is included in the personnel of pilot plant, which the administrative personnel is included in the laboratory personnel.

Training Requirement Outside the Country

| | <u>Number</u> | <u>Month</u> |
|--|---------------|--------------|
| Production Director | 1 | 6 |
| Factory Chief | 1 | 3 |
| Financing Supervisor | 1 | 1 |
| Personnel (Quality Control) (Chemist, Toxicologist) | 3 | 6 |
| Production Manager, Chemist and Operator | 9 | 18 |
| Chemical Engineer (Designer) | 1 | 3 |
| Mechanical Engineer and Technicians | 4 | 8 |
| | <hr/> | <hr/> |
| Total: | 20 | 45 |

Cost of Civil Construction *

| <u>Particulars</u> | <u>Cost US\$</u> |
|--|------------------|
| A. Process building | |
| Basement/Ground floor each 1300 sq.m.(= 2,600 sq.m) | |
| Mezzanine floor 600 sq.m. (\$ 880/sq.m.) | 2,816,000 |
| B. Office accommodation 100 sq.m.(\$ 1,000/sq.m) | 100,000 |
| C. Warehouse for raw materials 450 sq.m.(\$760/sq.m) | 342,000 |
| D. Warehouse for finished products 200 sq.m.(\$760/sq.m) | 152,000 |
| E. Building for utilities 570 sq.m.(\$840/sq.m) | 478,800 |
| F. Workshop, cafeteria, time office, etc. 300 sq.m. | |
| (\$ 840 sq.m.) | 252,000 |
| G. Research and Development Laboratory 860 sq.m. | |
| (\$ 1,000 sq.m.) | 860,000 |
| | <hr/> |
| Total cost of buildings | 5,008,000 |
| | ===== |

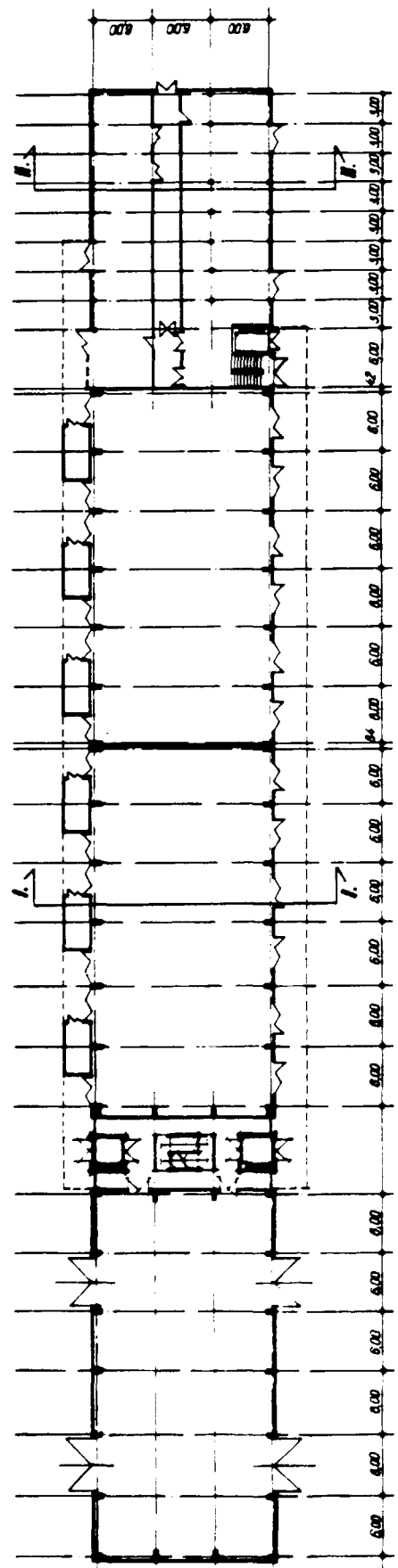
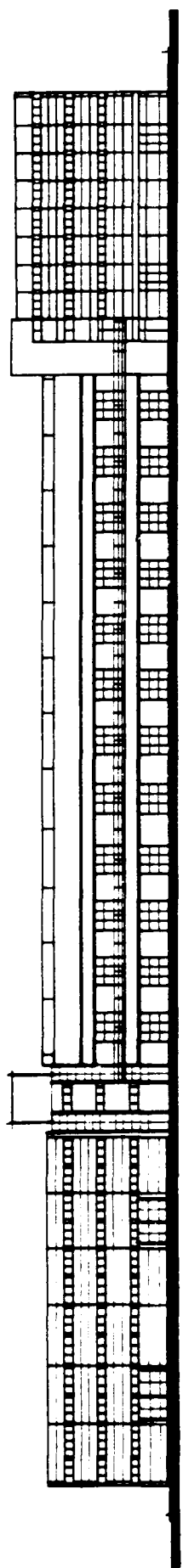
COST OF INSTALLED EQUIPMENT

| | <u>US\$</u> |
|---|------------------|
| A. Process equipment | 2,564,250 |
| B. Laboratory equipment | 250,000 |
| C. Equipment for utilites | <u>328,250</u> |
| Reserve for unforeseen equipment | 187,500 |
| Reserve for spare parts | 75,000 |
| Installation materials | <u>387,500</u> |
| Cost of equipment F.O. B. | 3,792,500 |
| Cost of equipment C.I.F. (25 percent F.O.B. cost) | 4,740,625 |
| Handling charges in Algeria | 125,000 |
| Installation charges | <u>250,000</u> |
| Total installed cost of equipment | <u>5,115,625</u> |

ESTIMATED COST OF THE PROJECT

| <u>Particulars</u> | <u>US \$</u> |
|---|----------------|
| Installed cost of equipment | 5,115,625 |
| Cost of civil construction | 5,008,000 |
| Transfer of Technology - technical know how | <u>944,375</u> |
| Total | 11,068,000 |

Multipurpose Pharmaceutical Hall
Lay-out

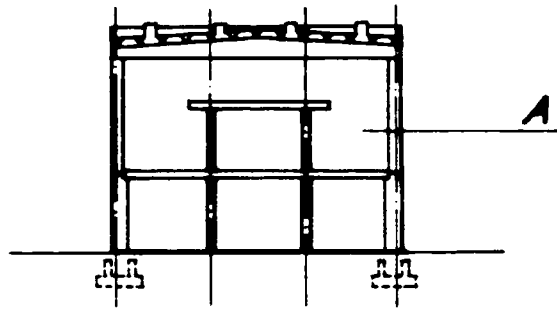


E UTILITIES ACCOMMODATION,
OFFICE CAFETERIA, TIME OFFICE
O/F W/DRINKING CAFETERIA, TIME OFFICE
6 RESEARCH AND DEVELOPMENT
LABORATORY

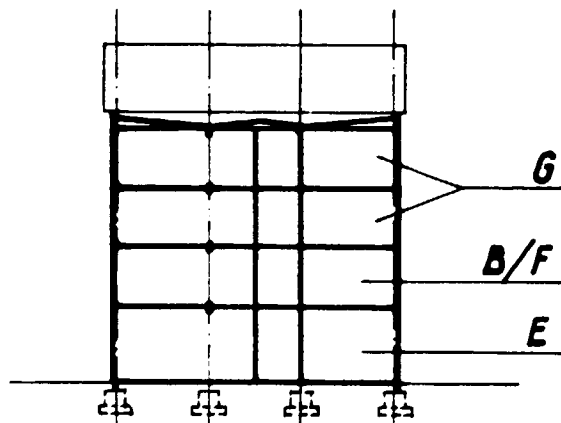
SECTION I
SECTION II
SECTION III
A PROCESS BUILDING

C/D WAREHOUSE FOR RAW MATERIALS
AND FINISHED PRODUCTS

SECTION I.



SECTION II.



Multipurpose Pharmaceutical Production Plant
Site plan

