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PHILIPPINES PHARMACEUTICAL INDUSTRY DEVELOPMENT STUDY

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PHILIPPINES

Technical report: Semi-synthesis of antibiotics*

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

Based on the work of Dr. Roberto Sciaky
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United Nations Industrial Development Organization
Vienna

* This document has not been edited.

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SUMMARY AND CONCLUSIONS

General considerations

The Philippines are an archipelago of some 7100 islands of the southeastern coast of the Asian mainland consisting of three major island groups namely: Luzon, Visayas and Mindanao.

According to the 1980 census, the population was 48 million and in 1985 was estimated to be 54.7 million people.

Projections to 1995 according to different assumptions give figures from 66.4 to 69.4 million people.

In 1985, crude birth rate was 26.3% and mortality 6.1%.

The first four causes of morbidity are bronchitis, diarrhea/gastroenteritis, influenza and upper respiratory tract infections.

The three leading causes of mortality are pneumonias, diseases of the heart and tuberculosis.

The health organization is partially public and partially private; about one third of the hospitals are governmental.

The pharmaceutical market

Drugs are purchased in different ways:

- purchase from abroad by Filipino and multinational Companies.
- purchase from the Department of Health through tenders.
- direct purchase from the Regions.
- smuggled goods, which escape any control.
- fake drugs imported or locally produced.
- donations from Charitable Institutions and International Organisations.

A market research has been done to pick out the antibiotics produced by direct fermentation or by semi-synthesis, a market large enough to deserve attention and to be taken into consideration for local production.

The following sources of information were checked:

- the Institute for Medical Statistics (IMS) data both for sales through drugstores and hospitals; we noticed through a cross check, that these figures are on the low side and for some products too low.

- the Business Statistics Monitor data which include weekly descriptive [illegible] reports by air or by sea.

- the procurement from the Department of Health for 1987 and the procurement program for 1988 for Rural Health Units.

- direct procurement by the Regions.

- meetings with marketing managers of the main Filipino and multinational Companies. Data concerning the local production of Ampicillin, Amoxycillin and Cloxacillin were supplied to us by Chemfields.

From all the data gathered, we could pick out some antibiotics with a sufficiently high consumption granting an investigation of the possibility of a local production (the veterinary and [illegible]technical consumation have been taken into account).

The antibiotics selected are: Penicillins G and V and their derivatives, Ampicillin, Amoxycillin, Cloxacillin, to which Cephalexin was added, since its market is growing and could be produced in the same plant without additional investments.

Other antibiotics selected are the Erythromycins (stearate, ethylsuccinate and thiocyanate) and Rifampicin.

To these products were added the 6-APA since it is prepared starting from Penicillins and it is of strategical importance for the production of semi-synthetic Penicillins and the hydrochlorides of Tetracycline and Oxytetracycline, starting from the free bases. Their production by direct fermentation is one of the options considered by the Expert in fermentation.

By a careful consideration of the different factors which could in some way influence the market size and growth of each antibiotic (population increase, the Gross National Product, the rational use of drugs, possible improvement of the health and sanitary conditions of the country, a possible shift to different drugs etc.), the following projections of the market size to 1995 were done:

Ampicillin	85 tons
Amoxycillin	75 tons
Cloxacillin	8 tons
Cephalexin	6 tons
Erythromycins	25 tons
Rifampicin	20 tons
Tetracycline hydrochloride	20 tons
Oxytetracycline hydrochloride	15 tons

For the production of the abovementioned quantities of semi-synthetic Penicillins, 110 tons of 6-APA would be required.

We stress the fact that these consumptions do not represent the total need of the country, but only the quantities that the market could absorb and the Department of Health could afford to supply to the Rural Health Units.

The proposed options

Based on this figures, the following options are proposed: (1)

1. a multipurpose plant for the production of Erythromycin derivatives (25 tons) and Rifampicin (20 tons)

2.) a plant for the production of beta-lactam antibiotics (Ampicillin, Amoxycillin, Cloxacillin and Cephalexin)

3.) a plant fc the production of 6-aminopenicillanic acid (6-APA) (110 tons)

4.) a plant for the production of the hydrochlorides of Tetracycline and Oxytetracycline (35 tons)

The plant under 2.) will have a capacity of 74 tons, since the already existing Chemfields facilities have a capacity of 100 tons. As to the priorities, 1.) and 2.) are short term projects, 1.) having top priority whereas 3.) and 4.) are strictly related to the implementation of a project for the local production of Penicillin and Tetracycline.

To stimulate investments, we would suggest that some incentives should be granted for a certain period of time, to improve the economics of the different projects among which:

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(1) related to the fact that the Expert in fermentation, will advance the options of two fermentation plants: one for Penicillin and a second, a multipurpose one, for the Tetracyclines, Erythromycin and Rifamycin B

1. exemption of import duties on machinery, equipment and raw materials.

2. tariff protection

3. income tax exemption

Our economic evaluation are made taking into account these assumptions especially 1 and 2 which have influence on the production cost and sales.

The production units

All the four options have been carefully examined and for each product the following data were reported: description of the product, principles and description of the method, batch dimensions, raw materials (quantity for one batch and factor for one kg taking into account the recovery of solvents), flow chart of the process, utilities, manpower, location and description of the plant, main equipment list, buildings, additional manpower needs for the auxillary services (quality control, engineering services, warehouse and administration) and manpower type and qualification.

The production costs, the estimated investments, as well as some economics are also included. The figures reported have been calculated to give a rough idea of the cost and an order of magnitude of the investment.

The semi-synthetic Penicillins plant

The plant will be located in the Chemfields factory, where room for expansion is available,especially because of the existing facilities and the presence of technicians having the required technical skill.

The production unit will be located in a 300 sq.mt building having two floors. In the ground floor together with some equipment are also located the powder area, the in-process control laboratory, lockers room etc.

Another air conditioned building will be also available as wearehouse.

At full capacity the plant will operate for 284 days a year on a two shifts basis to produce 74 tons of semisynthetic Penicillins; by working on a three shifts basis the capacity of the plant is higher than 100 tons. Also 28 tons of the Dane salt for Amoxycillin will be contemporaneously produced.

The plant consists of eight reactors ranging from one to five cu.mt. capacity, filters, tanks for solvents, centrifuges, driers and some minor equipment.

The present capacity for utilities of Chemfields will be incremented to cope with the new needs.

The investment, calculated to give a rough idea of the order of magnitude rather than exact figures, results to be 5,900,000 $. At full capacity, the manpower will consist of 31 people plus 14 people for the auxiliary services.

The projected production costs which include raw materials, (10% freight, insurance etc. included), utilities, manpower, general expenses and depreciation, assuming that the plant is run at full capacity, are as follows ($ per kg):

Ampicillin	(6-APA at 65 $ 10% freight etc.incl.)	79
Amoxycillin	(6-APA at 65,$ 10% freight,etc.incl.)	84
Cloxacillin	(6-APA at 64 $ 10% freight,etc.incl.)	78
Cephalexin		157

As to the selling prices, we present four assumptions:

1. products are sold at the international prices plus custom duties and other expenses evaluated globally at about 20%

2. products are sold 10% higher than the international prices, assuming a 10% advantage is granted to the local producers.

3. products are sold 20% higher than the international prices, assuming a 20% advantage is granted to the local producers.

4. products are sold at the current Chemfields prices. (50% of Amoxycillin sold to the Government).

With the above-mentioned assumption the following economics could be calculated

	Gross Profit on Sales	Pay-back Period
1.	15.2%	5.1 years
2.	21.7%	3.3 years
3.	27.3%	2.4 years
4.	27.7%	2.4 years

<u>The Erythromycin derivatives and Rifampicin plant</u>

Also this plant will be located in the Chemfieds factory because of the existence of the required facilities, organisation and staff which needs only to be slightly increased; furthermore, should the plant be placed in a new factory, the investment would increase from 1.5 to 2 times so the economics becoming less favourable.

The production unit will be located in a 200 sq.mt. building, the ground floor housing the powder area, the in-process control laboratory, locker room etc; in the first floor having a surface of 50 sq.mt. the main reactors are located. A 300 sq.mt. air conditioned building used as warehouse will be also provided.

At full capacity the plant will operate for 263 days a year working at one or two shifts; additional capacity can be reached by operating on three shifts.

The plant will consists of two stainless steel reactors, the larger having a capacity of 4,000lt,one filter,tanks for solvents, one centrifuge, one drier and some minor equipment.

The investment, calculated to give a rough idea of the order of magnitude rather than exact figures, results to be 1,530,000 $. At full capacity manpower will consist of 17 people plus 11 people for the auxiliary services.

The projected production costs, which include raw materials, utilities, manpower, general expenses and depreciation, assuming that the plant is run at full capacity, are as follows ($ per kg):

Erythromycin stearate	(Erythromycin at 105 $)	98
Erythromycin ethylsuccinate	(Erythromycin at 105 $)	144
Erythromycin thiocyanate	(Erythromycin at 105 $)	114
Rifampicin	(with imported 3-formyl-rifamycin SV)	199

As to the selling prices, we have made the three following assumptions:

1. products are sold at the international prices plus custom duties and other expenses evaluated globally at about 20%.

2. products are sold 10% higher than the international prices, assuming a 10% advantage is granted to the local producers.

3. products are sold 20% higher than the international prices assuming a 20% advantage is granted to the local producers.

With the abovementioned assumptions, the following economics could be calculated:

	Gross Profit on Sale	Pay-back Period
1.	8.3%	1.9 years
2.	17.2%	1.1 years
3.	23.1%	0.7 years

6-Aminopenicillanic acid plant

The plant will be located in the same building where recovery of Penicillin takes place so avoiding transportation of Penicillin to other plants; this option also semplifies recovery of the phenyl or phenoxyacetic acid formed during the splitting of the side chain and the recovery of the solvent which is the same used in the Penicillin extraction.

The production of the required 110 tons will be effected in 260 days.

The plant consists of two stainless steel reactors and two crystallizers having a capacity of 8,000 lt, one filter, tanks for solvents, one centrifuge, one drier and some minor equipment. The investment, calculated to give a rough idea of the order of magnitude rather than exact figures, results to be 1,530,000 $. At full capacity manpower will consist of 16 people plus 5 people for the auxiliary services.

The projected production cost, which includes raw materials (10% freight, insurance etc. included), utilities, manpower, general expenses and depreciation, results to be 58 $ / Kg.

As the production 6-aminopenicillanic acid constitutes only a minor part of the global Penicillins fermentation project, its economics will be included in the report of the Expert in fermentation.

The Tetracycline hydrochlorides plant

The plant will be located in the same building where recovery of Tetracycline takes place so limiting the investment and avoiding transportation of Tetracycline to other plants.

The production of the required 35 tons will be effected in 260 days.

The plant consists of two reactors (one glass lined) tanks for the solvents, one filter, one centrifuge, one drier and some minor equipment.

The investment, calculated to give a rough idea of the order of magnitude rather than exact figures, results to be 1,180,000 $. At full capacity manpower will consist of 16 people plus 5 people for the auxiliary services.

The projected production costs which include raw materials (10 % freight, insurance, etc. included), utilities, manpower, general expenses and depreciation, assuming that the plant is run at full capacity result to be 31$ for Tetracycline hydrochloride and 27 $ for Oxytetracycline hydrochloride.

As the production of the hydrochlorides of Tetracycline and Oxytetracycline constitutes only a minor part of the global Tetracycline fermentation project, its economics will be included in the report of the Expert in fermentation.

INTRODUCTION

As a general rule, antibiotics are products which are obtained by submerged fermentation with selected strains of microrganisms.

With a few exceptions also their industrial production occurs by fermentation.

With the aim of obtaining new molecules having new and better farmacological properties the molecules of the various antibiotics have been chemically modified.

Many of the new antibiotics so obtained had interesting properties and have been introduced in the clinical practice.

These new antibiotics which molecule is first otained by fermentation and successively modified by chemical means are named semi-synthetic antibiotics.

This report deals with the production by chemical synthesis of antibiotics starting from molecules first obtained by fermentation.

1.0 - GENERAL CONSIDERATIONS(1)

1.1 Geographic Situation

The Philippines is an archipelago consisting of some 1,700 islands and islets situated off the southeastern coast of the Asian mainland. It stretches 1,850 kilometers from north to south and 1,120 kilometers from west to east. It has an approximate land area of 300,000 square kilometers and a cost line stretching about 17,000 Kilometers. The climate is generally warm and humid most of the year. There are three seasons: the hot dry season from March to the end of May, the rainy season from June to the end of October and the cooler dry season from November to the end of February. Typhoons are common in the Philippines during the rainy season.

1.2 Human Geography

In the Philippines there are eighty-seven dialects spoken in the different parts of the country, most of which are interrelated. The most widely spoken are Pilipino (Tagalog), Cebuano, Ilongo, Ilocano, Bicol, Pampango and Pangalatok. English is widely spoken throughout the country and serves as common medium of communication. Pilipino and English are the official languages. The population is predominantly Roman Catholic (74%); there is an active Protestant minority (7%) and of Muslims (7%) concentrated mainly in the southernmost island of the Philippines.

1.3 Population

In 1980 the population of the Philippines was 48,098,000. With reference to the previous census (42,071,000 in 1975) a change of 14,3% is to be noticed. In 1985 the population was estimated to be 54,668,330; of this number, 40.7% is composed of young people from 0 to 14 years of age. Crude birth rate is estimated to be 26.3‰ with a decrease of 8.7% over the 1975 figures. For 1985 the total live births were 1.437.154, giving a fertility rate of 4.4 in consideration of the female population between the ages of 15-44 years of 12.913.036. The mortality in 1985 was 334.663 with a rate of 6.1‰..

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(1) Part 1.1-1.4 have been worked out together with the Expert in fermentation

Different death rates were noticed in the different regions, the highest being in region 1 with 7.8%, followed by the National Capital Region with 7.0%; all other regions had lower death rates, the lowest being 3.1 in region 12. The overall annual growth rate of the Filipino population is 2.4 percent. Life expectancy at birth increased from 61.0 years in 1975 to 63.3 in 1985. According to the 1980 census, the urban population was 17,943,897 and the rural one of 30,156,563 out of 48,098,490; the corresponding percentages are 37.3% and 62.7%.

In the last years urbanization has continued due to the difficulties encountered by the rural population, a fact that is pushing them to migrate to the large towns in the hope of earning a better salary and improve the quality of their lives.

Projections for the population of the Philippines to the year 2000 has been worked out and published by the "National Economic and Development Authority" with three different assumptions:

Low assumption:	rapid fertility decline and moderate mortality decline
Medium assumption:	moderate fertility decline and moderate mortality decline
High assumption:	slow fertility decline and moderate mortality decline.

The figures corresponding to the above mentioned assumptions are:

	1985	1990	1995	2000
Low assumption	54,488,016	60,670,677	66,415,638	71,319,761
Medium assumption	54,668,332	61,480,180	68,424,077	75,223,853
High assumption	54,761,950	61,894,361	69,447,233	77,209,296

One of the main objectives of the study is to examine the present market situation for pharmaceuticals and to assess whether there are possibilities for domestic production of active ingredients, in this case antibiotics, with particular emphasis to locally available raw materials.

Since the consumption of drugs is influenced by the size of the population and by the health situation of the country, the above reported figures are of the utmost interest to assess the size of a potential production. In consideration of the fact that the implementation of a fine chemicals production factory project requires a minimum of 3-5 years, we feel it would be realistic to take as basis of our calculations the projections of 1995.

2.0 - HEALTH SITUATION

2.1 Leading Causes of Morbidity

The health situation in the Philippines is better than in many other developing countries; nevertheless there are still some major problems especially due to communicable diseases, representing in 1986 the first six causes of morbidity.

The ten leading causes of morbidity for 1986 are reported hereunder together (rate per 100,000 population.) (1)

1)	Bronchitis	1112.4
2)	Diarrhea/gastroenteritis	1087.5
3)	Influenza	966.1
4)	Upper respiratory tract infections	939.9
5)	Pneumonias	351.3
6)	Pulmonary tuberculosis	293.1
7)	Malaria	243.4
8)	Accidents	209.4
9)	Diseases of the heart	170.4
10)	Parasitism	96.3

These figures are probably too low due to some facts such as:

- some cases are not properly diagnosed
- some cases, especially in the rural centers, escape diagnosis due to the difficulties of bringing people to undergo medical examination (especially valid for pulmonary tuberculosis).

  In case of less serious diseases physicians are not contacted, the cases escaping detection and classification. Probably, for some diseases the above mentioned figures have to be substantially increased.

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(1) Based on Regional Health Office Reports

We will discuss this point in the paragraphs devoted to the definition of potential production. Some data are different from the 1985 classified causes probably due to some changes in the criteria of classification.

2.2 Leading causes of mortality

According to official statistics the ten leading causes of death account for 60.0 percent of total deaths. (1986) In the following table are reported the causes of death (rate per 100,000 population) and the percent of total deaths.(1)

	CAUSE	Rate	Percent of Total Deaths
1.	Pneumonias	95.5	19.2
2.	Diseases of the Heart	44.7	9.0
3.	Tuberculosis, (all forms)	42.7	8.6
4.	Cardiovascular Diseases	35.5	7.2
5.	Malignant Neoplasms	23.7	4.7
6.	Accidents	22.4	4.5
7.	Diarrhoeas	15.6	3.1
8.	Diseases of the Circulatory System	7.3	1.5
9.	Senility	6.9	1.4
10.	Avitaminoses and other Nutritional Deficiencies	4.0	0.8
		Total	60.0

(1) Based on Regional Health Office Reports

As to the infant mortality, according to official statistics, the ten leading causes are reported in the following table together with the rate per 1, 000 live births and percent of infant deaths (1983).(1)

	C A U S E	RATE	Percent of Total Deaths
1.	Pneumonias	10.2	23.9
2.	Respiratory conditions of foetus and newborn	6.2	14.6
3.	Diarrhoeas	4.0	9.4
4.	Congenital Anomalies	1.9	4.6
5.	Avitaminoses and other Nutritional Deficiencies	1.7	4.0
6.	Measles	1.5	3.5
7.	Birth injury and difficult labor	1.1	2.6
8.	Acute Bronchitis and Bronchiolitis	0.7	1.6
9.	Septicemia	0.6	1.4
10.	Meningitis	0.6	1.3

In 1983, deaths under one year were 64,267, from one to four years 44. 316 and from five to nine years 10,660; globally deaths from zero to nine years were 119,243, out of 327, 260 representing 36.4 percent of total deaths. From these figures it emerges that the most critical period of life is from zero to nine years.

(1) Philippines Statistical Yearbook 1987

2.3 Health Organization

From the point of view of health, the Philippines population is divided into twelve health regions plus the National Capital Region (NCR). The health organization is partially governmental and partially private. In the following table some data concerning the hospitals are reported (1986).(1)

Number of Hospitals			Bed Capacity			Bed Capacity per 10,000 population
Total	Government	Private	Total	Gov't	Private	
1,846	617	1229	89,171	48,906	40,265	15.9

The hospital beds to population ratio results to be 1:629, not far from the standard ratio of one hospital bed per 500 persons. The ratio of Rural Health Units (RHUs) to the population in 1985 was 1:27,458 totalling then around 2000. The proportion of Barangay Health Stations (BHSs) to population in 1985 reached 1: 6,841, marking a significant progress with reference to the previous years.

(1) Philippine Statistical Yearbook 1987

3.0 - THE PROCUREMENT SYSTEM

In order to determine the market for antibiotics and to estimate the volume of the different antibiotics for which a potential local production could be taken into consideration, we have investigated the different ways in which drugs are purchased and introduced into the Philippines, either in bulk or in packaged form. We could identify the following main channels:

- Imports from Filipino and Multinational Companies with main suppliers in Europe, Japan, the United States and China.

- Purchases from the Department of Health through tenders; these purchases are especially devoted to the supply of essential drugs for the Rural Health Units.

- Direct purchases from the Regions.

- Smuggled goods which escape control and with quantities difficult to evaluate.

- F drugs imported and locally manufactured ; the amount seem to be relatively small.

- Donations from Charitable Institutions and International Organizations mainly from the United States and Western European countries; the quantity of drugs introduced into the Philippines by this way is rather small and irregular and consists essentially in analgesics and some antibiotics.

The largest part of drugs in bulk form are imported by the private sector, the Government being the second most important purchaser.

4.0 - THE PHARMACEUTICAL MARKET FOR ANTIBIOTICS

4.1 Sources of data

In order to reach a reasonable estimate of the consumption of antibiotics, a number of sources have been examined and the gathered data have been checked in order to reach more realistic figures.

The following documents were examined:

- The IMS (Institute for Medical Statistics) audit concerning sales through pharmacies (PDI); the data represent figures for all the pharmaceutical specialties and all pharmaceutical forms; the data are collected through a sample analysis of sales of 260 selected retail drugstores out of 6563 and figures are extended to cover the entire country measuring approximately 78% of the drug business (1). The reported figures, considered generally accurate as a whole, give an idea of the order of magnitude of sales of a given product, but are considered to be rather low especially for certain products.

- The IMS audit concerning sales through the hospitals (PHPA); containing figures for all the pharmaceutical specialties and all pharmaceutical forms with data collected through a sample analysis of sales of 100 selected hospitals (67 private and 33 government). Approximately 14 % of the total business pass through hospitals. Also in this case, figures are considered to be on the low side.

- Business Statistics Monitor (BSM) (edited by a private Company). This publication includes weekly descriptive arrival reports and is issued in two different series, one for the arrivals by air and one by sea. The set for pharmaceuticals includes for each product or specialty the following data: the quantity, the name or the description of the product, the name of the consignee, the name of the shipper (when available), the name of the ship, or air carrier the port of origin, the FOB price in US Dollars and the landed price in Pesos. Sometimes the description needs interpretation, but in any case it is an interesting publication by means of which it could be possible to check the imports of the private pharmaceutical sector. We examined both the data for 1987 and for the period January-May 1988. Also figures for antibiotics for veterinary and animal feed use are included in the monitor.

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(1) The audit is not extended to the Mercury retail chain of 201 main outlets.

- Procurement from the Department of Health for 1987 and the Annual Procurement Program for RHU medicines for 1988. These figures give an indication of the efforts of the Department of Health to cope with the needs for drugs in the RHU.

- Direct procurement by the Regions for 1987.

- Other information have been collected through meetings and discussions with managers of some domestic and foreign Companies, especially those involved with manufacture of drugs we might take into consideration for local production.

- As for the local manufacture of Ampicillin, Amoxycillin and Cloxacillin, the data were collected during visits to the producing plant of Chemfields and from discussions with the managers of the company.

4.2 The IMS Data

In the following tables, which are listed in alphabetical order, all the antibiotics that are sold in the Philippines as specialties through drugstores and hospitals pharmacies, are indicated. Antineoplastic antibiotics are not included because of their very specific activity, their patent position, their relatively sophisticated technology and the very limited volume. The quantities and the market value (at ex-factory sales prices) are indicated. The reported quantities are to be considered as minimum quantities; in selected cases some more realistic figures, together with a rationale will be given. We shall now examine each family of antibiotics with the objective of identifying some products that could be taken into consideration for local production. Both fermentation and semi-synthetic products will be considered. Each family will be discussed in detail with special attention to the most interesting products, especially from the point of view of the market size and of the interest of the country's health situation and economy.

Table 4.01

FAMILY : AMINOGLYCOSIDE ANTIBIOTICS

ACTIVE INGREDIENTS	DRUGSTORE VOLUME (Kgs)	DRUGSTORE VALUE (Pesosx1000)	HOSPITAL VOLUME (Kgs)	HOSPITAL VALUE (Pesosx1000)	TOTAL VOLUME (Kgs)	TOTAL VALUE (Pesosx1000)
AMIKACIN	22	10369	21	9471	43	19560
GENTAMYCIN	19	45761	10	10343	29	56104
NEOMYCIN	56	36046	7	1673	63	37683
PAROMOMYCIN	105	6768	4	249	107	7017
STREPTOMYCIN	3925	80478	202	2331	4127	82809
TOBRAMYCIN	4	4070	7	6855	11	10925
DIBEKACIN	1	776	0.2	214	1.2	990
NETILMICIN	2	4978	10	9746	12	14724
KANAMYCIN	6	308	3	132	9	440

Table 4.02

FAMILY : ERYTHROMYCINS and other MACROLIDE ANTIBIOTICS

ACTIVE INGREDIENTS	DRUGSTORE VOLUME (Kgs)	DRUGSTORE VALUE (Pesosx1000)	HOSPITAL VOLUME (Kgs)	HOSPITAL VALUE (Pesosx1000)	TOTAL VOLUME (Kgs)	TOTAL VALUE (Pesosx1000)
ERYTHROMYCIN BASE	1075	20493	65	1073	1140	21566
STEARATE	2297	32267	82	1603	2379	33870
ETHYLSUCCINATE	3167	49067	68	1220	3235	50287
ESTOLATE	673	19017	27	696	700	19713
LACTOBIONATE			95	179	95	179
SPIRAMYCIN	310	4448	6	90	400	4538

- Figures refer to 1987
- Prices are ex-factory prices

Table 4.03

FAMILY : PENICILLINS

ACTIVE INGREDIENTS	DRUGSTORE VOLUME (Kgs)	DRUGSTORE VALUE (Pesosx1000)	HOSPITAL VOLUME (Kgs)	HOSPITAL VALUE (Pesosx1000)	TOTAL VOLUME (Kgs)	TOTAL VALUE (Pesosx1000)
PENICILLIN G (Sod. or Pot. salt)	2578	50433	15	27	2593	53026
PENICILLIN V (Acid or Pot. salt)	12356	57567	2177	2598	14535	60165
PENICILLIN G BENZATHINE	95	3762	13	588	108	9612
PENICILLIN PROCAINE	500	8741	38	1322	538	10063

Table 4.04

FAMILY : POLIPEPTIDE ANTIBIOTICS

ACTIVE INGREDIENTS	DRUGSTORE VOLUME (Kgs)	DRUGSTORE VALUE (Pesosx1000)	HOSPITAL VOLUME (Kgs)	HOSPITAL VALUE (Pesosx1000)	TOTAL VOLUME (Kgs)	TOTAL VALUE (Pesosx1000)
GRAMICIDIN	1.7	1140	0.1	475	1.8	11915
POLYMIXIN B	34	47099	2	1966	36	48965

Table 4.05

FAMILY : POLYENE ANTIBIOTICS

ACTIVE INGREDIENTS	DRUGSTORE VOLUME (Kgs)	DRUGSTORE VALUE (Pesosx1000)	HOSPITAL VOLUME (Kgs)	HOSPITAL VALUE (Pesosx1000)	TOTAL VOLUME (Kgs)	TOTAL VALUE (Pesosx1000)
AMPHOTERICIN B	33	4846	0.1	4	33.1	4850
POLYMIXIN B	0.8	164			0.8	164

- Figures refer to 1987
- Prices are ex-factory prices

Table 4.06

FAMILY : RIFAMYCINS

ACTIVE INGREDIENTS	DRUGSTORE VOLUME (Kgs)	DRUGSTORE VALUE (Pesosx1000)	HOSPITAL VOLUME (Kgs)	HOSPITAL VALUE (Pesosx1000)	TOTAL VOLUME (Kgs)	TOTAL VALUE (Pesosx1000)
RIFAMPICIN	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

Table 4.07

FAMILY : SEMISYNTHETIC CEPHALOSPORINS DERIVED FROM 7-ACA

ACTIVE INGREDIENTS	DRUGSTORE VOLUME (Kgs)	DRUGSTORE VALUE (Pesosx1000)	HOSPITAL VOLUME (Kgs)	HOSPITAL VALUE (Pesosx1000)	TOTAL VOLUME (Kgs)	TOTAL VALUE (Pesosx1000)
CEPHALOTIN	40	3699	65	6067	105	9766
CEFUROXIME	19	4363	24	6570	43	10933
CEFOTIAM	3	647	8	2070	11	2717
CEFSULODIN	1	230	0.4	116	1.4	346
CEFTAZIDIME	16	5350	38	12947	54	18297
CEFTRIAXONE	19	9341	2	854	21	10195
CEFAMANDOL	8	810	21	2838	29	3648
CEFADROXIL	209	9512	34	486	243	9998
CEFAZOLIN	14	2183	0.4	67	14.4	2250
CEFUROXIME	3	571	3	632	6	1203
CEFOPERAZONE	5	1614	24	16450	29	18064
CEFOTAXIME	15	4303	17	4762	32	9065
CEFACLOR	202	10261	37	1745	239	12006
CEFOXITIN			4	808	4	808

- Figures refer to 1987
- Prices are ex-factory prices

Table 4.06

FAMILY : SEMISYNTHETIC CEPHALOSPORINS DERIVED FROM 7-ADCA

ACTIVE INGREDIENTS	DRUGSTORE VOLUME (Kgs)	DRUGSTORE VALUE (Pesosx1000)	HOSPITAL VOLUME (Kgs)	HOSPITAL VALUE (Pesosx1000)	TOTAL VOLUME (Kgs)	TOTAL VALUE (Pesosx1000)
CEPHALEXIN	2055	62918	438	17321	2493	80239
CEPHRADIN	214	11850	67	2668	281	14518

-Figures refer to 1987
-Prices are ex-factory prices

Table 4.09

FAMILY : SEMISYNTHETIC PENICILLINS

ACTIVE INGREDIENTS	DRUGSTORE VOLUME (kgs)	DRUGSTORE VALUE (Pesos x 1.000)	HOSPITAL VOLUME (kgs)	HOSPITAL VALUE (Pesos x 1.000)	TOTAL VOLUME (kgs)	TOTAL VALUE (Pesos x 1.000)
AMPICILLIN	19[illegible]26	352700	2123	5662	22101	358362
AMOXYCILLIN	9880	196946	665	20359	10545	217304
CLOXACILLIN	2505	67255	406	10477	2911	77732
CARBENICILLIN	1	47	1	56	2	103
EPICILLIN	565	9526	98	1887	661	11413
BECAMPICILLIN	1[illegible]72	36446	177	5116	2156	41562
MECILLINAM	7	273	0.1	122	7.1	395
METAMPICILLIN	78	1183	79	2002	157	3185
NAFCILLIN SOD.	7[illegible]	15[illegible]79	56	2539	786	17669
PIVAMPICILLIN	170	7265	15	808	185	8073
PIVMECILLINAM	70	4941	12	783	82	5724
[illegible]CACILLIN	81[illegible]	1[illegible]21	25	2942	[illegible]	22752
CICLACILLIN	232	3819	7	117	239	3936
MEZLOCILLIN	11	1663	13	1894	24	3557
PIPERACILLIN	9	963	43	4465	52	5428
SULBENICILLIN	41	3159	36	2513	77	5672
SULBACTAM	9	3292	10	1128	19	4420
TICARCILLIN	34	2067	9	1076	43	3140

- Figures refer to 1987
- Prices are ex-factory prices

Table 4.10

FAMILY : TETRACYCLINES

ACTIVE INGREDIENTS	DRUGSTORE VOLUME (Kgs)	DRUGSTORE VALUE (Pesosx1000)	HOSPITAL VOLUME (Kgs)	HOSPITAL VALUE (Pesosx1000)	TOTAL VOLUME (Kgs)	TOTAL VALUE (Pesosx1000)
TETRACYCLINE	4980	40659	185	1027	5165	41683
CHLORTETRACYCLINE	374	5475	0.06	8	5475	5483
OXYTETRACYCLINE	2269	59009	18	706	2287	59715
DOXYCYCLINE	1187	17108	16	1441	1203	18549
MINOCYCLINE	79	5378	2	113	81	5491

Table 4.11

FAMILY : OTHER ANTIBIOTICS

ACTIVE INGREDIENTS	DRUGSTORE VOLUME (Kgs)	DRUGSTORE VALUE (Pesosx1000)	HOSPITAL VOLUME (Kgs)	HOSPITAL VALUE (Pesosx1000)	TOTAL VOLUME (Kgs)	TOTAL VALUE (Pesosx1000)
BACITRACIN	7	4293	0.2	149	7.2	4442
CHLORAMPHENICOL	23370	113109	974	18793	24344	131902
CLINDAMYCIN	364	17089	28	4013	392	21102
FRAMYCETIN	12	7782	1.5	379	13.5	8161
GRISEOFULVIN	750	12256	15	234	765	12490
LINCOMYCIN	570	8857	47	729	617	9586

- Figures refer to 1987
- Prices are ex-factory prices.

Aminoglicoside antibiotics

In this class are two antibiotics prepared by partial synthesis: Amikacin and Dibekacin. The quantities involved are limited and the products are of no interest for local production. The most interesting in terms of market strength is Streptomycin. According to the IMS figures local consumption amount to about 4 tons per annum. Another more realistic figure, according to the data of the Philippine imports of antibiotic provided by the National Statistics Office mentioning 16.3 tons for 1987 and 11.3 tons for 1986. Streptomycin is an old antibiotic which is used as an antituberculosis agent. In more developed countries, it is considered to be obsolete and only a few remaining companies are still producing it. With the advent of Rifampicin and the new anti-TB treatment schemes on one side, as well as some undesirable side effects, on the other, the use of the product is declining all over the world and we do not recommend its production.(1) The market size of the product is limited, to be taken into consideration for manufacturing purposes. In any case, a production plant is not feasible, due to the recovery section, which is specific for this product and cannot be utilized for other purposes.

Erythromycins

The volume of local consumption of these products implies its importance. The figures given by IMS are too low. Erythromycin will be discussed in detail, later.

Penicillins

The strategic importance of Penicillins is based upon the interest in the product itself (Penicillins G and V, injectable forms and benzatine and procaine salt depot) and as a starting material for the preparation of 6-APA (6-aminopenicillanic acid), which is the starting point in the preparation of semi-synthetic Penicillins and of 7-ADCA (7-aminodesacetoxycephalosporanic acid),which is the basic material for two important derivatives, Cephalexin and Cephradin.

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(1) Its inclusion on the 1988 Investment Priority Plan could be reconsidered

Polipeptide antibiotics

This class of antibiotics do not seem to be of any interest, considering the limited quantities used in the country.

Polyene antibiotics

Also for this class, the considerations for polypeptide antibiotics are valid.

Rifamycins

This class which includes only Rifampicin is a very important class, especially in view of its therapeutic value in the TB treatment, its mechanism of action and the lack of cross-resistance with other antibiotics. The IMS figures are on the low side and do not take into account all the purchases from the Department of Health.

This product, which is prepared by partial synthesis from Rifamycin B, will be discussed in detail in the next pages.

Semi-synthetic Cephalosporins derived from 7-ADCA

(7-Aminodesacetoxycephalosporanic acid)

This class includes Cephalexin (1), an important antibiotic, for which an increase of the market is foreseen; notwithstanding the present rather limited quantity used, we will discuss this product in the following pages.

Semi-synthetic Cephalosporins derived from 7-ACA

(7-aminocephalosporanic acid)

This class includes some recent and valuable antibiotics some of them with specific activity spectrum. Because of the limited quantities used in the country these products will not be taken into consideration for local production.

(1) Not included in the WHO essential drug list

Semi-synthetic Penicillins

In this class are included some of the most widely used antibiotics e.g. Ampicillin and Amoxycillin. These two products together with Cloxacillin will be discussed in detail in the following pages due to their high volume of sales. The other antibiotics are of minor interest, either because they are therapeutically not much different from amoxycillin or they are still under patent protection, or they are present in the market with only one or two brands.

Tetracyclines

This class of antibiotics includes three products obtained by fermentation and two by semi-synthesis (Doxicycline and Minocycline). The quantities of tetracycline, chlotetracycline and oxytetracycline reported in IMS are lower than those obtained from other sources. Furthermore, Chlotetracycline is largely used as an animal feed supplement, the quantities involved being rather high. We will discuss in greater detail the products which are obtained by fermentation. As to the products obtained by semi-synthesis, the quantities involved are rather low and would seem not to be of any interest for local production.

Other antibiotics

This class encompasses all the antibiotics not included in other classes. Except for Clindamycins and Chloramphenicol, all the products are obtained by direct fermentation. The volume of their consumption and their rather specific spectrum of activity advise against a local production. It would seem also appropriate not to dissipate efforts and to concentrate on more widely used drugs. Chlorampenicol is largely used in the country, the quantity sold in 1987 being about 25 tons. In developed countries the use of this antibiotic is limited to specific cases and its consumption has gradually decreased, also due to some side-effects. Because of these reasons, in the United States Chloramphenicol and its esters have been delisted by FDA. These side effects could

contribute to the decrease of its prescription in the Philippines in the near future despite its being included in the essential drug list.(1) Furthermore, the technology for chloramphenicol production is controlled by a small number of companies and is not easily available and the quantities involved are insufficent from the point of view of production feasibility.

4.3 The Business Statistics Monitor Data

In the following tables are listed the quantities of the main antibiotics introduced officially in the country. They include products imported into the Philippines either by air or by sea.

The antibiotics are divided into different families and the range of F.O.B prices in us dollars at the origin is also reported.

The large price variations observed in some cases should be attributed mainly to the fact that the same product is imported both in the oral as well as in the injectable and more expensive form.

Landed prices are 20-25 percent higher due to transport costs as well as to import duties and taxes. Since the figures reported are based on the effective quantities introduced into the country, our opinion is that the BSM data seem more reliable than other sources of information.

The tables include two sets of figures: the ones related to the 1987 and the ones related to the period January - May 1988.

As the data for 1987 are related to one whole year we consider that these figures are more representative than the later of January-May 1988, with which they have been compared.

We will now examine in detail the various groups of antibiotics in order to identify those which could be appropriate for local production.

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(1) Due to the FDA measures taken on the USA, there are talks to delist this product in the Philippines, despite its high therapheutic value in the treatment of thyphoid fever.

Table 4.12

ARRIVAL BY SHIP OR PLANE IN 1987

FAMILY : CEPHALOSPORINS

ACTIVE INGREDIENTS	QUANTITY (Kgs)	PRICE * RANGE ($ Per Kg.)
CEPHALEXIN	2700	170-250
CEFADROXYL	600	600-670
CEFACHLOR	310	700-800
CEFADRINE	300	750-770
CEFAPERAZONE	30	N.A.
CEFAZOLIN	10	2300

Table 4.13

ARRIVAL BY SHIP OR PLANE IN 1987

FAMILY : ERYTHROMYCINS

ACTIVE INGREDIENT	QUANTITY (Kgs)	PRICE RANGE * ($ Per Kg.)
ERYTHROMYCIN BASE	1800	100-200
ERYTHROMYCIN STEARATE	4000	100-150
ERYTHROMYCIN ETHYLSUCCINATE	2700	140-210
ERYTHROMYCIN THIOCIANATE	2500	90-123
ERYTHROMYCIN ESTOLATE	1300	75-110

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* FOB PRICES

Table 4.14

ARRIVAL BY SHIP OR PLANE IN 1987

FAMILY : PENICILLINS

ACTIVE INGREDIENT	QUANTITY (BU)	PRICE RANGE * ($ Per BU)
PENICILLIN G POTASSIUM	13040	27-30
PENICILLIN G SODIUM	4770	50-65
PENICILLIN G BENZATHINE	250	70-80
PENICILLIN G PROCAINE (STERILE)	2500	45-65
PENICILLIN G PROCAINE (FEEDGRADE)	7700	28-31
PENICILLIN V POTASSIUM	41400	30-60
PENICILLIN V ACID	1600	27- 30

Table 4.15

ARRIVAL BY SHIP OR PLANE IN 1987

FAMILY : RIFAMYCINS

ACTIVE INGREDIENTS	QUANTITY (Kgs)	PRICE * RANGE ($ Per Kg.)
RIFAMPICIN	6600	200-500

Table 4.16

ARRIVAL BY SHIP OR PLANE IN 1987

FAMILY : STREPTOMYCINS

ACTIVE INGREDIENTS	QUANTITY (Kgs)	PRICE * RANGE ($ Per Kg.)
STREPTOMYCIN	11374	30-70

* FOB PRICES

Table 4.17

ARRIVAL BY SHIP OR PLANE IN 1987

FAMILY : SEMISYNTHETIC PENICILLINS

ACTIVE INGREDIENT	QUANTITY (Kgs)	PRICE RANGE * ($ Per Kg.)
AMPICILLIN TRIHYDRATE	1600	60-85
AMOXYCILLIN TRIHYDRATE	1800	100-115
CLOXACILLIN SODIUM	4900	160-250
AMPICILLIN SODIUM STERILE	270	500-750
EPICILLINE	760	300-320
NAFCILLINE	1500	300-400

Table 4.18

ARRIVAL BY SHIP OR PLANE IN 1987

FAMILY : TETRACYCLINES

ACTIVE INGREDIENT	QUANTITY (Kgs)	PRICE RANGE * ($ Per Kg.)
TETRACYCLINE HYDROCHLORIDE	16000	30-70
TETRACYCLINE BASE	500	25-30
OXYTETRACYCLINE HYDROCHLORIDE	11500	24-30
OXYTETRACYCLINE FEEDGRADE	4500	
CHLORTETRACYCLINE FEEDGRADE	30500	18-70

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* FOB PRICES

Table 4.19

ARRIVAL BY SHIP OR PLANE IN JANUARY-MAY 1988

FAMILY : CEPHALOSPORINS

ACTIVE INGREDIENTS	QUANTITY (Kgs)	PRICE * RANGE ($ Per Kg.)
CEPHALEXIN	239	250-390
CEFADROXYL	90	607-1600
CEFACHLOR	200	810
CEFADRINE	140	757
CEFAPERAZONE	4.6	3780

Table 4.20

ARRIVAL BY SHIP OR PLANE IN JANUARY-MAY 1988

FAMILY : ERYTHROMYCINS

ACTIVE INGREDIENT	QUANTITY (Kgs)	PRICE RANGE * ($ Per Kg.)
ERYTHROMYCIN BASE	100	135
ERYTHROMYCIN BASE STERILE	635	225
ERYTHROMYCIN ETHYLSUCCINATE	1767	139-218
ERYTHROMYCIN STEARATE	2063	235-240
ERYTHROMYCIN THIOCIANATE	990	88-97
ERYTHROMYCIN ESTOLATE	329	114-350

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* FOB PRICES

Table 4.21

ARRIVAL BY SHIP OR PLANE IN JANUARY-MAY 1988

FAMILY : PENICILLINS

ACTIVE INGREDIENT	QUANTITY (BU	PRICE RANGE * ($ Per BU)
PENICILLIN G POTASSIUM	3844	19.6-30.6
PENICILLIN G SODIUM	1450	17.5
PENICILLIN G PROCAINE	2732	27.5-33 (STERILE)
PENICILLIN V POTASSIUM	15400	27-38.5

Table 4.22

ARRIVAL BY SHIP OR PLANE IN JANUARY-MAY 1988

FAMILY : RIFAMYCINS

ACTIVE INGREDIENTS	QUANTITY (Kgs)	PRICE * RANGE ($ Per Kg.)
RIFAMPICIN	2727	195-520

Table 4.23

ARRIVAL BY SHIP OR PLANE IN JANUARY-MAY 1988

FAMILY : STREPTOMYCINS

ACTIVE INGREDIENTS	QUANTITY (Kgs)	PRICE * RANGE ($ Per Kg.)
STREPTOMYCIN	2970	29-72
DIHYDROSTREPTOMYCIN	200	65

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* FOB PRICES

Table 4.24

ARRIVAL BY SHIP OR PLANE IN JANUARY-MAY 1988

FAMILY : SEMISYNTHETIC PENICILLINS

ACTIVE INGREDIENT	QUANTITY (Kgs)	PRICE RANGE * ($ Per Kg.)
AMPICILLIN SODIUM	10.5	1076 (STERILE)
AMOXYCILLIN TRIHYDRATE	2000	60-87
CLOXACILLIN SODIUM	200	155
BECAMPICILLIN	120	275
EPICILLINE	450	195

Table 4.25

ARRIVAL BY SHIP OR PLANE IN JANUARY-MAY 1988

FAMILY : TETRACYCLINES

ACTIVE INGREDIENT	QUANTITY (Kgs)	PRICE RANGE * ($ Per Kg.)
TETRACYCLINE HYDROCHLORIDE	3950	27-70
TETRACYCLINE BASE	215	30.5
OXYTETRACYCLINE HYDROCHLORIDE	533	26-106
DOXYCYCLINE	30	1840
MINOCYCLINE	45	1585

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* FOB PRICES

Cephalosporins

In this group of antibiotics, only Cephalexin which is a derivative of 7-ADCA seems of interest in view of the market volume.

In consideration of the fact that a growth of the market is anticipated, we will discuss this antibiotic in the following pages.

Erythromycins

In its globality this family of important therapeutic agents reaches a level of consumption of more than twelve tons per year. This fact includes Erythromycins among the antibiotics which should be seriously considered for local production.

Penicillins

Taking into account the large quantities of this strategic antibiotic used as such in the country and the quantities used for the production of 6-APA and hence of Ampicillin and Amoxycillin, we are of the opinion that Penicillins are to be taken into consideration for local production, a point to be further developped.

Rifamycins

Rifampicin is an important antitubercular drug and a strategic product in the antituberculosis program supported by the DOH. Because of its importance and of the quantities involved, we will examine this antibiotic in more details.

Streptomycins

Although streptomycin is used in the country as one of the drugs against tuberculosis, for the reasons discussed in the IMS data section, (see paragraph 4.2) we do not consider the product interesting for local production.

Semi-synthetic Penicillins

The imported quantities in the preceding tables are on the low side. This apparent anomaly is explained by the fact that there is a local production of Ampicillin, Amoxycillin and lately some Cloxacillin, which meet to some extent the present consumption of the country.(1) In view of the importance of these products, they will be examined thoroughly in the following pages.

Tetracyclines

A large import of these antibiotics, both for human and for animal use, result from BSM figures. The quantity of more than 60 tons imported in 1987 is large enough to stimulate a deeper insight in order to determnine whether there is space for local production.(2)

4.4 Procurement for the Department of Health Data

A large quantity of drugs are directly purchased by the Department of Health to supply Rural Health Units. The figures supplied by the DOH for 1987 procurement for antibiotics are the following:

Erythromycins (Stearate or Ethylsuccinate)	Kg	1,100
Rifampicin		13,350
Amoxycillin Trihydrate		11,500

The annual procurement program for RHU medicines for 1988 included the following figures:

Erytromycins (Stearate or Ethylsuccinate)	Kg	3,900
Rifampicin		10,800
Amoxycillin Trihydrate		23,370

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(1) Apparently, Chemfields does not seem to supply Ampicillin and Amoxycillin to the government suppliers of finished medicines.

(2) The figure of 109,692 tons reported by the National Census and Statistics Office seems to be on the high side. We think that this figure could be explained by the fact that some batches of feed-grade Chlortetrocycline and Oxytetracycline having a 8 - 10 % content of the active principle, were considered 100% pure substance.

The projected quantities of Rifampicin correspond to the quantities required in 1988 for the antileprosy program (annual treatment of 40,000 people) and for the antituberculosis program (annual treatment of 140,000 cases).(1)

4.5 Direct Procurement from the Regions Data

The direct procurement from the regions, in accordance, refer to ten regions out of twelve. The volume of the products calculated from the amount of specialties purchased appear to be (1987):

Penicillin	G	400	Kg
Penicillin	V	1,300	Kg
Ampicillin		3.6	tons
Amoxycillin		1.6	tons
Tetracycline		830	Kg
Oxytetracycline		150	Kg
Erythromycins		280	Kg
Rifampicin		35	Kg

4.6 Chemfields Data

The annual manufactured volume of Chemfields could be summarized as follows:

Manufacture	1985	1986	1987
Ampicillin trihydrate	39.90T (70%)	30.75T (64%)	51.6T (68%)
Amoxycillin	16.30T (28%)	15.25T (32%)	22.5T (30%)
Cloxacillin	-	0.50T (1%)	-
Anhydrous Ampicillin	1.15T (2%)	1.56T (3%)	1.35T (2%)
T o t a l	57.35 T	48.06 T	75.44 T

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(1) see (1) page #49

4.7 Comparative data on consumption of drugs in different countries

It is known that the present Philippino pharmaceutical market represents only the quantity of drugs the population can afford and not its real needs.In order to roughly estimate the gap between the consumption and needs we have collected some data concerning pharmaceutical consumptions.
We report in the following table the figures for 1987 concerning some European contries, USA and Japan.

Country	Populati n (millions)	Pharmaceutical sales* (million $)	Average price of drugs to the public (in $)**	Expense per person per year (in $)
Italy	56.6	5962	6.29	168.59
France	54.3	6754	4.72	212.01
W.Germany	59.8	7606	13.45	263.46
U.K.	54.1	2496	8.91	98.28
Spain	37.6	2053	3.84	90.78
European)				
Econ.Com.)	---	27,305	7.03	---
USA	226.5	28,965	21.38	258.96
Japan	111.9	22,698	49.48	285.02
Philippines	54.7(1985)	500	---	9

* Ex-factory prices
** Public prices

The difference of the pharmaceutical sales in the various countries partly reflects the existing health system; e.g. in the United Kingdom where the health system is state controlled, the average price of drugss and the expense per person are lower than in other countries because of the existing limitations and restrictions.
According to some evaluations, in the Philippines in 1984 wealth was so distributed:

Very rich + rich	3 %
Middle class	20 %
Poor	51 %
Very poor	26 %
	100 %

The core of the pharmaceutical market is constituted by 23% of the population which covers about 80% of the private sector sales.About 75% of the population receive only a very limited amount of drugs, expecially through the RHUs although the morbidity is higher than in other developed countries due inter alia to the poor hygienic conditions.
Taking into account tha fact that the philippino pharmaceutical market is a free market from the above figures and considerations we estimate that the need of drugs by quantity is four to five times the present consumption to reach a reasonable level of population health and up to eight to ten times to reach the consumption of full developed countries.

5. GENERAL CONSIDERATIONS AND PROJECTIONS OF THE SELECTED PRODUCTS

5.1 Considerations on Single Products

Further to our previous comments concerning the status of available data in the majority of the developing countries, and as a result of our discussions with the private sector and among the Experts, as well as after the examination of various sources of information, we are of the opinion that the following estimates, without having necessarily a scientific base, represent reasonably acceptable levels. In this chapter will be discussed in detail the antibiotics produced by semi-synthesis, which in the preceeding pages appeared to be of interest for a potential local production.

In order to establish a relatively correct dimension of the productive capacity, projections up to 1995 have been made. A period of seven years has been selected, since the completion of a chemical plant and the start-up of operations requires a minimum of four to five years from the approval of the project; a seven years projection permits the establishment of a more flexible plant.

Except for specific reasons indicated under each antibiotic, the basic considerations taken into account when estimating the market sizes of the products, could be summarized as follows:

- The annual population growth of the Philippines reaching 68 millions in 1995
- The GNP growth projections and the distribution of wealth
- The family expenditures devoted to health care and purchase of medicines
- The prescription and automedication habits (a more rational use of drugs and a better knowledge of the medica profession of the specificity of each antibiotic); the usage of generics
- The DOH budget devoted to the drug procurement
- The health programmes for tuberculosis and leprosy, as well as other programmes and measures, resulting in a possible improvement of the general health situation and the sanitary conditions of the population
- The increase of potential prescribers by about 6000 # in 1995(1)

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(1) 781 passed the board examinations in 1988

The estimate do not represent the total needs of the country, but reflect only the market absorption capacity by the year 1995, including the private and public sectors.

Finally, the volume of smuggled goods, which will probably continue to exist in the future, has not been taken into consideration.

AMPICILLIN

According to the figures reported(1), the present production of Chemfields was of 51.6 tons in 1987; the official imports were of 2 tons, most of which was Ampicillin Sodium (the injectable salt imported in sterile vials).

As per the information received from various sources, there are smuggled goods which amount is difficult to determine but can be roughly estimated at 20 percent of the official production that is 10 tons per annum. The price of smuggled Ampicillin is lower than the locally produced one and ranges between 1850 and 2000 Pesos (obviously duties are not payed), against ₱ 2200 of the Chemfields product. An additional factor to be taken into consideration in order to make projections is the possible shift of the market from Ampicillin(2) to Amoxycillin could take place, thus limiting its growth potential.

Taking into consideration all the foregoing elements, a reasonable increase of the market in volume would be of +6% per year, the total quantity reaching 83 tons in 1995.

AMOXYCILLIN

This fast growing antibiotic is presently produced in the country by Chemfields with an output of 22.5 tons in 1987. The import was about 2 tons mainly of injectable sodium salt which is mainly imported in sterile vials.

In the same year, the Department of Health purchased 11.5 tons for the Rural Health Units. There is also a direct purchase by the Regions of limited quantities(2 tons).

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(1) 60 to 70 percent from 60 to 80 tons (12.8.1988)

(2) Presently its price is about 20 to 30 percent lower than that of Amoxycillin, which is not included in the WHO essential drug list.

Smuggled goods are also available in quantities, representing, according to some opinions, 20 percent of the official figures, thus reaching 5-8 tons annually.

In the procurement program of the Department of Health the volume for the RHUs in 1988 is 23.5 tons; Chemfields is also planning to increase its production.

In order to make a reasonable forecast, the following fact is to be taken into consideration, in addition to the general factors taken into account:

- a shift from Ampicillin to Amoxycillin could be taking place; hence is to be anticipated that its marked will show a larger increase than the one of Ampicillin (see also 5.2).

Taking into consideration all the factors, the following projections could be done:

The private sector market growth could be evaluated at 15% up to 1990 and at 8% up to 1995, giving a figure of 45 tons in that year. We understand the efforts undertaken by the Department of Health in doubling the procurement program for 1988 from 11.5 tons to 23.5 tons, but we think that in the future a more limited increase in the purchase of antibiotics could be expected.

Thus, for the period of 1989 to 1995, our projection will be 4 percent annually, reaching a volume of about 30 tons in 1995.

Our total projection for 1995 is of 75 tons.

CLOXACILLIN.

This antibiotic has a limited use in the Philippines with figures for 1987 reaching imports of 6 tons. Its market is rather steady and our projections are for a 4% annual growth rate and a market of 8 tons in 1995. This semi-synthetic penicillin could also be produced at the same plant used for Ampicillin and Amoxycillin production without additional investments.

CEPHALEXIN

The 1987 imports were about three tons and three brands were present on the market. Cephalexin is a rather expensive antibiotic derived from 7-ADCA and thence from Penicillin G or V.

This antibiotic(1) has a large growing market in the United States, in Japan and in Western Europe. We anticipate a 10 percent increase per year giving a total volume of 6 tons in 1995.

Cephalexin has been considered also, since its production could be undertaken in the same plant used for Ampicillin and Amoxycillin, so that spare capacity could be utilized without additional investments.

ERYTHROMYCINS.

The local projected production includes the preparation of the stearate and ethylsuccinate from Erythromycin base, which could be produced in the proposed multipurpose fermentation plant.

Erythromycin is an important broad spectrum antibiotic widely used all over the world. In 1987 the imports stood at about 12 tons, whereas the DOH procurement for RHU was of 1.1 tons. For 1988, the procurement program indicates about 4 tons in the form of stearate and ethylsuccinate.

In the projection for 1995, we have considered the following facts in addition to the general factors taken into account:

- as a broad spectrum antibiotic Erythromycin ranks among the most used products all over the world
- it has no competitors as in the case of Amoxycillin/Ampicillin.

For all these reasons, our projections are for a 6% growth of the private sector market up to 1991 and for a 4% up to 1995, thus reaching 17 tons in that year. With a 6% increase in the DOH procurement giving a quantity of 6 tons in 1995, the total consumption could reach 23 tons. Also in this case the quantities do not correspond to the total needs of the country but reflect only the market size and the volume the DOH could probably afford.

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(1) Not included in the WHO list of Essential Drugs

RIFAMPICIN

This antibiotic plays an important part in the antituberculosis and antileprosy programmes. Imports for 1987 were of about 7 tons and the DOH procurement reached more than 13 tons.

The procurement programme of the DOH for 1988 is 11 tons in finished form, quantity corresponding to the forecast for treatment of 40,000 cases of leprosy and 140,000 cases of tuberculosis.
The number of cases might be much higher considering the new cases, the recurrence and the fact that many of them are escaping diagnosis. The 140,000 represent most probably the number of persons which could be trated in 1988, connected to the availability of funds devoted to that programme.(1) For the coming years, the projections of DOH are (in kilograms of Rifampicin):

For Leprosy	1988	1989	1990	1991	1992
Paucibacillary	111	21	18	18	19
Multibacillary	416	405	92	92	88
Tuberculosis					
Short course chemotherapy	10,395	9565	8370	7790	7500
Total	10,922	9986	8480	7900	7607

Our projections are for a consumption of 9 tons in the private sector and of 11 tons in the procurement programs of the DOH up to 1995(2) the total volume projected being at 20 tons annually.

TETRACYCLINE HYDROCHLORIDE

This salt is to be taken into consideration when transforming the Tetracycline base obtained in the proposed multipurpose fermentation plant by the Expert on fermentation.

---

(1) Direct smear positive cases is 6.6 per 1,000 population, or 387,560 for a population of 58,721.307 in 1987

(2) The probability for a substantial increase in the DOH budget for this programme seem rather remote.

Imports of Tetracycline Hydrochloride reached 16 tons(1) for 1987. This product is a wide spectrum antibiotic having a relatively low price. For the projections up to 1995, the following additional considerations were kept in mind:

-Tetracycline is an old product with relatively limited market growth potential and with an annual increase which could be directly related to the population growth.

-The Department of Health does not supply this antibiotic to the RHUs.

-There is a certain overlapping of indications between the Tetracyclines and the semi-synthetic Penicillins

-Like with the Chloramphenicols, the shift of usage could also depend from price fluctuations

The increase in consumption is mainly due to the growth of the private sector market. For all these reasons a 3% annual growth of the market is anticipated, the 1995 consumption reaching about 20 tons.

OXYTETRACYCLINE HYDROCHLORIDE

Also this salt has been taken into account for the same reasons as for the Tetracycline hydrochloride, except that a very limited quantity is programmed by the DOH for the RHUs in the form of ophtalmic ointments (less than 1 kg). The 1987 import of this derivative was 11.5 t.Following considerations similar to those made for Tetracycline and assuming the same growth rate, a market size of about 15 tons is anticipated by 1995.

5.2 Projected requirements for the Years 1993, 1994, 1995.

Further to the projections made in the preceeding chapter, some, calculations have been made to determine the requirements for the years 1993, 1994, 1995. Based on the assumption that from the approval and financing of the project to the start-up of the industrial operation a minimum of three to four years are necessary and, assuming that the present project could be approved by mid 1989, a reasonable start of the production could be expected in 1993.

---

(1) The total volume of Tetracyclines imported in 1987 was 109,692 kg. With an average FOB price of US $ 19.64 /Kg (veterinary use included);see under Tetracycline point 4.3

The calculated figures for the projected requirements and/or production are (in metric tons):

		1993	1994	1995
Ampicillin		73.7	78.2	83.0
Amoxycillin	Private Sector	38.3	41.4	44.7
	Public Sector	28.6	29.7	30.9
Total Amoxycillin		66.9	71.1	75.6
Cloxacillin		7.6	7.9	8.2
Cephalexin		4.8	5.3	5.9
Total Semi-synthetic Penicillins		153.0	162.9	172.7
Erytromycins	Private Sector	15.5	16.0	16.6
	Public Sector	5.3	5.7	6.0
Total Erytromycins		20.8	21.7	22.7
Rifampycin	Private Sector	9.0	9.0	9.0
	Public Sector	11.0	11.0	11.0
Total Rifampicin		20.0	20.0	20.0
Tetracycline Hydrochloride		19.1	19.7	20.3
Oxytetracycline Hydrochloride		13.7	14.2	14.6

The rounded up figures for which the plants should be designed could be summarized as follows:(1)

Ampicillin	85 tons
Amoxycillin (2)	75 tons
Cloxacillin	8 tons
Cephalexin	6 tons
Erythromycin	25 tons
Rifampicin	20 tons
Tetracycline Hydrochloride	20 tons
Oxytetracycline Hydrochloride	15 tons

---

(1) Figures have been rounded up to a higher value to take into account the quantities directly purchased by the regions.

(2) In case the Amoxycillin purchases by the DOH do not follow the present growth trend and are shifted to Ampicillin having a similar therapeutic value at a lower cost, the production pattern could follow and instead of Amoxycillin, Ampicillin could be produced

We point out that the figures here reported represent the market projections up to 1995 for these antibiotics which are interesting for the country needs and consumption, and from an industrial point of view have a sufficient dimension to deserve a more detailed study.

Technical and economical considerations will be discussed in the following pages under the single headings.

6. RECCOMENDATIONS

6.1 General Criteria

The general criteria that have been followed in the selection of the antibiotics which could constitute the output of those industrial plants, whose implementation is recomended in the present report are listed here below:

- Consumption volume (or market size)
- Prevailing diseases and morbidity
- Government health programmes
- Strategic importance (such as Penicillin, which could serve as starting point for the manufacture of several other antibiotics)
- Patent position
- Availability of technologies
- World Market trends
- Availability of domestic raw materials (in particular agricultural products)
- Existence of down-stream facilities (e.g. Chemfields Inc. prcducts are all obtained starting from 6-APA and Penicillin)
- Presence of adequate and qualified human resources.

6.2 The Proposed Options

Taking into consideration the proposed fermentation plant and the products which could be manufacured locally, the projected quantities for the local consumption in 1995, as well as the present and potential production of the Chemfields factory, we propose the following options which will be examined in detail in the following pages.

1. A plant for the production of semi-synthetic beta-lactam antibiotics.

2. A plant for the production of 6-APA

3. A multi-purpose plant for the production of Erthromycin derivatives and Rifampicin.

4. A plant for the production of Tetracycline Hydrochloride and Oxytetracycline Hydrochloride from the corresponding bases.

We point out that options 2 and 4 have to be considered only if Penicillin and Tetracycline producing plants are installed in the country.

In this case, the two options are essential and should be considered as an integral part of the two projects.

The options to be implemented short-term are the Erythromycin derivatives and Rifampicin as well as semi-synthetic Penicillins projects whereas the 6-APA and Tetracycline Hydrochloride options are strictly connected with the implementation of corresponding fermentation projects and should be considered long-term proposals.

We will now discuss in some detail the options proposed in order to establish the viability of each.

7. THE BETA-LACTAM ANTIBIOTICS PROPOSED PLANT

The plant proposed in this section has the aim of producing beta-lactam antibiotics, to increase the present local production capacity (Chemfields) in order to satisfy the projected country consumption in 1995, estimated as follows.

Ampicillin	85 tons
Amoxycillin	75 tons
Cloxacillin	8 tons
Cephalexin	6 tons
	174 tons

Satisfactory technologies for Ampicillin, Amoxycillin and Cloxacillin are already available at Chemfields. Only the technology for Cephalexin should be obtained from external sources. Available technologies are updated and we do not have information of the existence of new ones; we are of the opinion that Chemfields technologies will remain competitive in the future.

Taking into account the present production capacity of Chemfields estimated to be about 100 tons/year (1) the proposed plant should have an additional capacity of 74 tons/year. Additional equipment is needed for the production of an intermediate (Dane Salt) in th Amoxycillin synthesis.

The Yearly Output of the plant will be:

Ampicillin	35 tons
Amoxycillin	30 tons
Cloxacillin	3 tons
Cephalexin	6 tons
Dane salt for Amoxycillin	28 tons

The proposal includes two different options; the first to produce the antibiotics by external supply of 6-APA; the second to use the 6-APA locally produced from Penicillin in a multi-purpose fermentation plant according to one option. Equipment, utilities ,manpower qualification and economics will be examined in detail at the end of the chapter.

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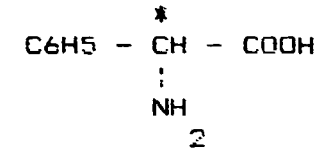
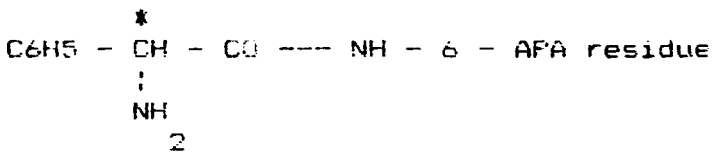
(1) In the existing set-up it would be almost impossible to reach a production of 13 batches per week on a three shift basis, with a batch size of 300 Kg. as claimed sometimes.

7.1 Ampicillin Trihydrate

Ampicillin, the first important semisynthetic Penicillin to be introduced into the market has a side chain derived from phenylglycine which has the following formula



Since it has an asymmetric carbon atom, the molecule is optically active; in the Ampicillin molecule it has the D(-) optical form. Ampicillin has the following formula:



$C_{16}H_{19}N_3O_4S \cdot 3H_2O$

m.w. 403.50 trihydrate

m.w. 349.42 anhydrous form

Determination of the Number of Batches

For the projected plant the batch dimension will be 300 kg. For the production of 35 tons 117 batches are required.

Principle of the Method

The proposed method consists in the condensation of the acid chloride derived from D(-) phenylglycine with 6-APA in which the carboxylic group is protected by sylilation. The synthesis is composed of the following steps:

1. Protection of the carboxylic group by sylilation
2. Condensation with phenylglycine chloride hydrochloride
3. Removal by hydrolisis of the protective group.

Description of the Method

The 6-APA is dissolved in anhydrous methylene

chloride and diethylamine and trimethylchlorosylane are added. After the reaction, dimethylaniline is added and, after cooling to -20 C, solid D(-) phenylglycine chloride hydrochloride is added portionwise. After the reaction has taken place, water is added to hydrolyze the sylilester. The dichloromethane phase is separated and the aqueous solution, after treatment with active carbon, is basified with triethylamine; the precipitated Ampicillin is centrifuged, washed and dried.

Yields

Theoretical yield	83 %
Weight yield	155 %

Raw Materials

Hereunder are the list of the main raw materials needed for one batch of 300 Kg and the corresponding quantities for one Kg. of Ampicillin trihydrate. The amount of solvents in brackets are the quantities used, while the the other figures pertains to the consumption considering a 70% recovery for dichloromethane and acetone

6-APA		194 Kg		0.647 Kg
Phenylglycine chloride hydrochloride		185 Kg		0.62 Kg
Trimethylchlorosylane		94 Kg		0.31 Kg
Dimethylaniline		180 Kg		0.61 Kg
Dichloromethane	(3800 Kg)	1140 kg	(12.6 Kg)	3.8 Kg
Triethylamine		105 kg		0.35 Kg
Acetone	(200 kg)	60 Kg	(0.66 kg)	0.2 Kg
Diethylamine		105 kg		0.35 Kg

Main Utilities for a 300 Kg Batch.

Electric Power	2400 KwH
Steam	2.10^6 Kcal
Liquid Nitrogen	5000 Kg

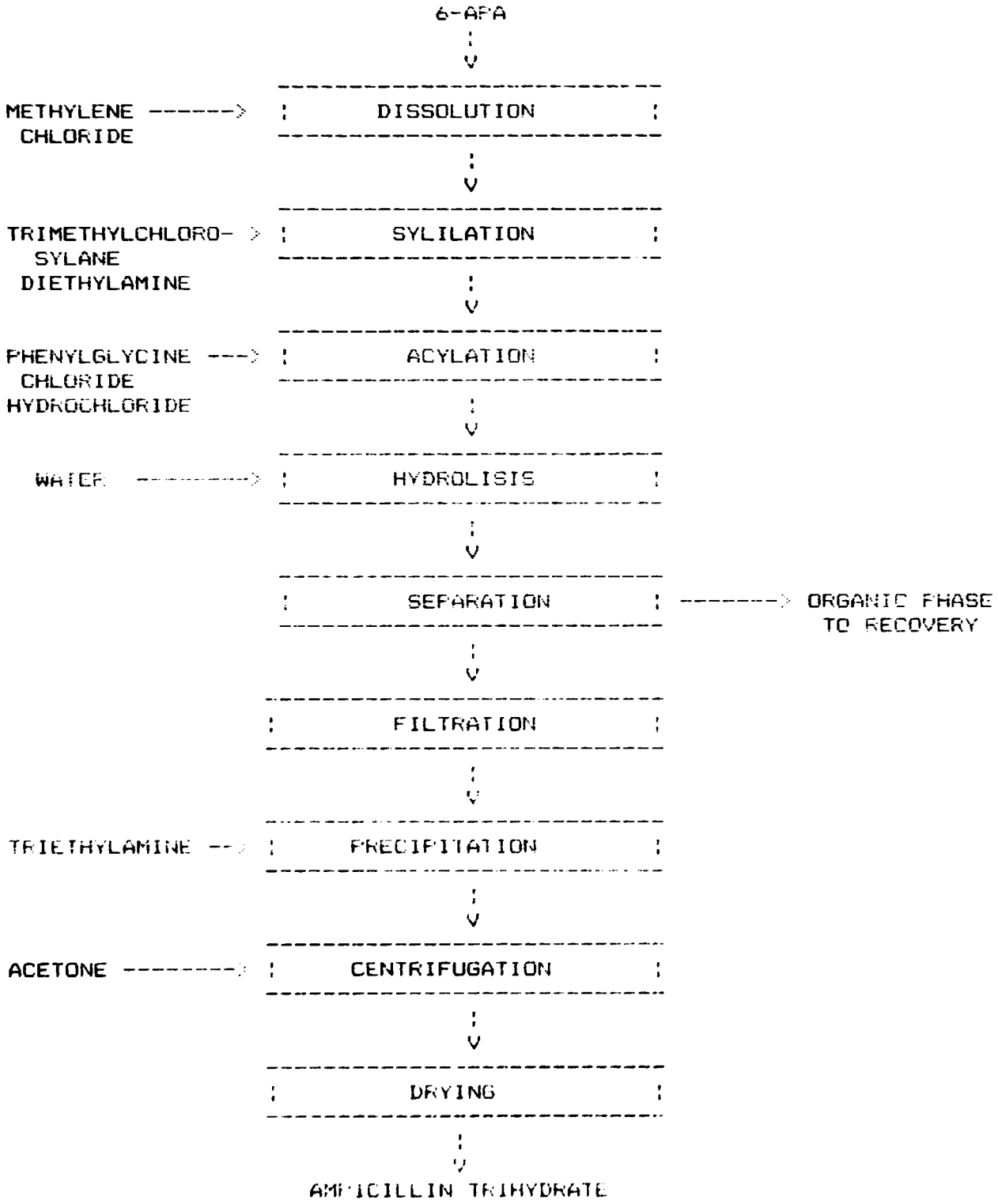
Production Plant and Equipment list

See 7.9 and 7.10

Manpower

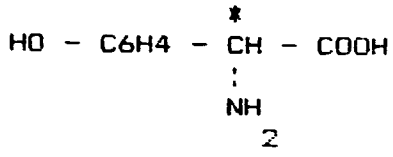
See 7.15

AMPICILLIN FLOW CHART

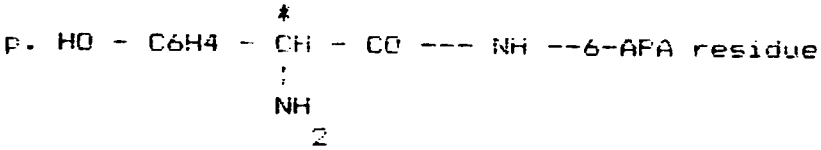


7.2 Amoxycillin Trihydrate

This important semi-synthetic Penicillin has a side chain derived from p. hydroxyphenylglycine which has the following formula



Since it has an asimmetric carbon atom this molecule is optically active;in the Amoxycillin molecule it has the D (-) optical form. It has the following formula:



Determination of the Number of Batches

For the projected plant the batch dimension will be 300 Kg. The production of 30 tons requires 100 batches.

Reaction Scheme

6 - APA	+	DANE SALT	------>	AMOXYCILLIN TRIHYDRATE
C H N O S		C H NO K		C H N O S . 3H O
8 12 2 3		14 16 4		16 19 3 5 2
m.w. 216.28		m.w. 301.38		m.w. 419.50 trihydrate
				m.w. 365.38 anhydrous form

Principle of the method

The proposed method consists in the condensation of the mixed anhydride derived from the Dane Salt (ethyl potassium) and ethylchlorocarbonate with salified 6-APA. The synthesis is composed by two steps:

1.) Preparation of the mixed anhydride
2.) Condensation with 6-APA

Description of the Method

1) Preparation of the mixed anhydride: The Dane salt (ethyl potassium) is introduced into the reactor containing anhydrous acetone followed by ethylchlorocarbonate and an organic base (amine). The mixed anhydride so prepared is very much moisture sensitive; it should be kept at 15-18 C and used as soon as possible.

2) Preparation of Amoxycillin : 6-APA is suspended in acetone water in a stainless steel reactor and dissolved by salification with triethylamine at -10 to -25 C . The solution of the mixed anhydride in acetone is then added keeping the temperature under 0 C. After the reaction has taken place,the resulting salt is hydrolysed by addition of hydrochloric acid. The solution is then extracted with dichloromethane - methylisobutylketone which extracts organic solvents and other products. After filtration, the Amoxycillin is precipitated from the aqueous phase by alkalinization, isolated by centrifugation, washed and dried. Amoxycillin trihydrate is obtained.

Yields

Theoretical yield	81%
Weight yield	155%

Raw materials

The main raw materials needed for one batch of 300 Kg and the corresponding quantities for one Kg are here reported.
The following percentage of recovery are considered:

Dichlorometane	70%
Methylisobutylketone	85%
Acetone	80%

6-APA		193.5 Kg		0.645 Kg
Dane salt,ethyl potassium		282 kg		0.94 Kg
Ethylchlorocarbonate		108 Kg		0.36 Kg
Acetone	(1050 Kg)	210 Kg	(3.5 Kg)	0.70 Kg
Dichloromethane	(960 Kg)	290 Kg	(3.2 Kg)	0.96 Kg
Methylisobutylketone	(780 Kg)	115 Kg	(2.6 Kg)	0.38 Kg
Triethylamine		99 kg		0.33 Kg

Concentrated Hydrochloric acid : Ammonia 28 Bé.

Main Utilities Used for a 300 Kg. Batch

Electric Power	4,200 Kwh
Brine	
Liquid nitrogen	5,000 Kg
Steam	22.10^5 Kcal

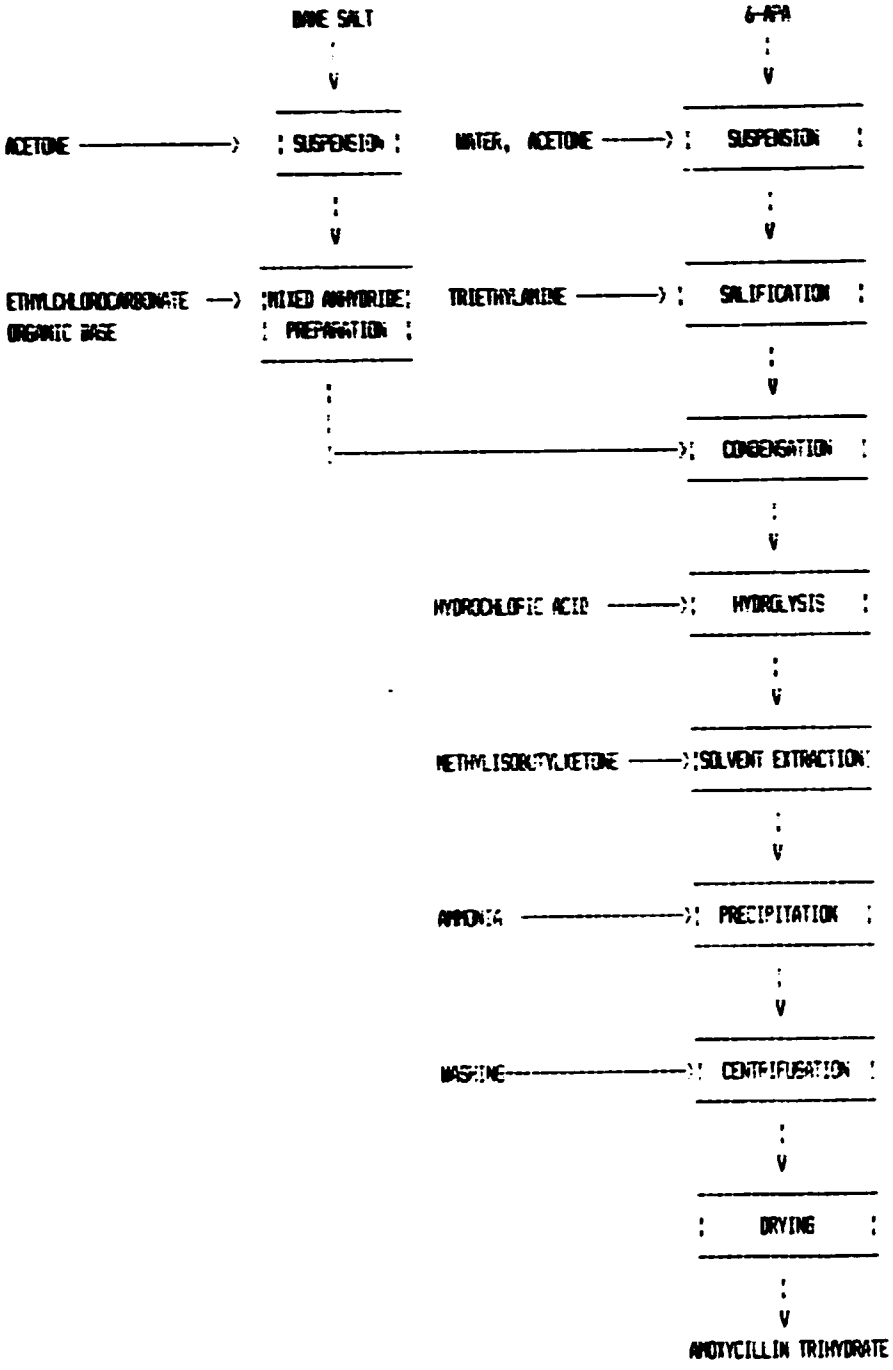
Production plant and Equipment list

see 7.10 and 7.11

Manpower

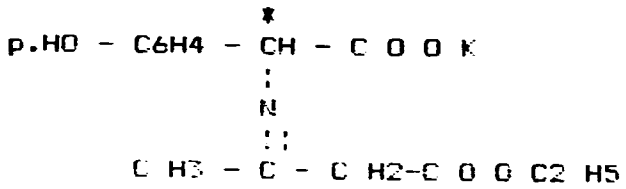
see 7.15

AMOXYCILLIN FLOW CHART



7.3 Dane Salt for Amoxycillin Production

Since the introduction of the side chain for the preparation of Amoxycillin requires the use of a reagent denominated Dane Salt, we suggest the local production of this intermediate in order to save money and foreign exchange. The required Dane salt has the following structure:



Formula : C 14 H 16 N O 4 K

[illegible] 301.38

[illegible] asymmetric carbon atom the [illegible] is optically active; the optical form is the D(-).

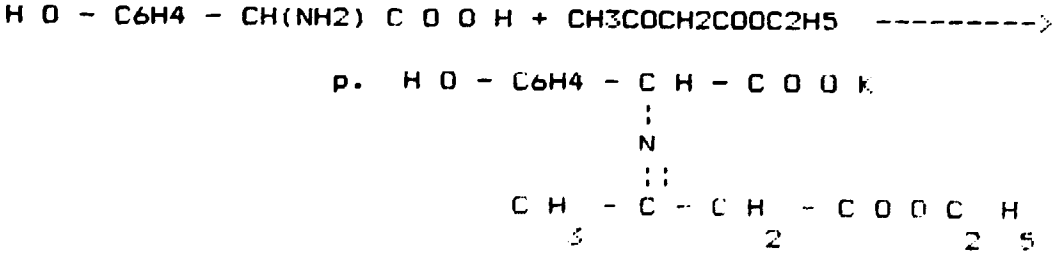
Determination of the quantity annually needed

Since for the production of one Kg of Amoxycillin, 0.94 Kg of Dane Salt are required, the total annual necessity will be 28.2 tons.

Determination of the number of batches

In the projected plant the dimension of each batch will be 500 Kg.For the production of 28 tons 56 batches are required.

Reaction scheme



Principle of the method

Condensation of D(-)p.Hydroxyphenylglycine with ethylacetoacetate and precipitation of the Dane salt with alkali.

Description of the method

D(-)p.hydroxyphenylglycine is dissolved in anhydrous ethanol and ethylacetate is added keeping the temperature low. By addition of alkali, the potassium Dane Salt precipitates, is filtered, washed with ethanol and dried. An additional quantity is obtainded by vacuum concentration of the mother liquors. It is filtered, washed and dried.

Yields

Theoretical Yield	91 %
Weight Yield	164 %

Raw Materials

Listed hereunder are the main raw materials needed for one batch of 500 Kg and the corresponding quantities for one Kg. of Dane salt.
A 80% recovery yield for ethanol is considered.

D(-)p.hydroxyphenylglycine		305 Kg	0.61	Kg
Ethylacetoacetate		260 Kg	0.52	Kg
Potassium Hydroxyde		102 Kg	0.204	Kg
Absolute Ethanol	(2400 Kg)	480 Kg	(4.8 Kg.) 9.96	Kg

Main utilities used for a 500 Kg batch

Electric Power	500 Kwh
Brine	
Steam	0.5×10^5 Kcal

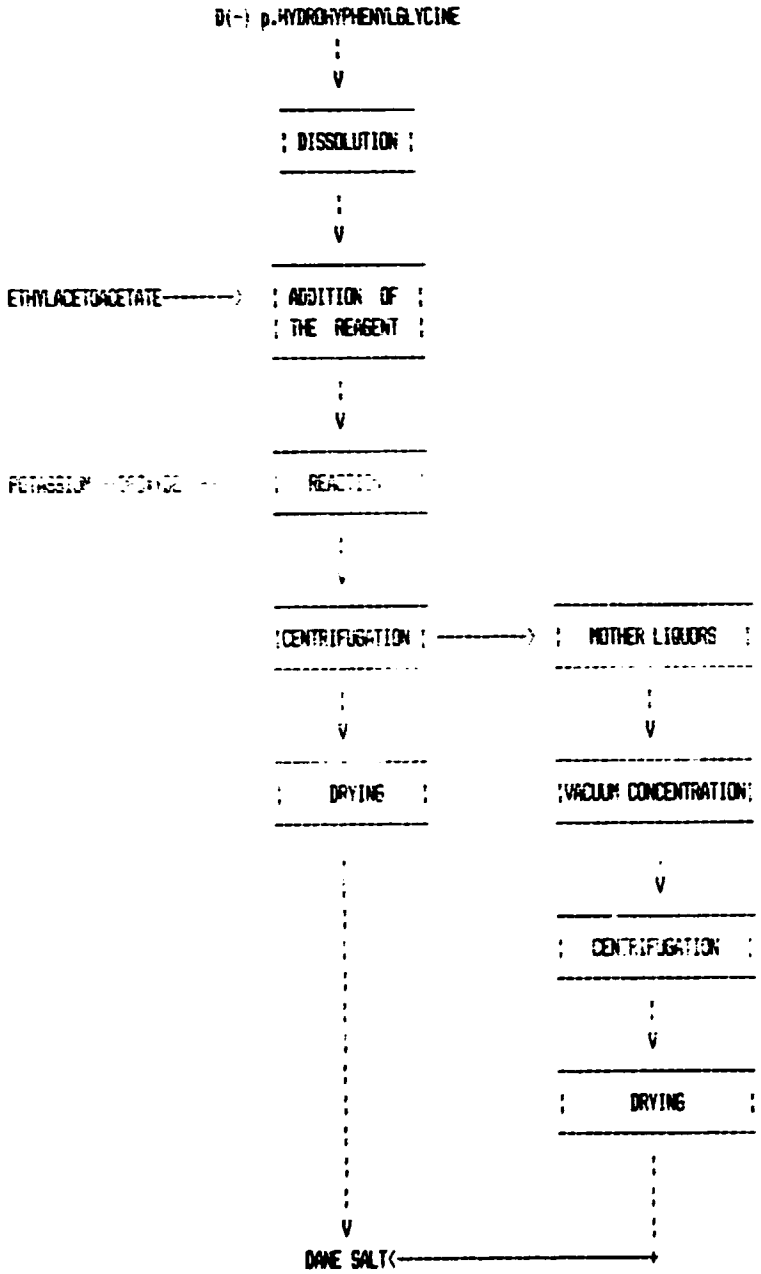
Production plant and equipment list

see 7.10 and 7.11

Manpower

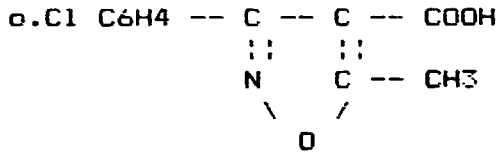
See 7.15

DANE SALT FLOW CHART

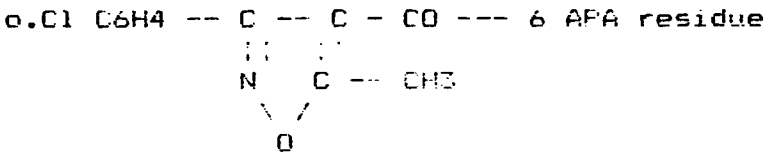


7.4 CLOXACILLIN SODIUM MONOHYDRATE

Cloxacillin, a semi-synthetic Penicillin having a specific activity against gram positive germs, has a side chain derived from 3 (2-chlorophenyl) -5-methyl-isoxazolyl-4-carboxylic acid, with the following structure:



This group is attached to the amino group of 6-APA through an amide linkage as in the other semisynthetic Penicillins. Cloxacillin has the following formula:



$C_{19}H_{18}N_3O_5ClS$

m.w. 435.89

Sodium Cloxacillin monohydrate

$C_{19}H_{17}N_3O_5ClSNa \cdot H_2O$

m.w. 475.87

Having one carboxylic group in the molecule Cloxacillin gives a sodium salt which has one molecule of water of crystallisation.

Determination of the number of batches

For the projected plant, the batch dimension will be 150 Kg.For the production of the requested 3 tons, 20 batches are needed.

Principle of the method

The proposed method consists in the acylation of the amino-group of 6-APA with 3 (2-chlorophenyl) -

5-methyl-isoxazolyl-4-carboxylic acid chloride. The sodium salt is precipitated from the solution by addition of sodium ethylhexanoate.

Description of the method

The 6-APA is acylated in aqueous acetone with the acid chloride in the presence of alkali. After extraction of acetone with dichloromethane Cloxacillin is extracted with methylisobutylketone and the solution dried. By addition of sodium ethylhexanoate solution the sodium salt precipitates.The suspension is centrifuged and the product dried. Sodium Cloxacillin monohydrate is obtained.

Yields

Theoretical yield	80%
Weight yield	175%

Raw materials

Hereunder are listed the main raw materials needed for one batch of 150 kg and the corresponding quantities for one kg.
A 70% recovery yield for bot solvents is considered.

6-APA	85.5 kg		0.57 kg	
Methylisobuthylketone	(1830 kg)	400 kg	(12.2 kg)	2.7 kg
Acetone	(975 kg)	200 kg	(6.5 kg)	1.3 kg
Sodium 2-ethylhexanoate	72 kg		0.48 kg	
3 (2-cniorophenyl)-5-methyl isoxazolyl-carboxychloride	108 kg		0.72 kg	
Sodium hydroxide	17 kg		0.11 kg	

Main Utilities for a 150 kg batch

Electric Power	2,400 kwh
Steam	$10 .10^5$ Kcal
Brine	

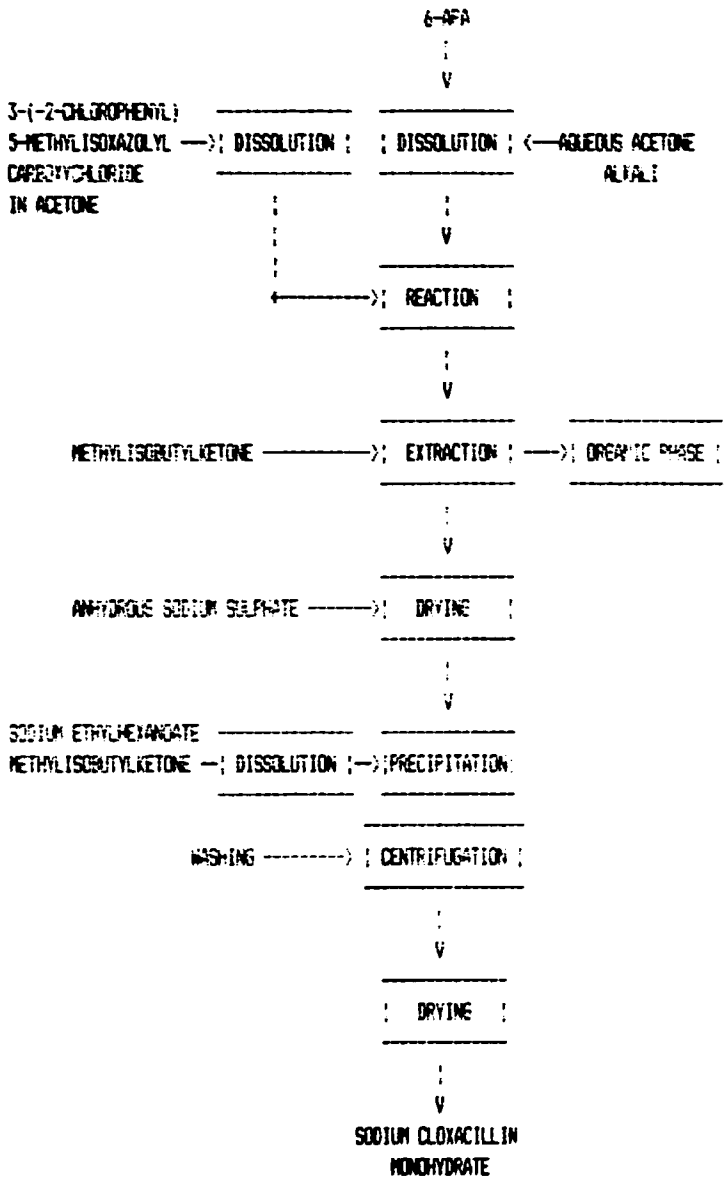
Production plant and equipment list

See 7.9 and 7.10

Manpower

See 7.15

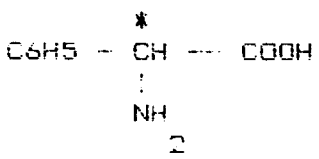
SODIUM CLOXACILLIN MONOHYDRATE FLOW CHART



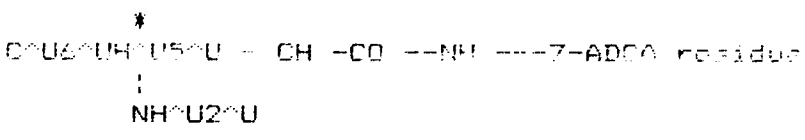
7.5 Cephalexin Monohydrate

Cephalexin is the most important member of the class of 3-desacetoxycephalosporins which are semi-synthetic antibiotics derived from 7-amino-desacetoxycephalosporanic acid. Since 7-ADCA can be conveniently prepared from penicillin G or V, later, if the proposed fermentation facilities for the production of Penicillins will be implemented, also 7-ADCA could be produced in the Philippines.

Its side chain, like Ampicillin, derives from phenylglycin which has the following formula:



Since it has asymmetric carbon atom its molecule is [illegible] the D (-) optical form. Cephalexin has the following formula:



C H N O S
16 17 3 4

m.w. 347.39

Determination of the number of batches

For the projected plant, the batch dimension will be 150 kg. For the production of the requested 6 tons, 40 batches are required.

Principle of the method

The proposed method consists in the condensation of the acid chloride derived from D (-) phenylglycine with 7-ADCA in which the carboxylic group is protected by sylilation.

Description of the method

The 7-ADCA is suspended in methylene chloride and acetone; diethylamine and trimethylchlorosylane are added and the sylilation carried out at 40 C. After cooling to 0-5 C D(-)phenylglycine chloride hydrochloride and dimethylaniline are added portionwise keeping the temperature low. Water is then added, the organic phase discarted and the acqueous, phase after active carbon treatment followed by filtration, is treated with triethylamine; the precipitated crude Cephalexin is centrifuged and washed.

The purification is performed by suspension in water and successive treatment with acetone. After centrifugation, washing and drying under vacuum, pure Cephalexin monohydrate is obtained.

Yields

Theoretical yield	75%
Weight yield	135%

Raw Materials

The main raw materials needed for one batch of 150 kg of Cephalexin Monohydrate and the corresponding quantitites for one kg are listed hereunder. A 70% recovery yield for dichloromethane and acetone is considered.

7-ADCA		111 kg	0.74 kg	
Phenylglycine chloride hydrochloride		95 kg	0.63 kg	
Diethylamine		39 kg	0.26 kg	
Trimethylchlorosylane		52 kg	0.345 kg	
Dimethylaniline		102 kg	0.68 kg	
Triethylamine		61 kg	0.41 kg	
Methylene chloride	(1,800 Kg)	540 kg	1.08 kg	(3.6 kg)
Acetone	(1,000 kg)	300 kg	0.60 kg	(2.0 kg)

Main utilities for a 150 kg batch

Electric power	1,200	Kwh
Steam	5 10	Kcal
Liquid nitrogen	2,300	kg
Brine		

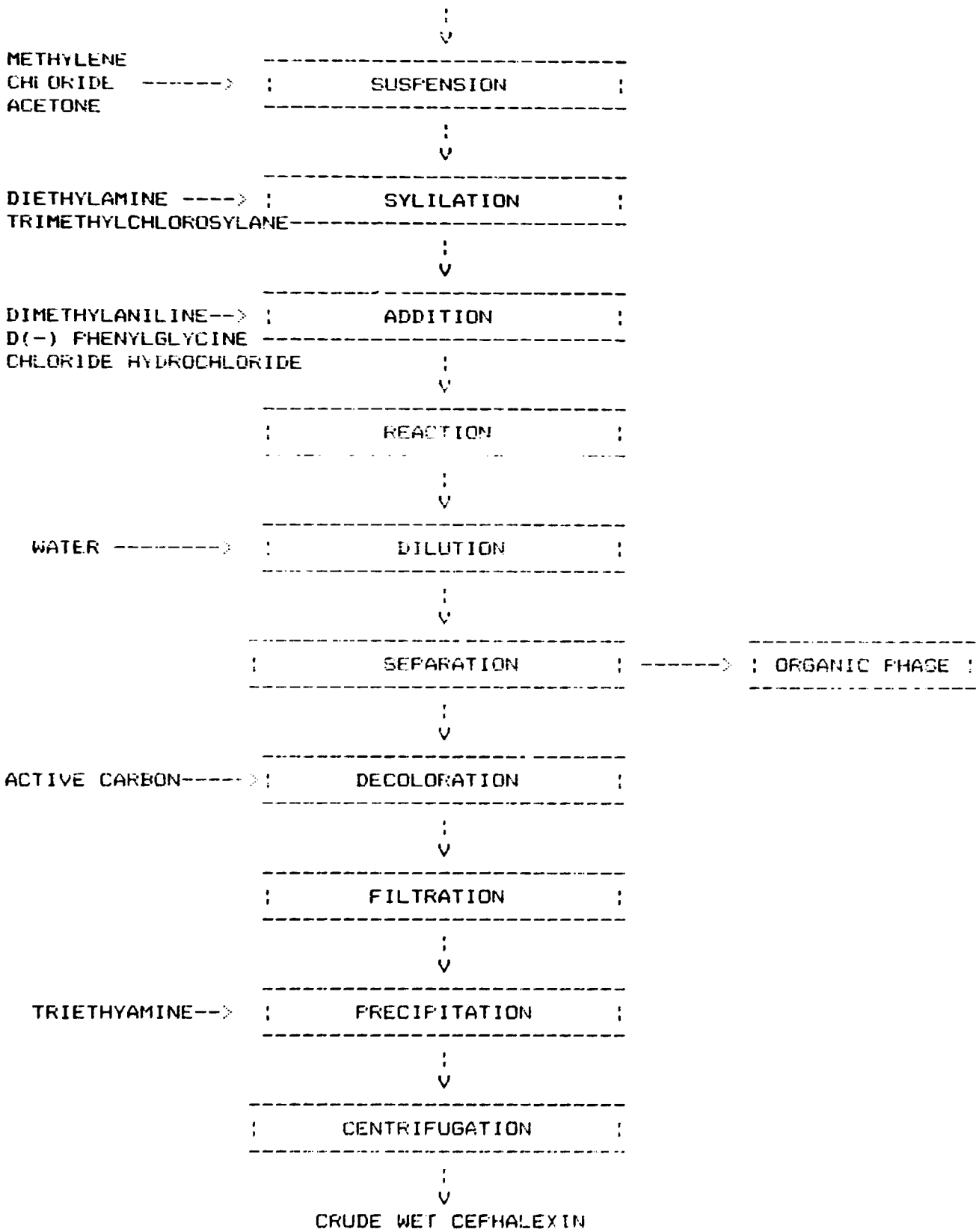
Production plant and equipment list

See 7.9 and 7.10

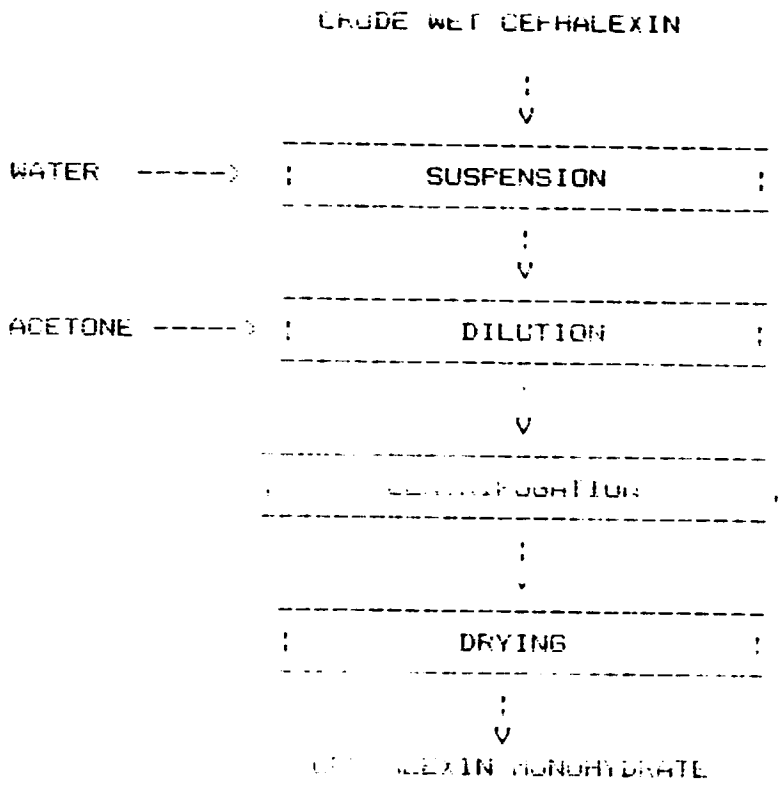
Manpower

See 7.15

CRUDE CEPHALEXIN FLOW CHART



CEPHALEXIN MONOHYDRATE FLOW CHART



7.6 Utilization of the Plant

The data concerning the duration of the operations for the production of the projected products, the number of batches required and the total time of utilization of the plant are as follows.

Product	Output per batch	Duration of each batch	Number of batches	Total working days
Ampicillin trihydrate	300 Kg	36 hours	117	117
Amoxycillin trihydrate	300 Kg	36 hours	100	100
Cloxacillin sodium monohydrate	150 Kg	36 hours	20	20
Cephalexin monohydrate	150 Kg	36 hours	40	40
Dane salt for Amoxycillin	500 Kg	36 hours	56	56

For all these productions the duration of the chemical step is about 15 hours the bottleneck being the drying which last 36 hours. With two driers it is possible to obtain one batch/day. When the plant will reach the full production capacity it will be occupied for the whole year, additional capacity being obtained with an increase of the number of batches by working on three shifts. Working days are globally 284 since the Dane salt is prepared at the same time of other productions using additional equipment.

7.7 Waste Treatment

The processes carried out in this plant produce both solid and liquid wastes. The solid wastes are mainly composed from active carbon containing small quantities of impurities and salts. We suggest that they will be taken away, or burned. The liquid wastes should be neutralized in the plant; they consist mainly of inorganic salts, residues of decomposed antibiotics and some excess of the reagents. By treatment with sodium hydroxide, the beta-lactam nucleus breaks giving rise to inactive products. After neutralization, they are treated with activated sludges in the existing plant of the Chemfields factory. In case its capacity is insufficient, it should be enlarged to cope with the new requirements.

7.8 Location of the Plant

Semisynthetic Penicillins are sophisticated products and beta-lactam antibiotics. For this reason, in order to avoid cross-contamination with other products, they must be produced in a plant devoted only to their production to comply with the " **Good Manufacturing Practice** " rules. Furthermore high technical skills are essential for their production. Since a production of beta-lactam antibiotics is already running in the Chemfields factory and as the technicians employed there are already well acquainted with the technology of semi-synthetic Penicillins, we suggest that the plant should be located in the Chemfields factory, where 5 hectares are available for expansion.
Furthermore, all the technical services (quality control, maintenance, warehouse, administration) and some spare capacity for utilities being already available in the factory, a limited increase of equipment and of people would be necessary to cope with the new needs, meaning a more limited investment. [illegible] costs etc.
Should the expansion be placed in a new factory, the investment would be much higher and roughly [illegible] 1.5-2 times the proposed one so the economics becoming unfavourable.

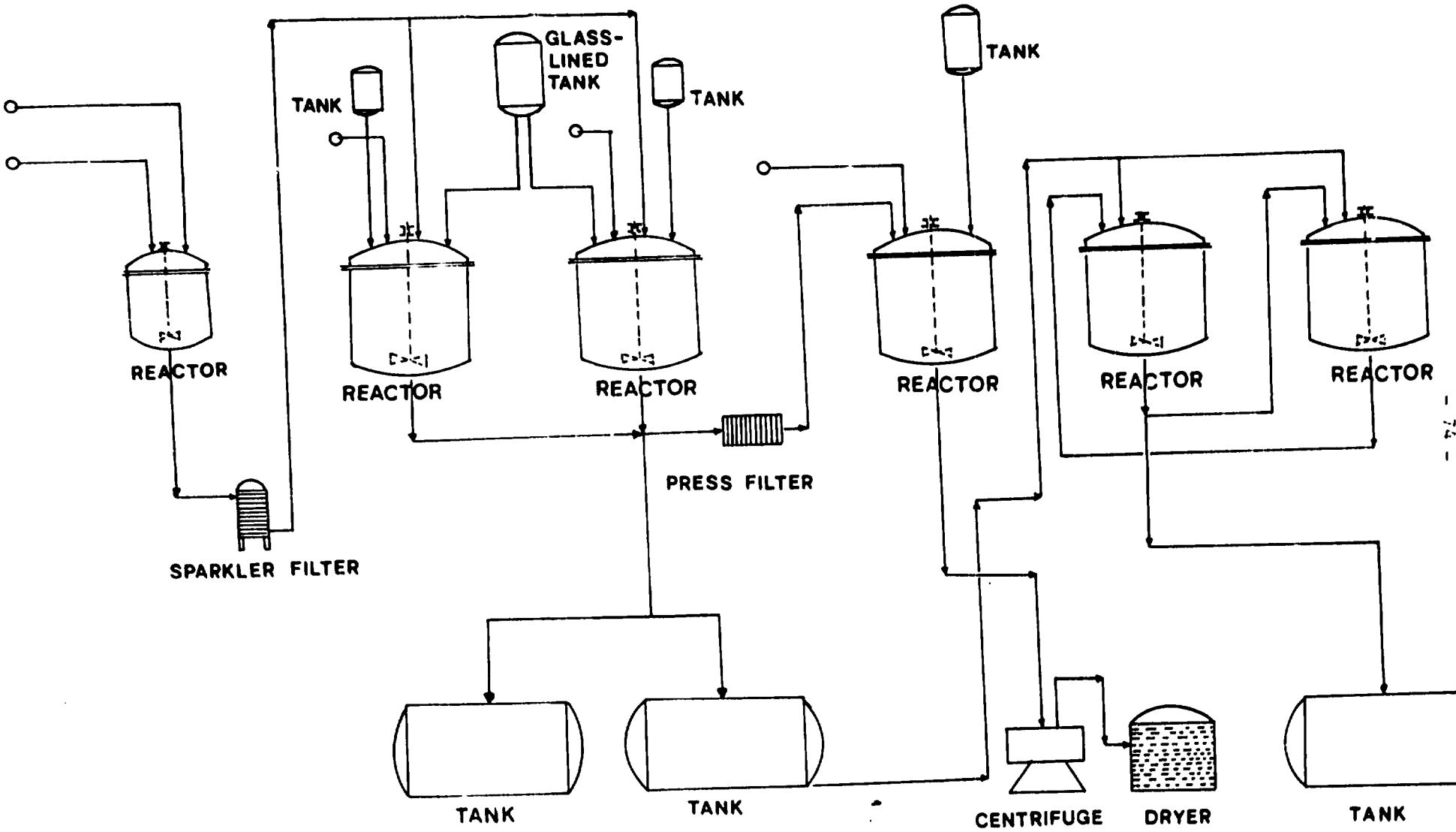
7.9 Description of the Plant

The plant proposed for the preparation of semi-synthetic Penicillins is composed from eight stainless steel reactors ranging from one to five cu.m. capacity, one press and one plate filter, some tanks for mother liquors, two stainless steel centrifuges and two driers. Minor equipment (centrifugal pumps, grinder, sieve etc.,) are also provided. Solvents come from external tanks through metering pumps. The following units for utilities will be required:

- One distillation unit to increase the present capacity of Chemfields taking into account also the recovery needs for the Erythromycin and Rifampicin production plant, which we suggested to be located in the same compound.

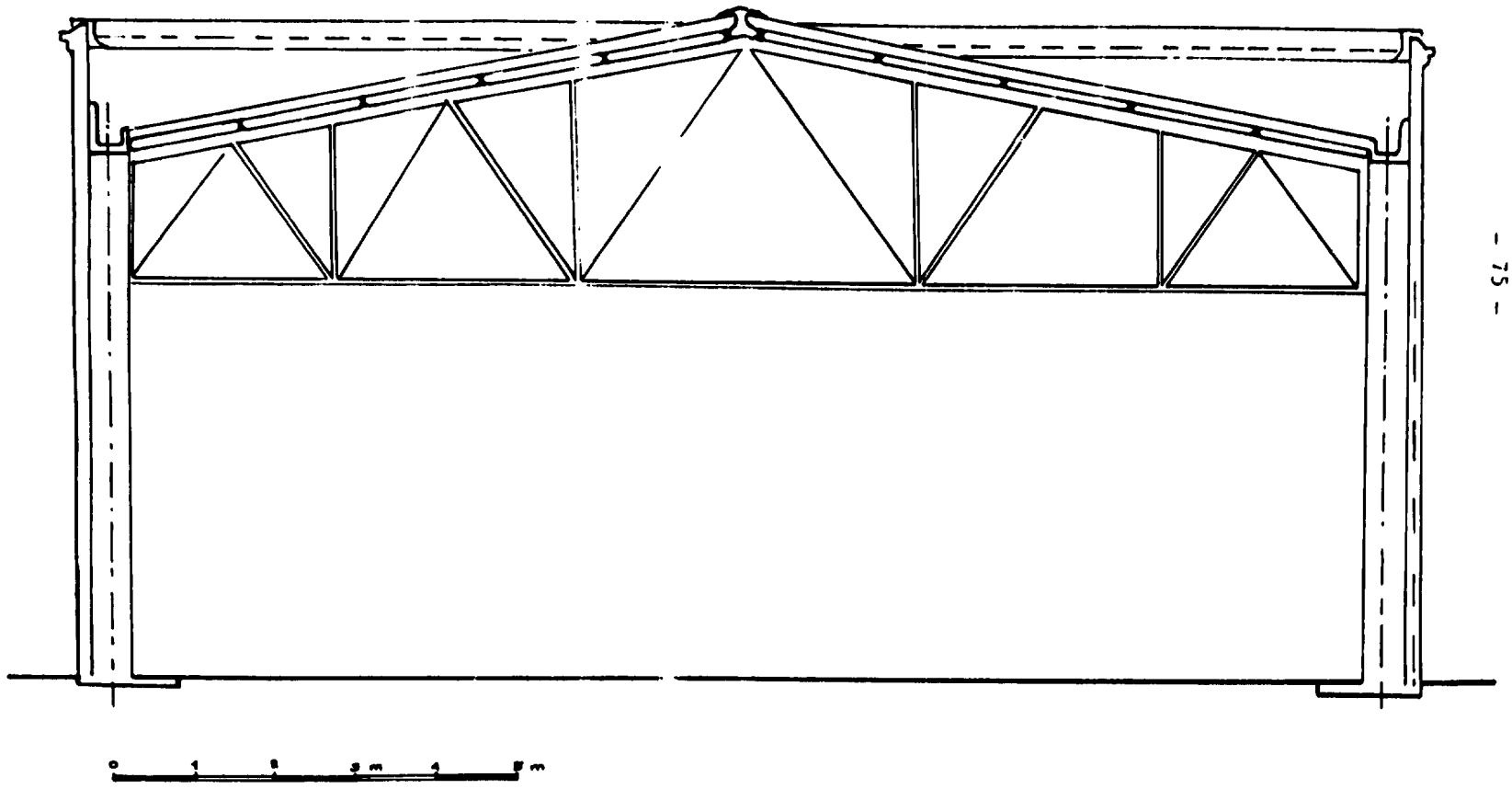
- One refrigeration unit for production of brine at - 30 C, 40 tons capacity
- One unit for demineralized water production
- One boiler for steam production
- One cooling tower for cooling water.

With this plant,working on a three shift basis it is possible to reach a production of more than 100 tons/year.



BETA-LACTAM ANTIBIOTIC PLANT

MANILA – AUGUST, 1988



BETA-LACTAM PRODUCTION UNIT

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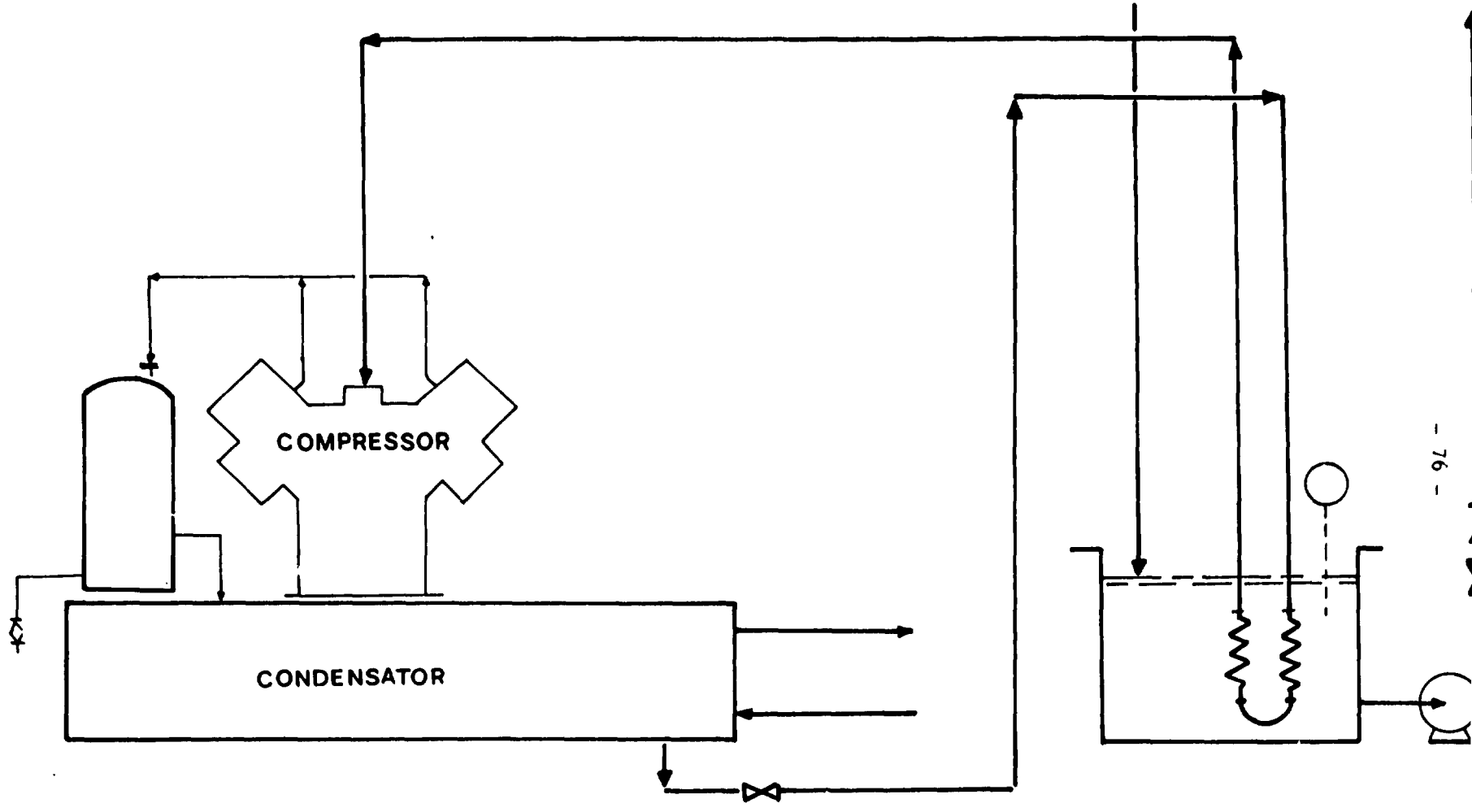
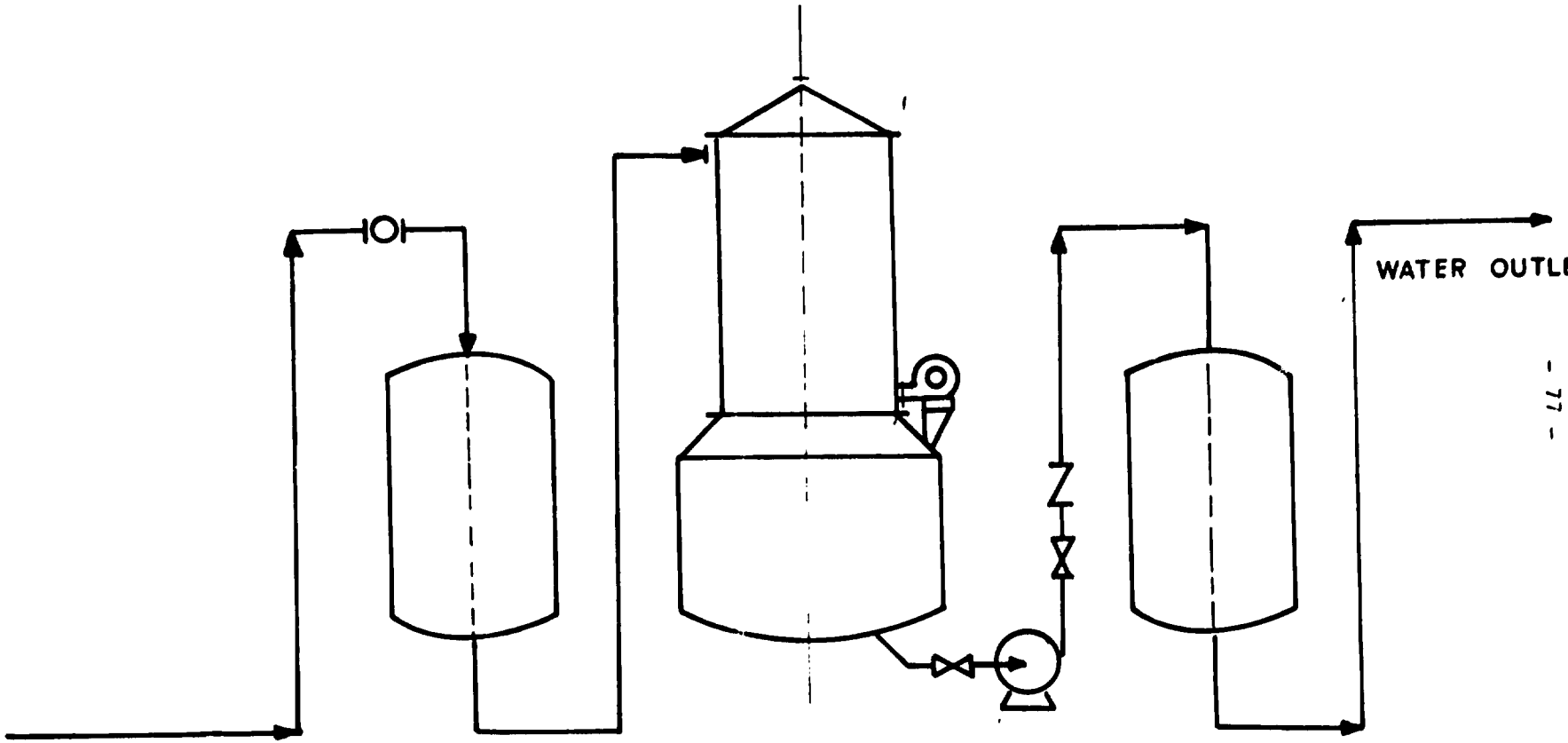


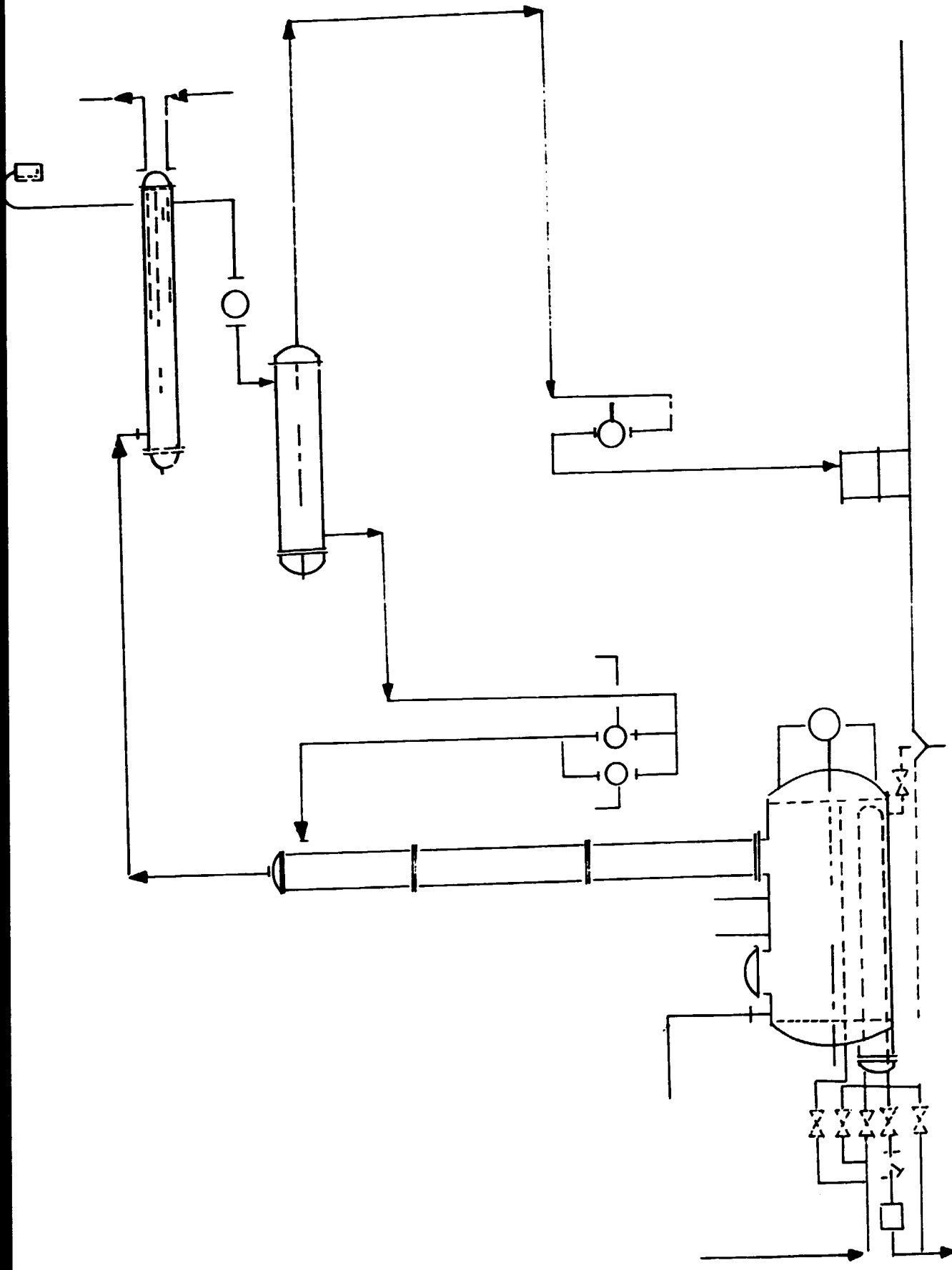
BRINE PRODUCTION UNIT

MANILA – AUGUST, 1988



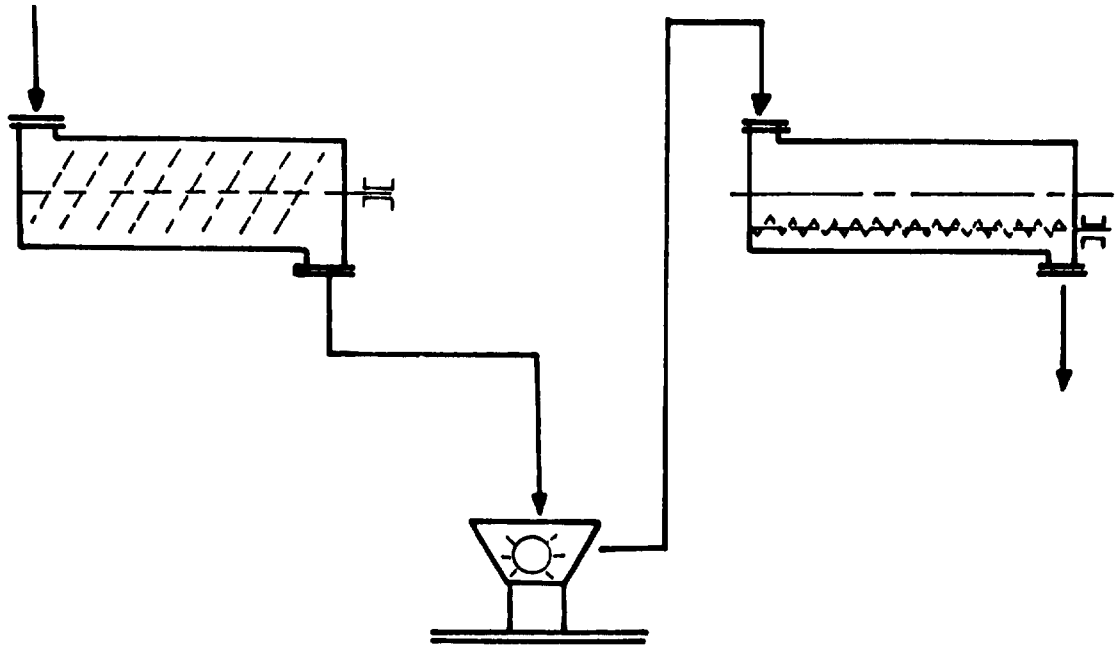
DEMINERALIZED WATER PRODUCTION UNIT

MANILA – AUGUST, 1988



SOLVENT RECOVERY PLANT

MANILA - AUGUST 1988



POWDER DRYING SECTION

MANILA– AUGUST, 1988

7.10 Equipment List

The main equipment needed for the production of semi-synthetic Penicillins and Cephalosporins is as follows.

Equipment	Number	Capacity	Material	Stirrer	Jacket
Reactor	1	2,000 lt	stainless steel	scraper	nitrogen cooling
Reactor	3	5,000 lt	s.s.	turbine	yes
Reactor	2	4,000 lt	s.s.	one anchor one turbine	yes yes
Reactor	1	1,000 lt	s.s.	impeller	yes
Reactor	1	1,000 lt	glass lined		
Tank	2	14,000 lt			
Tank	1	200 lt	s.s.		
Plate filter	1	7 sq.mt.			
Press filter	1	4 sq.mt.			
Centrifuge	2	ø 1500 mm	s.s.		
Fluid bed drier	2	3.5 cu.mt.	s.s.		
Distillation colomn	2		s.s.		
Demineralizer	1				
Refrigeration unit					
Boiler	1				
Cooling tower	1				

Minor equipment is not listed,but it will be considered for the investment. The vacuum insulated evaporator for storage of liquid nitrogen, could be locally rented. (Consolidated Industrial Gases Inc.)

7.11 Locally Available Equipment

In the Philippines, there are some producers in a position to supply stainless steel reactors and tanks. The production of the reactors requires several connections and welding of the stainless steel whereas the production of tanks is less sophisticated. The long term resistance of the local reactors as yet has not been fully proved.

For this reason, we think that tanks could be produced locally, whereas for the reactors it would be more advisable to be imported.

Pipes are locally produced but only in carbon steel and not in stainless steel, as required for the plant. With some exceptions control equipment should be imported. Good engineering companies, locally available, are in a position to prepare the project and to make the detailed engineering. They can also supervise [illegible] and the piping. We suggest that local engineering companies be consulted in case of implementation of the project.

7.12 Type of Utilities

For the production of the projected semi-synthetic Penicillins and Cephalosporins the following utilities should be available:

Steam	at 5 Kg/cm2
Brine	at - 30 C
Deionized water	
Electric power	at 380 V
Liquid nitrogen	

7.13 Buildings

For the production an area of 300 sq.m. for the building is required; the building would consist of two floors; in the upper one are placed, the reactors whereas the lower one houses the centrifuges. The surface of the upper floor should be about 70 sq. mt. The total surface includes the powder area where drying, grinding and sieving is performed, a laboratory for in-process controls, lockers room , W.C. etc. As to the warehouse, a covered air-conditioned building of 300 sq.mt. is required; this building is to be divided into two parts, one for raw materials and one for the finished products. We suggest that civil works should be locally planned and realized, since good

local construction capabilities have been identified. The civil works will have a concrete structure with reinforced concrete columns. It is essential to take into consideration the possibility of earthquakes. The walls will be in bricks and covered in light concrete prefabricated elements or equivalent.

7.14 Quality Control, Engineering Services, Warehouse, Administration.

The new expansion of the plant should take into consideration the new needs for the services from both points on view of equipment and personnel. In this section we will consider the increment of equipment for both plants of semi-synthetic Penicillins and Erytromycin derivatives,(see 7,16)whereas the personnel increment will be considered separately.The additional personnel required could be summarized as follows:

7.14.1 Technical Services

n.1 senior laboratory technician
n.1 inspector for quality control
n.2 laboratory technicians.

7.14.2 Engineering Services

n.1 utilities operator
n.2 mechanics/electrician

7.14.3 Warehouse

n.1 supervisor
n.1 stock clerk
n.3 warehouse aides.

7.14.4 Administration

n.2 clerks

For manpower qualification see 7.15

7.15 Manpower Type and Qualification

The plant will be run on a three shifts basis.

We suggest that the following manpower should be available:

n.1 plant manager
n.4 supervisors
n.8 senior production technicians
n.12 production technicians
n.6 production aides.

As to the qualification of manpower our suggestions are:

- The plant manager should have a master degree in chemistry, experience in running a plant and management capabilities. If not locally available we suggest that for a certain period of time (minimum one year) he should be flanked by one expatriate to gain experience in managing a chemical plant.

- The supervisor should have a masters degree in chemistry and technical experience in running a chemical plant. This experience could be gained by working in the Chemfields plant for instance. If an experienced one is not available, a master degree should be trained by working for a period of six months to one year in a fine chemicals plant abroad.

- The senior production technicians should have a [illegible] degree in chemistry and would have gained some practical experience in a fine chemical [illegible] if not available they should be trained for a period (six months) or at Chemfields plant or better abroad in a fine chemicals producing plant.

- The production technicians should have a bachelor degree in chemistry; for them a more limited experience is required since they will work together with the senior production technicians and could gain experience locally.

- For the production aides no previous experience is required.

The additional man power for the technical services department (see 7.14) should possess the following qualifications:

- The senior laboratory technicians should have a master degree in chemistry and a specialization in analytical chemistry with experience in the use of modern techniques such as gas chromatography, U.V. spectroscopy, HPLC. If the experience required is not available they should be trained for three-four months in the analytical department of a reputed Pharmaceutical Company.

- The Quality Control Inspector should have a master degree in chemistry and be familiar with the quality control procedures. If an experienced one is not available he should be trained for a six months period in the quality control department of a reputed Pharmaceutical Company.

- The laboratory technicians should have a bachelor degree in chemistry and some experience in chemical syntheses. If not available they might be trained in the Chemfields laboratory for synthesis.

The additional manpower for the engineering department (see 7.14) should possess the following qualification:

The utilities operator should have some knowledge of the use and regulation of the various utilities; he could be trained locally.The mechanic/electrician are qualified workers who might be locally available.
The additional manpower for the warehouse and the administration is locally available and could be hired without difficulty.

7.16 Investments

The investments reported, hereunder have been calculated to give only an idea of the order of magnitude of the investment. The reported figures do not include the land cost. The investment for the utilities (refrigeration unit, cooling tower, boiler, demineralizer, distillation columns) take into account also the utilities needed for the the Erythromycin and Rifampicin plant which will be located in the same factory. Some spare capacity being already available in the Chemfields plant for some utilities, the capacity to be installed will be lower than the total capacity required.

The investment is estimated at:(in US $)

Plant

Plant	2,350,000
Equipment (transportation included)	
Erection (piping, mounting, electrical parts, instrumentation, insulation, paintings etc.)	2,350,000
Engineering 7%	330,000
Assistance to the erection 7%	330,000
Cost of technology	165,000
Training of personnel	100,000
Laboratory equipment (additional)	120,000
Buildings	
Main building	70,000
Warehouse (air conditioned)	85,000
T o t a l	5,900,000

Since a satisfactory technology for Ampicillin, Amoxycillin and Cloxacillin is already available in the country, the cost of technology includes only Cephalexin. We assume that the import of machinery and equipment for the new plant will be exempt of import duties and taxes.

7.17 Production Cost

For the evaluation of the cost of production, two different options are taken into consideration for Ampicillin, Amoxycillin, and Cloxacillin (antibiotics derived from 6-APA).

1. the use imported 6-APA (at 65 $, 10% freight, insurance, etc. included)
2. the use of 6-APA produced locally.

For the calculation of the production costs we assume that the plant will be operating at full capacity to be probably reached three years after the start-up.

The raw materials cost includes freight, ins... and other expenses evaluated at about 10% of the cost.

The production costs include raw materials, utilities, manpower and general expenses (in US $)

Ampicillin (with imported 6-APA)	71
With 6-APA produced locally	62
Amoxycillin (with imported 6-APA)	76
With 6-APA produced locally	44
Dane Salt	22
Cloxacillin (with imported 6-APA)	70
With 6- APA produced locally	62
Cephalexin	149

For the calculation of the manpower, we have used a simplified criterion: the total amount of manpower cost for one year considering 1) a 13 month salary and 2) that cost to the company is the double of the salary received by the employee) was divided by the total output of the plant at full capacity to obtain the man-power incidence per Kg. of antibiotic produced. In this calculation, the Dane Salt was not considered; its production being simple and the batch quantity being large, we have assumed a manpower incidence of 0.5 /Kg ; this value take into consideration some elements which could have not been considered in the calculation of the total cost of manpower. General Expenses are globally estimated at US $ 180,000, a rather conservative evaluation which includes the incremental auxilliary services such as quality control, engineering services, warehouse,administration etc.

For the raw materials we have assumed that they are imported exempt of customs duties and taxes.

7.18 Economic Considerations

In the Philippines like in the other developing countries, in order to stimulate new investment in this field,it is advisable that incentives should be granted to improve the economics of the different projects.

Among the various incentives which could be granted, three are especially connected with the manufacturing cost and the selling prices of the locally manufactured product:

1. Exemption of import duties on machinery, equipment and raw materials
2. Tariff protection
3. Income tax exemptions

We suggest that these incentives should be granted for the new potential bulk pharmaceutical production, also because it is of strategical importance for the health situation of the country.

In the following economical considerations we make the following assumptions:

1.) a tariff protection will be granted
2.) a tax exemption will be granted
3.) income tax exemption will be granted

As to the depreciation, we assumed it as a straight line one for a 10 years period, for both equipment and buildings(1).

As a first approximation we have calculated the depreciation per kilogram by dividing the annual depreciation by the quantity produced at full capacity, that is 74 tons. For the semi-synthetic Penicillin plant the incidence per Kg results to be 8 US $ / Kg.

The production cost, including depreciation will be:
($ per Kg.)

Ampicillin	(with imported 6-APA)	79
	(with local 6-APA)	70
Amoxycillin	(with imported 6-APA)	84
	(with local 6-APA)	74
Cloxacillin	(with imported 6-APA)	78
	(with local 6-APA)	70
Cephalexin		157

(1) Although buildings could be depreciated for 20 years, due to the relatively small value, we have left all at 10 years.

The present international market prices (2) are (in US $):

Ampicillin	70-75
Amoxycillin	85-90
Cloxacillin	90-95
Cephalexin	180-190

The present selling prices of Chemfields are (per kg.): (3)

	in Pesos	in US $
Ampicillin	2200	104
Amoxycillin (to the Government)	2250	107
(to private Companies)	2750	131
Cloxacillin	3000	143

The economic calculation which follows take into account the quantities representing the production at full capacity:

Ampicillin	35 tons
Amoxycillin	30 tons
Cloxacillin	3 tons
Cephalexin	6 tons
Total	74 tons

(2) 1968 Prices
(3) Exchange rate at 1 US $ = 21 P

In the following table we report some figures concerning the production cost, the sales value with different hypotheses and the corresponding profits.

We have considered the following sales prices for comparative purposes:

1. The products are sold at the international prices plus 20 % which includes freight, insurance, custom duties and the value added taxes.

2. The products are sold 10 % higher than the international prices, assuming that a 10% advantage would be applied.

3. The products are sold 20 % higher than the international prices, assuming that a 20% advantage would be applied.

4. The products are sold at the present Chemfields selling prices.

For Amoxycillin:
under A)
- the price applied to the Government Institutions
and under B)
- the price applied to the private sector.

The total yearly gross profits are also reported.

COST, SALES AND GROSS PROFIT WITH IMPORTED 6-APA AND 7-ADCA

	Ampicillin		Amoxycillin	Cloxacillin	Cephalexin	TOTAL
Total Production cost ($ x 000)	2,765		2,520	234	942	6,461
1)Sales ($ x 000)	2,940 (70$+20%)		3,060 (85$+20%)	324 (90$+20%)	1,296 (180$+20%)	7,620
Profit	175		540	90	354	1,159
2)Sales (+10 % on international prices) ($ x 000)	3,185 (70$+30%)		3,315 (85$+30%)	351 (90$+30%)	1,404 (180$+30%)	8,255
Profit	420		795	117	462	1,794
3)Sales (+20 % on international prices) ($ x 000)	3,430 (70$+40%)		3,570 (85$+40%)	378 (90$+40%)	1,512 (180$+40%)	8,890
Profit	665		1,050	144	576	2,429
4)Sales at Chemfields Selling price	3,640 (104$)	A)	3,210 (107$)	429 (143$)	1,296 $ (180$+20%)	A) 8,575
		B)	3,930 (131$)			B) 9,295
Profit	875	A)	690	195	354	A) 2,114
		B)	1,410			B) 2,834

$ International Prices

From these figures the estimated profit on sales could be as follows:

Hypothesis 1 15.2%

Hypothesis 2 21,7%

Hyphotesis 3 27.3%

Hypothesis 4 27.7% (50 % of the production sold to the Government)

The corresponding pay-back periods are:

Hypothesis 1 5.1 years

Hypothesis 2 3.3 years

Hypothesis 3 2.4 years

Hypothesis 4 2.4 years

The above calculatiosn have been elaborated to give a rough indication of the economics of the project. A more in-depth analysis should be initiated.

We stress again the fact that the preliminary calculations are based on the following assumptions:

- the machinery and equipment are imported, exempt of taxes and tariff duties
- The raw materials are imported exempt of taxes and tariff duties
- the plant operates at full capacity
- The imported Ampicillin, Amoxicillin, Clo[illegible] and Cephalexin are subject to customs duties and income taxes

We suggest that the government should take a commitment to buy a part of the production for all the corresponding antibiotics purchased for the RHUs.

- In hypothesis 2 and 3 a 10 or 20% advantage on selling prices is given to the local production.

Calculations based on the assumption of local production of 6-APA will be dealt with in the report of the Expert in fermentation and will be based on the above reported figures for productions costs, investments and market prices.

In annex one some more economics on the semi-synthetic Penicillins are reported.

8. THE 6-AMINOPENICILLANIC ACID (6-APA) PRODUCING PLANT

This plant, included in the list of the proposed options, should be implemented only in case the option concerning the Penicillin fermentation plant is carried on.

The main use of Penicillin G or V according to this project, is to produce 6-APA to provide enough starting material for the local production of semi-synthetic Penicillins with significant economies. The projected output of the plant at full capacity will be 110 tons per year of 6-APA.
The technology should be supplied together with the ones concerning Penicillin fermentation and recovery.

8.1 6-Aminopenicillanic acid (6-APA)

6-APA is the starting material for the production of semi-synthetic Penicillins and in particular, according to one of the proposed options, of Ampicillin, Amoxycillin and Cloxacillin.

It is amphoteric having in the molecule a carboxylic and an amino group. Its formula is:

$$C_8H_{12}N_2O_3S$$

m.w. 216.28

6-APA is prepared by chemical or enzymatical splitting of the amide group of Penicillin G or V with removal of the side chain.

$$\underset{\text{PENICILLIN G}}{C_6H_5CH_2CO\text{-}NH\,C_8H_{11}NO_3S} \xrightarrow{H_2O} \underset{\text{PHENYLACETIC ACID}}{C_6H_5CH_2COOH} + \underset{\text{6-APA}}{C_8H_{12}N_2O_3S}$$

The proposed method is the enzymatic one which is the more economical.

Determination of the daily output

For the production of 110 tons in 260 working days, a 425 kg daily output is needed. This output will be obtained in three batches per day, each batch being of 142 kg.

Principle of Method

Splitting of the side chain of Penicillin G with supported enzymes.

Description of the Method

Penicillin G is suspended in deionized water, brought into solution by addition of alkali and the solution transferred into a reactor containing the supported enzyme; under stirring the reaction is carried on with continuous addition of alkali to control the Ph value. When the reaction is over the enzyme is filtered, methylisobutylketone is added, the Ph modified by addition of acids and the precipitated 6-APA filtered, washed with acetone and dried. From the mother liquors phenylacetic acid is recovered.

Yields

Theoretical yield	93%
Weight yield	54%

Raw Materials

Hereunder are the list of the main raw materials for one batch of 142 kg and the corresponding quantities for one kg of 6-APA.

A 80% recovery yield for butylacetate and 70% for acetone is considered.

Potassium Penicillin G		263 kg		1.85 kg
Supported enzyme(1)		263 kg		1.85 kg
Acetone	(120 kg)	37 kg	(0.84 kg)	0.26 kg
Butylacetate	(210 kg)	43 kg	(1.48 kg)	0.30 kg
Alkali				
Acids				

---

(1) The supported enzyme loses some activity during each batch. The total quantity of the supported enzyme consumption is three to four Kg. per ton of 6-APA produced.

Utilities for one batch of 142 kg

Electric power	900 kwh
Steam	10^5 Kcal

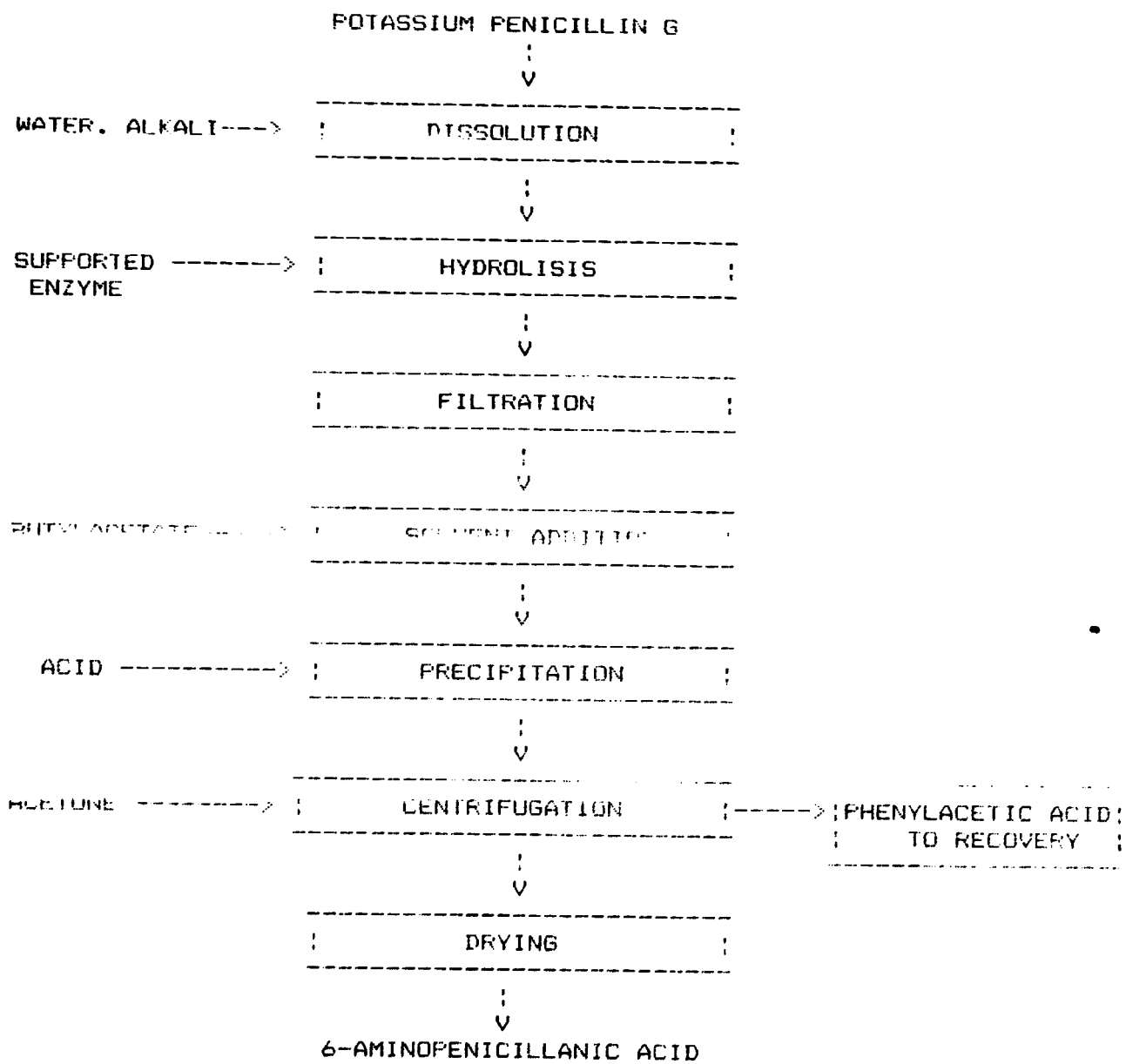
Production plant and equipment list

See 8.4 and 8.5

Manpower

See 8.10

6-AMINOPENICILLANIC ACID FLOW CHART



8.2 Waste Treatment

Wastes from the plant are essentially liquid wastes. They will be trated together with the main liquid effluents from the Penicillin production plant.

8.3 LOCATION OF THE PLANT

The plant for 6-APA production should be located near the fermentation plant for the production of Penicillins.

The main reasons are:

1) being a beta-lactam product it must be isolated from other chemical productions for cross-contamination reasons to fit the **"Good Manufacturing Practice"** rules.

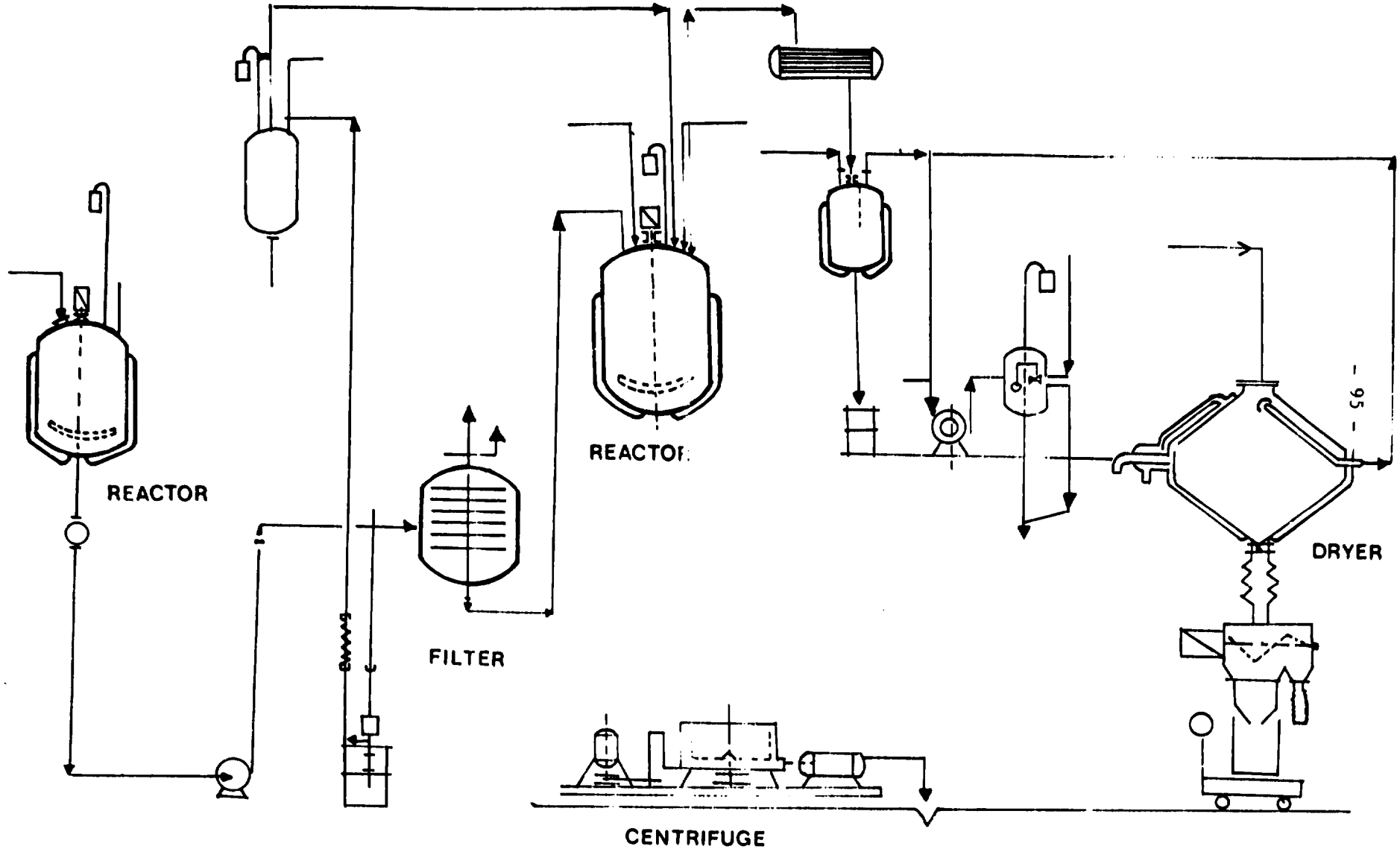
2) The starting material for its preparation being Penicillin G or V, the location of the 6-APA plant in the same place where Penicillins are produced avoid transportation to other plants and simplify the burocratic procedures.

3) The butylacetate extract contains phyenylacetic acid (from Penicillin G) or phenoxyacetic acid (from Penicillin V). These valuable intermediates could be directly recovered whithout previous isolation.

4) The solvent for extraction is the one used for Penicillin extraction; it can be added for recovery to butylacetate from the Penicillin recovery and the same tanks could be used, avoiding the need for different ones.

8.4 Description of the Plant

The proposed plant consists essentially of one reactor for the dissolution of Penicillin, one reactor for the enzymatic hydrolysis and two crystallizers. The isolation of 6-APA is carried out by centrifugation. Some tanks for acid and alkali addition, as well as a drier and a grinder are needed together with some minor equipment. Solvent come from external tanks through metering pumps. The utilities, would be those used in the fermentation plant.



MANILA - AUGUST, 1988

6-APA PRODUCING PLANT

8.5 Equipment List

The main equipment needed for the production of 6-APA is as follows:

Equipment	Number	Capacity	Material	Stirrer	Jacket
Reactor	1	2,000 lt	stainless steel	impeller	
Reactor	1	3,000 lt	s.s.	scraper	yes
Reactor	2	8,000 lt	s.s.	scraper	
Tank	2	15,000 lt	s.s.		
Filter	1		s.s.		
Centrifuge	1	1200 mm	s.s.		
Fluid bed drier	1	500 lt capacity			

8.6 Locally Available Equipment

see 7.11

8.7 Type of Utilities

For the production of 6-APA the following utilities are requested:

Demineralized water

Brine at -30 C

Steam at 5 Kg/cm2

Electric power at 380 V

8.8 Buildings

The production unit will be located in the same building where the recovery of Penicillin takes place. (See the fermentation Expert's report)

8.9 Quality Control, Engineering Services, Warehouse, Administration

The 6-APA production requires the following increase of the personnel already available in the Penicillin production plant.

8.9.1 Technical Services:

n. 1 analyst
n. 1 laboratory technician

8.9.2 Warehouse :

n. 2 warehouse aides

8.9.3 Administration:

n. 1 clerk

As to the other services, the already existing manpower could face all the needs.

For the manpower qualification see 7.15

8.10 Manpower, Type and Qualification

The plant will be run on a three shifts basis.

We suggest the following manpower:

n. 4 supervisors
n. 4 senior production technicians
n. 4 production technicians
n. 4 production aides

For the qualifications of the manpower see /.15

8.11 Investment

The investments reported hereunder have been calculated to give only an idea of the order of magnitude. The figures do not include buildings, since the plant will be located in the same building where the recovery of Penicillin takes place. We do not consider investments for the utilities, since they constitute only a small part of the ones used for the Penicillin production and as they are included in the

investment for Penicillin.

The investments are estimated as follows:

	(in US $)
Equipment	730,000
Erection (piping, mounting, electrical parts, instrumentation,insulation,painting,etc.)	730,000
Engineering 7%	35,000
Assistance to the erection 7%	35,000
T o t a l	1,530,000

In the investment we have not taken into account, the cost of technolog and the training of personnel which would be included in the investment for the Penicillin plant. We assume that the import of machinery and equipment for the new plant is exempt of customs duties and taxes.

8.12 Production Cost

The local production of 6-APA from Penicillin could be interesting only if a Penicillin production is started in the Philippines. For this reason the evaluation is made using the production cost of Penicillin which could be reached in case of local production. The production cost results to be 56 US $/Kg including raw materials, utilities, manpower, and general expenses.
The present market price for 6-APA is around 60 % / Kg.

The raw materials costs include freight, insurance and other expenses evaluated at about 10% of the cost.

For the calculation of the manpower incidence, we have used the criterion indicated at point 7.17.
General expenses are globally estimated at 110,000 US$, contributing to the total amount of general expenses of the Penicillin production plant.
We evaluate this figure conservative to include the incremental auxillary services such as quality control, engineering services, warehouse, administration etc. devoted to 6-APA production.
As to the raw materials we assume that they are imported, exempt of custom duties and taxes.

8.13 Economic Considerations

Calculations based on the assumption of local production of 6-APA will be dealt with in the report of the Expert in fermentation and will be based on the above reported figures for production costs, investments and market prices.
As to the depreciation, assuming it has a straight line for a ten years period, by dividing the yearly depreciation by the annual production at full capacity, it results to be 1.5 $ / Kg.; the 6-APA cost including depreciation results to be about 58 $.

9. THE ERYTHROMYCIN DERIVATIVES AND RIFAMPICIN PRODUCTION PLANT

The purpose of the proposed plant is to transform Erythromycin base which could be produced according to one option in a multipurpose fermentation plant, into the derivatives stearate and ethylsuccinate, which are the most common derivatives used in the medical practice together with the free base.

We do not take into consideration the estolate because only one multinational company is selling this product as specialty but will consider the thiocyanate which is used only in the veterinary field with a not very high consumption but still of some interest.

Another option could be the production of Erythromycin derivatives starting from imported Erythromycin base in case the project for its local production is not implemented or before the start-up of the fermentation plant. In this case the margin will be lower but it has the advantage to train people in this new technology.

The other antibiotic which will be produced in the plant is Rifampicin using as a starting material 8-formylrifamycinSV; should Rifamycin B be produced in the multipurpose fermentation plant, the chemical production of 8-formyl-rifamycin SV from Rifamycin B should be examined in detail.

At the beginning, in the period in which locally made Rifampicin is not yet available, we propose its production from an advanced intermediate, 8-formyl-rifamycin SV, available in some countries like China etc., in order to be acquainted with the production and gain some experience with the chemistry of this expensive antibiotic.

The different antibiotics will be produced in successive cycles e.g. three months Erythromycin stearate, two months ethysuccinate etc. The production program will be prepared according to the market requirements.

All these technologies are not presently available in the Philippines and should be obtained from external sources.

9.1 Output of the Production Plant

The proposed plant consists essentially of two reactors, the larger having a capacity of 4,000 and the other one of 15000 liters.
With such reactors the output of each batch will be :

Erythromycin stearate:	125 Kg.
Erythromycin ethylsuccinate:	165 Kg.
Erythromycin thiocyanate	165 Kg.
Rifampicin	330 Kg.

9.2 Erythromycin Derivatives

The projected quantities of Erythromycin derivatives are 25 tons per year. We propose the following subdivision into the three derivatives:

Erythromycin stearate	11 tons
Erythromycin ethylsuccinate	11 tons
Erythromycin thiocyanate	3 tons

In case of need it is possible to shift from one product to another, the total yearly production not being affected.

9.3 Erythromycin Stearate

Erythromycin stearate is a derivative of Erythromycin, used in the pharmaceutical solid forms (tablets). The structure of Erythromycin consists of a large ring (erytronolide) to which one sugar (cladinose) and one aminosugar (desosamine) are attached: it belongs to the family of macrolides (large ring) antibiotics; the stearic moiety salifies the amino group the structure being:

$$C_{37}H_{67}NO_{13} \cdot CH_3(CH_2)_{16}COOH$$

m.w. 1018.39

Determination of the Number of Batches

For the projected plant, the batch dimension will be 125 Kg. The producion of 11 tons requires 88 batches.

Principle of the Method

Salification of Erythromycin with stearic acid.

Description of the Method

Erythromycin base is dissolved in acetone and stearic acid is added. After treatment with activated carbon, the Eryhtromycin stearate is precipitated with water, isolated by centrifugation, washed and dried.

Yields

Theoretical yield	92.6 %
Weight yield	126.0 %

Raw Materials

Hereunder are listed the main raw materials needed for one batch of 125 Kg. and the corresponding quantities for one Kg. A 60% recovery yield for acetone is considered.

Erythromycin base		99 Kg		0.79 Kg
Acetone	(320 Kg.)	125 Kg	(2.56 Kg)	1.00 Kg
Stearic Acid		44 Kg		0.35 Kg
Activated carbon		2 Kg.		0.016 Kg

Main Utilities for a 125 Kg Batch

Electric power	275 Kwh
Steam	1.3 x 106 Kcal

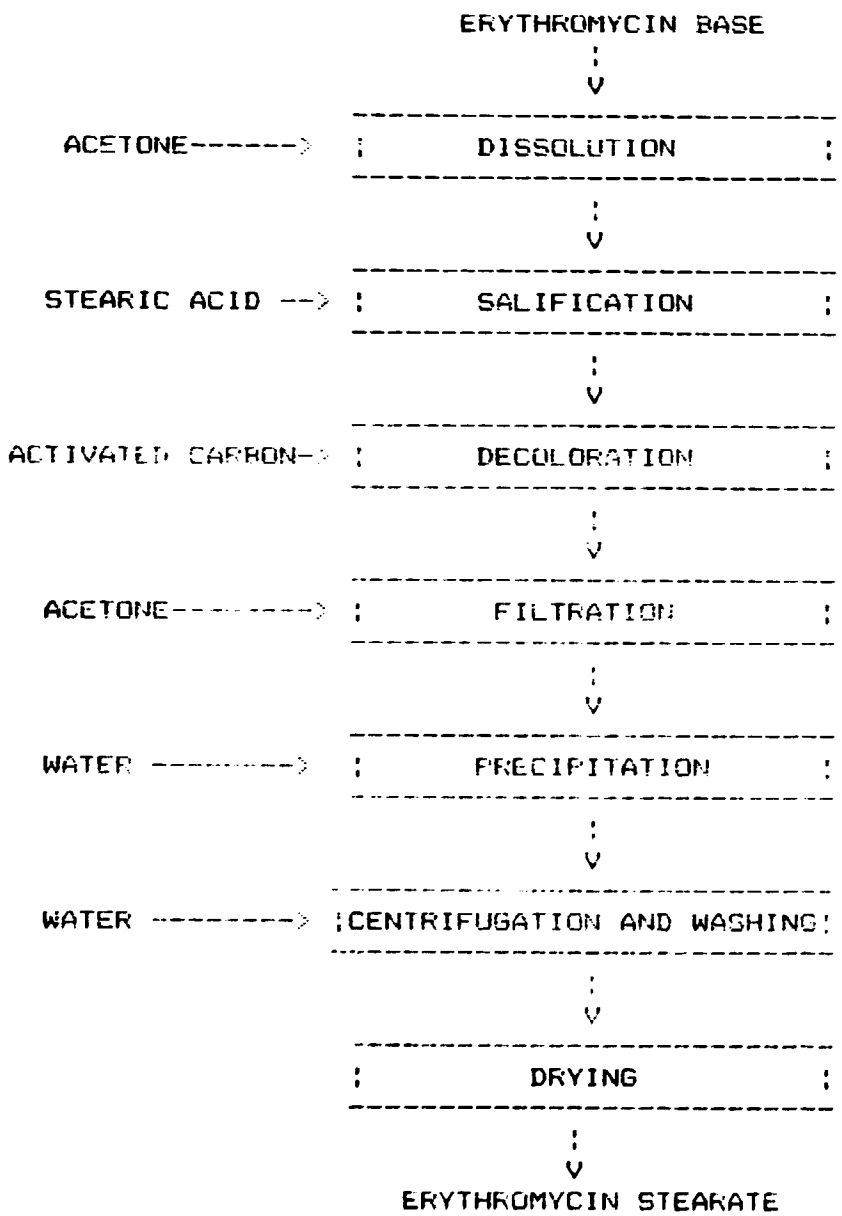
Production Plant and Equipment List

See 9.10 and 9.11

Manpower

see 9.16

ERYTHROMYCIN STEARATE FLOW CHART



9.4 Erythromycin Ethylsuccinate

Erythromycin ethylsuccinate is an ester derived from Erythromycin, its main use being in the pharmaceutical liquid forms (suspensions). The structure of Erythromycin consists of a large ring (erytronolide) to which one sugar (cladinose) and one aminosugar (desosamine) are attached; it belongs to the family of macrolide (large ring) antibiotics. The ethysuccinoyl moiety esterfying one hydroxy group, its structure being:

$$C_{37}H_{66}NO_{12}\text{--}O\ CO\ \text{-}(\ CH_2)_2\ \text{-}\ COOC_2H_5$$

m.w. 862.06

Determination of the Number of Batches

For the projected plant the batch dimension will be 165 Kg. The production of 11 tons requires 67 batches.

Principle of the Method

Esterification of Erithromycin with Ethylsuccinoyl chloride

Description of the Method

The Erythromycin base is dissolved in acetone and treated with ethylsuccinoyl chloride in the presence of alkali. After filtration of salts formed in the reaction, the Erythromycin ethylsuccinate is precipitated with water and isolated by centrifugation. The purification is effected by suspension in aqueous acetone, followed by isolation of the product by centrifugation, washing and drying.

Yields

Theoretical yield	72 %
Weight yield	85 %

Raw Materials

Hereunder are listed the main raw materials needed for one batch of 165 Kg. and the corresponding quantities for one Kg. A 60 % recovery yield for acetone is considered.

Erythromycin base		194 K	1.18 Kg
Ethylsuccinoyl chloride		53 Kg	0.32 Kg
Acetone	(750 Kg)	300 Kg	1.80 Kg
Alkali		112 Kg	0.68 Kg

Main Utilities for a 165 Kg. Batch

Electric power	150 Kwh
Steam	1.6×10^6 Kcal

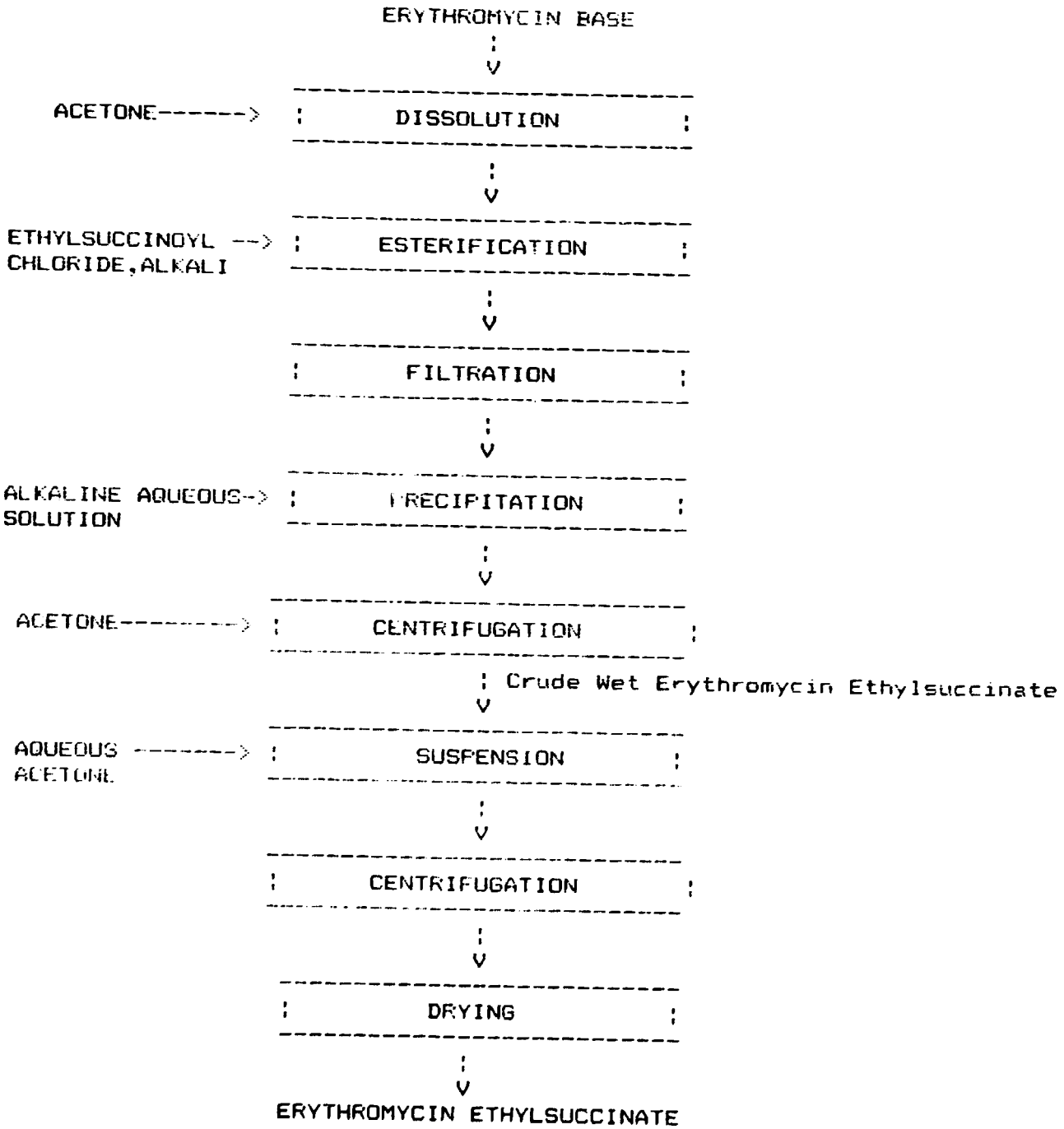
Production Plant and Equipment List

see 9.10 and 9.11

Manpower

see 9.16

ERYTHROMYCIN ETHYLSUCCINATE FLOW CHART



9.5 Erythromycin Thiocyanate

Erythromycin thiocyanate is a derivative of Erythromycin which is mainly used in the veterinary field. In this derivative the aminogroup of desosamine is salified with thiocyanic acid, its structure being:

$$C_{37}H_{67}NO_{13} \cdot HSCN$$

m.w. 793.04

In some recovery processes, Erhytromycin is isolated as the thiocyanate thus this salt being the less expensive derivative available. The recovery process proposed by the Expert in fermentation is different since the base is the first product to be isolated.

Determination of the Number of Batches

For the projected plant the batch dimension will be 165 Kg. The production of 3 tons requires 18 batches.

Principle of the Method

Salification of Erythromycin with potassium thiocyanate.

Description of the Method

The Erythromycin base is dissolved in an aqueous solvent and the salt is precipitated by addition of an aqueous solution of potassium thiocyanate. Water is added and Erythromycin thiocyanate is isolated by centrifugation, washed and dried.

Yields

Theoretical yield	95 %
Weight yield	100 %

Raw Materials

Hereunder are the list of the main raw materials needed for the production of 165 Kg. and the corresponding quantities for one Kg.
A 60 % recovery yield for the solvent is considered.

Erytromycin base		165 Kg		1.0 Kg
Potassium thiocyanate		24 Kg		0.145 Kg
Solvent	(600 Kg)	250 Kg	(3.6 Kg)	1.5 Kg

Main Utilities for a 165 Kg Batch

Electric power	320 Kwh
Steam	10^6 Kcal

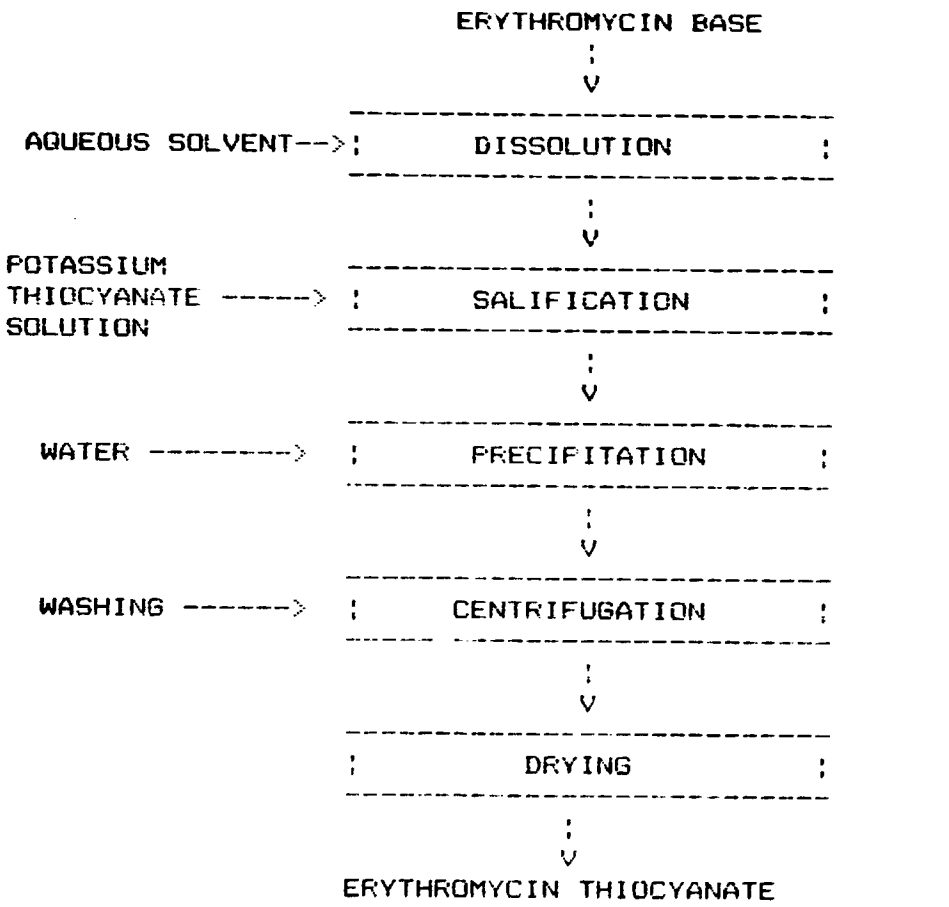
Production Plant and Equipment List

see 9.10 and 9.11

Manpower

see 9.16

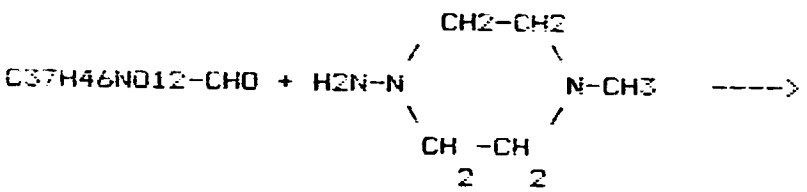
ERYTHROMYCIN THIOCYANATE FLOW CHART

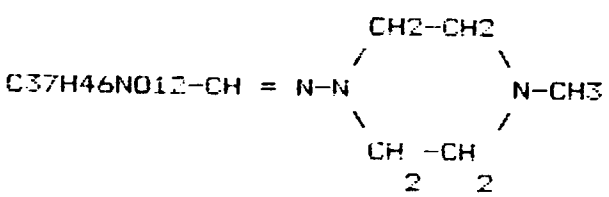


9.6 Rifampicin

Rifampicin is a semi-synthetic antibiotic derived from Rifamicin B through Rifamicin SV and the corresponding 8-formyl derivative. Its synthesis from Rifamicin B includes seven difficult steps the last one being the formation of the Schiff base between 8-formyl-rifamycin SV and 1-methyl-4-aminopiperazine.

The partial formulas for this step are the following evidentiating only the functional groups involved:





C43H58N4O12

m.w. 822.96

According to one option, Rifamycin B could be produced in a multipurpose fermentation plant.Since Rifamycin B option is a long term one, we suggest that at least a partial synthesis of Rifampicin should be taken into consideration in the short term.

The advatages of such an option are:

1. to start being acquainted with the chemistry of the product
2. to achieve some economies
3. to save on foreign exchange

In this section the production of Rifampicin from 8-formyl-rifamycin SV is described.

Determination of the Number of Batches

For the project plant, the batch dimension will

be 330 Kg. The production of 20 tons requires 61 batches.

Principle of the Method

Condensation of 8-formyl-rifamycin SV with 1-methyl-4-aminopiperazine.

Description of the Method

8-formyl-rifamycin SV is dissolved in acetone-ethylacetate and 1-methyl-4-aminopiperazine is added. After the reaction has taken place, the resulting solution is slowly introduced into a mixture of acetone-ethylacetate and the resulting suspension is slowly cooled to complete the precipitation of Rifampicin, which is isolated by centrifugation, washed and dried.

Yields

Theoretical yield	93 %
Weight yield	102 %

Raw Materials

Hereunder are the list of the main raw materials needed for the production of 330 Kg and the corresponding quantities for one Kg.

8-formyl-rifamycin SV		320 Kg		0.97 Kg
1-methyl-4-aminopiperazine		54 Kg		0.163 Kg
Acetone-ethylacetate	(2000 Kg)	600 Kg	(6.1 Kg)	1.9 Kg

A 70% recovery yield for the solvents is considered. The mixture of acetone-ethylacetate is recovered by distillation restoring the requested composition by addition of the lacking component.

Utilities for a 330 Kg. Batch

Electric power	220 Kwh
Brine at	-30 C

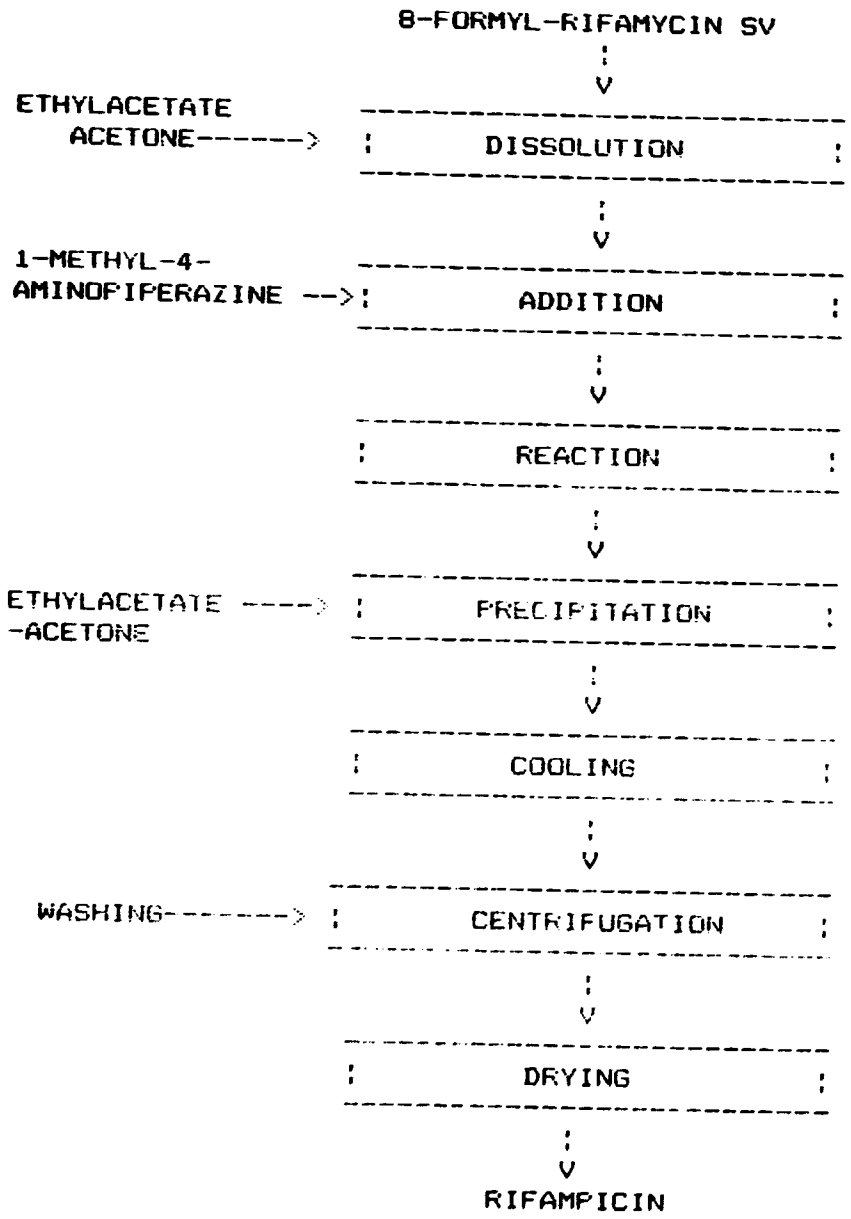
Production Plant and Equipment List

See 9.10 and 9.11

Manpower

See 9.16

RIFAMPICIN FLOW CHART



9.7 Utilization of the Plant

We have listed in the following table some data concerning the duration of the operations for the production of the projected products, the number of the batches required and the total time of utilization of the plant.

Product	Output per batch	Duration of each batch	Number of batches	Total Working days
Erythromycin stearate	125 Kg	1 day	88	88
Erythromycin ethylsucc.	165 Kg	1 day	67	67
Erythromycin thiocyan.	165 Kg	1 day	18	18
Rifampicin	330 Kg	36 hours	61	90
Total				263

263 days correspond more or less to the number of working days per year in the Philippines. That means that when the plant will be fully operational it will be working busy the whole year. Additional capacity can be reached by working with two or three shifts per day depending from the product.

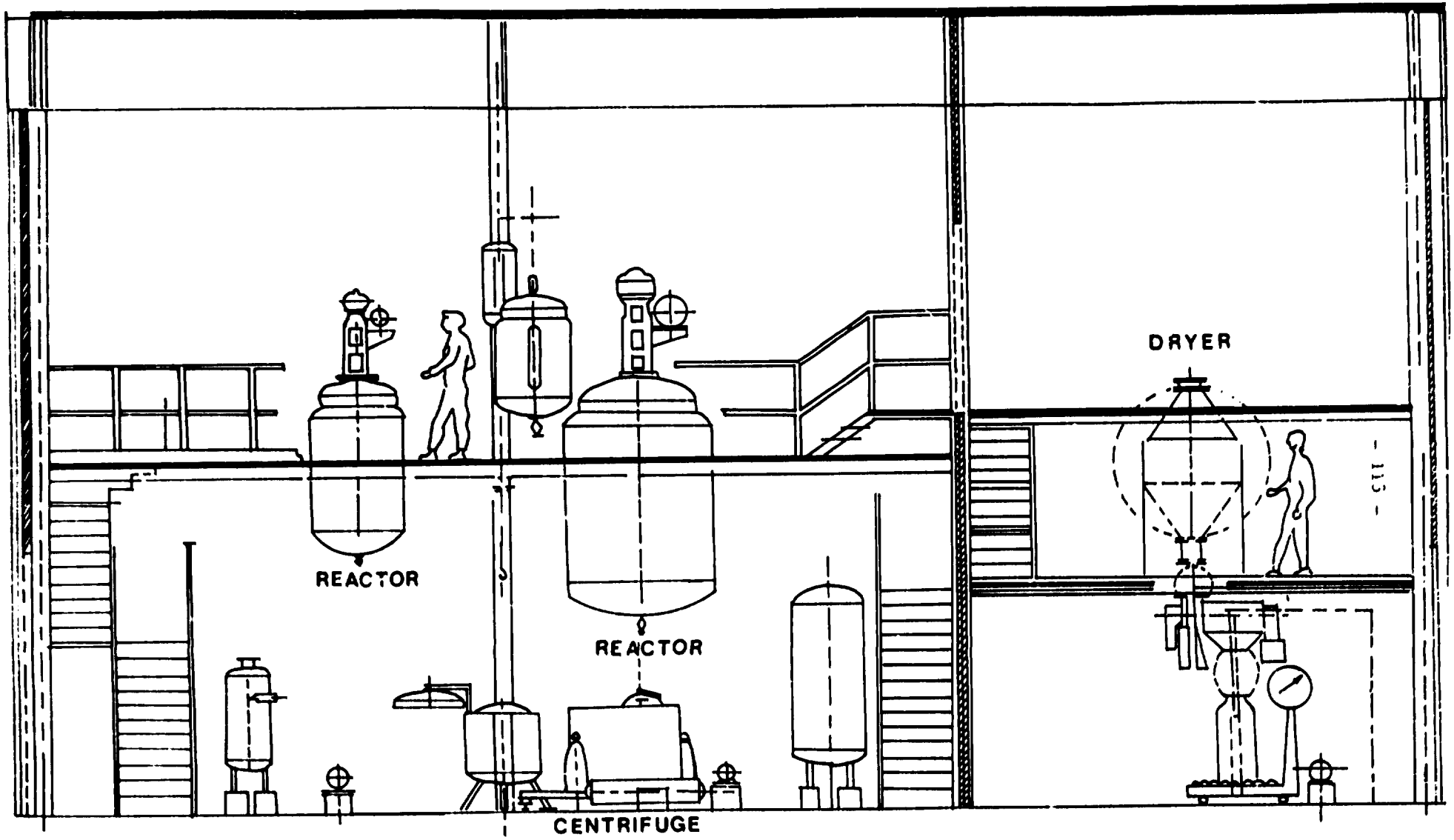
9.8 Waste Treatment

The quantities of solid waste are rather limited and are mainly composed from activated carbon. We suggest that they be burned or taken away. The liquid waste after neutralization, should be treated with activated sludges in the existing plant in the Chemfields factory.

9.9 Location of the Plant (1)

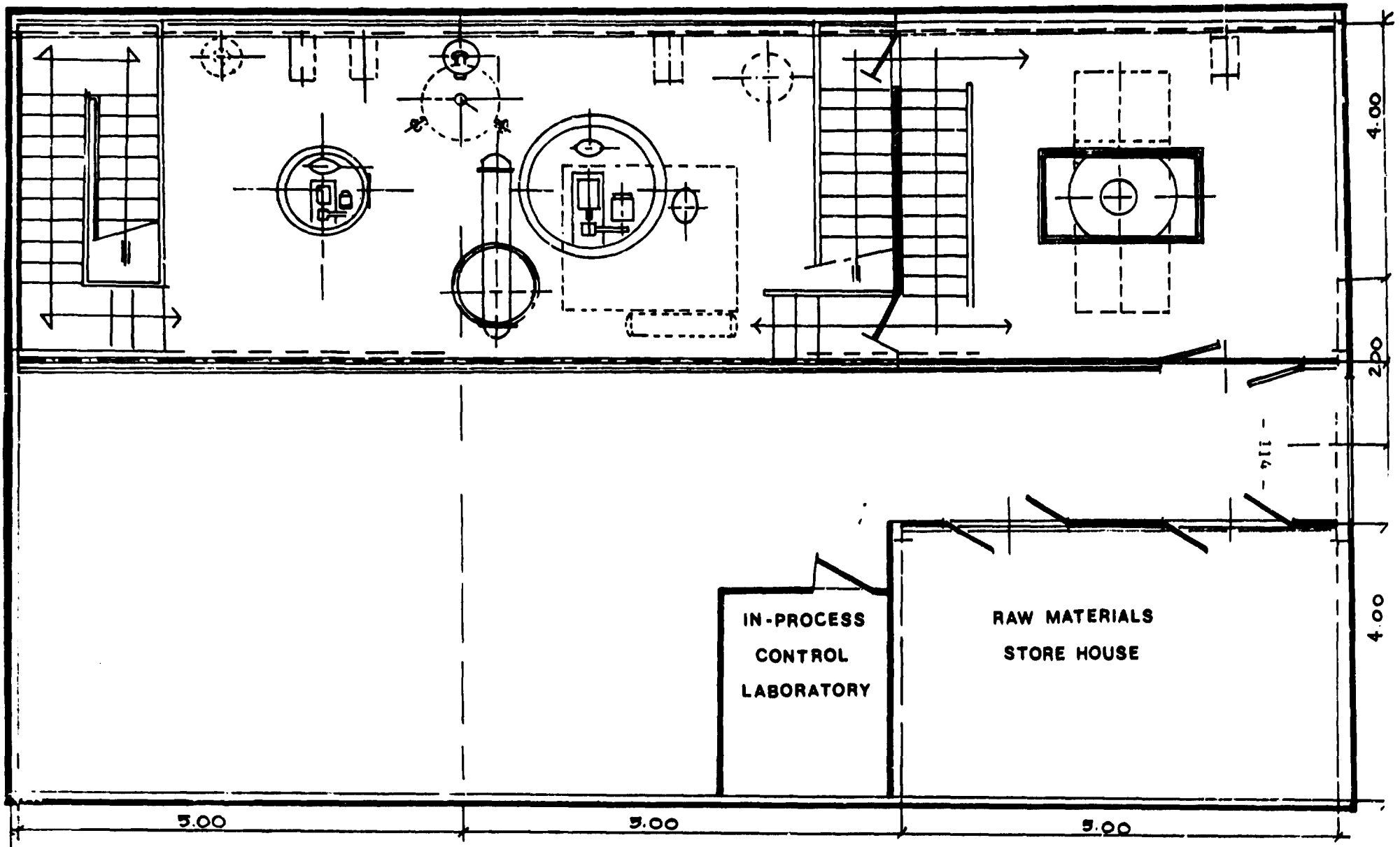
The production for Erythromycin derivatives and Rifampicin has limited dimensions. For economic reasons consideration, we don't think it is advisable to erect a new complex.Should the Erythromycin plant be placed in a new factory, the investment would be much higher, roughly evaluated 1.5-2 times the proposed one, so the economics becoming unfavourable. We suggest that the plant be placed in the Chemfields factory in a new building, which should be separated from the one for

(1) the potential to generate or provide capital for the expansion should also be taken into account.



SECTION OF THE ERYTHROMYCIN AND RIFAMPICIN PLANT

MANILA – AUGUST, 1988



PLAN OF THE ERYTHROMYCIN AND RIFAMPICIN PLANT

MANILA – AUGUST 1988

beta-lactam (semisynthetic penicillins) production to avoid cross-contamination. The Chemfields plant has all the required facilities, an existing organization and a staff which has to be slightly increased to cope with the new needs. Some of the existing utilities have spare capacity, thus it will be possible to limit the investment.

9.10 Description of the Plant

The plant proposed for the production of Erythromycin derivatives and Rifampicin consisits essentially of two stainless steel jacketed reactors with stirring, one press filter (or in alternative a Sparkler type filter) one centrifuge and tanks for mother liquors. One drier (or in alternative a fluid bed drier) and equipment for grinding and sieving the product are also provided. Solvents come from external tanks through metering pumps. Deionized water is produced in a separate unit. For circulation centrifugal pumps are installed. As to the utilities see 7.9

9.11 Equipment List

The main equipment needed for the production of Erythromycin derivatives and Rifampicin is as follows.

Equipment	Number	Capacity	Material	Stirrer	Jacket
Reactor	1	4,000 lt	Stainless steel	Anchor	yes
Reactor	1	1,500 lt	Stainless steel	Anchor	yes
Tank	1	2,000 lt	Stainless steel	--	--
Tank	1	1,000 lt	Stainless steel	--	--
Tank	2	1,500 lt	Stainless steel	--	--
Centrifugal pump	2		Stainless steel		
Press Filter	1	Frame 500 x 500 mm	Stainless steel		
Centrifuge	1	Ø 1,200 mm	Stainless steel		
Drier	1	500 Kg capacity	Stainless steel		
Scale	1				
Grinder	1				
Distillation column	1				

9.12 Locally Available Equipment

see 7.11

9.13 Type of Utilities

For the production of the projected products, the following utilities should be available:

Steam	at 5 Kg/cm^2
Brine	at -30 C
Deionized water	
Electric power	at 380 V

9.14 BUILDINGS

For the production unit a 200 sq. m. surface is needed, one part of the building having two levels to arrange the reactors (50 sq.mt). The surface includes the powder area where drying, grinding and sieving are performed, a small laboratory, locker rooms, W.C. etc. A 300 sq. mt., air conditioned warehouse divided into two parts for raw materials and finished products should also be provided.
Building could be locally projected considering the good local capabilities available. The civil works will have a concrete structure with reinforced concrete columns. Walls will be in bricks and covering in light concrete pre-fabricated elements or equivalent.

9.15 Quality Control, Engineering Services, Warehouse, Administration

The new Erythromycin plant should take into consideration additional needs for services from both points of view of equipment and personnel. The additional equipment (in particular laboratory equipment) is considered in semi-synthetic Penicillins plant, but a certain portion of the investment is allocated here (see 9.17).

The additional staff required for the Erythromycin plant is as follows:

9.15.1 Technical Services:

n. 1 senior laboratory technician
n. 1 quality control inspector
n. 2 laboratory technicians

9.15.2 Warehouse :

n. 3 warehouse aides
n. 1 supervisor
n. 1 clerk

9.15.3 Administration:

n. 1 clerk

For the manpower qualification see 7.15

9.16 Manpower Type and Qualification

In some cases, the plant will be running on three shifts a day basis.

We suggest the following manpower:

n.1 plant manager
n.4 supervisors
n.4 senior production technicians
n.4 production technicians
n.4 production aides

For the manpower qualification see 7.15

9.17 Investment

The investment level has been calculated to give an idea of the order of magnitude rather than to provide a precise figure. In the reported figures the land cost is not included. The investments for the equipment concerning some utilities such as a brine plant, steam plant, a new solvent recovery plant etc., will be considered in the part concerning semi-synthetic Penicillins which we suggest to be placed in the Chemfields factory.

An investment has been considered for the additional laboratory equipment (see 9.15).

The investment figures are:

Plant	In US $
Equipment (transportation Included)	400,000
Erection (Piping, mounting, electrical parts, instrumentation, insulation, painting etc.) ~~400,000~~	400,000
Engineering 7%	60,000
Assistance to the erection 7%	60,000
Cost of Technology	300,000
Buildings	
Plant	50,000
Warehouse (air conditioned)	85,000
Laboratory equipment (additional)	105,000
Sub-total	1,460,000
Training of Personnel	70,000
Grand Total	1,530,000

9.18 Production Cost

For the evaluation of the production costs, two different options are taken into consideration:

1. The use of imported starting material;
   (erythromycin base at 105$,10% freight, insurance etc. included)
   (8-formyl-rifamycin SV at 190$, 10% freight, insurance etc. included)
2. The use of starting material produced locally.

For the calculation of the production cost, we have assumed that the plant is operating at full capacity (the full potential capacity will be probably reached three years after the start-up of the plant).

The raw materials costs include freight, insurance and other expenses evaluated at about 10 % of the cost.
The production costs include raw materials, utilities, manpower and general expenses($ / Kg)

Erythromycin stearate	(erythromycin at 65$)	62
Erythromycin at 105 $	(10% freight,etc.included)	94
Erythromycin ethylsuccinate	(erythromycin at 65$)	95
Erythromycin at 105 $	(10% freight,etc.included)	140
Erythromycin thiocyanate	(erythromycin at 65$)	70
Erythromycin at 105 $	(10% freight,etc.included)	110

Rifampicin

Due to lack of reliable information, we assume that a reasonable figure for cost of locally produced 8-formyl-rifamycin SV is 130 $/Kg.

8-formyl-rifamycin SV at 130 $	141
8-formyl-rifamycin SV at 190 $	195

For the calculations of the manpower incidence we have used the criterion indicated at point 7.17.
General Expenses are globally estimated at 90,000 $. We think that this figure is large enough to include the incremental auxillary services such as quality control, engineering services, warehouse, administration etc. devoted to the Erythromycin and Rifampicin production. For the raw materials we assume that they are imported,exempt of customs duties and taxes.

9.19 Economic Considerations

As already mentioned, in order to stimulate new investment in the pharmaceutical field it is advisable that incentives be granted to improve the economics of the different projects. Among the various incentives which could be granted, three are especially connected with the manufacturing cost and the selling price of the locally manufactured products which are:

1) exemption of import duties on machinery, equipment and raw materials
2) tariff protection and
3) income tax exemption.

We suggest that these incentives should be granted to the new potential bulk pharmaceutical production, also because of its strategic importance for the health situation of the country.In the economic considerations we make the assumption that all the three incentives will be granted. As to the depreciation, we assume it has a straight line one for a 10 year period for both equipment and buildings (1). As the first approximation we have calculated the depreciation per kilogram by dividing the annual depreciation by the quantity produced at full capacity, that is 45 tons. For the Erythromycin derivatives and Rifampicin plant the incidence per kg. results to be about 4 $/kg.

---(1) Although buildings could be depreciated for 20 years, due to the relatively small value, we have left all at 10 year

The production cost including depreciation will then be ($ per Kg.)

Erythromycin stearate	
(with imported erythromycin)	98
(with local erythromycin)	66
Erythromycin ethylsuccinate	
(with imported erythromycin)	144
(with local erythromycin)	99
Erythromycin thiocyanate	
(with imported erythromycin)	114
(with local erythromycin)	74
Rifampicin (with imported 8-formyl-Rifamycin SV)	199
(with local 8-formyl-rifamycin SV)	145

The present international market prices (1) are (in US $):

Erythromycin	95-100
Eryhtromycin stearate	80-85
Erythromycin ethylsuccinate	130-135
Erythromycin thiocyanate	85-90
Rifampicin	190- 220

In the following table, we report some figures concerning the production cost, the sales value with different hypotheses and the corresponding profits. We have considered the following sales prices for comparative purposes:

1.) the products are sold at the international prices plus 20% which includes, freight, insurance, custom duties and the value added tax

2.) the products are sold 10 % higher than the international prices, assuming that a 10% advantage would be applied

3.) the products are sold 20 % higher than the international prices, assuming that a 20% advantage would be applied

Total yearly gross profits are also reported

---

(1) 1988 Prices

COSTS, SALES AND GROSS PROFITS WITH IMPORTED ERYTHROMYCIN AND 8-FORMYL-RIFAMYCIN SV

	Erythromycin stearate	Erythromycin ethylsuccinate	Erythromycin thiocyanate	Rifampicin	TOTAL
Total Production cost ($ x 000)	1,078	1,584	342	3,980	6,859
1)Sales	1,122	1,782	324	4,560	7,788
($ x 000)	(85$+20%)	(135$+20%)	(90$+20%)	(190$+20%)	
Profit	44	198	-18	580	804
2)Sales (+10 % on international prices)	1,215	1,930	351	4,940	8,436
($ x 000)	(85$+30%)	(135$+30%)	(90$+30%)	(190$+30%)	
Profit	137	346	9	960	1,452
3)Sales (+20 % on international prices)	1,309	2,079	378	5,320	9,096
($ x 000)	(85$+40%)	(135$+43%)	(90$+40%)	(190$+40%)	
Profit	231	495	36	1,340	2,102

From these figures the estimated profit on sales could be as follows:

Hypothesis 1 8.3%

Hypothesis 2 17.2%

Hypothesis 3 23.1%

The corresponding pay-back periods are:

Hypothesis 1 1.9 years

Hypothesis 2 1.1 years

Hypothesis 3 0.7 years

From the above figures it emerges that the profit on sales is not high but still acceptable and the pay-back period is relatively short because the investment is rather limited.

The above calculations have been elaborated to give a rough indication of the economics of the projects. A more in-depth analysis should be initiated.

We stress again the fact that these preliminary calculations are based on the following assumptions:

- the machinery and equipment are imported, exempt of taxes and tariff duties
- the plant operates at full capacity
- the imported Erythromycin derivatives and Rifampicin are subject to custom duties and income taxes.
- in the hypothesis 2 and 3 a 10 or 20 % advantage on selling prices is given to the local production.

We suggest that the government should take a commitment to buy a part of the production for all the corresponding antibiotics purchased for the RHUs. Calculations based on the assumption of local production of Erythromycin and Rifamycins B will be dealt with in the report of the Expert in fermentation and will be based on the above reported figures for the production costs, investments and market prices.

In annex two some more economics on the Erythromycins and Rifampicin plant are reported.

10. THE TETRACYCLINE HYDROCHLORIDES PRODUCTION PLANT

The plant for production of the hydrochlorides of Tetracycline and Oxytetracycline is proposed in order to transform the free bases which should be obtained in the proposed multipurpose fermentation plant, into the hydrochlorides which are the commercial salts.

Since the free bases have only a very limited use, this plant is essential in case the option of producing the Tetracyclines by submerged fermentation is taken.

The projected quantities of the two salts are the following:

Tetracycline hydrochloride	20 tons
Oxytetracycline hydrochloride	15 tons

The corresponding technologies should be obtained together with the ones concerning Tetracycline and Oxytetracycline fermentation and recovery.

10.1 Tetracycline Hydrochloride

Tetracycline hydrochloride is the most used derivative of the wide spectrum antibiotic Tetracycline. This name is due to the fact that its molecule contains four (tetra in Greek) cycles. In the hydrochloride, hydrochloric acid salifies the dimethylamino group of ring A.

Its formula is:

$$C_{22}H_{24}N_2O_8 \cdot HCl$$

m.w. 480.89

Determination of the number of batches

For the projected plant the batch dimension will be 270 kg. The production of 20 tons requires 74 batches.

Principle of the Method

Salification of Tetracycline with hydrochloric acid.

Description of the Method

The solution of Tetracycline in butanol-ethylcellosolve is treated with concentrated aqueous hydrochloric acid and filtered; by heating crystallisation of the hydrochloride takes place; the product is centrifuged, washed and dried.

Yields

Theoretical yield	92%
Weight yield	100%

Raw Materials

Hereunder are listed the main raw materials needed for one batch of 270 kg and the corresponding quantities for one kg. A 80% recovery yield for the mixture of solvents and 70% for acetone is considered.
The mixture of butanol-ethylcellosolve is recovered from the mother liquors by distillation. Water is first removed and then the mixture is distilled and the ratio between the two components is rearranged.

Tetracycline		270 kg		1.0 kg
Butanol	(1150 kg)	230 kg		0.85 kg
Ethylcellosolve	(120 kg)	24 kg	(0.44 kg)	0.09 kg
Concentrated hydrochloric acid		25 kg		0.09 kg
Acetone	(525 kg)	150 kg	(1.94 kg)	0.55 kg

Utilities for one 270 kg batch

Electric power	600 Kwh
Brine	$5 \cdot 10^5$ kcal
Steam	

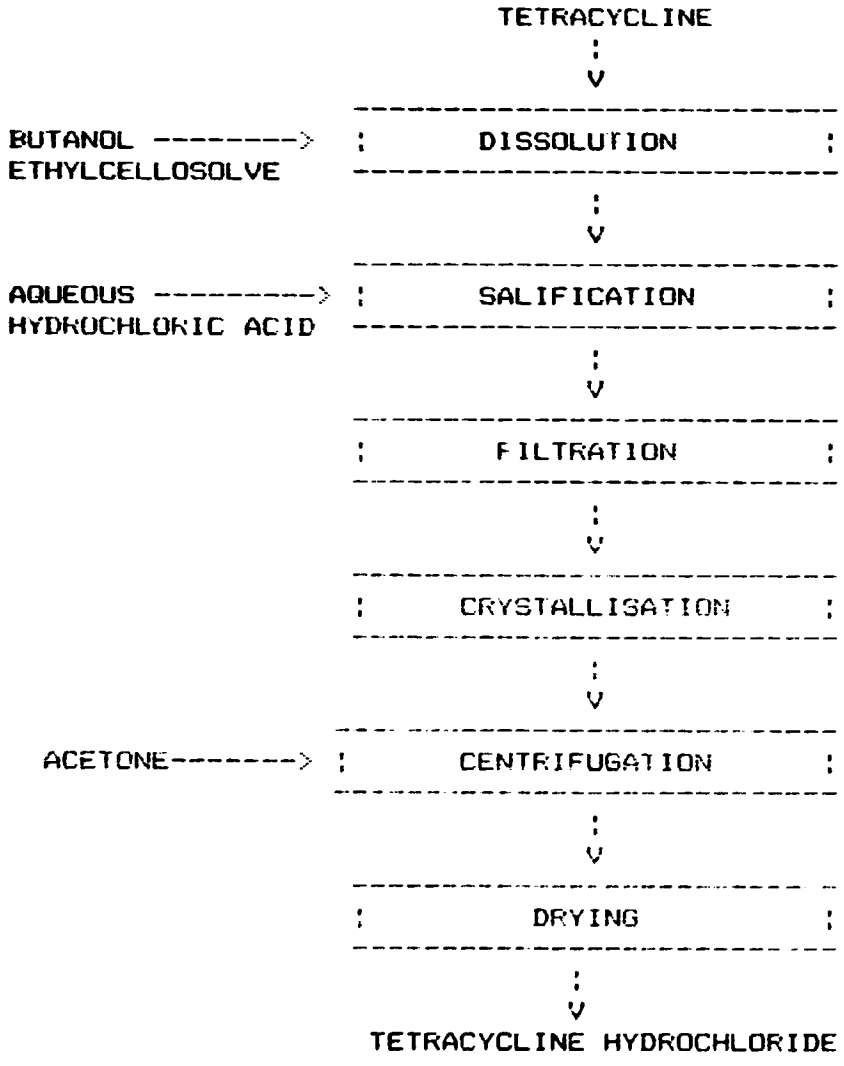
Production plant and equipment list

See 10.6 and 10.7

Manpower

See 10.12

TETRACYCLINE HYDROCHLORIDE FLOW CHART



10.2 Oxytetracycline Hydrochloride

Oxytetracycline hydrochloride is the most used derivative of the wide spectrum antibiotic Oxytetracycline. In the hydrochloride, hydrochloric acid salifies the dimethylamino group in ring A.

Its formula is:

$C_{22}H_{24}N_2O_9 \cdot HCl$

m.w. 496.90

Determination of the number of batches

For the projected plant the batch dimension will be 270 kg. For the production of 15 tons 56 batches are required.

Principle of the method

Salification of Oxytetracycline with hydrochloric acid.

Description of the method

Oxytetracycline is dissolved in a butanol-ethylcellosolve mixture and hydrochloric acid is added. After crystallization, the hydrochloride is separated by centrifugation, washed and dried.

Yields

Theoretical yield	89%
Weight yield	97%

Raw Materials

Hereunder are listed the main raw materials needed for one batch of 270 kg and the corresponding quantities for one kg. A 80% recovery yield for the mixture of solvents and 70% for acetone is considered.
The mixture of butanol-ethylcellosolve is recovered from the mother liquors by distillation. Water if first removed and then the mixture is distilled and the ratio of the two components is rearranged.

Oxytetracycline base		278 kg		1.03 kg
Butanol-ethylcellosolve mixture	(1,200 kg)	240 kg	(4.44 kg)	0.89 kg
Concentrated hydrochloric acid		24 kg		0.09 kg
Acetone	(525 kg)	150 kg	(1.94 kg)	0.55 kg

Utilities for a 270 kg batch

Electric power	600 Kwh
Brine	
Steam	10^5 Kcal

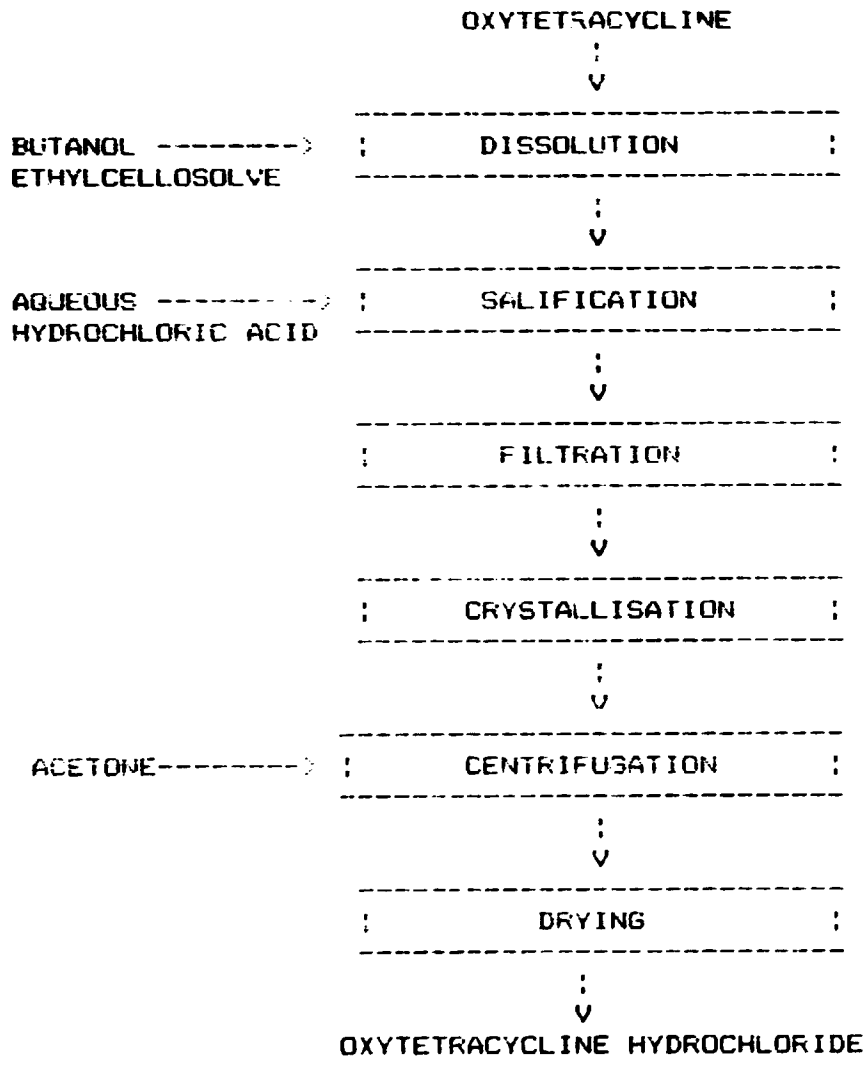
Production plant and equipment list

See 10.6 and 10.7

Manpower

See 10.12

OXYTEYTRACYCLINE HYDROCHLORIDE FLOW CHART



10.3 Utilization of the Plant

The data concerning the duration of the operations, the number of batches required and the total time of utilization of the plant are as follows:

Product	Output per Batch	Duration of each batch	Number of batches	Total working days
Tetracycline hydrochloride	270 Kg	42 hours	74	148
Oxytetracycline hydrochloride	270 Kg	42 hours	56	112
			260	260

260 days correspond more or less to the number of working days per year in the Philippines. It means that when the plant will be fully operational, it will be working the whole year. Additional capacity could be reached by adding more facilities for drying.

10.4 WASTE TREATMENT

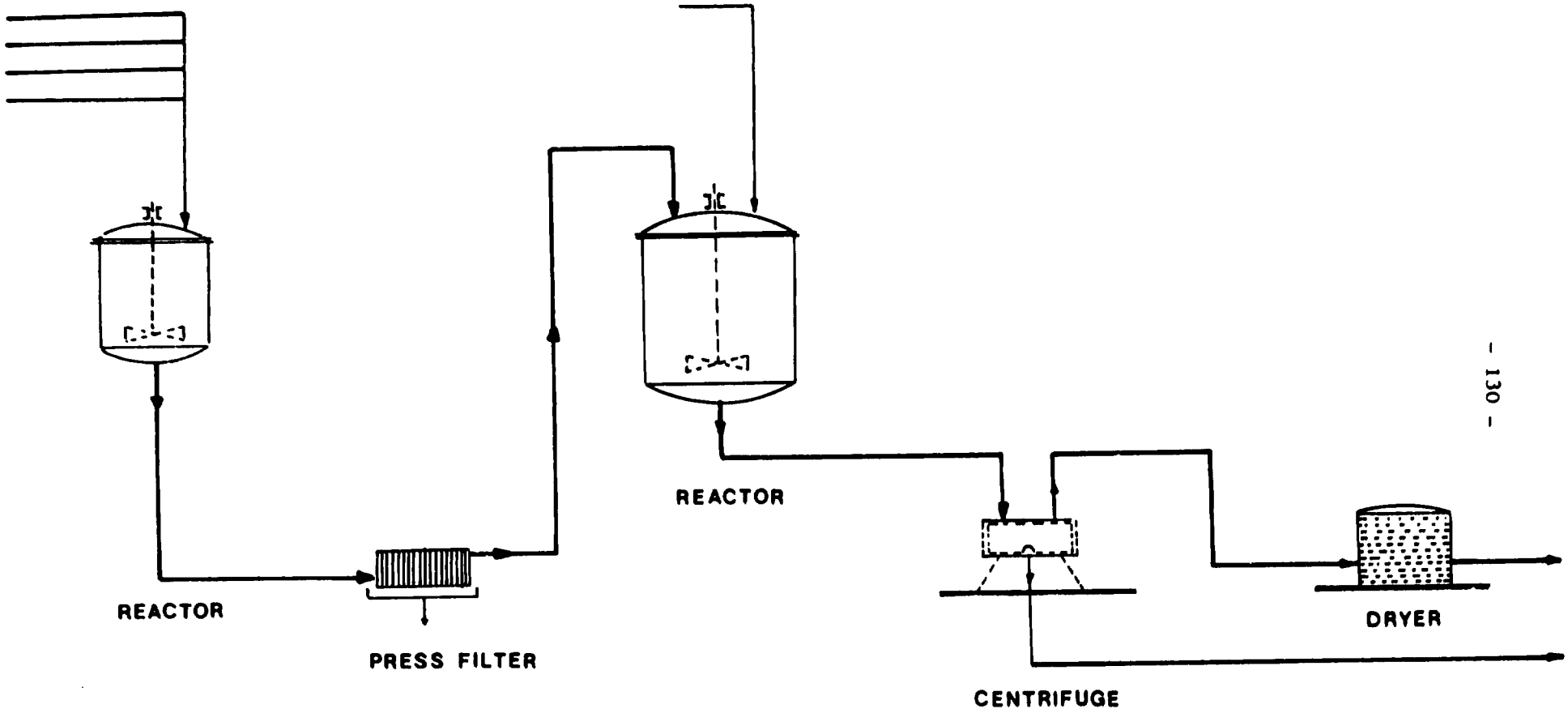
The waste from the plant are essentially liquid wastes. They will be treated together with the main liquid effluents from the Tetracyclines production plant.

10.5 Location of the Plant

Tetracycline and Oxytetracycline free bases have a very limited market, the main commercial products being the hydrochlorides. For this reason we suggest to locate the plant for the hydrochlorides production in the same building where the recovery of the Tetracyclines take place. So it is possible to avoid transportation of the free bases and duplication of the technical services and utilities required in a production plant.

10.6 Description of the Plant

The proposed plant consists essentially of one reactor where the reaction is carried out supplied with a tank for the addition of hydrochloric acid, a second one for the filtered solution, a centrifuge for the isolation of the products as well as one drier. Some minor equipment are also required. The solvents comes from external tanks through metering pumps.



TETRACYCLINES HYDROCHLORIDES PLANT

MANILA – AUGUST, 1988

10.7 Equipment List

The main equipment needed for the production of Tetracycline and Oxytetracycline hydrochlorides is here listed.

Equipment	Number	Capacity	Material	Stirrer	Jacket
Reactor	2	2,000 lt	glass lined	yes	yes
Tank	1	100 lt	fiberglass		
Centrifuge	1	Ø 1500 mm	stainless steel		
Drier	1		s.s.		
Filter press	1		s.s.		

As to the utilities the ones produced for the fermentation and recovery of Tetracycline and Oxytetracycline are utilized.

10.8 Locally Available Equipment

see 7.11

10.9 Type of Utilities

For the preparation of the Hydrochlorides of Tetracycline and Oxytetracycline the following utilities are needed:

Brine	at -30 C
Electric power	at 380 V
Steam	at 5 Kg / cm^2

10.10 Buildings

The production unit will be located in the same building were the recovery of Tetracycline takes place. See the report of the Expert in fermentation.

10.11 Quality Control, Engineering Services, Warehouse, Administration

The production of Tetracycline hydrochlorides requires an increase of the personel already available for the Tetracycline fermentation production plant. The technical services department will be incremented by :

10.11.1 Engineering Department

n.1 analyst
n.1 laboratory technician

10.11.2 Warehouse

n.2 warehouse aides

10.11.3 Administration

n.1 clerk

For other services the already existing manpower can face all the needs

10.12 Manpower type and Qualification

The plant will be run on a three shift basis.We suggest the following manpower should be available:

n.4 supervisors
n.4 senior production technicians
n.4 production technicians
n.4 production aides

As for the qualification of the manpower see 7.15

10.13 Investment

The level of investments reported hereunder have been calculated to give an idea of the order of magnitude of the investment. The figures do not include buildings, since the plant will be located in the same building where the recovery of Tetracyclines takes place. We do not consider investments for the utilities as they constitute only a very small part of the ones used for Tetracycline production and they are included in the investment for Tetracycline.

The investments could be summarized as follows:

	(in US $)
Equipment	550,000
Erection (Piping,mounting,electrical parts, instrumentation, insulation, painting etc.)	550,000
Engineering 7%	40,000
Assistance to the erection 7%	40,000
Grand total	1,180,000

In these investments we have not considered the cost of technology and the training of the personel, which should be included in the investment for the Tetracycline plant. We assume that the import of machinery and equipment for the new plant would be exempt of custom duties and taxes.

10.14 Production cost

The local production of the hydrochlorides of Tetracyclines and Oxytetracycline is interesting only if a Tetracycline producing plant is started in the Philippines. For this reason the evaluation is made using the eventual local production costs of Tetracycline and Oxytetracycline .

The raw materials costs include freight, insurance, and other expenses evaluated at 10 % of the cost.

The production costs include raw materials, utilities, manpower and general expenses (in US $).

Tetracycline hydrochloride	28
Oxytetracycline hydrochloride	24

The present (1988) market prices are:

Tetracycline hydrochloride	34
Oxytetracycline hydrochloride	30

For the calculation of the manpower costs, we have used the criterion indicated at point 7.17.
General expenses were globally estimated 35,000 US $. We evaluate this figure to be large enough to include the incremental auxillary services such as quality control, engineering services, warehouse, administration, etc. devoted to the Tetracyclines hydrochlorides production. For the raw material we assume that they are imported exempt of customs duty and taxes.

10.15 Economic Considerations

Calculation based on the assumption of a local productions of Tetracyclines hydrochlorides will be dealt with in the report of the Expert in fermentation and will be based on the above reported figures for the production costs, investments and market prices.
As to the depreciation, assuming it has a straight line one for a ten year period, dividing the annual depreciation by the quantity annually produced at full capacity that is 35 tons, it results to be 3.5 $ / Kg.
Total costs including depreciation result to be about 27$ for Oxytetracycline hydrochloride and 31 $ for Tetracycline hydrochloride.

11. ADDITIONAL MANPOWER NEEDS

The establishment of new production units in the Philippines generates new working places and new opportunities for employment. The new proposed plants will need both technicians and workers. When the plants will operate at full capacity, the following manpower will be utilized.

	Beta-Lactam antibiotics	Erythromycin and Rifampicin	6-APA	Tetracyclines Hydrochlorides
Plant manager	1	1	–	–
Supervisors	4	4	4	4
Senior Production Technicians	8	4	4	4
Productions Technicians	12	4	4	4
Production Aides	6	4	4	4
Total	31	17	16	16

The incremental manpower for the services to the production will be more limited due to the fact that technical people are already available in the factories.

The following are the list of incremental manpower needs for the four plants:

	Beta-Lactam antibiotics	Erythromycin and Rifampicin	6-APA	Tetracyclines hydrochlorides
Senior Laboratory Technician (analyst)	1	1	1	1
Laboratory Technician	2	2	1	1
Quality Control Inspector	1	1		
Utilities Operator	1			
Mechanics/Electrician	2			
Supervisor (warehouse)	1	1		
Stock Clerk	1	1		
Warehouse aides	3	3	2	2
Clerk (administration)	2	2	1	1
Total	14	11	5	5

Globally, if the four projets are implemented, 80 new working places willbe available for the production and 26 for the auxiliary services.

12. AVAILABILITY OF LOCALLY PRODUCED RAW MATERIALS

In order to check the local availability of solvents and other chemicals, chemicals producing companies have been contacted. No local production of intermediates and solvents used in the semi-synthesis of antibiotics was evidentiated. Only 95% ethanol is produced locally.
For the production of the Dane salt for Amoxycillin absolute ethanol is required.
Probably its production could be examined; one of the methods is the azeotropic distillation of a ternary mixture with the addition of benzene.
As to the other chemicals, sulphuric acid and sodium hydroxyde are locally available, but their consumption for the semi-synthetic antibiotics is very limited. Liquid nitrogen used as a cooling agent in the production of semi-synthetic Penicillins is locally produced and is available in large quantities.

13. EVALUATION OF THE LOCAL AVAILABILITY OF SKILLED MANPOWER

In order to identify the local skilled manpower, who could be hired for the proposed plants, Managers of some pharmaceutical industries as well as Professors of some Universities have been contacted.

Investigations were done in the Departments of Chemistry of the following Universities:

- University of the Philippines
- De La Salle University
- Ateneo University

We could gather also informationon on one Cebu University which was visited by one of our collegues.

The Department of Chemistry of the University of the Philippines (prof. Claro Llaguno) seems to be rather well organized and to have satisfactory teaching programs.

In its laboratories we noticed that some modern equipment such as I.R., U.V., G.C., Mass Spectrum, Electon Microscope etc. is available. The equipment, mainly of japanese origin,seems to be really utilized for teaching.

It is the only Institute in which studies on organic syntheses are carried out, the main focus being on plant products as in other Universities.

Ten to 15 BS and 5 to 8 MS graduate each year; recently in cooperation with the Ateneo University a common program was launched with the aim of graduating six PhD every two years; for them it is requested one academic year of training in a University abroad.

In the De La Salle University Professors of Chemistry, Chemical Engineering and Biology were contacted.

Teaching programs seems to satisfactory according to European and U.S. standards modern textbooks being used.

Also in this University during a visit to the laboratories we noticed the usual equipment (I.R., U.V., G.C. etc.) which seems to be used for teaching.

We have been expecially impressed by the Department of Chemical Engineering which seemed to us very well organized; notwithstanding the limitation of the financial means the Department do its best to supply th students with equipment to learn the basic principles of chemical engineering such as chemistry, mechanics, electronics etc.

Ten to 15 students graduate in chemistry each year.

In the Department of Chemistry work five PhDs which were trained abroad (West Germany and USA) for one year.

The main focus of the researches is on natural products (terpenes, branched chain [illegible]

In the Ateneo University we have visited the Philippine Institute for Pure and Applied Chemistry (PIPAC; prof. M. Chua). In this University 10 to 15 BS and 3 to 5 MS graduate each year. As mentioned before, the Department of Chemistry plans to graduate six PhDs two each year in cooperation with the University of the Philippines.

The equipment available at PIPAC is new and of good quality and mainly devoted to the chemistry but we noticed also one fermenter; most of the equipment is of japanese origin.

Unfortunately, because of limited financial means, the personnel working in the Institute is rather limited and the equipment is not much used.

PIPAC works mainly for external Organisations and Industries expecially in the analytical field.

The main problem it that technical people, because of the low salaries, often get a job abroad depriving the country of skilled technicians.

Summarizing the information collected and checking our findings with industrial managers, it is our opinion that in the Philippine Universities we have visited, considered among the best in the country, the educational level is good, but the practical experience of the students is rather limited, because of lack of economic means to perform a sufficient number of experiments and studies in chemistry.

As suggested at point 7.15, the technicians should be trained abroad for different periods according to experience required before being utilized in a chemical plant. In any case, they could be recruited in the Philippines.

ANNEX ONE

DATE : 09/29/88 TIME : 11:56

Project : SC000
Title : PENICILLINES
Currency: 1000 U.S. DOLLARS

YEARS : 10

DISCOUNT RATE: 10

FOR SECOND YEAR AT 100 % OF CAPACITY YEAR = 1996

TOTAL GROSS VALUE	= 7620
TOTAL COST	= 6802
FIXED PRODUCTION EXPENDITURE	= 1118
FINANCIAL CHARGES	= 466
DEPRECIATION	= 464

VALUE OF P&L ACCOUNT BREAK EVEN POINT FOR SECOND YEAR AT 100% CAPACITY	= 58%
VALUE OF INTERNAL RATE OF RETURN	= 17.80174 %

FEASIBILITY MODEL DATE: 09/29/1988 TIME: 11:56

Centre for the Development of Industry

APPENDIX I - INVESTMENT COST FINANCING TABLE 1. CAPITAL REQUIREMENTS AND TIME SCHEDULE OF EXPENDITURE

PENTACRYLIDES CURRENCY : 1000 U.S. DOLLARS

	TOTAL CAPITAL REQUIRED (1)+(2)	1	2								
LAND	0	0	0	0	0	0	0	0	0	0	0
INFRASTRUCTURE	0	0	0	0	0	0	0	0	0	0	0
FACTORY BUILDINGS	135	100	35	0	0	0	0	0	0	0	0
OFFICE BUILDINGS	0	0	0	0	0	0	0	0	0	0	0
STAFF HOUSES	0	0	0	0	0	0	0	0	0	0	0
MACHINERY (C.I.F.)	2350	1000	1350	0	0	0	0	0	0	0	0
FREIGHT AND INSTALLATION COSTS	2350	400	1950	0	0	0	0	0	0	0	0
TOOLS, SMALL EQUIPMENTS	0	0	0	0	0	0	0	0	0	0	0
FACTORY AND OFFICE EQUIPMENT	0	0	0	0	0	0	0	0	0	0	0
VEHICLES	0	0	0	0	0	0	0	0	0	0	0
FURNITURE AND EQUIPMENT STAFF HOUSES	0	0	0	0	0	0	0	0	0	0	0
TOTAL FIXED ASSETS BEFORE CONTINGENCIES	4835	1500	3335	0	0	0	0	0	0	0	0
CONTINGENCY	242	75	167	0	0	0	0	0	0	0	0
TOTAL FIXED ASSETS	5077	1575	3502	0	0	0	0	0	0	0	0
WORKING CAPITAL (NET)	0	0	0	1852	3016	3789	3810	3810	3810	3810	3810
PRELIM. EXPENS. & COSTS OF ESTABL.	1045	500	545	0	0	0	0	0	0	0	0
TOTAL FUNDS REQUIRED	6122	2075	4047	1852	3016	3789	3810	3810	3810	3810	3810

FIXED ASSETS BEFORE CONTINGENCY AND PRELIM. EXPENS. IN:

DOMESTIC CURRENCY	1292	475	817	1852	3016	3789	3810	3810	3810	3810	3810
FOREIGN CURRENCY	4830	1600	3230	0	0	0	0	0	0	0	0

FEASIBILITY MODEL DATE: 07/29/1988 TIME: 11:56

Centre for the Development of Industry

APPENDIX II - INVESTMENT COST FINANCING TABLE 1. PRODUCTION AND SALES FORECAST

PENICILLINES CURRENCY : 1000 U.S. DOLLARS

YEARS	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000
USE OF CAPACITY (QUANTITY)	0 %	0 %	50 %	80 %	100 %	100 %	100 %	100 %	100 %	100 %
PRODUCTION VALUE AT FACTORY SALES PRICE										
ITEM 1	0	0	1470	2352	2940	2940	2940	2940	2940	2940
ITEM 2	0	0	1530	2448	3060	3060	3060	3060	3060	3060
ITEM 3	0	0	162	259	324	324	324	324	324	324
ITEM 4	0	0	648	1039	1296	1296	1296	1296	1296	1296
ITEM 5	0	0	0	0	0	0	0	0	0	0
ITEM 6	0	0	0	0	0	0	0	0	0	0
ITEM 7	0	0	0	0	0	0	0	0	0	0
ITEM 8	0	0	0	0	0	0	0	0	0	0
ITEM 9	0	0	0	0	0	0	0	0	0	0
ITEM 10	0	0	0	0	0	0	0	0	0	0
PROD. VALUE AT FACT. SALES PRICES	0	0	3810	6096	7620	7620	7620	7620	7620	7620
INCREASE/DECREASE STOCKS FINISHED PRODUC	0	0	635	381	254	0	0	0	0	0
TOTAL NET SALES	0	0	3175	5715	7366	7620	7620	7620	7620	7620

FEASIBILITY MODEL DATE: 09/29/1988 TIME: 11:56

Centre for the Development of Industry

APPENDIX II - FINANCIAL DATA TABLE 2. OPERATING EXPENDITURE

PENICILLINES CURRENCY : 1000 U.S. DOLLARS

YEARS	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000
VARIABLE EXPENDITURES										
RAW MATERIALS	0	0	0	0	0	0	0	0	0	0
INTERMEDIATE MATERIALS	0	0	0	0	0	0	0	0	0	0
OTHER MATERIALS	0	0	0	0	0	0	0	0	0	0
SPARE PARTS	0	0	0	0	0	0	0	0	0	0
WATER	0	0	0	0	0	0	0	0	0	0
FUEL OIL	0	0	0	0	0	0	0	0	0	0
ELECTRICITY	0	0	0	0	0	0	0	0	0	0
PACKAGING	0	0	0	0	0	0	0	0	0	0
FREIGHT AND DISTRIBUTION	0	0	0	0	0	0	0	0	0	0
LABOUR	0	0	0	0	0	0	0	0	0	0
OTHER	0	0	2842	4547	5684	5684	5684	5684	5684	5684
TOT. VARIABLE OPERATING EXPEND.	0	0	2842	4547	5684	5684	5684	5684	5684	5684
FIXED EXPENDITURES										
MAINTENANCE	0	0	0	0	0	0	0	0	0	0
INSURANCE	0	0	0	0	0	0	0	0	0	0
TAX	0	0	0	0	0	0	0	0	0	0
OFFICE AND ADMIN. EXPENDITURES	0	0	0	0	0	0	0	0	0	0
PERSONNEL	0	0	0	0	0	0	0	0	0	0
RENT ON OFFICE AND FACTORY BUILDINGS	0	0	0	0	0	0	0	0	0	0
OTHER	0	0	186	188	188	188	188	188	188	188
TOT. FIXED OPERATING EXPEND.	0	0	186	188	188	186	188	186	188	186
TOTAL OPERATING EXPENDITURE	0	0	3030	4735	5872	5872	5872	5872	5872	5872

FEASIBILITY MODEL DATE: 09/29/1988 TIME: 11:56

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APPENDIX II - FINANCIAL DATA

TABLE 3. REPAYMENT OF LOANS AND FINANCIAL CHARGES

PENICILLINES

CURRENCY : 1000 U.S. DOLLARS

YEARS	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000
FOREIGN BANK 1-LOAN AT BEGINNING YEAR	2000	4883	4883	4883	4483	4083	3683	3283	2883	2483
REPAYMENT OF PRINCIPAL	0	0	0	400	400	400	400	400	400	400
PAYMENTS OF INTEREST	190	464	464	464	426	388	350	312	274	236
LOAN AT YEAR END	2000	4883	4883	4483	4083	3683	3283	2883	2483	2083
FOREIGN BANK-2 LOAN AT BEGINNING YEAR	0	0	0	0	0	0	0	0	0	0
REPAYMENT OF PRINCIPAL	0	0	0	0	0	0	0	0	0	0
PAYMENTS OF INTEREST	0	0	0	0	0	0	0	0	0	0
LOAN AT YEAR END	0	0	0	0	0	0	0	0	0	0
FOREIGN BANK-3 LOAN AT BEGINNING YEAR	0	0	0	0	0	0	0	0	0	0
REPAYMENT OF PRINCIPAL	0	0	0	0	0	0	0	0	0	0
PAYMENTS OF INTEREST	0	0	0	0	0	0	0	0	0	0
LOAN AT YEAR END	0	0	0	0	0	0	0	0	0	0
LOCAL BANK-1 LOAN AT BEGINNING YEAR	0	0	0	0	0	0	0	0	0	0
REPAYMENT OF PRINCIPAL	0	0	0	0	0	0	0	0	0	0
PAYMENTS OF INTEREST	0	0	0	0	0	0	0	0	0	0
LOAN AT YEAR END	0	0	0	0	0	0	0	0	0	0
LOCAL BANK-2 LOAN AT BEGINNING YEAR	0	0	0	0	0	0	0	0	0	0
REPAYMENT OF PRINCIPAL	0	0	0	0	0	0	0	0	0	0
PAYMENTS OF INTEREST	0	0	0	0	0	0	0	0	0	0
LOAN AT YEAR END	0	0	0	0	0	0	0	0	0	0
LOCAL BANK-3 LOAN AT BEGINNING YEAR	0	0	0	0	0	0	0	0	0	0
REPAYMENT OF PRINCIPAL	0	0	0	0	0	0	0	0	0	0
PAYMENTS OF INTEREST	0	0	0	0	0	0	0	0	0	0
LOAN AT YEAR END	0	0	0	0	0	0	0	0	0	0
TOTAL LOANS AT BEGINNING YEAR	2000	4883	4883	4883	4483	4083	3683	3283	2883	2483
TOTAL REPAYMENT OF PRINCIPAL	0	0	0	400	400	400	400	400	400	400
TOTAL PAYMENTS OF INTEREST	190	464	464	464	426	388	350	312	274	236
TOTAL LOANS AT YEAR END	2000	4883	4883	4483	4083	3683	3283	2883	2483	2083

FEASIBILITY MODEL DATE: 09/29/1988 TIME: 11:56

Centre for the Development of Industry

APPENDIX II - FINANCIAL DATA TABLE 4. DEPRECIATION AND TAX ON PROFITS

PENICILLINE CURRENCY : 1000 U.S. DOLLARS

YEARS	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000
TAX DEPRECIATION AND ALLOWANCES										
INFRASTRUCTURE	0	0	0	0	0	0	0	0	0	0
FACTORY BUILDINGS	0	4	4	4	4	4	4	4	4	4
OFFICE BUILDINGS	0	0	0	0	0	0	0	0	0	0
STAFF HOUSES	0	0	0	0	0	0	0	0	0	0
PLANT AND MACHINERY INCLUD. FREIGHT ETC.	0	346	346	346	346	346	346	346	346	346
VEHICLES	0	0	0	0	0	0	0	0	0	0
OTHER EQUIPMENT	0	0	0	0	0	0	0	0	0	0
PRELIMINARY EXPENDITURES	0	114	114	114	114	114	0	0	0	0
TOTAL DEPRECIATION	0	464	464	464	464	464	350	350	350	350
TAXABLE PROFIT/(LOSS)	-190	-928	-783	52	566	818	1048	1486	1124	1162
ACCUMULATED PROFITS/(LOSSES)	-190	-1118	-1901	-1849	-1283	-465	583	1669	2793	3955
TAX	0	0	0	0	0	0	0	543	542	581

FEASIBILITY MODEL DATE: 07/29/1988 TIME: 11:56

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APPENDIX II - FINANCIAL DATA TABLE 5. WORKING CAPITAL REQUIREMENTS

PENICILLINES CURRENCY : 1000 U.S. DOLLARS

YEARS	MONTHS	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000
CURRENT ASSETS											
CASH	1	0	0	0	0	0	0	0	0	0	0
RAW MATERIAL	3	0	0	0	0	0	0	0	0	0	0
INTERMEDIATE MATERIAL	3	0	0	0	0	0	0	0	0	0	0
OTHER MATERIALS/SPARE PARTS	3	0	0	0	0	0	0	0	0	0	0
WORK IN PROGRESS	3	0	0	952	1524	1905	1905	1905	1905	1905	1905
FUEL	3	0	0	0	0	0	0	0	0	0	0
PACKAGING ETC.	3	0	0	0	0	0	0	0	0	0	0
FINISHED PRODUCTS	2	0	0	635	1016	1270	1270	1270	1270	1270	1270
RECEIVABLES	1	0	0	265	476	614	635	635	635	635	635
TOTAL CURRENT ASSENTS		0	0	1852	3016	3789	3810	3810	3810	3810	3810
MINUS : CURRENT LIABILITIES											
RAW MATERIAL	1	0	0	0	0	0	0	0	0	0	0
INTERMEDIATE MATERIAL	1	0	0	0	0	0	0	0	0	0	0
OTHER MATERIALS/SPARE PARTS	1	0	0	0	0	0	0	0	0	0	0
FUEL	1	0	0	0	0	0	0	0	0	0	0
PACKAGING	1	0	0	0	0	0	0	0	0	0	0
CURRENT LIABILITIES		0	0	0	0	0	0	0	0	0	0
WORKING CAPITAL REQUIREMENTS		0	0	1852	3016	3789	3810	3810	3810	3810	3810
WORKING CAPITAL INCREASE/(DECREASE) P.A.		0	0	1852	1164	773	21	0	0	0	0

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APPENDIX II - FINANCIAL DATA TABLE 6. PROFIT AND LOSS ACCOUNT FORECAST

PENICILLINES CURRENCY : 1000 U.S. DOLLARS

YEARS	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000
TOTAL NET SALES	0	0	3175	5715	7366	7620	7620	7620	7620	7620
OPERATING EXPENDITURES	0	0	3030	4735	5872	5872	5872	5872	5872	5872
DEPRECIATION AND AMORTISATION	0	464	464	464	464	464	350	350	350	350
TOTAL COST OF PRODUCTION	0	464	3494	5199	6336	6336	6222	6222	6222	6222
LONG INTEREST	190	464	464	464	426	386	350	312	274	236
OVERDRAFT INTEREST	0	0	0	0	38	78	0	0	0	0
TOTAL FINANCIAL CHARGES	190	464	464	464	464	466	350	312	274	236
TOTAL COSTS	190	928	3958	5663	6800	6802	6572	6534	6496	6458
NET PROFIT/(LOSS) BEFORE TAX	-190	-928	-783	52	566	818	1048	1086	1124	1162
RETURN ON EQUITY %	0	0	0	1	11	16	21	11	11	12
APPROPRIATION OF PROFITS										
DIVIDENDS - AMOUNT	0	0	0	0	0	0	0	0	0	0
DIVIDENDS - % ON EQUITY	0	0	0	0	0	0	0	0	0	0
RETAINED EARNINGS FOR THE YEAR	-190	-190	-783	52	566	818	1048	543	562	581
CUMULATIVE RETAINED EARNING	-190	-1118	-1901	-1849	-1283	-465	583	1126	1688	2269

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APPENDIX II - FINANCIAL DATA TABLE 7. CASH FLOW

PENICILLINES CURRENCY : 1000 U.S. DOLLARS

YEARS	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000
SOURCES OF CASH										
EQUITY	1600	4400	0	0	0	0	0	0	0	0
LOANS	2000	2813	0	0	0	0	0	0	0	0
NET PROFIT/(LOSS) BEFORE TAX	-190	-928	-783	52	566	818	1048	1086	1124	1162
DEPRECIATION AND AMORTISATION	0	464	464	464	464	464	350	350	350	350
CASH INCOME	2810	6369	-319	516	1030	1282	1398	1436	1474	1512
WORKING CAPITAL DECREASE	0	0	0	0	0	0	0	0	0	0
SALE OF FIXED ASSET	0	0	0	0	0	0	0	0	0	0
TOTAL CASH AVAILABLE	2810	6369	-319	516	1030	1282	1398	1436	1474	1512
CASH REQUIREMENTS										
CAPITAL INVESTMENT/REPLACEMENT ASSETS	2075	4047	0	0	0	0	0	0	0	0
DIVIDENDS PAYMENTS	0	0	0	0	0	0	0	0	0	0
TAX PAYMENTS	0	0	0	0	0	0	0	0	543	562
WORKING CAPITAL INCREASE	0	0	1852	1164	773	21	0	0	0	0
PAYMENT OF PRINCIPAL	0	0	0	400	400	400	400	400	400	400
TOTAL CASH REQUIREMENTS	2075	4047	1852	1564	1173	421	400	400	943	962
CASH SITUATION AT YEAR END	735	2322	-2171	-1048	-143	861	998	1036	531	550

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APPENDIX II - FINANCIAL DATA TABLE 8. BALANCE SHEET PROJECTION

PENICILLINES CURRENCY : 1000 U.S. DOLLARS

YEARS	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000
ASSETS										
CASH	0	0	0	0	0	0	0	0	0	0
STOCKS	0	0	1587	2540	3175	3175	3175	3175	3175	3175
RECEIVABLES	0	0	265	476	614	635	635	635	635	635
RESERVE	0	0	0	0	0	0	0	0	0	0
TOTAL CURRENT ASSETS	0	0	1852	3016	3789	3810	3810	3810	3810	3810
FIXED ASSETS GROSS	2075	6122	6122	6122	6122	6122	6122	6122	6122	6122
DEPRECIATION AND AMORTIZATION	0	464	928	1392	1856	2320	2670	3020	3370	3720
NET FIXED ASSETS	2075	5658	5194	4730	4266	3802	3452	3102	2752	2402
TOTAL CURRENT LIABILITIES	2075	5658	7046	7746	8055	7612	7262	6912	6562	6212
LIABILITIES										
TAX PAYABLE	0	0	0	0	0	0	0	543	562	581
DIVIDENDS PAYABLE	0	0	0	0	0	0	0	0	0	0
CURRENT ACCOUNTS (MINUS = SURPLUS)	-735	-6164	-1822	274	560	-1162	-3158	-5230	-6292	-7392
CURRENT LIABILITIES	0	0	0	0	0	0	0	0	0	0
TOTAL CURRENT LIABILITIES	-735	-3057	-886	162	305	-556	-1554	-2047	-2559	-3090
LONG TERM DEBT	2000	4883	4883	4[illegible]	4083	3683	3283	2883	2483	2083
EQUITY (1)	1000	5000	5000	5000	5000	5000	5000	5000	5000	5000
RESERVES	-190	-1118	-1901	-1849	-1283	-465	583	1126	1688	2269
TOTAL SHAREHOLDERS EQUITY	810	3882	3099	3151	3717	4535	5583	6126	6688	7269
TOTAL LIABILITIES	2075	5658	7046	7746	8055	7612	7262	6912	6562	6212
DEBT: EQUITY RATIO (2)	2.5	1.3	1.6	1.4	1.1	0.8	0.6	0.5	0.4	0.3
SECURITY COVERAGE RATIO (3)	1.0	1.2	1.1	1.1	1.0	1.0	1.1	1.1	1.1	1.2
LIQUIDITY RATIO (4)	0.0	0.0	0.0	18.6	12.4	0.0	0.0	0.0	0.0	0.0

(1) Amount on Equity plus eventual future Increase
(2) Long Term Debt: Total Shareholders Equity
(3) Net Fixed Assets: Long Term Debt
(4) Total Current Assets: Total Current Liabilities

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APPENDIX II - FINANCIAL DATA TABLE 9. SENSITIVITY ANALYSIS FOR 2ND YEAR AT 100%

PENICILLINES CURRENCY : 1000 U.S. DOLLARS

RESULTS : NET PROFIT/(LOSS)BEFORE TAX

	SELLING PRICES OF FINISHED PRODUCTS						
	-30%	-20%	-10%	CONSTANT	+10%	+2-%	+30%
TOTAL OPER. EXPEND. +30%	-3230	-2468	1706	-944	-182	560	1342
TOTAL OPER. EXPEND. +20%	-2642	-1880	-1118	-356	406	1168	1930
TOTAL OPER. EXPEND. +10%	-2055	-1293	-531	231	993	1755	2517
TOTAL OPER. EXPEND. CONSTANT	-1468	-706	56	818	1580	2342	3104
TOTAL OPER. EXPEND. -10%	-881	-119	643	1405	2167	2929	3691
TOTAL OPER. EXPEND. -20%	-294	468	1230	1992	2754	3516	4278
TOTAL OPER. EXPEND. -30%	294	1056	1818	2580	3342	4104	4866

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APPENDIX II - FINANCIAL DATA

TABLE 11. NET PRESENT VALUE AND DISCOUNTED CASH FLOW

PENICILLINES CURRENCY : 1000 U.S. DOLLARS

YEARS	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000
NET PRESENT VALUE P.A. (NET SALES MINUS EXPENDITURE MINUS INVESTMENT FIXED ASSETS, DISCOUNTED AT 10 % P.A.)	-1500	-3032	120	736	1020	1085	987	897	815	741
SUM OF NET PRESENT VALUES (YEAR 1 TO 10)										1869
DISCOUNTED CASH FLOW RATE (INTERNAL RATE OF RETURN = DISCOUNTED RATE AT WHICH CASH FLOW YEARS 1 TO 10 EQUALS ZERO) (%)										17.80

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APPENDIX II - FINANCIAL DATA TABLE 1. FOREIGN EXCHANGE EARNINGS

PENICILLINES CURRENCY : 1000 U.S. DOLLARS

YEARS	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000
INFLOW										
EQUITY AND LOANS	2000	2833	0	0	0	0	0	0	0	0
IMPORT SUBSTITUTION	0	0	3810	6096	7620	7620	7620	7620	7620	7620
EXPORT EARNINGS	0	0	0	0	0	0	0	0	0	0
TOTAL	200	2833	3810	6096	7620	7620	7620	7620	7620	7620
OUTFLOW										
INTEREST (NET)	190	464	464	464	426	388	350	312	274	236
PRINCIPAL	0	0	0	400	400	400	400	400	400	400
DIVIDENDS (NET)	0	0	0	0	0	0	0	0	0	0
CAPITAL GOODS(NET OF DUTY TAXES)	1600	3230	0	0	0	0	0	0	0	0
IMPORT OF MATERIALS (NET)	0	0	2273	3678	4547	4547	4547	4547	4547	4547
TRANSFER PAYMENTS	0	0	0	0	0	0	0	0	0	0
TOTAL	1790	3694	2737	4542	5373	5335	5297	5259	5221	5183
SURPLUS/(DEFICIT) P.A.	210	-861	1073	1554	2247	2285	2323	2361	2399	2437
CUMULATED SURPLUS/DEFICIT)	210	-651	422	1976	4223	6508	8831	11192	13591	16028

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APPENDIX II - FINANCIAL DATA TABLE 2. FISCAL EFFECTS

PENICILLINES CURRENCY : 1000 U.S. DOLLARS

YEARS	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000
POSITIVE DIRECT EFFECTS										
TAX ON LAND ETC .	0	0	0	0	0	0	0	0	0	0
DUTY ON IMPORTED EQUIPMENT	0	0	0	0	0	0	0	0	0	0
EXCISE AND CONSUMPTION TAXES	0	0	0	0	0	0	0	0	0	0
CORPORATE TAX (ON PROFITS)	0	0	0	0	0	0	0	543	562	581
PERSONAL INCOME TAX	0	0	0	0	0	0	0	0	0	0
TAXES ON DIVIDENDS	0	0	0	0	0	0	0	0	0	0
TAXES ON INTEREST	0	0	0	0	0	0	0	0	0	0
TOTAL TAX PAYMENTS	0	0	0	0	0	0	0	543	562	581
NEGATIVE DIRECT EFFECTS										
LOSS OF IMP. DUTY ON LOCAL PROD. GOODS	0	0	381	609	762	762	762	762	762	762
NET TAX INCOME P.A.	0	0	-381	-609	-762	-762	-762	-219	-200	-181
CUMULATED TAX INCOME	0	0	-381	-990	-1752	-2514	-3276	-3495	-3695	-3876

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APPENDIX II - FINANCIAL DATA TABLE 3. CONTRIBUTION TO NATIONAL INCOME
20 YEAR FULL PROD.

PENICILLINES CURRENCY : 1000 U.S. DOLLARS

YEARS	1996
PURCHASES	5872
DEPRECIATION	464
TOTAL	6336
FACTOR COSTS (NET VALUE ADDED)	
SALARIES AND WAGES	0
INTEREST	466
RENT ON OFFICE & FACTORY BUILDINGS	0
NET PROFIT/(LOSS) BEFORE TAX	818
TOTAL NET VALUE ADDED	1284
GRAND TOTAL	7620

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APPENDIX II - FINANCIAL DATA

TABLE 10. CALCULATION OF BREAK-EVEN POINT
2ND YEAR FULL PROD.

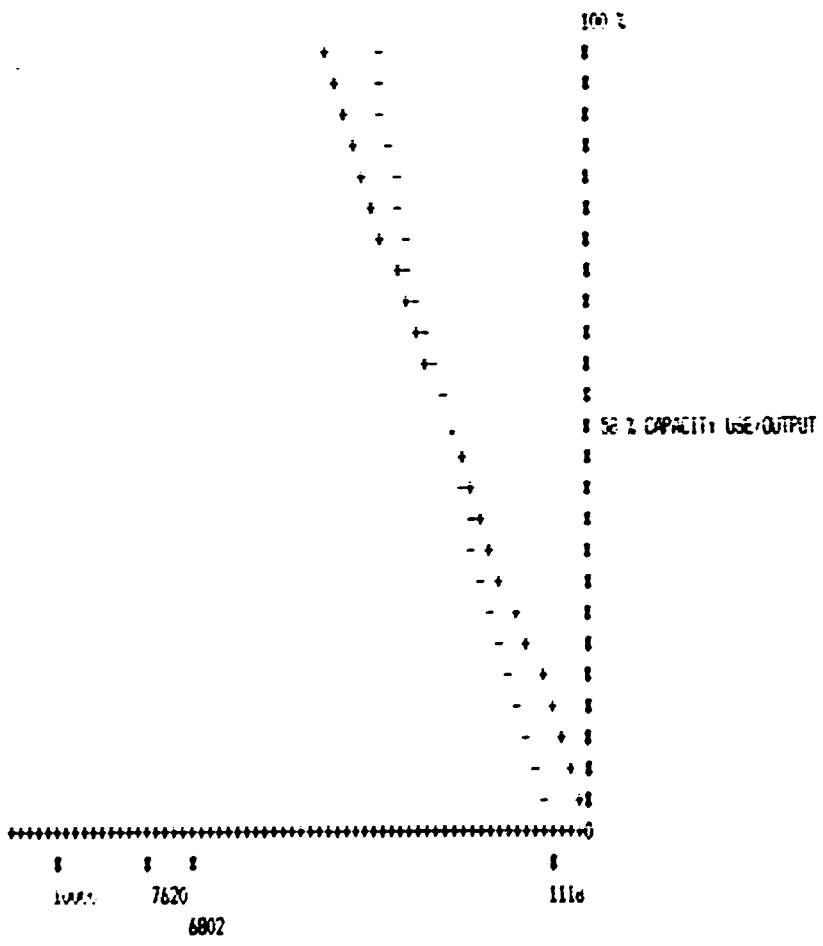
PENICILLINES

CURRENCY : 1000 U.S. DOLLARS

FOR SECOND YEAR AT 100 % OF CAPACITY YEAR = 1996

TOTAL OUTPUT VALUE	= 7620
TOTAL COST	= 6802
FIXED PRODUCTION EXPENDITURE	= 1118
FINANCIAL CHARGES	= 466
DEPRECIATION	= 464

VALUE OF P&L ACCOUNT BREAK EVEN POINT FOR SECOND YEAR AT 100% CAPACITY	= 587
VALUE OF INTERNAL RATE OF RETURN	= 17.60174 %



COST OF PRODUCTION/VALUE OF OUTPUT

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Project : ROBER ANNEX TWO
Title : Erythromycins
Currency : 1000 U.S. Dollars

YEARS : 10

DISCOUNT RATE : 10

FOR SECOND YEAR AT 100% OF CAPACITY

TOTAL OUTPUT VALUE	=	7768
TOTAL COST	=	6659
FIXED PRODUCTION EXPENDITURE	=	331
FINANCIAL CHARGES	=	73
DEPRECIATION	=	166
VALUE OF P&L ACCOUNT BREAK EVEN POINT FOR SECOND YEAR AT 100% CAPACITY	=	26%
VALUE OF INTERNAL RATE OF RETURN	=	34.23413

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APPENDIX I - INVESTMENT COST FINANCING EVALUATION

TABLE 1. CAPITAL REQUIREMENTS AND TIME SCHEDULE OF EXPENDITURE
CURRENCY :1000 U.S. Dollars

	TOTAL CAPITAL REQUIRED (1)+(2)	1	2								
LAND	0	0	0	0	0	0	0	0	0	0	0
INFRASTRUCTURE	0	0	0	0	0	0	0	0	0	0	0
FACTORY BUILDINGS	175	175	0	0	0	0	0	0	0	0	0
OFFICE BUILDINGS	0	0	0	0	0	0	0	0	0	0	0
STAFF HOUSES	0	0	0	0	0	0	0	0	0	0	0
MACHINERY (CIF)	925	350	575	0	0	0	0	0	0	0	0
FREIGHT AND INSTALLATION COSTS	409	159	250	0	0	0	0	0	0	0	0
TOOLS, SMALL EQUIPMENTS	0	0	0	0	0	0	0	0	0	0	0
FACTORY AND OFFICE EQUIPMENT	0	0	0	0	0	0	0	0	0	0	0
VEHICLES	0	0	0	0	0	0	0	0	0	0	0
FURNITURE AND EQUIPMENT, STAFF HOUSES	0	0	0	0	0	0	0	0	0	0	0
TOTAL FIXED ASSETS BEFORE CONTIGENCIES	1409	684	825	0	0	0	0	0	0	0	0
CONTINGENCY	73	32	41	0	0	0	0	0	0	0	0
TOTAL FIXED ASSETS	1533	667	866	0	0	0	0	0	0	0	0
WORKING CAPITAL (NET)	0	0	0	1892	3082	3872	3894	3894	3894	3894	3894
PRELIM. EXPENS.& COSTS OF ESTABL.	70	0	70	0	0	0	0	0	0	0	0
TOTAL FUNDS REQUIRED	1630	667	936	1892	3082	3872	3894	3894	3894	3894	3894
FIXED ASSETS BEFORE CONTINGENCY AND PRELIM. EXPENS. IN:											
DOMESTIC CURRENCY	678	317	361	1892	3082	3872	3894	3894	3894	3894	3894
FOREIGN CURRENCY	731	350	381	0	0	0	0	0	0	0	0

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APPENDIX II - FINANCIAL DATA TABLE 1. PRODUCTION AND SALES FORECAST

ERYTHROPOIETINE CURRENCY: 1000 U.S. DOLLARS

YEARS	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000
USE OF CAPACITY (QUANTITY)	0 %	0 %	50 %	80 %	100 %	100 %	100 %	100 %	100 %	100 %
PRODUCTION VALUE AT FACTORY SALES PRICES										
ITEM 1	0	0	3894	6230	7786	7788	7788	7788	7788	7788
ITEM 2	0	0	0	0	0	0	0	0	0	0
ITEM 3	0	0	0	0	0	0	0	0	0	0
ITEM 4	0	0	0	0	0	0	0	0	0	0
ITEM 5	0	0	0	0	0	0	0	0	0	0
ITEM 6	0	0	0	0	0	0	0	0	0	0
ITEM 7	0	0	0	0	0	0	0	0	0	0
ITEM 8	0	0	0	0	0	0	0	0	0	0
ITEM 9	0	0	0	0	0	0	0	0	0	0
ITEM 10	0	0	0	0	0	0	0	0	0	0
PROD. VALUE AT FACT. SALES PRICES	0	0	3894	6230	7786	7788	7788	7788	7788	7788
INCREASE/DECREASE STOCKS FINISHED PRODUC	0	0	649	389	260	0	0	0	0	0
TOTAL NET SALES	0	0	3245	5841	7526	7788	7788	7788	7788	7788

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APPENDIX II - FINANCIAL DATA TABLE 2. OPERATING EXPENDITURE

ERYTHROPOIETINS CURRENCY : 1000 U.S. DOLLARS

YEARS	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000
VARIABLE EXPENDITURES										
RAW MATERIALS	0	0	0	0	0	0	0	0	0	0
INTERMEDIATE MATERIALS	0	0	0	0	0	0	0	0	0	0
OTHER MATERIALS	0	0	0	0	0	0	0	0	0	0
SPARE PARTS	0	0	0	0	0	0	0	0	0	0
WATER	0	0	0	0	0	0	0	0	0	0
FUEL OIL	0	0	0	0	0	0	0	0	0	0
ELECTRICITY	0	0	0	0	0	0	0	0	0	0
PACKAGING	0	0	0	0	0	0	0	0	0	0
FREIGHT DISTRIBUTION	0	0	0	0	0	0	0	0	0	0
LABOUR	0	0	0	0	0	0	0	0	0	0
OTHER	0	0	3264	5222	6528	6528	6528	6528	6528	6528
TOT. VARIABLE OPERATING EXPEND.	0	0	3264	5222	6528	6528	6528	6528	6528	6528
FIXED EXPENDITURES										
MAINTENANCE	0	0	0	0	0	0	0	0	0	0
INSURANCE	0	0	0	0	0	0	0	0	0	0
TAX	0	0	0	0	0	0	0	0	0	0
OFFICE AND ADMIN. EXPENDITURES	0	0	0	0	0	0	0	0	0	0
PERSONNEL	0	0	0	0	0	0	0	0	0	0
RENT ON OFFICE & FACTORY BUILDING	0	0	0	0	0	0	0	0	0	0
OTHER	0	0	90	90	90	90	90	90	90	90
TOT. FIXED OPERATING EXPEND.	0	0	90	90	90	90	90	90	90	90
TOTAL. OPERATING EXPENDITURES	0	0	3354	5321	6618	6618	6618	6618	6618	6618

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APPENDIX II - FINANCIAL DATA

TABLE 3. REPAYMENT OF LOANS AND FINANCIAL CHARGES

ERYTHROMYCINS

CURRENCY : 1000 U.S. DOLLARS

YEARS	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000
FOREIGN BANK 1-LOAN AT BEGINNING YEAR	925	925	925	925	740	555	370	185	0	0
REPAYMENT OF PRINCIPAL	0	0	0	185	185	185	185	185	0	0
PAYMENTS OF INTEREST	88	88	88	88	70	53	35	18	0	0
LOAN AT YEAR END	925	925	925	740	555	370	185	0	0	0
FOREIGN BANK 2-LOAN AT BEGINNING YEAR	0	0	0	0	0	0	0	0	0	0
REPAYMENT OF PRINCIPAL	0	0	0	0	0	0	0	0	0	0
PAYMENTS OF INTEREST	0	0	0	0	0	0	0	0	0	0
LOAN AT YEAR END	0	0	0	0	0	0	0	0	0	0
FOREIGN BANK 3-LOAN AT BEGINNING YEAR	0	0	0	0	0	0	0	0	0	0
REPAYMENT OF PRINCIPAL	0	0	0	0	0	0	0	0	0	0
PAYMENTS OF INTEREST	0	0	0	0	0	0	0	0	0	0
LOAN AT YEAR END	0	0	0	0	0	0	0	0	0	0
LOCAL BANK 1-LOAN AT BEGINNING YEAR	0	0	0	0	0	0	0	0	0	0
REPAYMENT OF PRINCIPAL	0	0	0	0	0	0	0	0	0	0
PAYMENTS OF INTEREST	0	0	0	0	0	0	0	0	0	0
LOAN AT YEAR END	0	0	0	0	0	0	0	0	0	0
LOCAL BANK 2-LOAN AT BEGINNING YEAR	0	0	0	0	0	0	0	0	0	0
REPAYMENT OF PRINCIPAL	0	0	0	0	0	0	0	0	0	0
PAYMENTS OF INTEREST	0	0	0	0	0	0	0	0	0	0
LOAN AT YEAR END	0	0	0	0	0	0	0	0	0	0
LOCAL BANK 3-LOAN AT BEGINNING YEAR	0	0	0	0	0	0	0	0	0	0
REPAYMENT OF PRINCIPAL	0	0	0	0	0	0	0	0	0	0
PAYMENTS OF INTEREST	0	0	0	0	0	0	0	0	0	0
LOAN AT YEAR END	0	0	0	0	0	0	0	0	0	0
TOTAL LOANS AT BEGINNING YEAR	925	925	925	925	740	555	370	185	0	0
TOTAL REPAYMENT OF PRINCIPAL	0	0	0	185	185	185	185	185	0	0
TOTAL PAYMENTS OF INTEREST	88	88	88	88	70	53	35	18	0	0
TOTAL LOAN AT YEAR END	925	925	925	740	555	370	185	0	0	0

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APPENDIX II - FINANCIAL DATA TABLE 4. DEPRECIATION AND TAX ON PROFITS

ERYTHROMYCINS CURRENCY : 1000 U.S. DOLLARS

YEARS	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000
TAX DEPRECIATION AND ALLOWANCES										
INFRASTRUCTURE	0	0	0	0	0	0	0	0	0	0
FACTORY BUILDINGS	0	0	14	14	14	14	14	14	14	14
OFFICE BUILDINGS	0	0	0	0	0	0	0	0	0	0
STAFF HOUSES	0	0	0	0	0	0	0	0	0	0
PLANT AND MACHINERY INCLUD. FREIGHT ETC.	0	87	139	139	139	139	139	139	139	139
VEHICLES	0	0	0	0	0	0	0	0	0	0
OTHER EQUIPMENT	0	0	0	0	0	0	0	0	0	0
PRELIMINARY EXPENDITURES	0	0	15	15	15	15	15	0	0	0
TOTAL DEPRECIATIONS	0	87	168	168	168	168	168	153	153	153
TAXABLE PROFIT/(LOSS)	(88)	(229)	(441)	273	671	929	967	999	1017	1017
ACCUMULATED PROFIT/(LOSS)	(88)	(317)	(758)	(485)	186	1115	2082	3081	4098	5115
TAX	0	0	0	0	0	0	0	500	509	509

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APPENDIX II - FINANCIAL DATA TABLE 5. WORKING CAPITAL REQUIREMENTS

ERYTHROMYCINS CURRENCY : 1000 U.S. DOLLARS

YEARS	MONTHS	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000
CURRENT ASSETS											
CASH	1	0	0	0	0	0	0	0	0	0	0
RAW MATERIALS	3	0	0	0	0	0	0	0	0	0	0
INTERMEDIATE MATERIALS	3	0	0	0	0	0	0	0	0	0	0
OTHER MATERIALS/SPARE PARTS	3	0	0	0	0	0	0	0	0	0	0
WORK IN PROGRESS	3	0	0	973	1557	1947	1947	1947	1947	1947	1947
FUEL	3	0	0	0	0	0	0	0	0	0	0
PACKAGING ETC.	3	0	0	0	0	0	0	0	0	0	0
FINISHED PRODUCTS	2	0	0	649	1038	1298	1298	1298	1298	1298	1298
RECIEVABLES	1	0	0	270	487	627	649	649	649	649	649
TOTAL CURRENT ASSETS		0	0	1892	3082	3872	3894	3894	3894	3894	3894
MINUS: CURRENT LIABILITIES											
RAW MATERIAL	1	0	0	0	0	0	0	0	0	0	0
INTERMEDIATE MATERIAL	1	0	0	0	0	0	0	0	0	0	0
OTHER MATERIALS/SPARE PARTS	1	0	0	0	0	0	0	0	0	0	0
FUEL	1	0	0	0	0	0	0	0	0	0	0
PACKAGING	1	0	0	0	0	0	0	0	0	0	0
CURRENT LIABILITIES		0	0	0	0	0	0	0	0	0	0
WORKING CAPITAL REQUIREMENTS		0	0	1892	3082	3872	3894	3894	3894	3894	3894
WORKING CAPITAL INCREASE/ (DECREASE) P.A.		0	0	1892	1190	790	22	0	0	0	0

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APPENDIX II - FINANCIAL DATA TABLE 6. PROFIT AND LOSS ACCOUNT FORECAST

ERYTHROMYCINS CURRENCY : 1000 U.S. DOLLARS

YEARS	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000
TOTAL NET SALES	0	0	3254	5841	7528	7788	7788	7788	7788	7788
OPERATING EXPENDITURES	0	0	3354	5312	6618	6618	6618	6618	6618	6618
DEPRECIATION AND AMORTISATION	0	87	168	168	168	168	168	153	153	153
TOTAL COST OF PRODUCTION	0	87	3522	5480	6786	6786	6786	6771	6771	6771
LOAN INTEREST	98	88	88	88	70	53	35	18	0	0
OVERDRAFT INTEREST	0	54	76	0	1	20	0	0	0	0
TOTAL FINANCIAL CHARGES	88	142	164	88	71	73	35	18	0	0
TOTAL COSTS	86	229	3686	5568	6857	6859	6821	6789	6771	6771
NET PROFIT/(LOSS) BEFORE TAX	-88	-229	-449	273	671	929	967	999	1017	1017
TAX	0	0	0	0	0	0	0	500	509	509
PROFIT/(LOSS) AFTER TAX	-88	-229	-441	273	671	929	967	499	508	508
RETURN ON EQUITY %	0	0	0	7	17	23	24	12	13	13
APPROPRIATION OF PROFITS										
DIVIDENDS - AMOUNT	0	0	0	0	0	0	0	0	0	0
DIVIDENDS - % ON EQUITY	0	0	0	0	0	0	0	0	0	0
RETAINED EARNINGS FOR THE YEAR	-88	-229	-441	273	671	929	967	499	508	508
CUMULATIVE RETAINED EARNINGS	-88	-317	-758	-485	186	1115	2082	2581	3089	3597

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APPENDIX II - FINANCIAL DATA TABLE 7. CASH FLOW

ERYTHROMYCINS CURRENCY : 1000 U.S. DOLLARS

YEARS	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000
SOURCES OF CASH										
EQUITY	100	1000	2900	0	0	0	0	0	0	0
LOANS	0	0	925	0	0	0	0	0	0	0
NET PROFIT/(LOSS) BEFORE TAX	-88	-229	-441	273	671	929	967	999	1017	1017
DEPRECIATION AND AMORTISATION	0	87	168	168	168	168	168	153	153	153
CASH INCOME	12	858	3552	441	839	1097	1135	1152	1170	1170
WORKING CAPITAL	0	0	0	0	0	0	0	0	0	0
SALE OF FIXED ASSET	0	0	0	0	0	0	0	0	0	0
TOTAL CASH AVAILABLE	12	858	3552	441	839	1097	1135	1152	1170	1170
CASH REQUIREMENTS										
CAPITAL INVESTMENT/REPLACEMENT ASSETS	667	936	0	0	0	0	0	0	0	0
DIVIDENDS PAYMENTS	0	0	0	0	0	0	0	0	0	0
TAX PAYMENTS	0	0	0	0	0	0	0	0	500	509
WORKING CAPITAL INCREASE	0	0	1892	1190	790	22	0	0	0	0
PAYMENT OF PRINCIPAL	0	0	0	185	185	185	185	185	0	0
TOTAL CASH REQUIREMENTS	667	936	1892	1375	975	207	185	185	500	509
CASH SITUATION AT YEAR END	-665	-78	1660	-934	-136	890	950	967	670	661

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APPENDIX II - FINANCIAL DATA

TABLE 8. BALANCE SHEET PROJECTION

ERYTHROMYCINS

CURRENCY : 1000 U.S. DOLLARS

YEARS	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000
ASSETS										
CASH	0	0	0	0	0	0	0	0	0	0
STOCKS	0	0	1622	2529	3245	3245	3245	3245	3245	3245
RECEIVABLES	0	0	270	487	327	649	649	649	649	649
RESERVE	0	0	0	0	0	0	0	0	0	0
TOTAL CURRENT ASSETS	0	0	1892	3082	3872	3894	3894	3894	3894	3894
FIXED ASSETS GROSS	667	1603	1603	1603	1603	1603	1603	1603	1603	1603
DEPRECIATION AND AMORTISATION	0	87	255	423	591	759	927	1080	1233	1386
NET FIXED ASSETS	667	1516	[illegible]	1180	1012	844	[illegible]	523	370	[illegible]
TOTAL ASSETS	667	1516	3240	4262	4884	4738	4570	4417	4264	4111
LIABILITIES										
TAX PAYABLE	0	0	0	0	0	0	0	500	509	569
DIVIDENDS PAYABLE	0	0	0	0	0	0	0	0	0	0
CURRENT ACCOUNT (MINUS=SURPLUS)	355	541	-927	7	147	-747	-1697	-2664	-3334	-3995
CURRENT LIABILITIES	0	0	0	0	0	0	0	0	0	0
TOTAL CURRENT LIABILITIES	355	[illegible]	-927	7	147	-747	[illegible]	[illegible]	[illegible]	[illegible]
LONG TERM DEBT	925	925	925	740	555	370	185	0	0	0
EQUITY (1)	100	1100	4000	4000	4000	4000	4000	4000	4000	4000
RESERVES	-88	-317	-758	-485	186	1115	2062	2581	3089	3597
TOTAL SHAREHOLDERS EQUITY	12	783	3242	3515	4186	5115	6062	6581	7089	7597
TOTAL LIABILITIES	667	1516	3240	4262	4884	4738	4570	4417	4264	4111
DEBT: EQUITY RATIO (2)	77.1	1.2	0.3	0.2	0.1	0.1	0.0	0.0	0.0	0.0
SECURITY COVERAGE RATIO (3)	0.7	1.6	1.5	1.6	1.8	2.3	3.7	0.0	0.0	0.0
LIQUIDITY RATIO (4)	0.0	0.0	0.0	440.3	27.1	0.0	0.0	0.0	0.0	0.0

(1) Amount of equity plus eventual future increase
(2) Long Term Debt : Total Shareholders Equity
(3) [illegible]
(4) Total Current Assets : Total Current Liabilities

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APPENDIX II - FINANCIAL DATA TABLE 9. SENSITIVITY ANALYSIS FOR 2ND YEAR AT 100%

ERYTHROMYCINE CURRENCY : 1000 U.S. DOLLARS

RESULTS :NET PROFIT/(LOSS) BEFORE TAX

	SELLING PRICES OF FINISHED PRODUCTS						
	-30%	-20%	-10%	CONSTANT	+10%	+20%	+30%
TOTAL OPER. EXPENS. +30%	-3393	-2614	-1835	-1056	-278	501	1280
TOTAL OPER. EXPENS. +20%	-2731	-1952	-1176	-395	384	1163	1942
TOTAL OPER. EXPENS. +10%	-2069	-1290	-512	267	1046	1825	2604
TOTAL OPER. EXPENS. CONSTANT	-1407	-629	150	929	1708	2487	3265
TOTAL OPER. EXPENS. -10%	-746	33	812	1591	2370	3148	3927
TOTAL OPER. EXPENS. -20%	-84	695	1474	2253	3031	3810	4589
TOTAL OPER. EXPENS. -30%	578	1357	2136	2914	3693	4472	5251

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APPENDIX II - FINANCIAL DATA TABLE 11. NET PRESENT VALUE AND DISCOUNTED CASH FLO

ERYTHROMYCINS CURRENCY : 1000 U.S. DOLLARS

YEARS	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000
NET PRESENT VALUE P.A. (NET SALES MINUS EXPENDITURE, MINUS INVESTMENT FIXED ASSETS, DISCOUNTED AT 10% P.A.)	-635	-750	-90	397	622	726	660	600	546	496
SUM OF NET PRESENT VALUES (YEAR 1 TO 10)										2572
DISCOUNTED CASH FLOW RATE (INTERNAL RATE OF RETURN = DISCOUNTED RATE AT WHICH CASH FLOW YEARS 1 TO 10 EQUALS ZERO)(%)										34.23

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APPENDIX II - DEVELOPMENT CONTRIBUTION — TABLE 1. FOREIGN EXCHANGE EARNINGS

ERYTHROMYCINS — CURRENCY : 1000 U.S. DOLLARS

YEARS	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000
INFLOW										
EQUITY AND LOANS	925	0	0	0	0	0	0	0	0	0
IMPORT SUBSTITUTION	0	0	3500	5600	7000	7000	7000	7000	7000	7000
EXPORT EARNINGS	0	0	0	0	0	0	0	0	0	0
TOTAL	925	0	3500	5600	7000	7000	7000	7000	7000	7000
OUTFLOW										
INTEREST (NET)	88	88	88	86	70	53	35	18	0	0
PRINCIPAL	0	0	0	185	185	185	185	185	0	0
DIVIDENDS (NET)	0	0	0	0	0	0	0	0	0	0
CAPITAL GOODS (NET OF DUTY TAXES)	335	575	0	0	0	0	0	0	0	0
IMPORT OF MATERIALS (NET)	0	0	0	0	0	0	0	0	0	0
TRANSFER PAYMENTS	0	0	0	0	0	0	0	0	0	0
TOTAL	438	663	88	273	255	238	220	203	0	0
SURPLUS/(DEFICIT) P.A.	487	-663	3412	5327	6745	6762	6780	6797	7000	7000
CUMULATED SURPLUS/(DEFICIT)	487	-176	3236	8563	15308	22070	28850	35647	42647	49647

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APPENDIX II - DEVELOPMENT CONTRIBUTION TABLE 2. FISCAL EFFECTS

ERYTHROMYCINS CURRENCY : 1000 U.S. DOLLARS

YEARS	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000
POSITIVE DIRECT EFFECTS										
TAX ON LAND ETC.	0	0	0	0	0	0	0	0	0	0
DUTY ON IMPORTED EQUIPMENT	0	0	0	0	0	0	0	0	0	0
EXCISE AND CONSUMPTION TAXES	0	0	0	0	0	0	0	0	0	0
CORPORATE TAX (ON PROFITS)	0	0	0	0	0	0	0	500	509	509
PERSONAL INCOME TAX	0	0	0	0	0	0	0	0	0	0
TAX ON DIVIDENDS	0	0	0	0	0	0	0	0	0	0
TAXES ON INTEREST	0	0	0	0	0	0	0	0	0	0
TOTAL TAX PAYMENTS	0	0	0	0	0	0	0	500	509	509
NEGATIVE DIRECT EFFECTS										
LOSS OF IMP. DUTY ON LOCAL PROD. GOODS	0	0	400	640	800	800	800	800	800	800
NET TAX INCOME F.E.	0	0	-400	-640	-800	-800	-800	-300	-291	-291
CUMULATED TAX INCOME	0	0	-400	-1040	-1840	-2640	-3440	-3740	-4031	-4322

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APPENDIX II - DEVELOPMENT CONTRIBUTION TABLE 3. CONTRIBUTION TO NATIONAL INCOME 2ND YEAR FULL PRODUCTION

ERYTHROMYCINS CURRENCY : 1000 U.S. DOLLARS

YEAR	1996
PURCHASES	6616
DEPRECIATION	168
TOTAL	6784
FACTOR COSTS (NET VALUE ADDED)	
SALARIES AND WAGES	0
INTEREST	73
RENT ON OFFICE & FACTORY BUILDINGS	0
NET PROFIT/(LOSS) BEFORE TAX	929
TOTAL NET VALUE ADDED	1002
GRAND TOTAL	7788

ERYTHROMYCINS

FOR SECOND YEAR AT 100% OF CAPACITY YEAR = 1996

TOTAL OUTPUT VALUE	= 7788
TOTAL COST	= 6859
FIXED PRODUCTION EXPENDITURE	= 331
FINANCIAL CHARGES	= 73
DEPRECIATION	= 168

VALUE OF P&L ACCOUNT BREAK EVEN POINT FOR
SECOND YEAR AT 100% CAPACITY = 26%
VALUE OF INTERNAL RATE OF RETURN = 34.23413

CURRENCY : 1000 U.S. DOLLARS