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REPORTS ON DRUGS FROM THE NATIONAL DRUG LIST WHICH BECAUSE OF THEIR ESSENTIALITY COULD BE PRODUCED IN THE DEVELOPING COUNTRIES *

by

C.N. Chari**
in co-operation with
the secretariat of UNIDO

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** Managing Director, Hindustan Antibiotics Ltd., India.

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C O N T E N T S

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INTRODUCTION

With the growing emphasis on health care in the developing countries, the demand for drugs and pharmaceuticals is ever on the increase. As the National Health Programmes gain momentum and adequate finances are made available to support the same, the demand for drugs is bound to grow further. For example, the consumption of drugs and pharmaceuticals in one of the developing countries in Latin America in 1974 amounted to about US$800,000,000 and the growth rate has been over 15% per year. However, most of the developing countries don't have a well established drug and pharmaceutical industry and they have to depend upon imported bulk drugs to meet their requirements expending valuable foreign exchange. This in its turn limits the availability of drugs so vital to the health and well being of the people in the developing countries.

From the National Drug list, eleven drugs have been identified jointly by WHO/UNIDO. These drugs cover a wide spectrum and could be produced in the developing countries because of their essentiality and wide spread usage. Detailed reports are presented on these drugs indicating the process, raw materials required, investment involved for an economical unit, the names of major producers and patent holders, quantities consumed and the prices prevalent in the International market as well as the developing country. Fortunately sophisticated technologies for most of these drugs are available in some of the developing countries and it has been the strategy of UNIDO to encourage technical co-operation amongst the developing countries. An industrial profile is also presented for a multipurpose plant to manufacture four of the synthetic drugs along with several other drugs commonly used in the developing countries.

The authors gratefully acknowledge the cop-operation extended by Alta Laboratories, Haffkeine Institute, Hindustan Antibiotics, Karanth Pharma Chemical, Indian Drugs and Pharmaceuticals and National Chemical Laboratory - of India in the preparation of these reports.

I. ANALGESICS

A. ACETYL SALICYLIC ACID (600 t)

(From SALICYLIC ACID)

1. General

It occurs in the form of esters in several plants. It was first developed in 1899. In 1960 many synthetic processes have been developed for this drug. It is employed as an antipyretic and analgesic in a variety of conditions.

2. Producers

a. Bayer, F.R.G.

b. Merck Darmstadt

c. Rhone-Progil, France

d. Monsanto Chemicals, U.S.A., U.K.

e. Bofors, Sweden

f. Kerr-McGee, U.S.A. (Patent holder)

g. Smith Kline and French, U.S.A.

h. Alta Laboratories, 532 Senapati Bapat Marg, Dadar, Bombay, India (Willing to offer technology)

3. Process

Acetyl Salicylic Acid is prepared by Acetylation of Salicylic Acid with Acetic Anhydride. Excess Acetic Anhydride over the theory is used to get hard tabular crystals, as well as a stable product.

The crystals are centrifuged and washed with water and dried.

The mother liquor containing Acetic Acid, Acetic Anhydride and dissolved Aspirin is distilled to recover Acetic Acid as by-product.

The sludge in distillation still containing Aspirin is decomposed with Caustic Soda solution, and after purification Salicylic Acid is precipitated out with dilute Sulphuric Acid to recover Aspirin as Salicylic Acid.

Aspirin crystals after drying are sifted to separate oversize and fines. Middle fraction is sold as crystals while oversize and fines are milled and sold as powder.

The product produced by this process shall meet B.P. and U.S.P.

4. Raw Materials

Following are the major raw materials required for manufacture of Aspirin.

a. Salicylic Acid Sublimed.

b. Acetic Anhydride

c. Caustic Soda Flakes

d. Sulphuric Acid 98%

5. By-products Obtained

a. Acetic Acid Glacial Technical

b. Salicylic Acid Technical

6. Economical Size of the Plant

Based on the experience of a developing country, 600 Metric Tonnes of Acetyl Salicylic Acid B.P./U.S.P. per annum will be an economical size for developing countries. The capacity of production is based on three shifts a day, seven days a week and 300 days working in an year excluding the maintenance downtime.

7. Raw material prices, consumption and utilities requirement

The raw material prices are taken as international prices as quoted in various publications. Consumption of raw materials and utilities is based on the experience of a developing country.

a. Raw Material Cost:

Raw Material.	International price per M.T. in US $ C.I.F.	Requirement per ton of F.P.	Cost in US $ per M.T. of F.P.
Salicylic Acid Sublimed	1650	0.960 M.T.	1584
Acetic Anhydride	500	0.960 M.T.	480
Caustic Soda	250	0.120 M.T.	30
Sulphuric Acid	30	0.125 M.T.	6
Other raw materials	-	-	4
			2104
By products			
Acetic Acid Glacial Tech.	350	0,500 M.T.	175
Salicylic Acid Tech.	1220	0.125 M.T.	152
			323
Nett R.M. Cost Per Ton		.... U.S. $	1777

	Requirement per ton of F.P.
b. Power - only for Aspirin, Acetic Acid and recovery of Salicylic Acid	400 UNITS
c. Steam for Aspirin, for recovery of Acetic Acid and Salicylic Acid	5500 kgs.
d. Cooling Water - make up	50 M^3
e. Process Water	10 M^3

8. Labour Requirement

Category of Labour	Number Required	Assumed Rate per Month in US $	Amount in US $
Unskilled	12	50	600
Semiskilled	12	55	660
Skilled	8	60	480
Supervisory	4	75	300
Administrative	2	60	120
Clerical	1	55	55
Managerial	1	150	150
Security	7	50	350
			2715
Other Administrative Expenses			285
		TOTAL	3000

10. Other Capital Costs (Based on Indian Conditions)

a. Land - 1.5 Hectare 3000 US $
Land development and roads 7000 US $
10000 US $

b. Building

	Sq. Mtr.	Rate Per Sq. mtr. in US $	Amt. in US $
Factory Building	280	200	56000
Boiler House	55	50	2750
Godowns	280	50	14000
Other Buildings	150	50	7500
Office Building	110	100	11100
			91350

c. Utilities — US $

Boiler - 1000 kgs/hr. steam generation at 10 kg/sq. cm. including cost of equipment, installation, piping, instrumentation — 60000

Cooling and process water - including cost of pumps, pipelines, cooling towers — 20000

Power - Cost of transformer, cables, wiring Panel boards, etc. — 10000

Storage Tanks - For water, oil, etc. — 10000
100000

11. Working Capital

2 months raw materials	US $ 209000	
1 month's finished product	125000	
1 month's wages, fuel, stores & packing material	33250	
	367250	367250

12. Total Investment of the Project

a. Land and Land Development	10000
b. Buildings	91350
c. Plant and Machinery	460000
d. Utilities	100000
e. Working Capital	367250
	1028600
f. Contingencies	21400
	1050000
g. Interest during construction	50000
	1100000

Cost of Production

Qty. 600 M.T. per year	US $
Raw materials	1068000
Wages	36000
Power	11250
Fuel	25000
Depreciation - 10% on plant and machinery 5% on building (56000 + 4500)	60500
Total C/F	1200750
Total B/F	1200750
Maintenance - 4% on cost of equipment 1% on cost of building	23400
Overheads - 1.5 times direct wages	54000
Interest on investment as loans 70% of total capital at 10%	77000
Packing at US $ 75 per ton	45000
Selling and distribution 2% on Factory cost	27000
	1397150

∴ cost per ton . . . US $ 2328

14. Total Sales Realisation

The selling price fixed is $2500 per ton which is very reasonable on the basis of international price.

Total sales - 2500 x 600	1500000
Total cost of production	1397150
Total gross profit	102850
Add depreciation	60500
Total profit	163350

∴ RETURN ON CAPITAL INVESTMENT 14.85%

$$\frac{163350}{110000} \times 100 = 14.85\%$$

15. Technical know-how fee of M/S Alta Laboratories, India $50,000

Detailed engineering fee - 10% of the cost of plant and equipment.

B. ACETYL SALICYLIC ACID (645 t)
(From basic raw material - Phenol)

The partioulars under 1. General and 2. Producers are the same as given under I A.

3. Process

a. Salicylic Acid Sublimed

Salicylic Acid Technical grade is produced batchwise by reacting Phenol and Caustic Soda to give Sodium Phenate solution. Sodium Phenate solution is then subjected to evaporation to produce Sodium Phenate dry powder. Carbondioxide under pressure is introduced to react and convert Sodium Phenate to Sodium Salicylate. Some quantity of Phenol generated in the reaction is recovered, and Sodium Salicylate is dissolved, and the solution of Sodium Salicylate is purified and filtered. Salicylic Acid is precipitated out from Sodium Salicylate solution by adding dilute Sulphuric Acid. The precipitated slurry of Salicylic Acid is then centrifuged, washed and Salicylic Acid wet cake is dried to get Technical grade of Salicylic Acid.

Technical grade of Salicylic Acid is further subjected to sublimation on a continuous sublimer to give Salicylic Acid Sublimed, which is the raw material for manufacture of Acetyl Salicylic Acid.

b. Acetyl Salicylic Acid (Aspirin)

Acetyl Salicylic Acid is prepared by acetylation of Salicylic Acid with Acetic Anhydride. Excess Acetic Anhydride over the theory is used to get hard tabular crystals, as well as a stable product.

The crystals are centrifuged and washed with water and dried. The mother liquor containing Acetic Acid, Acetic Anhydride and dissolved Aspirin is distilled to recover Acetic Acid as by-product.

The sludge in distillation still containing Aspirin is decomposed with Caustic Soda solution, and after purification Slicylic Acid is precipitated out with dilute Sulphuric Acid to recover Aspirin as Salicylic Acid.

Aspirin crystals after drying are sifted to separate oversise and fines. Middle fraction is sold and oversise and fines are milled and sold as powder.

The product produced by this process shall meet B.P. and U.S.P.

Raw Materials

Salicylic Acid Technical and Sublimed

Following are the major raw materials required for manufacture of Salicylic Acid Technical:

i. Phenol
ii. Caustic Soda
iii. Carbondioxide
iv. Sulphuric Acid
v. Carbon, Hydrosulphite, Etc.

Acetyl Salicylic Acid

i. Salicylic Acid Sublimed
ii. Acetic Anhydride.
iii. Caustic Soda Flakes.
iv. Sulphuric Acid 98%

By-products obtained:

a. Acetic Acid Glacial Technical
b. Salicylic Acid Technical

5. Economical Size of the Plant

a. Salicylic Acid Technical & Sublimed

Based on the experience of a developing country, a plant to produce 660 M.T. per annum of Salicylic Acid Technical, which on sublimation should give about 620 M.T. of Sublimed Salicylic Acid per annum will be economical size for developing countries. This quantity of Sublimed Salicylic Acid can produce ultimately 645 M.T. of Aspirin. The production is based on 3 shifts a day, 7 days a week and 300 days working per year excluding maintenance and other downtime.

b. Acetyl Salicylic Acid

Based on the experience of a developing country, a 645 M.T. of Acetyl Salicylic Acid B.P./U.S.P. per annum will be an economical plant for developing countries. The capacity of production is based on three shifts a day, seven days a week and 300 days working per year excluding the maintenance downtime.

6. Raw Material Prices, Consumption and Utilities Requirement

a. Salicylic Acid Sublimed

The raw material prices are taken as International prices as quoted in various publications. Consumptions of raw materials and utilities is based on experience of a developing country.

1. Raw material cost per ton of Salicylic Acid Sublimed:

Raw Material	International price per M.T. in US $ CIF	Requirement per ton of S.P. in M.T.	Cost in US $ per M.T. of S.A.
Phenol	580	0.816	470
Caustic Soda	250	0.410	103
Carbondioxide	150	0.535	80
Sulphuric Acid	52	0.535	28
Other raw materials	-	-	19
			700

ii. Power for Salicylic Acid Technical and Sublimed — 1000 Units per M.T. of F.P.

iii. Steam for Salicylic Acid Tech. and Sublimed — 16500 kgs per M.T. of F.P.

iv. Cooling Water - make up — 100 M^3 per M.T. of F.P.

v. Process Water — 10 M^3 per M.T. of F.P.

Note: It is assumed that Carbondioxide used for Salicylic Acid will be from bottles and cylinders and no separate Carbondioxide plant is provided.

7. Labour Requirement

a. Salicylic Acid Technical and Sublimed Plant

Category	No. required	Assumed rate per month	Total Wages in US $
Unskilled	35	50	1750
Semiskilled	27	55	1485
Skilled	16	60	960
Supervisory	9	75	675
		Total C/F	4870
		Total B/F	4870
Administrative	2	60	120
Clerical	2	55	110
Security	7	50	350
Managerial	1	150	150
Maintenance	7	60	420
Analytical	2	75	150
			6370
		Other administrative expenses	380
		Total Wages per month	6750

8. List of Major Equipment

a. Salicylic Acid Technical and Sublimed
(Cost based on Indian conditions and prices prevailing in India).

Name of Equipment	Material of Construction	Qty. Nos.	Total Cost in US $
Phenol Melter	M.S.	1	3000
Caustic Dissolver	M.S.	1	2000
Phenate Mixer	M.S.	1	12000
Phenate Egg	M.S.	1	3000
Autoclaves Complete	M.S.	3	225000
Ejectors	M.S.	2	4000
Storage tanks main and various in plants	M.S./S.S.	-	25000
Purifiers	S.S.	1	20000
Filter Press	Wooden	2	8000
Purified Liq. Tank	S.S.	1	12000

Name of Equipment	Material of Construction	Qty. Nos.	Total Cost in US $
Precipitators with coil and agitators	Wooden	2	60000
Centrifuges	S.S.	6	80000
Drier	M.S./S.S.	1	30000
Phenol Concentrator	M.S.	1	16000
	Total C/F		500000
	Total B/F		500000
Pumps	M.S./S.S.	12	20000
Other equipments	-	-	60000
			580000
Sublimation Plant imported with 100 kgs/hr. capacity complete with spares at CIF Cost.	Aluminium/ M.S.		400000
			980000
Installation 15%			145000
Piping 10%			98000
Electrical 5%			49000
Instrumentation 2%			20000
Lagging 3%			30000
Spare Parts			30000
Contingencies			28000
			1380000

All the costs are based on bare cost which does not include packing, forwarding, import duty, transport, etc.

9. Other Capital Cost

Based on Indian Conditions.

a. Land - 3 Hectares 60000 US $
Land Development and Roads 60000
120000

b. Buildings:

Building	Area sq. m.	Rate per sq.m.	Amt. in US $	
Factory Bldg.	460	200	92000	
Boiler House	100	60	6000	
Other Bldgs.	150	60	9000	
Godowns	300	50	15000	
Office Bldg.	150	100	15000	
			137000	137000

C. Utilities

		US $
i.	Boiler - 3000 kgs/hr. at 10 kg./sq.cm. including main header, fittings, instrument and water softening plant complete with installation and lagging.	80000
ii.	Power - 500 KVA Transformer with 440 V 3 phase 50 cycles complete with Transformer House, Control Panels, Cables, etc.	20000
iii.	Cooling and Process water system complete with pumps for cooling and process water, cooling tower sedimentation and treatment arrangement, filter and pipe header with fittings, etc. complete with installation.	30000
iv.	Inert Gas System for Sublimer - Complete	20000
v.	Tanks for Water Storage, Furnace Oil Storage, etc.	15000
		314000

10. Working Capital

a. Salicylic Acid Sublimed

2 months raw materials	77000	
½ month's material in process	33000	
1 month's wages, fuel, stores & packing material, etc.	20000	
½ month's F.P.	49500	
	179500	179500

11. Total Investment of the Project

a. Salicylic Acid Technical & Sublimed

i.	Land & Land development	12000
ii.	Buildings	132000
iii.	Plant & Machinery	1300000
iv.	Utilities	315000
v.	Working Capital	179500
vi.	Interest during construction	100000
		1923500

12. **Cost of Production**

a. Salicylic Acid Sublimed 620 M.T. Per Year

	US $
Raw Materials	434000
Wages	81000
Power - 1000 Units for production and 500 units for others	25000
Fuel - Only for Salicylic Acid Tech. & Sublimed	84500
Depreciation - 10% on Plant & M/c. (154500)	161350
5% on Buildings (6850)	
Maintenance - 4% on cost of equipment (46000)	47370
1% on cost of Buildings (1370)	
Overheads - 1.5 times wages	121500
Interest on investment as loan 70% of the total investment at 10%	138150
Packing at $50 per ton	31000
	1123870

. . cost per M.T. of Salicylic Acid sublimed $1812.69

13. Raw Material Prices, Consumption and Utilities Requirement

b. Acetyl Salicylic Acid (Aspirin)

The raw material prices are taken as international prices as quoted in various publications. Consumptions of raw materials and utilities is based on experience of a developed country.

i. Raw Material Cost per ton of Acetyl Salicylic Acid

Raw Material	International prices per M.T. in US $ CIF	Requirement per ton of F.P. in M.T.	Cost in US $ per M.T. of F.P.
Salicylic Acid	1812.67	0.960	1740
Acetic Anhydride	500.00	0.960	480
Caustic Soda	250.00	0.120	30
Sulphuric Acid	52.00	0.120	6
Other raw materials	-	-	4
			2260
Less by-products			
Acetic Acid - 0.500 M.T. $350 = 175			383
Salicylic Acid 0.130 at $1600 = 208			
			1877

ii. Power - for Acetic Acid and recovery of Salicylic Acid — 400 units per M.T. of F. P.

iii. Steam for Aspirin and Acetic Acid (Recovery of Salicylic Acid to be done in Salicylic Acid Plant). — 4000 kgs per M.T. of F.P.

iv. Cooling water - make up — 50 M^3 per M.T. of F.P.

v. Process Water — 10 M^3 per M.T. of F.P.

14. Labour Requirement

b. Acetyl Salicylic Acid Plant

Category of Labour	No. Reqd.	Assumed rate $/month	Total amt. in US $
Unskilled	12	50	600
Semiskilled	12	55	660
Skilled	8	60	480
Supervisory	4	75	300
			2040
		Administrative Expenses	160
			2200

Note: Other categories of labour are not considered as it is already considered in salicylic acid plant.

15. List of Major Equipment

b. Acetyl Salicylic Acid Plant

Name of Equipment	Material of Construction	Qty. Nos.	Total Cost in US $
Aspirin Reactors - vertical agitated vessel with jacket	S.S.	3	45000
Centrifuges	S.S.	3	50000
Dryer	M.S./S.S.	2	15000
Sifter	S.S.	1	6000
Acetic Acid distillation still with condenser and receivers	s.s.	1	20000
Pumps	S.S./M.S.	8	13000
Chilling Plant	-	1	15000
Filters	S.S.	1	3000
Tanks for Acetic Anhydride, Acetic Acid, Caustic, Sodium Salicylate solution, etc.	-	-	35000
Other sundry equipment	-	-	50000
	C/F		272000
	Equipment Cost - C/F		272000
Installation 15%	40800		
Piping 10%	27200		
Electrical 5%	13600		
Instruments 2%	5440		
Lagging 3%	8160		
	95200		95200
Spare parts			20000
Contingencies			17800
	Total Equipment Cost		305000

16. Other Capital Cost (Based on Indian conditions)

a. Acetyl Salicylic Acid Plant

i. Land & Land development	nil
ii. Building - Factory building 280 sq. mtr. area @ $ 200 sq. m.	56000
iii. Utilities - Only steam headers, water headers and electrical cables from main transformer	20000
iv. Storage tanks, cooling tower, etc.	10000
	86000

17. Working Capital

a. Acetyl Salicylic Acid Plant

2 months raw materials except Salicylic acid	55000 US $
1 month's finished product	134500
1 month's wages, consumable stores and packing materials, etc.	15000
	204500

18. Total Capital Investment

b. Acetyl Salicylic Acid Project	nil
Land & land development	nil
Buildings	56000
Utilities	20000
Tanks and others	10000
Plant and Machinery	305000
Working Capital	204500
Other working capital	25000
Interest during construction at 10%	40000
	660500

19. Cost of Production

b. Acetyl Salicylic Acid

Cost of production of Aspirin based on consumption of all 620 M.T. of Salicylic Acid Sublimed. Total Aspirin production 645 M.T.

Raw Materials - 1877 x 645	1210670
Wages - 2200 x 12	26400
Power - $\frac{400 \times 645 \times 0.20}{8}$	6450
Fuel - $\frac{4000 \times 645 \times 2.2 \times 0.75}{25 \quad 8}$	21300
(only equivalent Furnace oil requirement)	
Depreciation - 10% on Plant & M/c. (33500) 5% on buildings (2800)	36300
Maintenance - 4% on Cost of equipment (9925) 1% on cost of building (560)	10485
Overheads 1.5 times of wages	43200
Interest on investment as loan 70% of the total investment at 10%	46235
C/F	1401040

Total B/F	1401040	US $
Packing $ 100 per ton	48375	
Selling and distribution - 2% on Factory Cost	29025	
	1478440	

∴ cost per ton .... US $ 2292

20. Total Realization on sale

Acetyl Salicylic Acid

Total realisation on sale at $2500 per M.T.	1612500
Cost of Production	1478440
Gross Profit	134060
Add depreciation of Salicylic Acid and Aspirin (161350 + 36300 = 197650)	197650
Total gross profit before depreciation	331710

21. Total Capital Investment & Return on Investment

a. Salicylic Acid Technical & Sublimed	1973500
b. Acetyl Salicylic Acid	660500
Total	2634000

∴ Return on Investment $\frac{331770 \times 100}{2634000}$ = 12.60%

22. Technical Know-how fee of M/s Alta Laboratories, India US $ 150,000

Detailed engineering fee - 10% of the cost of the plant and equipment.

C. PARACETAMOL (100 t)
(From basic raw material - Paranitro Chloro Benzene)

1. General

It is a mild analgesic used to relieve pains arising from muscles and joints and peripheral nerve conditions. It was first synthesized in 1878.

2. Producers

a. Bayer, F.R.G.
b. Hoechst, F.R.G.
c. Merck-Darmstadt
d. Rhone-Poulene, France
e. Roussel - Uclaf
f. Eisai, Japan
g. Warner Lambert (Patent holder)
h. Winthrop, U.S.A.
i. Indian Drugs and pharmaceuticals, India
j. Alta Laboratories, Dadar, Bombay, India
(Willing to offer technology)

3. Process

P-nitrochlorobenzene is the starting raw material. P-nitrochlorobenzene is first hydrolised by Sodium Salt of para nitrophenol by boiling with dilute Caustic Soda under pressure. Unreacted PNCB is recovered by distillation and Para-nitrophenol is precipitated out by addition of dilute Sulphuric Acid. The slurry is centrifuged and para-nitrophenol is washed with water.

Reduction of Para-nitrophenol (PNP) is carried out in a reduction vessel by means of iron powder where P-nitrophenol gets converted to P-aminophenol (PAP). P-aminophenol is in dissolved condition. The solution is then filtered to remove residue of iron sludge. The sludge is washed with hot water and washings are added in the filtrate.

The filtered solution of P-aminophenol is now cooled and Acetic Anhydride is added to acetylate P-aminophenol to P-acetyl aminophenol. After the reaction is completed, excess Acetic Anhydride and Acetic Acid formed during the reaction are neutralised with Soda Ash. The slurry is cooled and centrifuged wet cake is washed with water. The product Acetyl P-aminophenol is crude. Purification of crude Paracetamol is done by dissolving the material in water, high temperature, treating the solution with Activated carbon. The solution is filtered hot and cooled slowly to separate Paracetamol as crystalline form. The slurry is then filtered, washed and Paracetamol is dried. The product is sold as such or pulverised and sold as Paracetamol Powder. The product obtained shall meet pharmacopeial specifications for B.P. or U.S.P.

4. Raw Material Requirement

Following are the major raw materials required for manufacture of Paracetamol:

a. P-nitro chloro benzene

b. Caustic Soda Lye

c. Sulphuric Acid

d. Iron Powder

e. Acetic Anhydride

f. Soda Ash

g. Sodium Sulphite, Activated Carbon, Etc.

5. Economic Size of the Plant

Based on the experiment of a developed country, a 100 M. Tonne per annum plant of Paracetamol will be suitable for developing countries, although this may not be an economic capacity plant. The capital

investment being high, and demand being low, it is better to start with a medium sized plant and further expand it along with the demand in the market. The capacity of production is based on three shifts a day, seven days a week, and 300 days working per year excluding downtime for maintenance.

6. Raw material prices, consumption and utilities requirement

The raw material prices which are available in international market are taken and the balance raw material prices are assumed very near to the international market. Consumption of raw materials i.e. coefficient of consumptions and utilities is based on the experience of a developing country.

a. Raw Material Cost

Raw Material	International price per M.T. in US $CIF	Requirement per ton of F.P.	Cost in US $ per M.T. of F.P.
P-Nitrochlorobenzene	650	1.600	1040
Sod. Hydroxide (100%)	250	0.980	245
Sulphuric Acid	52	0 830	43
Iron Powder	60	1.550	93
Acetic Acid Glacial	350	0.060	21
Acetic Anhydride	500	1.400	700
Sodium Carbonate	55	0.900	50
Sodium Sulphite	450	0.015	7
Activated Charcoal	400	0.200	80
Ethylene Glycol (make-up)	520	0.020	10
	Total R.M. Cost		2289 say 2290

b. Power - 7000 units per ton for manufacturing only; and say 1000 units for other purpose — 8000 units/ton

c. Steam - for production — 12500 kgs/ton

d. Cooling water - make up — 50 M^3

e. Process Water — 10 M^3

7. Labour Requirement

Category of labour	Number Reqd.	Assumed rate/ month in US $	Amount in US $
Unskilled	12	50	600
Semiskilled	8	55	440
Skilled	8	60	480
Supervisory	4	75	300
Administrative	2	60	120
Clerical	1	55	55
Managerial	1	150	150
Maintenance	8	55	440
Security	8	50	400
			2985
Other Administrative Expenses			215
Salary per month			3200

8. List of Equipment

(Cost based on Indian conditions and prices prevailing in India).

Name of Equipment	Material of Construction	Qty. Nos.	Total Cost in US $
PNCB Hydrolyser - S.S. Agitated vessel with jacket, working pressure 5 kgs/sq. cm. with condenser and receiver 3000 lit.	S.S.	2	62500
Storage Tank for Sulphuric Acid, O.H. Tank for Sulphuric Acid, Storage tanks for Caustic Soda, Acetic Anhydride, etc.	MS/SS	8	37500
Pumps for Caustic, Sulphuric, Acetic Anhydride, Process pumps, etc.	MS/SS	10	12500
Total C/F			112500
Total B/F			112500
Air Compressor with pressure tank and charging egg.	M.S.	1	5500
Centrifuges	S.S.	3	45000
Reduction Vessels 3000 lit. cap. agitated with coil & condenser	S.S.	2	60000
Filter Unit	M.S.	2	5000
Acetylator S.S. Unit 3000 lit. capacity with agitator & jacket	S.S.	2	60000
Refrigeration Plant - 30 tons at -15°C complete with cooling tower and pumps	-	1	37500

Name of Equipment		Material of Construction	Qty. Nos.	Total Cost in US $
Treatment vessel S.S. agitated with heating arrangement and pressure filtration system, capacity 4000 lit.		S.S.	1	35000
Crystallisation Vessel S.S. agitated with cooling coil 4000 lit. capacity		S.S.	1	35000
Cabinet Dryer 48 trays capacity		M.S.	2	8000
Pulveriser for milling of powder		S.S.	1	3000
Other equipment		-	-	16000
				430000
Installation 10%	43000			
Piping 10%	43000			
Electrical 5%	21500			
Instruments 2%	8600			
Lagging 3%	12900			
	129000			129000
				559000
Spare parts				21500
Contingencies				19500
Total Equipment Cost				600000

9. Other Capital Cost

a. Land 1.5 Hectares
Land Development and Roads

	3000
	7000
	10000

b. Buildings

	Sq. Mtr.	Rate per Sq. Mtr.	
Factory Building	400	100	40000
Boiler House	60	50	3000
Godowns	300	50	15000
Other Buildings	150	50	7500
Office Building	110	100	11000
			76500

e. Utilities

Boiler - 600 kgs/hr. steam generation at 10 kgs/sq.cm. including cost of equipment, installation, headers, piping, instrumentation and lagging.	37500
Cooling & Process Water System - Cooling & Process Water pumps including Header, cooling tower lines, instrument, etc.	15000
Power - Cost of Transformer, cables, wiring, panel boards, etc.	10000
Storage tanks for Furnace Oil, Sedimentation tanks, etc. TOTAL UTILITIES	10000 72500

10. Working Capital

2 months' stock of raw materials	45500
0.5 month's material in process	17500
1 month's wages, fuel, stores and packing material	25000
1 month's finished product	40000
	128300

11. Total Investment in the Project

a.	Land and land development	10000
b.	Buildings	76500
c.	Plant and Machinery	600000
d.	Utilities	72500
e.	Working capital	128300
f.	Contingencies	12700
g.	Interest during construction	45000
		945000

12. Cost of production

Qty. 100 M.T. per annum

Raw material - 2290 x 100	229000
Wages - 3200 x 12	38400
Power - $\frac{5000 \times 100 \times 0.2}{8}$	20000
Fuel - $\frac{12500 \times 2.2 \times 100 \times 0.75}{6 \times 25}$	10500
Depreciation - 10% on Plant & M/C (67250) 5% on Bldg. (3825)	71075
Maintenance - 4% on cost of equipment (20050) 1% on cost of building (765)	20815
Overheads - 1.5 times of wages	57800
Interest on investment - 70% of total capital at 10%	66150
Packing at 80$ per ton	8000
Selling & Distribution 2% on Factory Cost	10435
	532175

. . cost per ton US $ 5322

13. Total Sales Realisation

If the product is sold at US $ 5500 per ton, which is very reasonable as compared with the International Price of US $ 5000 per ton, the total sales realisation will be:

Total Sales Realisation	550000
Less Production Cost	532175
Profit after depreciation	17825
Add depreciation	71075
	88900

∴ return on investment before depreciation = $\frac{88900}{945000} \times 100 = 9.41\%$

14. Technical know-how fee of M/S Alta Laboratories, India US $ 25,000

Detailed engineering fee - 10% of the cost of the plant and equipment.

II A [illegible]

A. PENICILLIN

1. General

Penicillin was first reported by Alexander Fleming in 1929. Further research was carried out by Fleming, Florey and Chain in 1940. This is a narrow spectrum antibiotic.

2. Producers and Patent Holders

a) Abbott Laboratories, U.S.A.

b) Aktiebolaget Astra, Sweden

c) Bristol-Meyers Co., U.S.A.

d) Glaxo Laboratories, U.K.

e) Hindustan Antibiotics, India

f) Hoechst A.G., F.R.G.

g) Indian Drugs and Pharmaceuticals Ltd., India

h) Meiji Seika Kaisha Ltd., Japan

i) Novo Industries A/S, Denmark

j) Pfizer Inc., U.S.A.

k) E.R. Squibb Inc., U.S.A.

l) Standard Pharmaceuticals, India

m) Toyo Jozo Co., Japan

n) Wyeth Laboratories, U.S.A.

3. Process

Penicillin is manufactured by the submerged fermentation process using the microbial strain Penicillium Chrysogenum. The antibiotic is recovered from the filtered fermented broth utilizing counter current liquid extraction with an organic solvent such as butyl acetate. Penicillin in the form of salt is precipitated out with potassium acetate or by azeotropic distillation. For parenteral administration, benzyl penicillin salts of potassium, sodium, procaine, benzathine etc. in sterile form are prepared. For oral administration, phenoxymethyl penicillin salts of potassium or in the acid form are manufactured.

4. Raw Materials

a) Lactose, sucrose or glucose

b) Peanut oil, lard oil

c) Corn steep liquor

d) Peanut meal, cotton seed flour

e) Calcium carbonate

f) Phenyl/Phenoxy Acetic acid

g) Organic Solvents

h) Procaine Hydrochloride,
N.E.E. Diacetate

5. By-Products Obtained

The By-Product is the mycelium Cake obtained on filtration of fermented broth. This is to be utilised as fertilisers in paddy fields.

6. Economical Size of the Plant

Based on prices prevailing in countries like India, it is estimated that the minimum economic plant to be set up would be of about 122.5 ton/annum of penicillin which could be further converted into 35 T of ampicillin and about 63 T of sterile penicillin bulk. The requirement of potassium penicillin non sterile for the above final product would be as follows:

1) For ampicillin 35 T, 52.5 T of penicillin non sterile.

2) For 63 T of sterile penicillin bulk - 70 T of potasium penicillin non sterile.

7. RAW MATERIAL PRICES, CONSUMPTION AND UTILITIES REQUIREMENT

The prices are taken as international prices wherever available and in other cases indigenous prices are adopted. Consumption of raw materials and utilities are based on actual experience of the working of one of the biggest plants in India.

a) Raw material cost: the same is shown as per annexure I

b) Power

c) Steam

d) Refrigeration as Chilled water

e) Process Water

8. Labour Requirements

Category of labour	Number Required Non Sterile Pen.	Bulk Pen.	Assumed rate per month in U.S. $	Amount in U.S. $ Non Sterile Pen	Per ann Bulk Pe
Unskilled	20	5	940.17	18,803	4,701
Semi skilled	20	5	1,477.41	29,548	7,387
Supervisory	6	3	1,880.34	9,402	5,641
Administrative	-	-	--	--	--
Clerical	-	-	--	--	--
Security	-	-	--	--	--
Managerial - Junior	8	4	2,014.62	16,117	8,059
- Senior	3	2	3,378.00/	10,134	6,711
	57	19	3,355.50		

9. List of Major Equipments
(Cost based on India conditions and prices prevailing in India (In case of imported items only c.i.f. prices are given).

Name of Equipment	Material of Construction	Quantity Nos.	Total amount in U.S. $
Seed vessel	S.S.	2	1,22,000
Fermentors 125 KL	S.S.	2	[illegible]
High Horse Power Agitator	S.S.	2	[illegible]
Sterile Air System	S.S.	1	2,44,000
Continuous Addition System	SS/MS	1	2,44,000
Metering Pumps	S.S.	2 sets	[illegible]
Broth Holding Tank	S.S.	1	1,22,000
Pre-coat Filters	S.S.	2	1,22,000
Filter Broth Tank	S.S.	[illegible]	[illegible]
Brine Refrigeration Unit		150 tones	1,4 ,000
Miscellaneous			
Storage Mixing Tank	SS/MS		[illegible]
Decalin [illegible]	S.S.		[illegible]
Extraction Tanks	S.S.		1,4 ,000
Condenser	S.S.	3	2,50,000
Cosoform Dryers	S.S.	4	[illegible]
Crystallisers	S.S.	2	1 ,000
Evaporator		4	12,000
Batch Distillation Stills	S.S.	2	24,000
Centrifuges	S.S.	2	24,000
Shelf Dryer		1	1 ,000
Procaine System			2,44,000
Phenathine Pen. System			2,44,000
Solvent Recovery			4,89,000
Miscellaneous			
TOTAL EQUIPMENT COST			5,100,000
Services Equipment			
Air Compressors	5000 SCFM	2	2,44,000
Chilled Water Refrigeration units		3	4,89,000
Boilers 12,000 kg/hour		2	2,44,000
Electricals like Transformer, Cables, etc.			4,40,000
Water Treatment			2,44,000
Effluent Disposal			2,44,000
Miscellaneous including Safety, Laboratory, etc.			2,44,000
TOTAL			2,100,000

Instruments	
Instruments like Temperature Recorder, Controllers, Flow Recorder Controllers, Pressure safety valves etc.	85,000
Piping approximately 10%	7,00,000
Spares	1,68,000
Steam and Insurance	3,90,000
	1,343,000
OTHER CAPITAL COST (Based on Indian Conditions)	
Preliminary expenses	12,000
Consultancy Services	1,22,000
Land development & Roads	1,83,000
Buildings	
Process Building	3,66,000
Services Building	36,000
Administration Building	2,44,000
Contingencies	2,82,000
TOTAL CAPITAL COST	1,245,000

10. **Working Capital**

	122.5 MT Non Sterile Pen. US $	63 Tonnes Pot. Pen. Bulk US $
1 month's raw materials	100,244	29,304
1 month's finished Product	86,203	89,377
Month's wages, fuel, stores & packing material		
40 days work in process	229,792	238,095
Stores and spares (ad hoc)	73,240	5,105
7 days sundry debtors	40,171	41,634
Less 1 month sundry creditors	100,244	29,304
TOTAL	429,426	375,213

11. **Total Investment of the Project**

a) Land and Land Development	1,83,000
b) Buildings	6,45,000
c) Plant & Machinery)	
d) Utilities, consulting etc.)	8[illegible],[illegible],000
e) Working capital	4,00,000
f) Contingencies	2,82,000
g) Interest during construction	
	10,187,000

12. Cost of Production (per kg. in $)

	Non sterile Pen.	Pot. Pen. Bulk
Raw materials, inc. inter-mediate	0.82	34.11
Wages	0.39	0.35
Power	0.52	0.01
Fuel	1.41	1.39
Depreciation	2.03	0.68
Maintenance	0.15	0.09
Overheads	2.17	1.07
Conversion Cost	1.14	1.00
$ per kg.	23.45	39.45

13. Price in the International Market - $ 23.00/kg.

Price in India, Potassium Penicillin G Sterile - $ 122/kg

14. Consumption in India

200 tons.

Annexure I

MAJOR RAW MATERIALS

Potassium Penicillin Non-Sterile

S.No.	Raw Material	Unit	Cost per Unit US $	Qty. per kg. Finished Product	Cost per Finished Product US $
1	Caustic Soda	Kg.	0.217	0.308	0.07
2	N. Butyl Alcohol	Kg.	0.500	1.408	0.70
3	Activated carbon	Kg.	0.690	0.107	0.07
4	Lard Oil	Lit.	1.220	0.314	0.38
5	Groundnut Oil	Kg.	0.890	0.293	0.26
6	Sulphuric Acid	Kg.	0.089	0.087	0.01
7	Urea	Kg.	0.125	0.169	0.02
8	Pharma Media	Kg.	0.620	0.630	0.40
9	Phenyl Acetic Acid	Kg.	4.800	0.306	1.47
10	Sugar	Kg.	0.252	4.970	1.25
11	Other raw materials				5.19
			US$ per kg.		9.82

Bulk Penicillin

1	N. Butanol	Kg.	0.500	5.43	2.72
2	Acetone	Kg.	0.300	6.98	2.09
3	Others				6.29
			US$ per kg.		11.10

II B. TETRACYCLINE:

1. GENERAL:

Tetracyclines were discovered in 1948 and Tetracycline in 1953 by Lederle Laboretories and Chas Pfizers. This is a broad spectrum antibiotic.

2. PRODUCERS AND PATENT HOLDERS:

a) American Cyanamid, U.S.A.

b) Ankerfarm, Italy

c) Bristol Mayers, U.S.A.

d) Gruppo Lepetit, Italy

e) Hoechst A.G., F.R.G.

f) Indian Drugs and Pharmaceuticals, India

g) Novo Industries, Denmark

h) Pfizer Inc., U.S.A.

i) Roussel - UCF, France

j) E.R.Squibb, U.S.A.

k) Synbiotics, India,

l) Takeda Chemical Industries, Japan

m) Upjohn Co., U.S.A.

3. PROCESS:

Tetracycline is manufactured by the submerged fermentation process. The crude base is precipitated out from the filtered fermented broth. This is dissolved in methanolic calcium chloride treated with methanolic hydrochloric acid and concentrated under vacuum when Tetracycline hydrochloride crystallizes out. This antibiotic is administered in the form of Tetracycline hydrochloride and some times as Tetracycline base.

4. RAW MATERIALS:

a) Cereals such as Sorghum, Rice

b) Peanut meal

c) Peanut oil

d) Corn Steep Liquor

e) Organic Solvents

f) Inorganic Acids.

5. ECONOMICAL SIZE OF THE PLANT:

Based on needs of the developing countries and the price structure existing in the country, it is considered that the minimum capacity of 50 tonnes per annum of Tetracycline would be an economical size.

6. RAW MATERIAL PRICES, CONSUMPTION & UTILITIES REQUIREMENT:

The Raw Material prices are taken at International prices on imported items and at Indian prices on materials available locally. The consumption of raw materials and utilities are based on data from the developing country:

No.	Raw material	Intl./ Indigenous price per Kg	Qty. per Kg.	Cost per Kg. F.P.
1	Corn Steep liquor	0.15	2.59	0.39
2	Groundnut oil	1.51	5.25	7.93
3	Soyabean flour	0.58	2.45	1.42
4	Oxalic Acid	1.17	3.66	4.28
5	Maize Starch	0.54	10.32	5.57
6	Sodium Hydroxide	0.27	2.90	0.78
7	Hydrochloric acid	0.07	11.94	0.83
8	Resin SBS 3	42.42	0.05	2.12
9	Butanol	0.78	2.48	3.93
	Other materials			3.85
				29.10

7. LABOUR REQUIREMENTS:

Category of labour	Number required	Assumed rate per month in US $	Amount in US $
Unskilled	20	940.17	18,803
Semi-skilled	20	1,477.41	29,548
Supervisory	5	1,880.34	9,402
Administrative			
Clerical			
Managerial (Junior)	8	2,014.62	8,059
" (Senior)	3	3,378.00	10,134
Security			
	56		

8. LIST OF MAJOR EQUIPMENT:

(Cost based on Indian conditions and prices on imported equipments c.i.f. prices are indicated)

Name of equipment	Material of construction	Qty. Nos.	Total amount in US $
Seed vessels	S.S.	2	24,000
Fermentors 50 KL	S.S.	2	4,88,000
Sterile Air system	M.S.	1	61,000
Rotary Vacuum Filter		1	61,000
Glass lined vessels		5	1,22,000
Glass lined Nutsch Filters		5	30,000
Reactors and Tanks		6	1,00,000
Dryers		2	24,000
Boilers		5	6,000
Miscellaneous			
			7,30,000

	Total amount in US $
Utilities:	
Steam Boiler	61,000
Air Compressor	61,000
Refrigeration	60,000
Water Treatment	40,000
Sewage Disposal	40,000
Electricity	50,000
Laboratory	36,000
Miscellaneous	
	4,02,000
Instruments:	
Flow Recorder Controllers) Temperature Recorder Controller) Sagety Valves) Temperature Indicator, etc.)	61,000
Piping	1,00,000
Spares	24,000
Freight & Insurance	61,000
Installation etc.	1,27,000
Contingencies	41,000
	4,14,000
9. **OTHER CAPITAL COST** (Based on Indian conditions)	
Preliminary expenses	12,000
Consultancy services	1,22,000
Land	
Land Development and roads	1,22,000
Buildings:	
Process	60,000
Services	60,000
Administrative	36,000

10. WORKING CAPITAL :

	Total amount in US $
One Month's raw materials	1,21,245
½ month's finished product	1,00,000
40 days work in progress	2,66,300
Stores and spares	30,525
Sundry debtors	46,642
Less: one month's creditors for raw material	- 1,21,245
	4,43,467

11. TOTAL INVESTMENT OF THE PROJECT:

a) Land and Land Development	1,22,000
b) Buildings	1,56,000
c) Plant and Machinery)	16,89,000
d) Utilities, Consultancy)	
e) working capital	4,43,467
f) Contingencies	41,000
g) Interest during construction	
	24,51,467

12. COST OF PRODUCTION:	Per kg US $
Raw Materials	29.10
Conversion Cost	13.82
Depreciation	3.61
Overheads	3.68
Per kg US $ ..	50.21

13. Price in the International Market: US $ 28 / Kg.
US $ 79.3 / Kg.

14. Consumption in India : 180 tons in 1976.

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II C. AMPICILLIN:

1. GENERAL:

Ampicillin is a Semi-synthetic Penicillin. It was first prepared by Doyle in 1961. This is particularly useful in treatment of cases, which are resistant to Penicillins.

2. PRODUCERS AND PATENT HOLDERS:

a) Beecham Research Laboratories, U.K.

b) Hindustan Antibiotics, India

c) Lederle Laboratories, U.S.A.

d) Parke-Davis & Co., U.S.A.

e) Smith Kline Corpn., U.S.A.

f) Wyeth Laboratories, U.S.A.

3. PROCESS:

The manufacture of Ampicillin is carried out in two stages. In the first stage, Penicillin is converted into 6-Amino Penicillinic Acid (6-APA) by chemical method or enzymatic process. 6-APA is then converted by chemical method to Ampicillin trihydrate/Ampicillin anhydrous.

4. RAW MATERIALS:

a) Potassium Benzyl Penicillin

b) Phenyl Glycine chloride hydrochloride

c) Dimethyl Aniline

d) Dimethyl Dichloro silaene

e) Organic Solvents

f) B-Naphthalene Sulphonic Acid.

5. ECONOMICAL SIZE OF THE PLANT:

Based on the prices prevailing in developing countries like India, it is considered that the most economical size of the plant would have a capacity of 35 tonnes per year of Ampicillin Trihydrate.

6. RAW MATERIAL PRICES, CONSUMPTION AND UTILITIES REQUIREMENT:

Raw material	International price per Kg. in US $ C.I.F.	Requirement per Kg. of F.P.	Cost in US $ per Kg. of F.P.
Chloroform	0.457	14.000	6.40
Phosphorus Pentachloride	25.030	0.900	22.53
Phenyl Glycerine Chloride HCC	34.20	0.733	25.07
Methyl Chloride	0.962	26.000	25.01
Triethyl Amine	4.051	1.085	4.40
Acetone	0.300	3.200	0.96
			1.65
		U.S.$ per Kg.	86.02

7) LABOUR REQUIREMENT:

Category of labour	Number required.	Assumed rate per year U.S. $	Amount in US $ per annum.
Unskilled Semi-skilled	14	940.17	13,162
Skilled	14	1,477.41	20,684
Supervisory	8	1,880.34	15,043
Administrative Clerical Managerial	5	2,128.00	10,940
Security			
	41		

8. LIST OF MAJOR EQUIPMENT:

(Cost based on Indian conditions and prices prevailing in India)

Name of Equipment	Material of construction	Quantity No.	Total amount in US $
Reactors & Storage Tank	S.S.	5	1,50,000
PVC Tanks		2	6,000
Filter Presses	S.S.	2	24,000
Centrifuges	S.S.	2	50,000
Fluid Bed Dryer		2	50,000
Pulveriser		1	4,000
Conoform Dryer		2	50,000
	Total		3,66,000

	Total amount in U.S. $
Services	
Boilers	60,000
Refrigeration	2,50,000
Water Treatment	40,000
Effluent Treatment	40,000
Laboratory	30,000
	4,20,000
Instrument:	
Piping	1,00,000
Spares	20,000
Freight and insurance	50,000
Construction etc.	1,00,000
Contingencies	40,000
	3,10,000

9. OTHER CAPITAL COSTS: (Based on Indian conditions)

Preliminary Expenses	12,000
Consultancy Services	1,72,000
Land:	
Land development and roads	60,000
Building:	
Process	60,000
Services	30,000
Administrative	30,000

10. WORKING CAPITAL:

	Total amount in U.S. $
1 months raw materials	2,50,794
½ month's finished product	2,21,123
40 days work-in-progress	5,89,011
Stores & spare parts	18,315
7 days Sundry Debtors	1,03,052
Less one month creditors for raw materials	2,50,794

11. TOTAL INVESTMENT OF THE PROJECT:

a) Land and land development	60,000
b) Buildings	1,20,000
c) Plant and machinery including utilities and contingencies	12,30,000
d) Working capital	9,31,501
	23,41,501

12. COST OF PRODUCTION:

	U.S. $ per Kg
Qty. 35 T. per year	
Raw materials and intermediate drug	127.24
Wages	1.71
Power	4.35
Fuel	5.43
Depreciation	3.86
Other conversion cost	3.03
Maintenance	0.50
Overheads	4.97
	151.09

13)	Price in the International Market	....	U.S. $ 80 / Kg.
	Price in India	....	U.S. $ 236 / Kg.
14)	Consumption in India	....	36 tons in 1976.

III. ANTIMALARIALS

A. CHLOROQUINE DIPHOSPHATE

1. GENERAL:

Chloroquine diphosphate is an antimalarial drug effective against the erythrocytic forms of plasmodiary falsiparum and plasmodium Vivax. By virtue of its high concentration in the liver and the other organs, it is effective in the treatment of extra-intestinal amoebiasis. It is also effective in the treatment of chronic discoid lupus erythematosus, rheumatoid arthritis and cardiac arrhythmias.

Chloroquine was synthesised and developed in 1940 as antimalarial drug, but later it was found to be useful in the treatment of amoebiasis.

2.(a) PRODUCERS

a) I.C.I. Pharmaceutical, U.S.A.

b) Winthrop, U.S.A.

c) Bayer, U.S.A.

d) May & Baker, U.S.A.

f) Hilton-Davis Chemicals, U.K.

g) Medimpex, Hungary.

German Pat. 683692 (1939)
U.S. Pat. 2233970 (1941)
A.R.Surrey, H.F.Hammer, JACS 68 113 (1946)
R.L.Kenyon, J.A. Wiesner, C.E.Kwartler,
Ind. Eng. Chem. 41, 654 (1949)

b) PROCESS:

One method of preparation is substitution of 4,7 Dichloroquinoline. Industrial profile is presented for the process using meta-chloro-aniline and novoldiamine.

c) INVESTMENT:

The fixed capital requirement of a plant with a production capacity of 80 tonnes per annum (within the battery limit) is U.S. $ 1.8 million.

d) BUILDING:

The area required for the plant (within the battery limit) would be 3,000 sq.meters. The building will have two floors, each floor having an area of 1,400 sq.meters.

e) International price : US $ 52.7 / Kg.

Consumption in India : 386 tonnes in 1976.

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3. LIST OF MAJOR REQUIREMENT REQUIRED:

Sl.No.	Description	Qty.(Nos.)
1.	Reactor, Stainless Steel, 3200 L.	6
2.	Reactor, Mild Steel Tile Linerd, 4000 L.	1
3.	Reactor, Mild Steel Tile Lined, 3200 L.	2
4.	Reactor, Cast Iron Glass Lined, 2000 L.	3
5.	Reactor, Stainless Steel, 2000 L.	2
6.	Reactor, Stainless Steel, 1600 L.	3
7.	Reactor, Mild Steel, 1600 L.	1
8.	Reactor, Mild Steel, 630 L.	2
9.	Reactor, Stainless Steel, 400 L.	2
10.	Horizontal Receiving Tank, Mild Steel, 5000 L.	1
11.	Horizontal Receiving Tank, Stainless Steel, 4000 L.	1
12.	Horizontal Distillation Still, Stainless Steel, A = 4 M^2.	1
13.	Horizontal Receiving Tank, Mild Steel, 2000 L.	1
14.	Measuring Tank, Mild Steel, 2000 L.	2
15.	Measuring Tank, Stainless Steel, 1600 L.	3
16.	Measuring Tank, Mild Steel, 1600 L.	3
17.	Measuring Tank, Mild Steel, 1600 L.	4
18.	Measuring Tank, Mild Steel, 630 L.	2
19.	Measuring Tank, Stainless Steel, 630 L.	1
20.	Measuring Tank, Mild Steel Tile Lined, 3200 L.	1
21.	Measuring Tank, Mild Steel FRP Lined, 630 L.	2
22.	Measuring Tank, Stainless Steel, 400 L.	2
23.	Measuring Tank, Mild Steel, 400 L.	2
24.	Measuring Tank, Stainless Steel, 250 l.	2

Sl.No.	Description	Qty. (No.)
25.	Measuring Tank, Mild Steel, 250 L.	8
26.	Measuring Tank, Stainless Steel, 100 L.	2
27.	Heat Exchanger, Mild Steel, 4 M^2.	6
28.	Heat Exchanger, Mild Steel, 6 M^2	1
29.	Heat Exchanger, Stainless Steel, 4 M^2.	4
30.	Centrifuge, Mild Steel Rubber Lined, 1000 mm.	2
31.	Bell type Heat Exchanger, Cast Iron Glass Lined, 4 M^2.	1
32.	Nutsch Filter, Mild Steel Tile Lined, 2x1x1 M.	1
33.	Centrifuge, Stainless Steel, 1200 mm.	4
34.	Air Circulation Dryer, Stainless Steel Trays, 1 M^2, Mild Steel Cabinet	2
35.	Leaf Filter, Mild Steel, 65 L.	2
36.	Heat Exchanger, Mild Steel, 16 M^2.	3
37.	Heat Exchanger, Mild Steel, 10 M^2.	1
38.	Leaf Filter, Stainless Steel, 65 L.	4
39.	Vacuum Dryer 24 Trays, Stainless Steel, 10.6 M^2.	2
40.	Centrifuge, Stainless Steel, ϕ = 1000 mm.	2
41.	Submerged Pump, Stainless Steel, 3 M^3/Hr.	1
42.	Packed Column, Stainless Steel, ϕ = 400 mm, H =6 M.	1
43.	Horisontal Distillation Still, Mild Steel, 4000 L, A = 8 M^2.	1
44.	Packed Column, Mild Steel, ϕ = 600 mm, H = 6 M.	1
45.	Centrifugal Pump, Cast Iron, 6 M^3/Hr, H = 30 M.	1
46.	Vacuum Pump, Cast Iron, 8.6 M^3/Min.	3

4. REQUIREMENT OF RAW-MATERIALS:

Sr. No.	Raw-material	Purity (%)	Qty. required per Kg. of product.
1.	Meta Chloroaniline	97	0.61 Kg.
2.	Ethoxy methylene Malonic ester.	Specific gravity 1.07 at 20°C.	1.09 Kg.
3.	Diphenyl Oxide	Specific gravity 1.07 at 20°C.	0.51 Kg.
4.	Phosphorous Oxychloride	99	0.79 Kg.
5.	Benzene	Tech.	1.60 Kg.
6.	Benzene	Distilled	2.39 Kg.
7.	Novoldiamine	95.33	0.57 Kg.
8.	Phenol	98.0	0.21 Kg.
9.	Acetic Acid	99.5	0.64 Kg.
10.	Phosphonic Acid	90.0	0.67 Kg.
11.	Aqueous Ammonia	25.0	1.37 Kg.
12.	Kerosene	Dry.	0.57 Kg.
13.	Activated Carbon	--	0.33 Kg.
14.	Sodium Hydroxide	47	3.96 Kg.
15.	Hydrochloric acid (Tech.)	31	3.66 Kg.
16.	Methanol	95	1.52 L.
17.	Absolute Ethyl Alcohol	99	12.00 L.

5. REQUIREMENT OF SERVICES:

Sl. No.	Service	Quantity required per tonne of product.
1.	Steam, 3 Kg/cm^2.	48 tonnes
2.	Steam, 6 kg/cm^2.	3 tonnes
3.	Water, 32°C.	3760 M^3.
4.	Water, 18°C.	5590 Th.K.Cal.
5.	Water, 5°C.	615 Th.K.Cal.
6.	Brine, -5°C.	2880 Th.K.Cal.
7.	Inert Gas	1555 M^3.
8.	Process Water	22 M^3.
9.	Distilled water	3 M^3.
10.	Power	22400 K.W.H.

6. REQUIREMENT OF OPERATING PERSONNEL:

Senior Supervisors	...	3
Supervisors	...	10
Analysts.	...	7
Skilled Workers	...	98
Unskilled workers	...	10
TOTAL	...	88

III ANTIMALARIALS

A. PRIMAQUINE

1. General

Primaquine is an important antimalarial drug particularly in malaria resistant cases. It is often administered in combination with chloroquin, Amodiaquine and Pyrimethanine. It was developed in 1940 as an antimalarial drug.
B.P. (73), U.S.P. (17th rev.), Martindale Ex. Pharm. (25th ed.)

2. Producers

a) I.C.I., U.K. (latest holders)
b) Melimpex, Hungary

3. Process

6 Methoxy-8-amino quinoline is synthesized by Skraup Synthesis by three steps starting from p-anisidine. This is treated with 1-4 dibromopentane and potassium phthalimide followed by Hydrazin Hydrate in three steps to obtain primaquine (8-4-Amino-1-methyl butylamino 1-6-methoxy quinoline).

4. Raw Materials

a) P- Anisidine
b) Acetic Anhydride
c) Glycerine
d) Arsenic Acid
e) Hydrazine Hydrate
f) Potassium Phthalimide
g) 1-4 Dibromopentane
h) Organic solvents

5. Investment and Cost of Production

Data found in the literature on the production procedures are very sketchy and estimates made on the basis of these are found to have very large margin of errors. The overall yields reported in the literature are about 55-70% and all the raw materials except 1,4-dibromopentane are available in India at reasonable prices. The economic viability of the process depends to a large extent on the price of 1,4-dibromopentane.

6. Consumption in India

40 tons in 1974.

7. References

1) J.Am. Chem. Soc., 4811 (1955)
2) Ibid., 1525 (1946)
3) U.S. 2,504,474; C.A. 44, 2777f.
4) C.A. 52, 10091f.
5) C.A. 20, 5532
6) Ber. 48, 629; C.A. 24, 1637
7) C.A. 52, 12356

9) J.Chem. Soc. 3252 (1954)
9) Brit. 310, 559; C.A. 24 6283
10) C.A. 34, 3685
11) C.A. 47, 4832h
12) C.A. 50, 13891e
13) C.A. 54, 7231

IV ANTI INFECTIVE

A. MEBENDAZOLE

1. General

Mebendazole is highly active against nemodes and cestodes. It can kill the larval stages of cestodes. Mebendazole was discovered by Van Gelder et al (Janssen Pharma Ceutica, Belgium). Potentially this drug can replace Thiabendesol and partly piperazine and Tol-Tetramizole and other anthelmentics.

2. Producers

a) Janssen Pharma Ceutica, Beerse, Belgium (patent holders).

Patents: To Janssen Pharma Ceutica 1971-72
German patent 2,029,637 corresponds to
U.S. patent 3,657,267

3. Process

5-Benzoyl Fluorobenzene is synthesized from Flurobensene and benzoyl chloride by Friedel and craft reaction. Then it is nitrated to get 5-Benzoyl-6-Nitro Fluorobensene. This is then treated with Ammonia to get 5-Benzoyl-6-Nitro Aniline. This is then reduced by Iron and Hydrochloric Acid to get 5-Benzoyl-Orthophenelenediamine.

In the second step, thio urea is treated with dimethyl sulphate to obtain Psedothio urea. This is then treated with methyl chloroformate to obtain Psedothiourea methyl carbonate.

In the third step, 5-Benzoyl orthophenylene diamine is treated with Psedo thiourea methyl carbonate to obtain Mebendazole (5-Benzoyl 2-benzimidazole carbamate).

4. Raw Materials

a) Fluorobenzene
b) Benzoylchloride
c) Thiourea
d) Methyl Chloroformate
e) Dimethyl Sulphate
f) Other chemicals include mineral and organic acids, alkali and organic solvents.

5. Investment and Cost of Production

Data available in the literature on the production procedures are very sketchy and any estimate made on this basis is bound to have a very large margin of error. The overall yield reported in the literature is satisfactory. The economic viability of this project primarily depends on the price of Fluorobenzene, which is the main raw material.

IV B. PIPERAZINE

1. GENERAL:

Piperazine hexahydrate (Diethylene diamine hydrate) and its salts - Piperazine citrate, Piperazine Phosphate and Piperazine adipate are very effective against most species of round worms, pin and hook worms and enterobiasis. It is used both in human and veterinary medicines.

Piperazine was first synthesised in 1853. Its anthelmintic activity was established in 1949.

2. (a) PRODUCERS:

a) Dow Chemicals (Patent Holder), U.S.A.

b) Jafferson Chemicals (Patent Holder)

c) Merck Sharp & Dhome, U.S.A.

d) Wellcome Lab., U.S.A., U.K.

e) Allen & Hanburys.

(b) Process:

Mono-ethanol-amine is the starting material for the synthesis of Piperazine Hexa hydrate. The latter is converted into Adipate, citrate and phosphate by reacting with the respective acids:

Ger. 1,046,057

USSR. 164,287

Ger. 1,170,960

U.S. 2,910,477

U.S. 3,064,001

U.S. 3,038,904

U.S. 2,873,274

Brit.	8,71,754
Ital.	69[illegible],938
Japan	7,411,712
French	2,066,197
Swed.	330,699

(c) Investment:

The fixed capital requirement of the plant with a production capacity of 80 tonnes / annum of Piperazine Hexahydrate and its salts (Piperazine citrate 30 tonnes, Piperazine phosphate 20 tonnes and Piperazine Adipate 30 tonnes) is U.S. $ 0.92 million.

(d) Building:

The floor area required for the plant (within the battery limit) would be 700 sq.meters.

(e) Price in the International Market : US $ 4.8 / Kg.
to US $ 11.3 / Kg.

Consumption in India : 100 tons in 1976.

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3. LIST OF EQUIPMENT REQUIRED:

Sl.No.	Description	Qty. (Nos.)
1.	Reactor, S.St. 1000 L.	5
2.	Reactor, CI. GL, 630 L.	12
3.	Evaporator (Reactor), CI. GL, 1000 L.	1
4.	Measuring Tank, St, 250 L.	2
5.	Measuring Tank, St, FRP, 250 L	3
6.	Receiving Tank, S.St. 250 L.	4
7.	Measuring Tank, St. 400 L.	2
8.	Receiving Tank, St. 630 L.	1
9.	Holding Tank, St, FRP, 630 L.	1
10.	Holding Tank, S.St, 1000 L.	1
11.	Holding Tank, St, FRP, 1000 L.	1
12.	Holding Tank, St, 2000 L.	1
13.	Holding Tank, St, 6000 L.	1
14.	Heat Exchanger, St, 10 M^2.	2
15.	Heat Exchanger, S.St. 10 M^2.	2
16.	Centrifugal Pump, CI, 3 M^3/Hr. H = 23 M	1
17.	Fan with Motor, CI, 2000 M^3/Min.	1
18.	Water ring vacuum pump, CI, 3 M^3/Min.	1
19.	Steam water mixer, Al, ø 160 mm.	1
20.	Nutsch filter, St. tile lined, 1.5 M^2.	2
21.	Ejector, Faclite, 50 lit/min. of water	10
22.	Centrifuge, S.St, ø 800 mm.	1
23.	Leaf filter, S.St, 60 L.	2
24.	Air circulation Dryer, S.St. trays, 19.2M^2 (Apt.)	1
25.	Fitz Mill, S.St.	1
26.	Sifter, S.St. 60 Kg/ Hr.	1

4 A. REQUIREMENT OF RAW MATERIALS FOR THE PRODUCTION OF PIPERAZINE HEXAHYDRATE

Sl. No.	Raw material	Purity (%)	Qty. required Kg. per Kg. of product
1.	Monoethanol Amine	99	1.58
2.	Hydrochloric acid	31	3.03
3.	Ammonium Chloride	99	0.35
4.	Recovered Ammonium Chloride	--	0.89
5.	Sodium Hydroxide Lye	47	2.14
6.	Sodium Hydroxide flakes	95	0.038

4 B REQUIREMENT OF RAW-MATERIALS FOR THE PRODUCTION OF PIPERAZINE ADIPATE

Sl.No.	Raw-material	Purity (%)	Qty. required Kg. per Kg. of product.
1	Piperazine Hexahydrate	100	1.00
2	Adipic Acid	Tech.	0.77
3	Carbon	Tech.	0.008
4.	Sodium Hydrosulphite	—	0.002

4 C. REQUIREMENT OF RAW-MATERIALS FOR THE PRODUCTION OF PIPERAZINE CITRATE

Sl.No.	Raw-material	Purity (%)	Qty. required Kg. per Kg. of product
1.	Piperazine Hexahydrate	100	0.94
2.	Citric Acid	99	0.69
3.	Activated Carbon	Tech.	0.086
4.	Rectified Spirit	95	0.825 (L)
5.	Sodium Hydrosulphite	--	0.0068

4 D. REQUIREMENT OF RAW MATERIALS FOR THE PRODUCTION OF PIPERAZINE PHOSPHATE.

Sl.No.	Raw material	Purity (%)	Qty. required Kg. per Kg. of product
1.	Piperazine Hexahydrate	100	1.18
2.	Phosphoric Acid	83	0.79
3.	Activated Carbon	Tech.	0.015
4.	Sodium Hydrosulphite	—	0.0025

5 A. REQUIREMENT OF SERVICES FOR THE PRODUCTION OF PIPERAZINE HEXAHYDRATE

Sl.No.	Service	Qty. required per tonne of product.
1.	Steam, 3 Kg/Cm^2	4 tonnes
2.	Steam, 10 Kg/cm^2.	3.5 tonnes
3.	Water, 32°C.	3800 M^3.
4.	Water, 18°C	1100 Th.K.Cal.
5.	Brine, -5°C	5000 Th.K.Cal.
6.	Compressed Air	275 nM^3
7.	Power	1620 K.W.H.

5 B. REQUIREMENT OF SERVICES FOR THE PRODUCTION OF [illegible] SALTS

Sl.No.	Service	Qty. required per tonne of product
1.	Steam, 3 Kg/cm^2	1.2
2.	Water, 5°C.	300 Th.K.Cal.
3.	Brine, -5°C	750 Th.K.Cal.
4.	Compressed Air	250 m^3.
5.	Power	1350 K.W.H.

6. REQUIREMENT OF OPERATING PERSONNEL:

Senior Supervisors	...	3
Supervisors	...	8
Analysts	...	4
Skilled workers	...	30
Unskilled Workers	...	10
TOTAL	...	55

V. ANTITUBERCULOSIS

A. ISONIAZID

1. General

Isoniazid is one of the most widely used drugs in the treatment of Tuberculosis. It is the most potent tuberculostatic antibacterial agent. It is also employed as a prophylactic for use in persons constantly exposed to tubercular patients. This drug was first synthesised in 1912 and its synthesis for manufacturing process was developed in 1952. Its antituberculostatic affect was investigated in 1953.

B.P. (73), U.S.P. (17th rev.), Martindale Ex. Pharm. (26th Ed.)

2. Producers

a) Bayer, F.R.G.

b) Merck-Darmstadt

c) Rhone Poulenc, France

d) Carlo Erba, Italy

e) Farmitalia, Italy

f) A.B. Bofors, Sweden

g) Synbiotics, India

h) Dr. Karanth's Pharma-chemical Industry, Sanatnagar, Hyderabad, India (willing to offer technology)

3. Process

For countries depending on imported Gamma Picoline, it is more economic to manufacture INH from 4-Cyano Pyridine. The process consists in catalytically hydrolyzing 4-Cyano Pyridine into the amide and condensing with Hydrazine Hydrate. The equipments involved for these two reactions are cheaper and less complicated. The cost of raw-materials for production of INH by this method is detailed below.

The synthesis of INH from Gamma Picoline consists in the following steps:-

1) Oxidation of Gamma Picoline into Isonicotinic acid.

2) Esterification of the acid.

3) Conversion of the ester into the Hydrazide.

Oxidation of Gamma Picoline is carried out in an economic manner by Nitric acid of 55 to 60% strength in a glass reactor at 190-200°C, neutralizing and precipitating Isonicotinic acid from the reaction mixture. Dilute Nitric acid obtained thereby can be concentrated to the original strength and re-used or utilised in the manufacture of other commercial products like Sodium Nitrate. The yield of Isonicotinic acid from Gamma Picoline is more than 75% and can therefore be considered efficient enough. The process is generally carried out in a series of glass flasks of 50-100 litres capacity with glass condensers and receivers, heated by electric heating mantles. At a some what higher investment, a glass-lined reactor heated by Dowtherm can be more efficiently employed.

Dry Isonicotinic acid is esterified with excess of 95% Ethyl alcohol in presence of Sulphuric acid. Part of the excess alcohol is recovered, so also unreacted Isonicotinic acid, as the Copper salt. The reaction mixture is carefully neutralized and extracted by Trichloro Ethylene. The solvent is recovered under partial vacuum and the crude ester is distilled in vacuum. The yield of the distilled ester is 90% of the theoretical yield. Trichloro Ethylene used in the process is recovered to the extent of 70%. Distilled ester is reacted with Hydrazine Hydrate 80% using Ethyl alcohol as solvent. The reaction mixture is centrifuged, washed and dried in vacuum. A net yield of more than 90% of INH from the ester is obtained. A small portion of Hydrazine Hydrate originally used, can also be recovered as its sulphate.

4. Investment and Cost of Production

The details given below for various raw-materials are ruling prices in the Indian market, excluding local taxes. The international prices for the same may be much lower and the cost of various raw-materials in other Countries can be calculated from the quantity mentioned and the ruling prices in respective countries. For example: the international price of Hydrazine Hydrate is $2.20/kg against $4.30/kg mentioned below and proportionately the cost of raw-materials would go down if this or any other raw-material is available at international price. The approximate cost of equipments is similarly based on ruling price in India.

COST OF RAW MATERIALS FOR MANUFACTURE OF ISONICOTINIC ACID

A. [illegible] ACID

S. No.	Raw-material	Qty/kg	Price/kg	$/kg
1	γ-Picoline	1.0	3.00	3.00
2	Nitric acid 55% (rett)	4.0	0.24	0.96
3	Sulphuric acid	1.5	0.10	0.15
4	Soda ash	1.5	0.16	0.24
				5.25 per kg

B. ISONICOTINIC ACID HYDRAZIDE

1	Isonicotinic acid (cost of raw-materials only)	45	0.12	5.65
2.	Ethyl alcohol (rett)	2	0.24	0.48
3	Trichloroethylene (rett)	10	0.04	0.40
4	Sulphuric acid	2	0.10	0.20
5	Soda ash	2	0.16	0.32
6	Hydrazine Hydrate	40	0.07	2.80
7	Miscellaneous chemicals			0.37
				10.42 per kg

Less cost on raw-materials if γ-Picoline and Hydrazine Hydrate are available at international prices of $1.75 and $2.20 per kilo 3.68

6.74 per kg

COST OF EQUIPMENT AND INSTALLATION FOR A PLANT FOR THE PRODUCTION OF 2000 KG OF ISONICOTINIC ACID HYDRAZIDE PER MONTH

		Approximate Price in India Ruling US$
1.	8 sets of 50 ltr. capacity glass-flasks, with receivers, condensers, heating mantles etc.	6,098
2.	Acid concentration stills of 100 litres (2 sets) (careful handling of equipment is necessary to avoid breakage)	4,878
3.	S.S. Transport vessel 100 litres	915
4.	S.S. Precipitation tank with stirring gear 1000 litres	2,439
5.	S.S. Centrifuge 800 mm dia.	6,098
6.	Air drier 24 trays	2,439
7.	Miscellaneous vessels	2,439
8.	One glass-lined reactor of 800 litres capacity with distillation assembly	15,854
9.	Precipitation tank 1000 litres, Stainless Steel, jacketed, anchor stirrer	2,439
10.	Solvent recovery still 250 litres with condenser, receiver etc. 2 nos. (stainless steel)	6,098
11.	Extraction unit mild steel with stirring 1000 litr.	610
12.	Vacuum distillation unit electrically heated, 80 litres with glass receivers	2,439
13.	Centrifuge, stainless steel 800 mm.	6,098
14.	Mixer, jacketed 400 litres with stirring s.s.	1,829
15.	Rubber-lined tank 1000 litres	915
16.	Vacuum Pumps 4 nos.	2,439
17.	Vacuum Drier, 10 shelves with hot water circulation	3,049
18.	Ball Mill	610
19.	Various tanks in stainless steel	3,659
20.	Rectification plant, 250 litres S.S.	3,049
21.	Chilled Water plant 4 T.	12,195
22.	Boiler 1500 litres Steam/kg	6,098
23.	Water supply, pumps, cooling tower etc.	1,829
24.	Installation of equipment and pipe lines etc.	24,390
25.	Laboratory	3,049
		121,955

LAND AND BUILDING

An area of 4000 sq.yards is envisaged as a reasonable requirement for the factory site, since a lot of open space is required for keeping containers of nitric acid. The oxidation reaction is carried out in a separate shed measuring approximately 20 feet x 30 feet = 600 sq.ft. with roof height of 15 feet. The main building may be a shed of 30 feet x 80 feet= 2400 sq.feet.

Total factory area	=	3000sq.ft. x $3.66 =	$10,980
Offices and Laboratory	=	1500sq.ft. x $6.10 =	9,146
Stores	=	2000sq.ft. x $2.44 =	4,878
			25,004
Land 4000 sq.yards at $4.88			19,512
			$44,516

The total investment for this manufacture therefore comes to $166,420.

An approximate idea of the direct monthly expenses are calculated as follows:-

A. Staff & Workers	
30 workers at $37 per worker per month	$ 1,110
3 Supervisors at $55 per supervisor per month	165
3 Chemists at $85 per chemist per month	255
1 Manager at $146 per month	146
Administrative staff (3)	146
	1,822
B. Depreciation is calculated at 15% on machinery $\frac{18,293}{12}$	1,524
C. Depreciation on building at 10% $\frac{2,500}{12}$	208
D. Steam and Electricity	336
E. Other expenses	976
	$ 4,896 per month

OR $2.44 per kg.

Therefore the nett cost of production will be:-

On raw materials	$10.98 per kg
Direct expenses	$ 2.44 per kg
	$13.42 per kg

(or less by $3.66 if raw materials are available at international prices) The selling price in India today ranges from $15.85 to $17.68 per kilo, leaving a margin of $2.44 to $4.27 per kilo.

PRODUCTION CAPACITY: This is based on 3 shift working of the section manufacturing Isonicotinic acid and one shift working for the remaining process.

INH FROM 4-CYANO PYRIDINE

S.No.	Raw-material	Qty/kg	Price/$/kg	Amt/$
1	4-Cyano Pyridine	1.0	4.39	4.39
2	Hydrazine Hydrate	0.7	2.20	1.54
3	Other chemicals		0.60	0.60
(International prices without duty)				6.53

Cost of equipment and building can be taken as half that required for the manufacture of INH from Picoline. Hence, the direct cost of manufacture can be estimated at $1.22 per kilo.

5. Other Products

The same plant can be profitably utilised for the manufacture of Niacinamide from 3-Cyano Pyridine. Catalytic hydrolysis of 3-Cyano Pyridine into Niacinamide is quantitative and can be converted into the pure product by crystallisation in Methyl Isobutyl Ketone. From 1 kg of 3-Cyano Pyridine, more than a kilo of Niacinamide can be obtained. In the set-up involves a reactor for hydrolysis, filter, a vacuum concentrator, drier and crystalliser.

NIACINAMIDE FROM 3-CYANO PYRIDINE

3-Cyano Pyridine	0.7	4.29	4.39
Other chemicals			0.61
Total on raw materials			5.00
Direct manufacture cost			0.61
			5.61

7. **Production in India**

About 200 tons per annum

8. **Price**

Price in India $15.25 to $17.43 per 1 kg.
International price $4.00 to $10.00 per 1 kg.

9. **References**

1) Montash. 33, 700 (1912)

2) Pharm. Ind., 3[illegible] (1952)

3) Recz. chem. 1[illegible] (1953)

4) U.S. 2, 630, 434

V B. RIFAMPICIN

1. GENERAL:

Rifamycin (Rifampicin) is an antibiotic complex of five components. It was isolated and developed by Gruppo Lepetit Laboratories from Streptomyces mediterrance in 1959. It is mainly used in initial or retreatment of pulmonary tuberculosis. It is also a promising drug in the treatment of leprosy.

2. PRODUCERS:

a) Gruppo Lepetit, S.P.A. Italy (Patent holder)
Belgium Patent No. 643-965 dated 1964

b) Archifar, Italy.

3. PROCESS:

Rifamycin is manufactured by the submerged fermentation process with the strain S. mediterrance 21-271 which specifically produces Rifampicin S and Rifampicin SV(1). The filtered fermented broth is extracted with Chloroform and concentrated. The concentrate is chromatographed using silica in the column. The product crystallises on concentrating the eluate. In an alternative method, the filtered fermented broth is acidified and extracted with Ethyl acetate. The extract is washed, concentrated and further treated as above.

4. RAW MATERIALS:

a) Glucose

b) Glycerol

c) Peanut flour

d) Soyabean meal

e) Organic solvents including Chloroform and ethyl acetate

f) Inorganic salts

5. ECONOMICAL SIZE OF THE PLANT:

In a developing country where this product has yet to be established, the minimum economical size of the plant would be about one tonne per year.

Data available in literature on Rifampicin are very sketchy and estimates based on these will have large margin of error. So comparable figures from other antibiotics such as Penicillin are taken as the basis for estimates.

6. LIST OF MAJOR EQUIPMENT:

(Cost based on Indian conditions and prices prevailing in India)

Name of equipment	Material of construction	Quantity Nos.	Total amount in US $
Ball Tonnes		3	40,000
Fermenter 40 M³		1	1,22,000
Boiler tank			20,000
Air filter system			20,000
Rotary Vacuum Filter			60,000
Agitated [illegible] tanks	S.S.	12	2,40,000
Filter press	S.S.	1	30,000
[illegible]		1	60,000
Centrifuge	S.S.	2	30,000
Spray dryer		1	80,000
Misc.			
	TOTAL		7,52,000

	Total amount in US $
Services	
Boilers	60,000
Air Compressors	60,000
Refrigeration equipment	60,000
Water Treatment	40,000
Effluent treatment	40,000
Electricity	60,000
Laboratory equipment	40,000
Miscellaneous	
	4,00,000
Instruments:	
Flor Recorder Controllers Temperature Recorder Controllers Temperature Recorder etc.	2,00,000
Piping	1,30,000
Spares	40,000
Freight & Insurance	80,000
Contingencies	60,000
Installation	1,78,000
	6,28,000

		Total amount in US $
7.	OTHER CAPITAL COSTS	
	Preliminary cost	12,000
	Consultancy services	1,22,000
	Land and development	12,000
	Buildings:	
	Process	60,000
	Services	25,000
	Administrative	25,000
8.	WORKING CAPITAL	
	One month's raw materials	73,260
	Two months finished product	45,910
	40 days work in process	1,22,466
	Stores & spares	30,525
	Sundry Debtors	21,490
	Less: One month creditors for raw materials	- 73,260
		2,20,391
9.	TOTAL INVESTMENT OF THE PROJECT:	
	a) Land & Land Development	12,000
	b) Buildings	1,10,000
	c) Plant & Machinery including utilities, Contingencies	19,55,000
	d) Working Capital	2,20,391
	TOTAL ..	22,97,391

10. COST OF PRODUCTION
(1 tonne per annum)

	Per kg U S $
Raw materials	879.37
Conversion costs	135.90
Depreciation	197.44
Overheads	56.29
U.S. $ per Kg. ...	1269.00

11. Price from Italian Sources: US $ 763 / Kg. to 1584 / Kg.

MULTIPURPOSE PLANT

Single product plants are feasible only when the requirement of a particular drug is large enough to put up a special plant for the same. However, in many of the developing countries, small quantities of a variety of drugs are required. In such cases a multipurpose plant is more suited. This will also involve the lowest possible investment.

The main advantages of a multipurpose plants are that they are suitable for the manufacture of a number of products either sequentially or to some extent simultaneously using a signle/double series of equipment. Secondly sophisticated automation is generally not required. Further the average life of the multipurpose plant is higher. Above all a modern plant for drugs must provide for the manufacture of an extensive line of basic pharmaceutical chemicals particularly of small volume normally required by most of the developing countries. This plant should also be versatile enough to take care of new products for which technology might be under development. The multipurpose plant is ideal under these conditions. Flexibility is built into its design to cater to the varying and everchanging demands of the pharmaceutical market. The design will also facilitate a substantial increase in the capacity by mariginal additional investment.

The cost of such a multipurpose plant for synthetic druge will vary according to the range of drugs selected and the source of supply of the equipment. The grouping of products in a multipurpose plant could best be done according to the kind of equipment to be utilised.

An industrial profile is presented for a multipurpose plant to manufacture primarily four of the seven synthetic drugs as described below:

S.No.		Quantity
1.	Acetylsalicylic acid	700
2.	Paracetamol	100
3.	Chloroquine diphosphate	60
4.	Isoniazid	20
	TOTAL	880

In addition to the four drugs mentioned above, a number of other products could be manufactured in the same multipurpose plant and these are shown in Annexure I. The details of investment for the above multipurpose plant are given in Annexure II.

As regards profitability, it will be appreciated that a clear cut separation between several productions running simultaneously in a multipurpose plant is rather difficult to make. It is, therefore, more practical to assess the working results of the entire operation in the course of one year. A rough estimate of profitability of a multipurpose plant is shown in Annexure III. Out of the 18 drugs listed therein, 5 turned out to be uneconomical although the operations as a whole showed some profit. Four highly uneconomical products have not been included in this list. Hence a multipurpose plant of the size proposed is economically viable thus making it feasible to produce few uneconomical items which might be vital for the developing country. A list of representative consulting firms and suppliers of equipment for pharmaceutical plants including multipurpose synthesis plants is given in Annexure IV.

ANNEXURE I

Other products which could be manufactured in the rpose plant.

No.	Product	Quantity (tons)
.	Bensyl Nicotinate	2
.	Calcium Bensoyl PAS	100
.	Diethylphenyl malonate	30
.	Ethyl nicotinate	25
.	Furasolidone	10
.	Guaicol glyceryl ether	10
.	Metronidasole	5
.	Niacinamide	100
.	Nikethamide	10
.	Nitrofurasene	5
.	Potassium phenyl acetate	15
.	Phenytion - Sodium	5
.	Phthalyl Sulphathiasole	20
.	Thiacetasone	20
.	Dapsone	5
.	Ethyl phenyl acetate	30
.	Niridasole	2
.	Phenobarbitone	20
		414

ANNEXURE II

Investment for multipurpose plant

Type of Investment	Amount (Mio US $)
Construction	
Buildings	2.20
Equipment	
a. Process	4.27
b. Utilities	3.59
c. Laboratory	0.40
Know-how and Engineering fee at 5%	0.52
Total Investment	10.98
Depreciation / yr.	
Buildings at 10%	0.22
Equipment at 20%	1.65
Manpower including overheads	0.06
Utilities	0.24
Annual Cost	2.17

Piping, electrial wiring and electronic control equipment included.

ANNEXURE III

Working Results of Multi-purpose Plant

US $

Sl. No.	Product	Production Cost	Sales value
1.	Acetyl Salicylic Acid	1,692,518	1,841,000
2.	Paracetamol	405,991	315,000
3.	Chloroquine diphosphate	628,854	660,000
4.	Isoniazid	122,340	96,000
5.	Benzyl Nicotinate	17,363	14,037
6.	Ca-Benzoyl-PAS	526,671	548,000
7.	Diethyl-Phenyl-malonate	208,159	240,000
8.	Ethyl nicotinate	194,462	443,250
9.	Furosolidone	50,026	78,400
10.	Guaicolglyceryl ether	76,901	79,500
11.	Metronidazole	1,30,298	99,550
12.	Niacinamide	537,562	5,54,000
13.	Nikethamide	75,393	113,200
14.	Nitrofurazone	87,753	33,638
15.	Potassium Phenylacetate	54,509	67,500
16.	Phenytoin Sodium	80,963	55,150
17.	Phthalyl-Sulpha-thiazole	152,993	140,000
18.	Thiacetazone	283,652	314,600
		5,206,196	5,692,885
	Plant operation cost during change over and maintenance	385,726	
	Excess amount of working capital charged to individual products		1,050,589
	Total	5,591,922	67,43,354
	Profit		1,151,432

ANNEXURE IV

List of some representative consulting firms and suppliers of equipment for pharmaceutical plants including multipurpose synthesis plants

General planning, integrated units:

Austroplan, Osterreichische Gesellschaft fur Planung,

A-1102 Vienna, Triesterstrasse 33, Austria

The Badger Company Inc., Cambridge, Mass. 02142, USA

The A. P. V. Company Ltd., Crawley, West Suesex, RH 102, QB, Great Britain

Buehler-MIAG GmbH, Braunschweig, 33 Braunschweig, Ernst-Amme-Strasse 19, FRG

Chemical Plant and Machinery Assoc. of India, Mackinnen Mackensie Building, Ballard Estate, Bombay 400 038, India

Chemocomplex, 1062 Budapest, Nepkoztarsasag utja 60, Hungary

R. L. Dalal and Cy/Dalal Consultants and Engineers Private Ltd., 86 Dr. Annie Besant Rd., Worli Naka, Bombay 400018, India

INGECO SpA, Via M. Gonzaga 7, I-20123 Milan, Italy

Pharmaconsult, D-6900 Heidelberg, Kubmaulstrasse 10, FRG

SPEICHIM, 106 Rue d'Ameterdam, Paris 9 ieme, France

Zimmer Aktiengesellschaft, D-6000 Frankfurt 60, Borsigallee 1-7, FRG

Representing several Japanese consulting firms:
NISSHO-IWAI CO. LTD.
Lugeck 1-2/7/40
1010 Vienna

Reactors; heat exchangers

Henry Balfour Co. Ltd., Leven, Fife, Scotland, Great Britain

Gebr. Boehler Co., AG, D-4000 Duesseldorf 11, Hansa-Allee 321 FRG

De Dietrich Cie, F-67110 Niederbronn-les-Bains, France

Lampart, H-1475 Budapest, Box 41, Hungary

Pfaudler-Werke AG, D-6830 Schwetzingen, Scheffelstrasse 55, FRG

Schwelmer Eisenwerk Mueller Co., GmbH, D-583 Schwelm, Loherstrasse 1, FRG

Vereinigte Edelstahlwerke AG (VEW), A-1010 Vienna, Elisabethstrasse 1, Austria

Centrifuges:

Alfa-Laval AB Celleco, Box 94, S-14700 Tumba, Sweden

Ellerwerk, Otto Ellerbrock Maschinen fabrik, D-2000 Hamburg 60, Steilhooperstrasse 102-116, FRG

Ferrum AG, Maschinenfabrik, CH-5102 Ruppeswil, Switzerland

Rousselet S.A., Rue Montalivet B. P. 129, F-07104 Annonay, France

Extractors:

Baker Perkins Chemical Machinery Ltd., Westfield Road, Peterborough PE 1 5TA, Great Britain

Dryer:

Titus, D-6148 Heppenheim

Pumps:

Chemiepumpenbau AG, CH-4800, Zofingen, Switzerland

W. Dickow Pumpenfabrik, D-8264 Waldkraiburg, Siemensstrasse 22, FRG

Friedrichsfeld GmbH., D-6800 Mannheim 71, Steinzeugstrasse 50, FRG

W. Heinrich Vakuumanalgen, D-6331 Katzenfurt, FRG

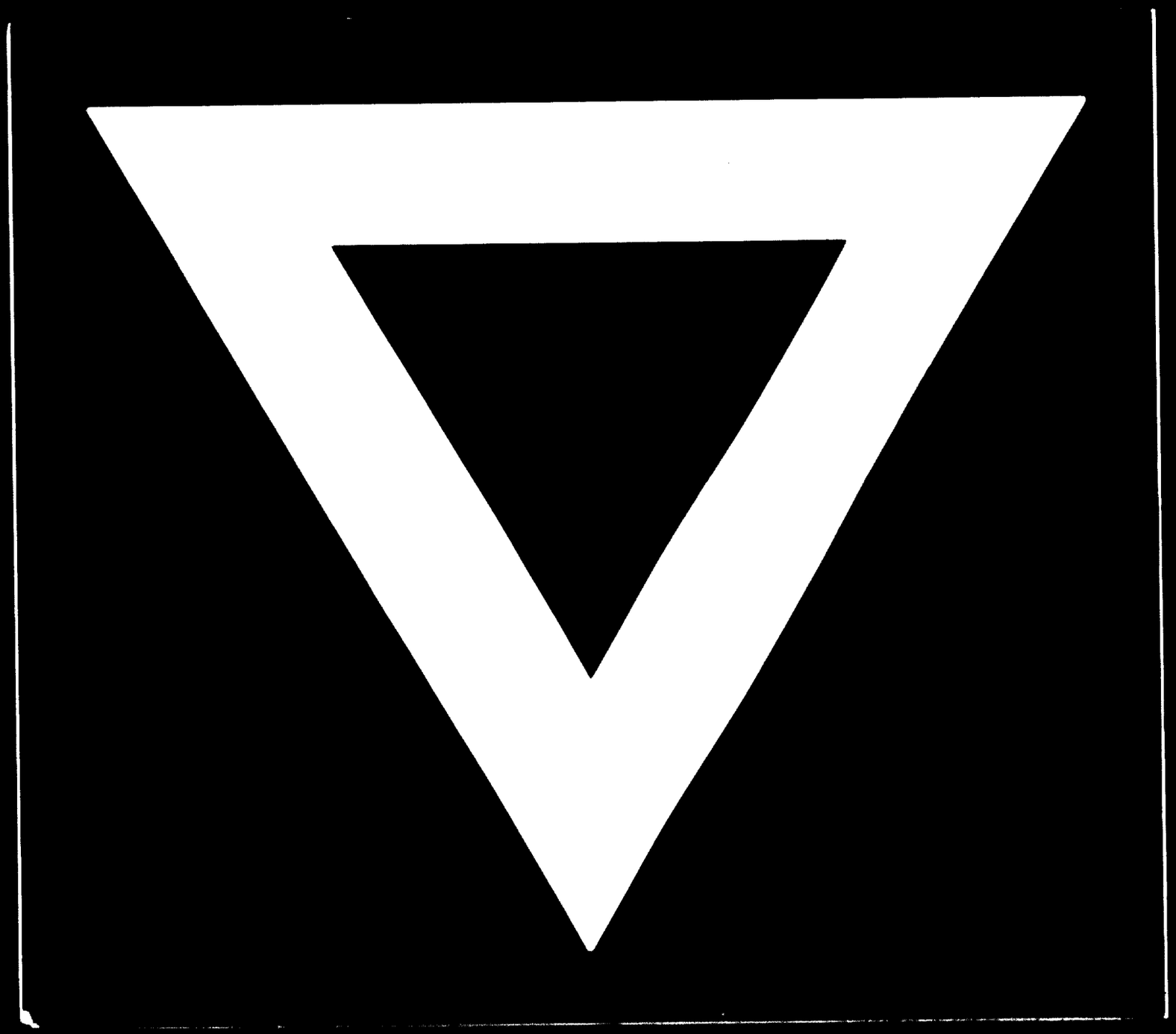
Gebser Sohn GmbH Co, A-4020 Linz, Austria

Waste water treatment:

DAMAG Verfahrenstechnik GmbH, D-6308 Butzbach, Wetzlarer-strabe 136, FRG

Norr Oliver Inc., New York, USA

G-664



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