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# PHARMACEUTICAL INDUSTRY DEVELOPMENT

SI/ZIM/84/802

ZIMBABWE

## Technical report: Transfer of Technology*

Prepared for the Government of the Republic of Zimbabwe

by the United Nations Industrial Development Organization,

acting as executing agency for the United Nations Development Programme

Based on the work of A. Ramachandran,
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Vienna

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## I. SUMMARY

The Government of Zimbabwe have decided to achieve self-sufficiency to a reasonable extent in the production of basic drugs (Pharmaceutical Chemicals) in the country. This objective cannot be achieved in a short time and the only way to go about it is to go in for a multipurpose plant as a first step for the reasons mentioned below:

(1) There is not a single bulk drug produced in the country and no technology is available locally.

(2) At present there is no base in the country to receive the technology even if it is available from outside.

(3) Skilled man power is not available to take up manufacture of basic drugs in the country.

(4) The existing seven Pharmaceutical Companies (three of these are multi-nationals) do not have any facilities nor have they any plans to go for bulk drugs production.

(5) The choice automatically falls on CAPS (PVT.) LTD. - the Government holds 40% of the shares of the Company. This Company is the biggest in the country and contributes to around 70% of the total formulations market.

The gaps between the facilities available and goal to be achieved can be filled only by establishing a multipurpose pilot plant.

(6) It must be made clear that this pilot plant will be a step in the right direction to achieve self-sufficiency. The pilot plant can produce some drugs needed for the country but it will not be really viable from the financial angle during initial stage as the cost of production will be higher than the landed cost of the basic drug. But the big advantage that will come out of the pilot plant is a technological base for the country. Besides producing small quantities of drugs, this base will serve as a training ground to develop technical skill in the country. The technical base so built up will make technology transfer easy at a later stage. The pilot plant also can generate a lot of design data that will be handy for designing new plants.

The proposal to achieve self-sufficiency is made for establishing a multipurpose pilot plant. This proposal will include the following:

(a) An equipment list to produce the bulk drugs (Pharmaceutical Chemicals).

(b) Procuring the know how from any source in the world.

(c) A detailed and intensive training programme for the operating personnel in the polot plant. This has to be arranged outside the country.

(d) Assistance to locate sources for the supply of specialised equipment and also the required raw materials that are needed for the production of bulk drugs.

Various alternatives and the final recommendations with justification

Before taking a final decision, it may be better to analyse the various alternatives, other than pilot plant. One alternative is to go in for a bulk drug plant.

To fix the size of the bulk drug plant, the quantities of drugs imported into the country to produce formulations have to be ascertained. Detailed information could be obtained from M/s. Caps (PVT) Ltd., who contribute to more than 70% of the total information was also obtained from M/s. Dat Labs and Sterling Winthrop.

Taking into account future potential of the various drugs, a product mix with quantities of production has been given below:

| Name of Drug | Average Consumption CAPS | DATALABS | STERLING | Total | Proposed Annual Cap. Tons |
|---|---|---|---|---|---|
| 1. Paracetamol | 60.0 | 7.0 | 4.5 | 71.5 | 100.0 |
| 2. Aspirin | 30.0 | 30.0 | 13.0 | 73.0 | 100.0 |
| 3. Chloroquin Phosphate | 4.0 | 2.0 | 9.0 | 15.0 | 20.0 |
| 4. Trimethoprim | 0.7 | - | - | 0.7 | 1.0 |
| 5. Sulphamethoxazole | 3.0 | - | - | 3.0 | 5.0 |

Annexure 11 gives outline of the process involved in the manufacture of the various bulk drugs.

Annexure 1 gives the total cost of production compared with Landed Cost.

Annexure 2 gives details of raw materials.

While observing the cost of production, it may be observed in many cases that the cost of production is much higher than the Landed Cost. In some cases there is a big gap and it is quite clear that the bulk drug plant visualised will not at all be viable from the financial point of view.

Now what is the alternative left if this proposed bulk drug plant is not viable and how to go about in the direction of achieving self reliance in the bulk drug production. The only way is to go for a multi-purpose pilot plant and produce a variety of drugs in small quantities. The production batches taken in the pilot plant can be gainfully used for captive consumption if they meet the Pharmacopoeial standards (BP or USP). This type of pilot plant will have the following advantages:

(1) This will give the base for developing technical skill to produce bulk drugs in the country.
(2) This pilot plant will serve as a base to receive and use the technology from outside.
(3) The personnel working in the plant will, in course of time, develop technical competence to expand the plant or go in for a new plant.
(4) The pilot plant can generate lot of technical data which will be very useful while designing the new plant.

In short, this plant will form the nucleus for developing technical skill and competence in the country to produce bulk drugs.

While comparing the cost of production with Landed Cost of a particular drug, one important point cannot be overlooked. The international prices are often artificial prices and they differ from country to country. The value of the plants of the big companies who produce their drugs on a very large scale would have been depreciated to a great extent. Drugs are supplied at high prices with good margin to some customers while to others they are supplied at

low prices, even recovering the variable costs and part of fixed expenses. Hence the prices in the international markets are artificial and subjected to wide variations and sometimes the drugs themselves will not be available.

It can be well appreciated that the only way to move in the direction of self-reliance for drugs is to go in for a multi-purpose pilot plant.

## INTRODUCTION

Zimbabwe, being a developing country, is quite keen to achieve the goal of self-sufficiency in the production of bulk drugs. UNDP's assistance has been requested for the same. As a first step, a study is done to assess the status of the pharmaceutical industry and make suitable recommendations taking into account the infra-structure available in terms of equipment availability, technical man power and raw materials etc.

It is quite clear that not a single bulk drug is produced in the country. There are technical people working in formulation plants. They are not suitable for Chemical processes as they mainly handle physical operations like mixing, granulating, compressing, etc. Similarly there are people working in heavy chemical factories like fertiliser plants who are not suitable as the production of heavey chemicals involves more continuous processes and automation. For the production of Pharmaceutical Chemicals we need people with good knowledge of chemistry and knowledge of Good Manufacturing Practices (GMP) are needed, since drugs meant for numan consumption are involved. The drugs produced must meet high and rigid standards of B.P. (British Pharmacopoeia) or U.S.P. (United States Pharmacopoeia). The only way to get the technical skill is to get the personnel trained outside the country in similar drug plants.

## JUSTIFICATION & RECOMMENDATIONS

At present the country depends entirely on imports for the bulk drugs and the Government of Zimbabwe is keen to take some steps to achieve self-sufficiency to reasonable extent, in the years to come.

There are very few chemical plants in the country where sulphuric acid, super phosphate, ammonia, hydrogen gas are produced. So most of the Chemicals required today are imported.

## Present status of Pharmaceutical Industry

The total pharmaceutical market in Zimbabwe is around 28 million US dollars and as per discussions with important persons in the industry, it is estimated that the growth rate will be around 8 to 10%. The total pharmaceutical sales are controlled by the following Companies. The major share of the sales is taken by M/s. CAPS (Pvt) Ltd. and DATALABS. This will be around 80%.

1. Caps (Pvt.) Ltd., Harare
2. Datlabs Pvt. Ltd., Bulawayo
3. Sterling Winthrop, Harare (Multinational, Winthrop Group USA)
4. Ian Wilson (Multinational - Wellcome Group UK)
5. Dab Marketing, Harare
6. Wallace Labs., Bulawayo
7. Pfizer Pvt. Ltd., Harare (Multinational, Pfizer USA)

None of the above Companies produces bulk drugs nor do they have any plans to go in for bulk drug production.

It has already been discussed in detail and recommended that the only way to go for self-reliance in bulk drugs production is to set up a multi-purpose plant. Various factors are to be considered before arriving at a suitable product mix for the pilot plant:

(1) The quantities of drugs imported into the country by various Companies.
(2) The availability of technology for various drugs.
(3) The growth potential of drugs - their future needs.
(4) The level of sophistication of technology and the size of the investment called for.

Annexure 2 gives the various items selected for the pilot plant. Care has been taken such that all the equipment in the pilot plant are fully utilised. Anti-biotics like tetracycline, penicillin, have been avoided since they need sophisticated technology involving fermentation and the investments will be high. The economical scale of the plant will be such that the output will far exceed the requirement.

Products like corticosteroids, hormones, have been omitted because of the high degree of skill required for these processes and it may not be advisable to go for these drugs in the beginning when the operating man power is still not fully developed.

## FEASIBILITY STUDY
### Selection of Equipment

The list of equipment has been finalised taking into account the various unit operation processes involved. The total occupation time for each operation and process has been calculated for various steps and the size of the equipment has been fixed. Care has been taken to see there is maximum utilisation of the equipment. In other words, different products will be campaigned at different periods of time and no equipment as such will be dedicated to one drug production. There will be separate stands on which the main equipment like reactors will be erected. These reactors will have all the utilities connected with flexible pipes to facilitate connecting any of the utilities like water, steam, chilled water, brine, etc. This type of connections gives a lot of flexibility to carry out many types of reactions in the same vessel. Even when we go in for a new product, the same reactor can be used by some minor or no changes. In other words, at a later stage, the pilot plant can produce an entirely new product mix.

Another major advantage of the pilot plant is that it can generate design data that can be gainfully used for designing a bigger plant or even new plants. Whatever data one may get from Laboratory cannot be used for a commercial plant as the conditions of working are entirely different in a commercial plant. Pilot plant is an ideal bridge between the laboratory to commercial plant. We can afford to have failures of batches in pilot plant but not in the main plant as the losses will be very heavy.

In short, the multipurpose pilot plant proposal justifies itself in many ways - as an excellent training ground for the operating personnel, Chemists and Engineers. This plant offers flexibility to change the product mix and finally provides a base to receive and try the new technologies. Many of the units in the pilot plant are glasslined and stainless steel units (S.S.316) that can handle most of the chemicals at various temperatures, pressures and pH conditions.

## Material of Construction

A critical study of the process parameters will reveal that highly corrosive acids like hydrochloric and sulphuric acids, and sometimes organic medium like methanol at fairly high temperatures need to be handled. No material of construction can stand other than glass. In other areas SS 316 has been recommended to stand chemical corrosion. In some cases, rubber-lined, epoxy lined equipment are suggested while in other cases high density polyethylene or fibre glass equipment is recommended.

## Sizing of equipment

The capacity of a reactor will be related to the batch time of a process The batch will have certain quantity of output and the capacity of the plant is calculated from the batch output. Most of the equipment recommended are standard size equipment so that changing of parts or replacements can be easily done. Even one equipment can be shifted from one portion to other. The balancing equipment like storage vessels, intermediate tanks, are also selected with particular capacities to match with the main reactors.

Pumps like centrifugal, compressed air or Nitrogen are used for transfer of material from one vessel to another. This arrangement also gives lot of flexibility to pilot plant to campaign different products.

For filtration, S.S. plate and frame filter, leaf filters are included. Centrifuges of different sizes, stainless steel and rubber lined, are provided.

As for drying, there are hot air circulators, air dryers and fluidised bed driers. Vacuum driers are provided to dry the thermolabile materials.

## Safety

Safety has to be given the highest priority since corrosive and dangerous chemicals like acids and inflammable substances like ethyl alchol and other solvents are to be handled. Lot of care is taken to alert the operators well in advance to take the proper steps to avoid accidents. During the training course, operating personnel will be given a full and intensive training on safety aspects.

As far as the equipment is concerned, explosion proof fittings will be used to avoid the electrical hazards. Since the production schemes are bound to change all the fittings in the electrical system will be explosion proof to take care of solvents handling.

First Aid box will be arranged in every production section. Gas masks to work in different atmospheres will be kept handy. Air masks will be provided with compressed air pipe line system. Further quick opening taps to deal with accidents where a person has to be washed with copious amounts of water will be installed. Each production area will be provided with necessary safety appliances which can be easily available to the operating personnel. Operators will be allowed to work on a process only after thorough training is given to them, stress being given to the safety aspects.

Since it is not safe to allow accumulation of fumes, solvent vapours, both local ventilation and general ventilation are provided. This gives the operating staff fresh air at the same time toxic gases being removed at the source.

Most modern concepts of GMP (Good Manufacturing Practice) are incorporated in the layout of the pilot plant. The areas, after the drug is filtered, are marked as Pharmacopoeial areas and there is complete segregation from chemical areas where the reactions are carried out.

Ventilation system is separate and only filtered air allowed to circulate in the Pharmacopoeial area. The equipment for drying the materials are installed in clean areas where filtered air is circulated. The size of the filters used is 5 microns.

## Infrastructure Facilities in Zimbabwe

### Engineering Industry:

The following are reasonably big Companies:

(1) Cochrane Stork, Zimbabwe
(2) Stainless Steel Industries Ltd.
(3) Satcow Steel
(4) AMA Welders
(5) Wrap Engineering

Among the above, the best is Cochrane Stork. They have all the expertise and facilities to fabricate the stainless steel and mild steel equipment of any size. They have made tanks upto 60 $M^3$ and can make reactors of any size, with jackets and agitator systems. Except centrifuges, fluidised bed driers, they can make all the rest. Of course, glasslined equipment has to be imported from abroad.

### Raw Materials Supply

Chemical industry in the country is in the stage of infancy. The have some ethanol plants since they have good sugar industry. There are also some fertilizer plants making super phosphate, sulphuric acid, ammonia and hydrogen gas. So, it is quite clear that almost all the chemicals have to be imported.

### Work Schedule

The total time required to complete the project will be 36 months. A bar chart showing the various activities is given in Annexure 8.

A fairly reasonable estimate of the investment involved on the equipment and building is also given in Annexures 5 & 6.

Acknowledgement

The writer expresses his deep appreciation and offers his grateful thanks for the help, guidance and co-operation he received from concerned organisations and Ministry of Industry and Technology, Government of Zimbabwe, UNDP Harare and New Delhi, and UNIDO, Vienna.

ANNEXURE 1.



## COST OF PRODUCTION OF VARIOUS DRUGS

(Per Kg.) (All in US $)

| | Para-cetamol | Aspirin | Sulphame-thoxazole | Trime-thoprim | Chloroquin-Phosphate |
|---|---|---|---|---|---|
| 1. Cost of Raw Material | 9.64 | 4.28 | 42.30 | 36.40 | 37.80 |
| 2. Cost of Utilities | 0.20 | 0.25 | 0.53 | 1.50 | 0.45 |
| 3. Cost of labour & Overheads | 5.00 | 6.00 | 7.50 | 7.12 | 7.12 |
| 4. Cost of Depreciation and Mainetnance | 3.50 | 4.00 | 3.50 | 3.29 | 2.75 |
| 5. Cost of Interest | 4.00 | 4.00 | 8.50 | 6.10 | 4.80 |
| 6. Cost of Insurance | 0.35 | 0.35 | 0.65 | 0.40 | 0.31 |
| Total Cost of Production | 22.69 | 18.88 | 62.98 | 54.81 | 53.23 |
| Market Price | 9.8 | 4.0 | 30.00 | 45.00 | 27.00 |

ANNEXURE - 2

## RAW MATERIAL REQUIREMENT FOR THE PRODUCTION OF PHARMACEUTICAL CHEMICALS

| No. | Name of Pharmaceutical Chemical | Raw Materials required | Requirement per 100 kg product Kg. | Unit Cost of raw materials US $/kg. | Raw material cost per 100 kg. product US $ | Annual Requirement of raw materials tons | Annual cost of raw materials Imported US $ |
|---|---|---|---|---|---|---|---|
| 1. | Nicotinamide Annual proposed production 1 Ton | 1. 3-cyanopyridine | 138 | 6.15 | 848.70 | 13.8 | 8487.0 |
| | | 2. Sodium Hydroxide 50% solution | 26 | 0.50 | 13.00 | 2.6 | 130.0 |
| | | 3. Active carbon | 4 | 2.2 | 8.80 | 0.04 | 88.0 |
| | | 4. Liquor ammonia | 4 | 0.25 | 1.00 | 0.04 | 10.0 |
| | | 5. Resin IRA-402 | 2 | 15.00 | 30.00 | 0.02 | 300.0 |
| | | | | | 901.50 | | 9015.0 |
| 2. | Paracetamol Annual proposed production 30 tons | 1. P.Aminophenol | 96 | 15 | 960.00 | 28.8 | 288.000 |
| | | 2. Acetic anhydride | 90 | 1.2 | 108.00 | 27.0 | 32.400 |
| | | 3. Sodium hydrosulfite | 1.8 | 1.2 | 2.16 | 0.03 | 0.600 |
| | | 4. Active carbon | 3 | 2.2 | 6.60 | 0.90 | 0.900 |
| | | | | | 1076.76 | | 321,900 |
| 3. | Metronidazole proposed annual production 1.5 tons | 1. 2-Methyl-5-Nitro Imidazole | 190 | 10.0 | 1900.00 | 2.85 | 28,500 |
| | | 2. Formic Acid | 448 | 1.40 | 627.20 | 6.75 | 9,450 |
| | | 3. Ethylene oxide | 334 | 11.00 | 3674.00 | 5.00 | 55,000 |
| | | 4. Liq. ammonia | 534 | 0.25 | 133.80 | 8.00 | 2,000 |
| | | 5. Sodium chloride | 500 | 0.70 | 350.00 | 7.25 | 5,075 |
| | | 6. Ethanol | 156 | 2.50 | 390.00 | 2.50 | 6,250 |
| | | 7. Active carbon | 7 | 2.2 | 15.4 | 105 kg. | 924 |
| | | | | | 7090.40 | | 107,199 |
| 4. | Aspirin Proposed annual Production 30 tons | 1. Salicilic acid | 96 | 3.7 | 355.20 | 28.80 | 106,560 |
| | | 2. Acetic anhydride | 95 | 1.2 | 114.00 | 28.50 | 34,200 |
| | | 3. Sulfuric acid | 4.5 | 0.12 | 0.54 | 1.35 | 162 |
| | | 4. Sodium hydroxide | 3.5 | 0.5 | 1.75 | 1.05 | 565 |
| | | | | | 471.49 | | 141,487 |

## RAW MATERIAL REQUIREMENT FOR THE PRODUCTION OF PHARMACEUTICAL CHEMICALS

| No. | Name of Pharmaceutical Chemical | Raw Materials required | Requirement per 100 kg product Kg. | Unit Cost of raw materials US $/kg. | Raw material cost per 100 kg. product US $ | Annual Requirement of raw materials tons | Annual cost of raw materials Imported US $ |
|---|---|---|---|---|---|---|---|
| 5. | Sulfamethoxazole proposed annual production 4 tons | 1. Acetone | 82 | 1.8 | 147.60 | 3.3 | 5.900 |
| | | 2. Active Carbon | 0.8 | 2.2 | 1.76 | 32.0 | 704 |
| | | 3. Pacetylamino benzene sulfonyl chloride | 195 | 4.5 | 877.50 | 8.0 | 35,100 |
| | | 4. Liq. Ammonia | 737 | 0.25 | 184.25 | 30.0 | 7,350 |
| | | 5. Benzene | 33 | 0.5 | 16.50 | 1.3 | 660 |
| | | 6. Diethyl oxalate | 205 | 6.0 | 1230.00 | 8 | 49,200 |
| | | 7. Hydroxylamine Sulfate | | | | | |
| | | 8. Methanol | 326 | 1.8 | 586.80 | 13.0 | 23,472 |
| | | 9. M.I.B.K. | 152 | 1.4 | 212.80 | 6.1 | 8,512 |
| | | 10. Pyridine | 97 | 5.5 | 533.50 | 4.0 | 21,340 |
| | | 11. Sodium Hydrosulfite | 6 | 1.2 | 7.20 | 0.3 | 288 |
| | | 12. Sodium hydroxide | 133 | 0.5 | 66.50 | 5.3 | 2,660 |
| | | 13. Sodium hypo chloride 12% | 64 | 0.20 | 12.80 | 2.6 | 512 |
| | | 14. Sodium metal | 34 | 16.0 | 544.00 | 1.4 | 21,760 |
| | | 15. Sulfuric acid | 252 | 0.12 | 30.24 | 10.0 | 1,210 |
| | | 16. Toluene | 94 | 0.5 | 47.00 | 4.0 | 1,880 |
| | | | | | 4498.45 | | 179,938 |
| 6. | Trimethoprim Proposed annual production 10 tons | 1. Acetic acid | 224 | 1.0 | 224.00 | 2.24 | 2,240 |
| | | 2. Acrylonitrile | 44 | 1.2 | 52.80 | 0.4 | 5,280 |
| | | 3. Active Carbon | 12 | 2.2 | 26.40 | 0.12 | 260 |
| | | 4. Liq. ammonia | 104 | 0.25 | 26.00 | 1.04 | 260 |
| | | 5. Aniline | 56 | 1.02 | 57.12 | 0.56 | 571 |
| | | 6. Dimethyl Sulfoxide | 123 | 2.5 | 307.50 | 1.23 | 3,075 |
| | | 7. Guanidine hydrochloride | 95 | 6.7 | 636.50 | 1.0 | 6,365 |
| | | 8. Isopropanol | 16 | 3.0 | 48.00 | 0.16 | 480 |
| | | 9. Morpholine | 66 | 3.47 | 229.00 | 0.66 | 2,290 |
| | | 10. Sodium Hydroxide | 41 | 0.5 | 20.50 | 0.4 | 205 |
| | | 11. Sodium Methoxide | 10 | 4.0 | 40.00 | 1.0 | 4,000 |
| | | 12. 3,4,5-trimethoxy benzaldehyde | 1199 | 20.0 | 2380.00 | 1.2 | 23,800 |
| | | | | | 4047.82 | | 48,474 |

## RAW MATERIAL REQUIREMENT FOR THE PRODUCTION OF PHARMACEUTICAL CHEMICALS

| No. | Name of Pharmaceutical Chemical | Raw Materials required | Requirement per 100 kg product Kg. | Unit Cost of raw materials US $/kg. | Raw material cost per 100 kg. product US $ | Annual Requirement of raw materials tons | Annual cost of raw materials Imported US $ |
|---|---|---|---|---|---|---|---|
| 7. | Chloroquine Phosphate Proposed annual Production 10 tons | 1. 4 Hydroxy-7 chloro-quinoline | 47 | 55 | 2585.00 | 4.7 | 258,500 |
| | | 2. Phosphorous oxychloride | 94 | 1.5 | 141.00 | 9.4 | 14,100 |
| | | 3. Dichloroethane | 187 | 2.4 | 448.80 | 18.7 | 44,880 |
| | | 4. Novoldiamine | 43.5 | 16.3 | 709.00 | 4.35 | 70,900 |
| | | 5. Ammonia | 75 | 1 | 75.00 | 7.5 | 7,500 |
| | | 6. Phosphoric acid | 64.7 | 0.35 | 22.50 | 6.4 | 2,250 |
| | | 7. Ethanol | 58.8 | 2.5 | 147.00 | 5.8 | 14,700 |
| | | 8. Carbon | 5 | 2.2 | 11.00 | 0.5 | 1,100 |
| | | 9. Phenol | 23.5 | 0.8 | 14.10 | 2.35 | 1,410 |
| | | 10. Benzene | 29 | 0.5 | 14.50 | 2.9 | 1,450 |
| | | 11. Caustic lye | 73 | 0.5 | 36.50 | 7.3 | 3,650 |
| | | | | | 4204.40 | | 420,440 |
| 8. | Chloramphenicol Proposed annual production 3 tons | 1. L Base | 70 | 48 | 3,360 | 2,100 | 100,800 |
| | | 2. Methyl dichloracetate | 60 | 5.0 | 300 | 1,800 | 9,000 |
| | | 3. Methanol | 160 | 0.75 | 120 | 4,800 | 3,600 |
| | | | | | 3,780 | | 113,400 |
| 9. | Thiamine Hydro-chloride Proposed annual production 500 kg. | 1. Thio thiamine | 100 | 50 | 5,000 | 25,000 | 25,000 |
| | | 2. Hydrogen peroxide | 50 | 0.7 | 35 | 175 | 175 |
| | | | | | 5,035 | | 25,175 |

## RAW MATERIAL REQUIREMENT FOR THE PRODUCTION OF PHARMACEUTICAL CHEMICALS

| No. | Name of Pharmaceutical Chemical | Raw Materials required | Requirement per 100 kg product Kg. | Unit Cost of raw materials US $/kg. | Raw material cost per 100 kg. product US $ | Annual Requirement of raw materials tons | Annual cost of raw materials Imported US $ |
|---|---|---|---|---|---|---|---|
| 10. | Vitamin $B_2$ 5' Phosphate Proposed annual production 100 kg. | Riboflavin (Vit. $B_2$) | 100 | 45 | 4,500 | 4,500 | 4,500 |
| | | Phosphorous oxychloride | 70 | 1.5 | 105 | 105 | 105 |
| | | | | | 4,605 | | 4,605 |
| 11. | Thioacetazone Proposed annual Production 1000 kg. | 1. Hydrazine hydrate 80% | 900 | 2.0 | 180.0 | 900 | 1,800 |
| | | 2. Ammonium Thiocynate | 154 | 1.8 | 277,2 | 1540 | 2,772 |
| | | 3. Acetone | 20 | 1.8 | 36.2 | 200 | 360 |
| | | 4. Carbon | 4 | 2.2 | 8.8 | 40 | 88 |
| | | | | | 502.00 | | 5,020 |
| 12. | Chloropropamide Proposed annual production 1000 kg. | 1. Chlorosulphonic acid | 600 | 0.7 | 420 | 6,000 | 4,200 |
| | | 2. Chlorobenzene | 140 | 1.2 | 168 | 1,400 | 1,680 |
| | | 3. Urea | 50 | 1.0 | 50 | 500 | 500 |
| | | 4. Xylene | 100 | 0.6 | 60 | 1,000 | 600 |
| | | 5. Ethanol | 186 | 2.5 | 465 | 1,860 | 4,650 |
| | | 6. n Propylamine | 40 | 1.8 | 72 | 400 | 720 |
| | | 7. C.S. Flakes | 180 | 1.0 | 180 | 1,800 | 1,800 |
| | | | | | 1,415 | | 14,150 |

ANNEXURE 3

## FUNDS REQUIRED

## SUMMARY

| | | | US $ |
|---|---|---|---|
| I. | Cost of Installed equipment | | 1,734,793 |
| II. | Cost of Laboratory Equipment | | 301,000 |
| III. | Cost of civil construction | | 642,500 |
| IV. | Requirement of Working Capital | US $ | |
| A. | Margin money for imported raw materials (4 months inventory) | 517,809 | |
| B. | Margin money for indigenous raw material | 5,000 | |
| C. | Stock in process 15 days stock | 64,726 | |
| D. | Cost of finished product for 1 month | 129,369 | |
| E. | Provision for interest | 300,000 | |
| | Provision for 1 month labour cost | 60,000 | |
| | Total Working capital | | 1,706,904 |

ANNEXURE 4

## LIST OF EQUIPMENT & ESTIMATED COST

| Serial No. | Item - Process Equipment | Capacity | No. | Unit Cost US$ | Total Cost US$ |
|---|---|---|---|---|---|
| A. | Glasslined Reactor Assembly | | | | |
| 1. | Jacketed glass-lined reactor with agitator | 1,000 l | 2 | 40,000 | 80,000 |
| 2. | G.L. Condenser | 4 sq.m. | 2 | 8,000 | 15,000 |
| 3. | G.L. Receiver | 600 l | 1 | 12,000 | 12,000 |
| | S.S. Reactor Assembly | | | | |
| 4. | Jacketed S.S. reactor with agitator | 1,000 l | 4 | 9,000 | 36,000 |
| 5. | S.S. Condenser | 4 sq.m. | 4 | 3,000 | 12,000 |
| 6. | S.S. Receiver | 600 l | 2 | 3,000 | 6,000 |
| 7. | Jacketed s.s. reactor with agitator | 600 l | 4 | 7,000 | 28,000 |
| 8. | S.S. Condenser | 3 sq.m. | 4 | 2,000 | 8,000 |
| 9. | S.S. Receiver | 500 l | 2 | 3,000 | 6,000 |
| 10. | Jacketed S.S. concentration pan with agitator | 400 l | 1 | 4,000 | 4,000 |
| 11. | Jacketed S.S. Vacuum still pot with agitator | 200 l | 1 | 4,000 | 4,000 |
| 12. | S.S. Condenser | 1.5 sq.m. | 1 | 1,000 | 1,000 |
| 13. | Jacketed S.S. Receiver | 200 l | 1 | 2,000 | 2,000 |
| | Centrifuges | | | | |
| 14. | S.S. basket centrifuge | 1 metre dia. | 2 | 8,000 | 16,000 |
| 15. | S.S. basket centrifuge | 0.75 metre dia. | 1 | 6,000 | 6,000 |
| | Filters | | | | |
| 16. | Mild steel rubber lined filter box | 600 l | 2 | 4,000 | 8,000 |
| 17. | S.S. Filter box | 600 l | 1 | 8,000 | 8,000 |
| 18. | S.S. Sparkler filter | | 1 | 8,000 | 8,000 |
| 19. | S.S. pressure leaf filter | | 1 | 3,000 | 3,000 |
| | Dryers - Air Circulation & Vacuum | | | | |
| 20. | Forced draft dryer | 94 trays | 1 | 25,000 | 25,000 |
| 21. | Forced draft dryer | 40 trays | 3 | 13,000 | 39,000 |
| 22. | Fluidised Bed | 30 trays | 1 | 18,700 | 18,700 |
| 23. | Fluidised Bed | 10 trays | 1 | 10,000 | 10,000 |
| 24. | Vacuum shelf dryer with condenser | | 1 | 9,000 | 9,000 |
| 25. | Water ring vacuum pumps | 7 h.p. | 4 | 2,000 | 8,000 |
| 26. | High Vacuum Pump | 2 h.p. | 1 | 1,000 | 1,000 |

## LIST OF EQUIPMENT & ESTIMATED COST

( Continued )

| Serial No. | Item - Process Equipment | Capacity | No. | Unit Cost US$ | Total Cost US$ |
|---|---|---|---|---|---|
| | Transfer Pumps | | | | |
| 27. | S.S. Centrifugal pump | 50 lbm at 25 m | 4 | 2,000 | 8,000 |
| 28. | M.S.R.L. pump | 50 lbm at 25 m | 2 | 1,000 | 2,000 |
| | All Glass Assembly | | | | |
| 29. | All glass reactor | 100 l | 2 | 2,000 | 4,000 |
| 30. | S.S. Pulveriser | | 1 | 2,000 | 2,000 |
| 31. | S.S. Mechanical sieve | | 1 | 2,000 | 2,000 |
| 32. | S.S. Resin column | 0.6 mo 1.5 m high | 2 | 2,000 | 4,000 |
| 33. | S.S. blender | | 1 | 3,000 | 3,000 |
| 34. | S.S. vent. condenser | 1.5 sq.m. | 5 | 1,000 | 5,000 |
| 35. | Dial type balance | to weigh 50 kg. | 2 | 1,500 | 3,000 |
| 36. | Miscellaneous Equipment - lump sum | | | | 6,000 |
| | | | | | 413,700 |

## LIST OF EQUIPMENT & ESTIMATED COST

| Serial No. | Item - ~~Process~~ Equipment | Capacity | No. | Unit Cost US$ | Total Cost US$ |
|---|---|---|---|---|---|
| B. | Tank Farm Equipment | | | | |
| 1. | Tank tor storing hydrochloric acid, high density poly thene | 10,000 l | 1 | 2,000 | 2,000 |
| 2. | M.S. storage tank for sulfuric acid | 10,000 l | 1 | 5,000 | 5,000 |
| 3. | M.S. storage tank for caustic soda | 10,000 l | 1 | 4,000 | 4,000 |
| 4. | M.S. storage tank for benzene | 10,000 l | 1 | 4,000 | 4,000 |
| 5. | M.S. storage tank for toluene | 10,000 l | 1 | 4,000 | 4,000 |
| 6. | M.S. storage tank for acetone | 10,000 l | 1 | 4,000 | 4,000 |
| 7. | M.S. storage tank for ethanol | 10,000 l | 1 | 4,000 | 4,000 |
| 8. | M.S. storage tank for methanol | 10,000 l | 1 | 4,000 | 4,000 |
| 9. | M.S. storage tank for diesel | 10,000 l | 2 | 4,000 | 8,000 |
| 10. | C.I. subermsible pump for solvent | | 5 | 2,000 | 10,000 |
| 11. | C.I. pump for sulfuric acid | | 1 | 1,000 | 1,000 |
| 12. | C.I. pump for caustic soda | | 1 | 1,000 | 1,000 |
| 13. | Polypropeline pump for hydrochloric acid | | 1 | 1,500 | 1,500 |
| 14. | M.S. vent condensers | 1 sq.m. | 5 | 1,000 | 5,000 |
| 15. | C.I. pump for diesel oil | | 1 | 1,000 | 1,000 |
| | | | | | 58,500 |
| C. | Utilities Equipment | | | | |
| 1. | Steam generator to generate steam at 10 atm | 500 kg/hr | 2 | 30,000 | 60,000 |
| 2. | Demineralized water unit | 3 $m^3$/hr | 1 | 15,000 | 15,000 |
| 3. | Soft water unit dealkalizer | 3 $m^3$/hr | 1 | 10,000 | 10,000 |
| 4. | H.D.P. storage tank for D.M. water | 10,000 l | 2 | 2,000 | 4,000 |
| 5. | H.D.P. storage tank for soft water | 10,000 l | 2 | 2,000 | 4,000 |
| 6. | S.S. pump for D.M. water | 25 l pm at 25 m | 1 | 1,500 | 1,500 |
| 7. | C.I. pump for soft water | 25 l pm at 25 m | 1 | 500 | 500 |
| 8. | Refrigeration unit for chilled water as SC | 30 tr | 2 | 30,000 | 60,000 |
| 9. | Refrigeration unit for chilled brine | 10 tr | 1 | 10,000 | 10,000 |
| 10. | Cooling Tower | 150 tr | 1 | 15,000 | 15,000 |
| 11. | C.I. cooling water pump | 1,500 l pm at 25 m | 2 | 3,000 | 6,000 |
| 12. | C.I. chilled water pump | 500 lpm at 25 m | 2 | 2,000 | 4,000 |
| 13. | C.I. Chilled brine pump | 100 lpm at 25 m | 2 | 1,500 | 3,000 |

## LIST OF EQUIPMENT & ESTIMATED COST

( continued )

| Serial No. | Item - Process Equipment | Capacity | No. | Unit Cost US$ | Total Cost US$ |
|---|---|---|---|---|---|
| 14. | Hot oil circulation unit | 70,000 K.cal/hr | 1 | 15.000 | 15,000 |
| 15. | Air Compressor | | 2 | 3,000 | 6,000 |
| 16. | Electric Substation 50 KVA | | 1 | 25,000 | 25,000 |
| 17. | Diesel generator 50 KVA | | 1 | 20,000 | 20,000 |
| 18. | Incinerator | | 1 | 2,500 | 2,500 |
| | Material Handling equipment | | | | |
| 19. | Hydraulic hand pallet truck | 1.5 ton | 3 | 1,000 | 3,000 |
| 20. | Battery operated truck | 1.0 ton | 3 | 900 | 2,700 |
| 21. | Fork lift truck | 1.5 ton | 1 | 10,000 | 10,000 |
| | Effluent Treatment Plant (Small Plant) | | | | |
| 22. | Neutralization & Biological treatment | | | 1,00,000 | 1,00,000 |
| | | | | | 3,77,200 |

| | |
|---|---|
| A. | 4,13,700 |
| B. | 58,500 |
| C. | 377,200 |
| | 849,400 |

ANNEXURE 5

## COST OF INSTALLED EQUIPMENT

| | | US $ | US $ |
|---|---|---|---|
| A. | Cost of Process Equipment | 413,700 | |
| B. | Cost of Tank Farm Equipment | 58,500 | |
| C. | Cost of Service Equipment | 377,200 | |
| | Total A, B & C | | 849,400 |
| D. | Cost of spares (for 3 years trouble free service) | | 84,940 |
| | | | 934,340 |
| | Total ex-works Cost of Equipment | | |
| E. | Handling charges to convert to ex-works cost to FOB | | |
| F. | CIF charges in Zimbabwe | | |
| G. | Handling Charges in Zimbabwe | | 233,585 |
| | Cost of Installation | | |
| | i) Cost of labour | 93,434 | |
| | ii) Cost of installation materials | 380,000 | |
| | iii) 10% for Explosion proofing | 93,434 | |
| | | | 566.868 |
| | Total installed cost of equipment | | 1,734,793 |

(Data collected from personal experience and cost of fabrication in India).

ANNEXURE - 6

## COST OF CIVIL CONSTRUCTION

| | | | US $ |
|---|---|---|---|
| A. | Cost of Process building - Basement/Ground Floor each 600 sq.m. Mezzanine floor 300 sq.m. (300 US $ / sq.m.) 1500 x 300 | | 450,000 |
| B. | Cost of Office accommodation, 50 sq.m. | | 15,000 |
| C. | Cost of warehouse for raw materials, 250 sq.m. | (250 x 250) | 62,500 |
| D. | Cost of warehouse for finished products, 100 sq.m. | | 25,000 |
| E. | Cost of building for utilities, 200 sq.m. | | 60,000 |
| F. | Workshop, cafeteria, time office,etc., 100 sq.m. | | 30,000 |
| | Total cost of Civil Construction | | 642,500 |

ANNEXURE - 7

## ANALYTICAL LABORATORIES

| A. | Equipment for Analytical Laboratory | Quantity |
|---|---|---|
| 1. | a) Metler semimicro balance | 1 |
| | b) Single pan balance | 1 |
| | c) Rough balance (Avery type) | 1 |
| 2. | Melting point apparatus | 1 |
| 3. | Laboratory drying oven (0 to 250°C) | 2(1 vac. oven) |
| 4. | Muffle furnace | 1 |
| 5. | Karl Fischer apparatus | 1 |
| 6. | Refractometer | 1 |
| 7. | Spectro Calorimeter | 1 |
| 8. | T.L.C. equipment | 1 |
| 9. | Vacuum pump | 1 |
| 10. | Heating mantles | 3 |
| 11. | Hot plates | 3 |
| 12. | PH Meter | 1 |
| 13. | U.V. - viewing cabinet | 1 |

| B. | Glass Ware and Other Laboratory Items | |
|---|---|---|
| 1. | Burette (10, 25 and 50 cc capacity) | 1 doz each |
| 2. | Pipettes (1, 2, 5, 10, 25 and 50 cc) | 20 each |
| | Lamda pipettes (5, 10 and 25) | 3 each |
| | Graduated pipettes (1, 5 and 10) | 10 each |
| 3. | Beakers (25, 50, 100, 250 and 500) | 2 doz each |
| | 1,00 cc | 1 doz each |
| 4. | Conical flasks (25, 50, 100, 250, 500 and 1,000 cc)Erlenmeyer | 1 doz. |
| | Idometric flask (250 ml) | 1 doz. |
| 5. | Kjaldhal distillation units (Kjaldhal flasks) | 2 |
| | Kjaldhal distillation units 500 ml. | 6 |
| | Kjaldhal distillation units 300 ml. | 6 |
| 6. | Platinum crucibles and tongs with pt. tip | 2 |
| 7. | Nickel crucibles | 2 |
| 8. | Silica (Vitreosol) crucible | 1 doz |
| 9. | Miscellaneous items (such as stand, clamps, etc.) | |
| 10. | Round bottom flask with standard joints (D-24) (100, 250 and 500 ml.) | 1 doz. each |

| | | |
|---|---|---|
| 11. | a) Thermometer (ordinary 0 to 250°C) | 6 |
| | b) Thermometer (Q.F.C. 250°C) | 3 |
| 12. | Standard glass joints, adapters, glassenheeds, etc. | |
| 13. | Separating funnel (50, 100, 250 and 500 cc) | 6 each |
| | Ordinary funnels | 1 doz |
| 14. | Weighing bottles | 1 doz |
| 15. | Sintared glass crucibles | 1 doz |
| 16. | Filteration flask (50, 100, 250, 500, 1 ltr.) | 6 each |
| 17. | Glass condenser for various types | 1 doz. |
| | Coiled type | 1 doz. |
| 18. | Glass cylinders (10, 25 and 100) | 1 doz each |
| 19. | Nesler tubes (25, 50 and 100) | 1 doz |
| 20. | Volumetric flasks ( 10, 25, 50 and 100) | 1 doz each |
| | 25, 500 and 1 ltr. | 6 |
| 21. | Test tubes - all sizes | 2 doz. |
| 22. | Dessiccators ordinary | 4 |
| | Vacuum | 2 |
| 23. | Specific gravity bottle and pyknometers | 10)<br>25) 3 each<br>50) |
| | Pyknometers | 4 |
| 24. | 100 l all-glass assembly | 1 |

Total estimated cost of Laboratory Ware A and B US $ 50,000

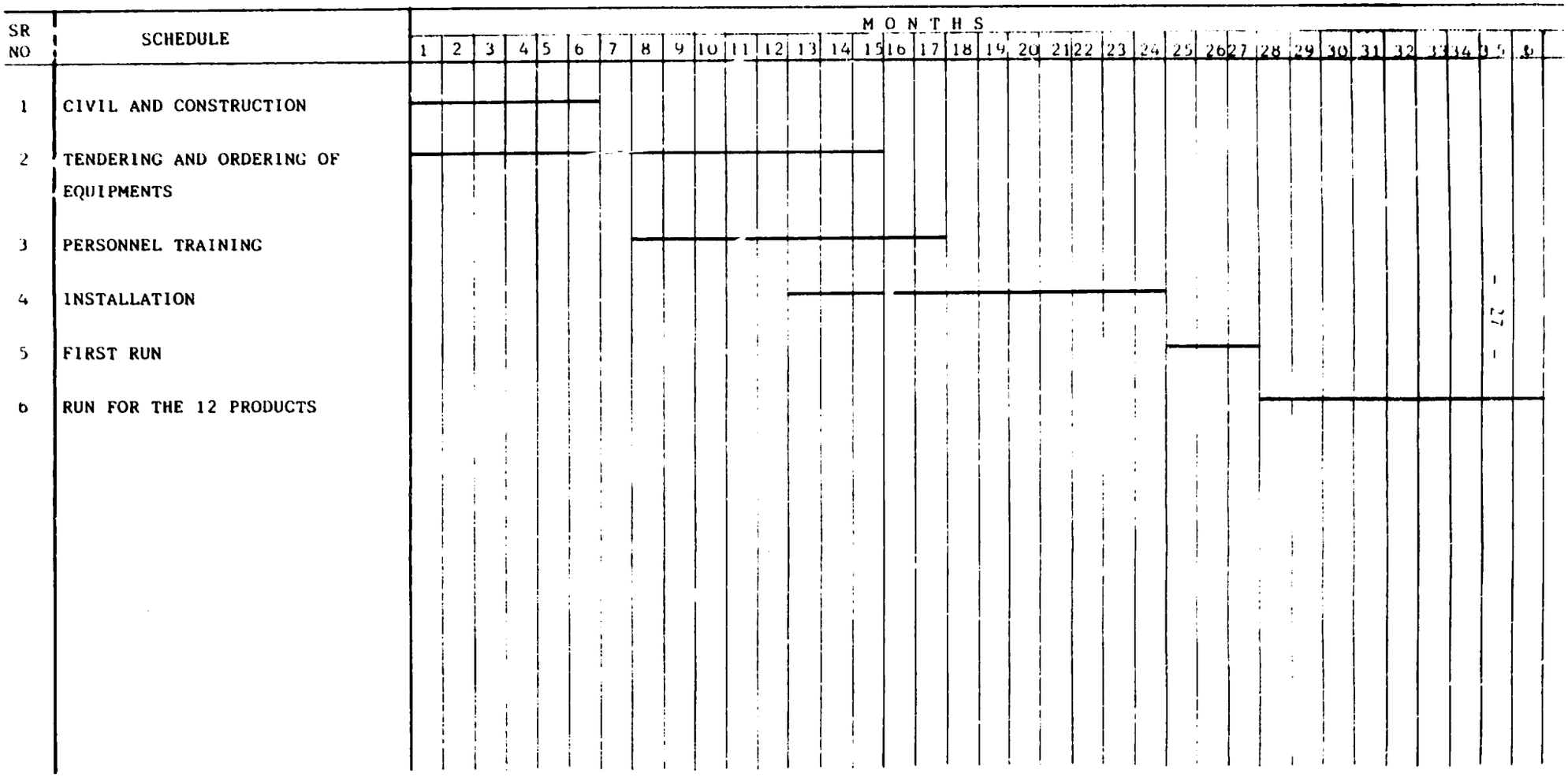
| C. | | US $ |
|---|---|---|
| 1. | Perkin-Elmer Series 4 high pressure liquid chromatograph complete with all spares and accessories c.i.f. | 58,800 |
| 2. | Perkin-Elmer Model 241 polarimeter complete with all spares and accessories c.i.f. | 20,000 |
| 3. | Beckman Acculab infrared spectrophotometer complete with all spares and accessories c.i.f. | 33,600 |
| 4. | Erweka unit for formulation complete with all spares and accessories c.i.f. | 40,000 |
| 5. | Atomic absorption spectrometer ) | |
| 6. | Gas chromatograph ) | 48,600 |
| | Total | US$ 251,000 |
| | Total A + B + C US$ | 301,000 |

ANNEXURE - 8

WORK SCHEDULE

FOR

MULTIPURPOSE PILOT PLANT



ANNEXURE - 9

## Personnel Requirement for the Plant

| | Production | Laboratory | Maintenance | Administration | Purchase | Finance | Services |
|---|---|---|---|---|---|---|---|
| Plant Manager, Chemist and high-level personnel | 9 | 3 | 2 | 1 | 1 | 1 | - |
| Operators Technicians, Clerk | 4 | 3 | 3 | 3 | 2 | 3 | 1 |
| Skilled Workers | 6 | 1 | 6 | 1 | 1 | 1 | 1 |
| Unskilled Workers | 15 | - | 3 | - | - | - | 6 |
| Total | 34 | 7 | 14 | 5 | 4 | 5 | 8 |

Total need: 77

## Training Requirement Outside the Country

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

ANNEXURE - II

## TECHNICAL INFORMATION

## ON THE VARIOUS DRUGS

1. Nicotinamide
2. Paracetamol
3. Metronidazole
4. Aspirin
5. Sulphamethoxazole
6. Trimethoprim
7. Chloroquin Phosphate
8. Chloramphenicol
9. Vitamin $B_1$ Hcl.
10. Vitamin $B_2$ 5' Phosphate
11. Thioacetazone
12. Chloropropamide

## 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.

## 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

## 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.

# 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

## 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 sulfanil 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

## 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 methylcinnamonitrile. 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.

## CHLOROQUIN PHOSPHATE

Chemical Name : $N^4$-(7-chloro-4-quinolinyl)-N'N'-diethyl-1,4-pentane-diamine phosphate

Use : Antimalarial

Brief description of the process:

4,7-Dichloroquinoline is reacted with Novolodiamine (1-diethyl-amino-4-aminopentane) for 7 hours at 180°C. The reaction mixture is then dissolved in dilute acetic acid and then basified by sodium hydroxide. The free base is extracted in an organic solvent and isolated by removal of the solvent from the dried extract and distilling the residue.

The free base i.e. chloroquin is then reacted with phosphoric acid to give the diphosphate.

Intermediates : 1) 4,7-Dichloroquinoline

2) Novolodiamine (1-diethylamino-4-aminopentane)

## CHLORAMPHENICOL

Chemical Name : D(-) threo-2,2-dichloro-N-[B-hydroxy-2-(hydroxy-methyl)-P-nitrophenethyl] - acetamide

Use : Antimicrobial / Antibacterial

Brief Description of Process:

L-Base is reacted with methyl dichloroacetate for 2 hours at 100°C. The residue is washed with petroleum ether and recrystallised from ethyl acetate to give chloramphenicol.

Intermediates:

1) L-Base
2) Methyl dichloroacetate

## VITAMIN $B_1$ HCl

### Thiamine Hydrochloride

Chemical Name : Thiamine Hydrochloride

Use : Enzyme Co factor Vitamin

Brief Description of process:

Thio thiamine is reacted with hydrogen peroxide. The base is precipitated by dumping in water - reaction with Hcl. - The thiamine Hcl. formed is crystalised out from alcohol - air dried.

Intermediate : Thio thiamine

## Vitamin $B_2$ 5' phosphate Sodium Salt

## Riboflavine-5'-phosphate-sodium salt

Use : Vitamin, has increased water solubility compared to riboflavin.

Brief Description of Process:

Riboflavin is reacted with phosphorous oxychloride to give the phosphate. The product is suspended in alcohol and pH adjusted by careful addition of sodium hydroxide solution to give the sodium salt of Vit. $B_2$-5'-phosphate.

Intermediates : 1) Riboflavin - Vit $B_2$

2) Phosphorous oxychloride

# THIACETAZONE

Chemical Name : N-[4-[[(Aminothioxymethyl) hydrazo] methylene] phenyl] acetamide.

Use : Antibacterial (tuberculostatic)

Brief description of process:

: p-Acetamimobenzaldehyde is reacted with thiosemicarbazide in ethanol at reflux temperature to give thiacetazone.

Intermediates: : 1) P-Acetylaminobenzaldehyde

2) Thiosemicarbazide.

## CHLOROPROPAMIDE

Chemical Name : 4 - chloro -N- [(propylamino) carbonyl) benzene sulfonamide

Use : Oral hypoglycemic

Brief description of process : 4- Amino-5-bromomethyl-2-methylpyrimidine is reacted with 5-(2-hydroxyethyl)-4-methyl thiazole to give Thiamine hydrobromide. This on reaction with silver chloride (or with ion exchange) gives thiamine hydrochloride.

Intermediates : 1) 4-Amino-5-Bromomethyl-2-methylpyrimidine

2) 5-(2-Hydroxyethyl)-4-methylthiazole.