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PHILIPPINES PHARMACEUTICAL INDUSTRY DEVELOPMENT STUDY

DP/PHI/87/019

PHILIPPINES

Technical report: Manufacture of Antibiotics through fermentation*

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. V. Gallo
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United Nations Industrial Development Organization
Vienna

* This document has not been edited.

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1 - SUMMARY

1.1 SCOPE OF THE WORK

Purpose of the present report is to provide inputs pertaining to manufacture of antibiotics in the Philippines through fermentation, and to evaluate whether a local production of some of these antibiotics could be feasible on an industrial scale, in accordance with one of the main objectives of the National Drug Policy, that is to achieve self-reliance with respect to bulk pharmaceutical chemicals.

1.2 Analysis of the present status

A preliminary research on the domestic antibiotics market has been done, through the evaluation of the following sources:

- Institute of Medical Statistics (IMS) data for sales through drugstores and hospitals

- Business Statistics Monitor data, which include weekly descriptive arrival reports by air or by sea

- Procurement of the Department of Health for 1987 and Procurement Program for 1988 for Rural Health Units

- Direct Procurement by the Regions

- Production data relevant to Chemfield Inc.,the only local bulk antibiotics plant, manufacturing semi-synthetic Penicillins.

On the basis of all the gathered data, some projections have been made in order to estimate the antibiotics demand in the next years.

1.3 General assessment

A detailed investigation has been performed on the Philippines specific situation, in order to identify locally available raw materials and energy sources for the manufacture of antibiotics and to evaluate local skilled manpower, infrastructure and plant construction capabilities.

As far as raw materials are concerned, agricultural products and agro-waste materials are of great importance and in particular:

- Products from sugar factories, such as raw sugar, molasses or cane juice. These products can constitute the source of the carbohydrate requirement of the fermentation processes and their local prices could greatly improve the project profitability

- Products from corn wet milling factories, such as starch, corn-steep liquor, dextrine and glucose solution.

It is to be underlined that sugar factories might supply also the energy source, which could be the Bagasse. In fact, this by-product, presently available at very low price, could be utilized for the production of the large amounts of electric power, commonly required for a large scale fermentation plant.

From these considerations, it appears that it would be convenient to install the future fermentation plant adjacent to an existing sugar factory. This possibility has been considered with great interested by officials of the Sugar Regulatory Administration.

1.4 Recommendations

According to the writer, two main options should be examined in order to reach a reasonable degree of self-reliance, as far as the local antibiotics production is concerned:

a - Establishment of a fermentation pilot plant for antibiotics
b - Implementation of an industrial scale plant for Penicillin production, mainly Penicillin G, Penicillin V and 6 APA

1.4.1 Fermentation pilot plant

The main objectives of the pilot plant should be:

- To investigate the local availability of raw materials, the main condition for the implementation of a large scale fermentation plant.
- To train technical personnel in the fermentation technology.

The pilot plant should be, at least in a first phase, "Development Oriented" and not mainly "Research Oriented" (strains improvement should be left to a second phase devoted to research. The main technical features of the Pilot-Plant have seen outlined by the writer (see chapter 6.0),but it has also been underlined that a fermentation pilot-plant already exists at BIOTECH Los Banos, characterized by modern equipment and complete infrastructures, recommended to be utilized in the implementation of the new fermentation pilot-plant project for antibiotics.

Two institutions can be identified as possible centers for the management of the pilot plant project:

- ITDI (Industrial Technology Development Institute), under the supervision of the DOST.
- BIOTECH, Los Banos, that is connected with U.P. Manpower resources of both of these institutions seems to be severely lacking both in quantity and quality, to be able to handle the above mentioned project. Also from this point of view a concentration of efforts of the two groups would lead to an optimization in utilization of local resources. It is, however, realized, that there could be complications and difficulties from a logistic, management and financial point of view.

A preliminary investment cost estimate, as far as machinery, equipment and engineering are concerned, is between US$ 1.5 and 2.0 millions (not including training and consultants costs).

A saving of 40 to 50 % of this cost could be expected, if the existing facilities of BIOTECH, Los Baños, are utilized.

The local technical personnel required for handling the above mentioned project could be estimated at about 20 persons (for the qualifications see paragraph 6.4).

1.4.2 Penicillins Plant

The proposed plant should cover all local requirements of the Beta-lactam antibiotics in 1995, except Cephalosporins.

The fermentation unit capacity is:

250 Tons per year of Penicillin G Potassium

45 Tons per year of Penicillin V Potassium

The main part of Penicillin G would be converted into 6-APA (6-amino-penicillanic acid) to cover the requirements relevant to the semi-synthetic penicillins production (Ampicillin, Amoxicillin, Cloxacillin, etc), while the rest of Penicillin G would be utilized to produce injectable Penicillins such as Pen G Procaine, Pen G Sodium or Potassium and Pen G Benzathine as well as feed grade Penicillins such as Pen G Procaine.

The most important criteria that led the writer to this recommendations are:

a - Consumptions volumes - Penicillins constitute by far the most important family of antibiotics in the Filipino market, both from a volume and value point of view. No other antibiotic could be the object of a simple line production, because the quantities are too low to allow the viability of an Industrial plant.

b - Prevailing diseases and morbidity - Penicillins are characterized by a broad spectrum activity, allowing their utilization in the treatment of a wide variety of infectious diseases prevalent in the country.

c - Government Health Programs - It appears from the data concerning DOH drugs supply to the RHU's, that Penicillins and especially Amoxicillin and Ampicillin are among the most important drugs both by volume and value.

d - Strategic importance - Penicillin G is the starting point for the production of several other antibiotics such as Semi-synthetic Penicillins (Ampicillin, Amoxicillin, etc) through 6-APA, Semi-sysnthetic Cephalosporins (Cephalexin, Cephradine, etc) through 7-ADCA, injectable and retard Penicillins (Procaine, Benzathine, etc) and feed grade Penicillins.

e - World Market Trends - It appears from data concerning the World Market Trend for antibiotics (see chapter 5.0) that Penicillins will probably be characterized by the highest growth rate in most of the developing countries, compared with other families of Antibiotics.

f - Patent position and available technologies - Almost all international patents relevant to Penicillin G and V have already expired. Good technologies are available in some western countries, at reasonable prices.

g - Available domestic raw materials - As already mentioned in paragraph 1.3, some raw materials that play important role in the Penicillin manufacturing cost as the carbohydrate source (that can be either glucose solution, molasses or cane sugar) are locally available, thus increasing the project profitability, decreasing foreign exposure and saving foreign exchange.

h - Existence of down-stream facilities - As already underlined, a Semi-synthetic Penicillins Plant already exists in the Philippines and is characterized by a satisfactory economic situation. This plant utilizes at present imported 6-APA as main raw material. The local production of Pen G and 6-APA would therefore allow the Philippines to cover with national products the entire line of Penicillins requirements.

The manpower required by the Penicillin Plant has been evaluated at about 190 persons (for the breakdown and qualifications see paragraph 7.8).

The investment level relevant to the above mentioned Penicillin Plant has been estimated in about US $30 millions.

The total sales have been estimated at about US$ 11.63 millions per year, while the Net Profit after Taxes has been projected to be in the vicinity of US $1.45 million annually.

The Return on Sales would represent about 19% during the first four year of life of the plant (charaterized by income tax holiday) and 12.5% after the 4th year.

An annual Rate of Return on Investment of 11.0% has been estimated with a Payback time of about 7 years.

All these data have been calculated on the basis of the present local situation as far as incentives are concerned (see paragraph 7.9)

A price regulatory policy, for instance, would be of great relevance in improving the profitability of a fermentation plant.

To evaluate the impact of such an incentive on the project economics, an alternative calculation of profitability has been made, considering the case that all products prices would be increased by 10%, as a consequence of a price regulatory policy(1). In these conditions the economic evaluation indexes for the Penicillin Plant would become:

- Return on sales :26% (for the first 4 years) and 17% after the 4th year
- Payback time :about 5 years
- Rate of return on investment: 14%

Besides the above-mentioned recomendations, a third option has been considered, consisting of a multipurpose plant for Erythromycin, Rifampicin and Tetracyclines production. Also in this case, the production capacity has been defined assuming to cover the local requirements of these antibiotics in 1995:

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(1) In other words the locally manufactured pharmaceutical chemicals could be sold on the domestic market at prices 10% higher than the prevailing international ones.

- Erythromycin Base 26 Tons per year
- Rifampicin 20 Tons per year
- Tetracyclines 85 Tons per year

On the basis of the analysis made by the writer (see Chapter 8), this latter option seems to be, for the time being, less attractive from a profitability point of view, but it could still be considered as a longer-term object in the achievement of a relative self-reliance in the antibiotic production, in the case that some changes occur in the future in the international market conditions, as well as in the local situation concerning regulatory policies for the pharmaceutical industry.

2 - INTRODUCTION

Definition of Antibiotics

Antibiotics can be described as chemical and/or metabolic substances derived from various microorganisms that inhibit the growth or reproduction of, or even destroy, other microorganisms.

Most of the chemically useful antibiotics are manufactured from species of the mold *Penicillium* and various *Streptomyces* bacteria.

Antibiotics act directly on the microorganisms that cause infections, rather than enhancing the immunological response of the infected host.

The antimicrobial activity of antibiotics is selective, i.e. some microbes are affected by antibiotics, and other are not affected at all or only to a limited degree. No antibiotic is effective against all microorganisms; each one is characterized by a specific antimicrobial spectrum of activity against different organisms. Some have a broad spectrum of activity and are effective against various bacteria ranging from gram-positive to grain-negative types; while others have a narrow spectrum and are active against members of a specific groups of microbes. Table 2.1 addresses the sensitivity of bacteria to major antibiotics.

Distribution channels

There are basically three types of enterprises participating in the market place of antibiotics: bulk manufacturers, dosage form formulators and fully intergrated pharmaceutical manufacturers. Bulk manufacturers are those firms which produce bulk antibiotics (and/or semi-synthetics) only. They do not manufacture any dosage form materials. Dosage form formulators, on the other hand, do not manufacture any of their bulk material; they purchase it on the open market. They take the purchased bulk material, formulate it into the various final dosage forms, package it and market it. Fully integrated pharmaceutical manufacturers have the capability of manufacturing their own bulk material, as well as the capacity to perform their own final dosage form formulation and packaging. These manufacturers also sells their excess (or non-captive) bulk material to dosage form formulators through brokers and/or directly. Firms that successfully supply bulk antibiotics to the market place have the following charateristics:

TABLE 2.1 SENSITIVITY OF BACTERIA TO MAJOR ANTIBIOTICS

ANTIBIOTICS \ BACTERIA		Gram-Positive				Gram-Negative									Others			
		Coccus				C.	Bacillus											
		Staphylo-coccus																
		PC-G																
		Sensitive	Resistant	Streptococcus	Enterococcus	Gonococcus	Escherichia Coli.	Pneumobacillus	Citrobacter	Enterobacter	Serratia	Pseudomonas aeruginosa	Proteus	Acinetobacter	Bacteroides	Actinomyces	Mycoplasma	Treponema Pallidum
Penicillin	Ampicillin	X		X	X	X	X						X					X
	Phenethicillin	X		X		X												X
	Cyclacillin	X	X	X	X		X	X	X				X					
	Amoxycillin	X	X	X	X	X	X						X					
	Carbenicillin	X	X	X			X	X				X	X					
	Sulbenicillin	X	X	X	X		X	X	X	X		X	X					
	Piperacillin	X	X	X	X		X	X	X	X	X	X	X	X	X			
	Pivmecillinam						X	X	X	X			X		X			
	Ticarcillin						X			X		X	X					
C.P.	Chloramphenicol		X	X	X	X	X	X					X					
Tetra-cycline	Doxycycline	X	X	X	X	X	X	X										
	Minocycline (O)	X	X	X	X	X	X	X	X	X		X	X					X
	Minocycline (I)		X	X			X	X		X		X		X				
Cephalosporin	Cephalcridine	X	X	X		X	X	X					X					
	Cephalexin	X	X	X	X	X	X	X		X			X					
	Cefazolin	X	X	X	X		X	X					X					
	Cephacetrile	X	X	X			X	X										
	Ceftezol	X	X	X			X	X					X					
	Cephradine	X	X	X			X	X					X					
	Cefatrizine	X	X	X			X	X					X					
	Cefmetazole						X	X					X		X			
	Cefoxitin						X	X					X		X			
Macro-lide	Josamycin	X	X	X	X													
	Midecamycin	X	X	X	X													
	Erythromycin	X	X	X	X	X											X	X
Amino-glycoside	Kanamycin	X	X			X	X	X				X	X					
	Fradiomycin						X											
	Gentamicin		X				X	X		X	X	X	X					
	Sekanamycin	X	X	X	X		X					X	X					
	Dibekacin		X				X	X				X	X					
	Amikacin						X	X	X	X	X	X	X					
	Tobramycin						X	X		X		X	X					
Other	Polymixin						X	X		X		X						

Notes: C = Coccus; PC-G = Penicillin G; C.P. = Chloramphenicol O = Oral; I = Injectable.

Source: Medicina Vol. 17, No. 10, 1980-10.

a - They have the ability to manufacture the material at low cost, resulting in competitive market place prices.

b - They have flexible manufacturing facilities that allow them to manufacture different products, not just one.

c - They have established relationships with major customers.

d - They have a reputation for consistent quality, timely delivery and good customer relations.

3.0 ANALYSIS OF THE PRESENT STATUS AND PROJECTIONS

3.1 - GENERAL CONSIDERATIONS (1)

3.1.1 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 coast 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.

3.1.2 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.

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(1) Part 3.1-3.4 have been worked out together with the Expert in semi-synthesis of antibiotics.

3.1.2 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 °/oo, with a decrease of 8.7 °/oo 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 °/oo .

Different death rates were noticed in the different regions, the highest being in region 1 with 7.8 °/oo, followed by the National Capital Region with 7.0 °/oo; 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 projection of 1995.

3.2 - HEALTH SITUATION

3.2.1 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)	Diarrhoea/gastroenteritis	1087.5
3)	Influenza	966.1
4)	Upper respiratory tract infection	939.9

(1) Based on Regional Health Office Reports

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 diagnozed
- 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.

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.

3.2.2 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)

	C A U S E	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.	Cardio Vascular Diseases	35.5	7.2
5.	Malignant Neoplasms	23.3	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 YEAR BOOK 1987

3.2.3 Health Organization

From the point of view of health care, 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	1,229	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

3.3. 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.
- Fake 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.

3.4. THE PHARMACEUTICAL MARKET FOR ANTIBIOTICS

3.4.1 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 brands.

- 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.

- 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.

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

- Other information have been collected through meetings and discussions with managers of some domestic and foreign Companies, especially the companies 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.

3.4.2 <u>The IMS Data</u>

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 3.01

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	10389	21	9471	43	19860
GENTAMYCIN	19	45761	10	10343	29	56104
NEOMYCIN	56	36046	7	1673	63	37683
PAROMOMYCIN	105	6768	4	249	109	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

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

Table 3.02
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 3.03

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)	12358	57567	2177	2598	14535	60165
PENICILLIN G BENZATHINE	95	3762	13	588	108	9612
PENICILLIN PROCAINE	500	8741	38	1322	538	10063

Table 3.04

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	1866	36	48965

Table 3.05

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 3.06

FAMILY : RIFAMYCINS

ACTIVE INGREDIENTS	DRUGSTORE VOLUME (Kgs)	DRUGSTORE VALUE (Pesosx1000)	HOSPITAL VOLUME (Kgs)	HOSPITAL VALUE (Pesosx1000)	TOTAL VOLUME (Kgs)	TOTAL VALUE (Pesosx1000)
RIFAMPICIN	6492	202872	228	6125	6720	208997

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

Table 3.07

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
CEFTAZIDINE	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 3.08

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 3.09

FAMILY : SEMISYNTHETIC PENICILLIN

ACTIVE INGREDIENTS	DRUGSTORE VOLUME (Kgs)	DRUGSTORE VALUE (Pesosx1000)	HOSPITAL VOLUME (Kgs)	HOSPITAL VALUE (Pesosx1000)	TOTAL VOLUME (Kgs)	TOTAL VALUE (Pesosx1000)
AMPICILLIN	19978	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	563	9526	98	1887	661	11413
BECAMPICILLIN	1913	36446	177	5116	2150	41562
MECILLINAM	7	273	0.1	122	7.1	395
METAMPICILLIN	78	1183	79	2002	157	3185
NAFCILLIN SOD.	730	15070	58	2539	788	17609
PIVAMPICILLIN	170	7265	15	808	185	8073
PIVMECILLINAM	70	4941	12	783	82	5724
OXACILLIN	816	19810	29	2942	845	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

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

Table 3.10

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 3.11

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
CLINDANYCIN	364	17089	28	4013	392	21102
FRAMYCETIN	12	7782	1.5	379	13.5	8161
GRISEOFULVIN	750	12256	15	237	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 prepared 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 is mentioning 16.3 tons for 1987 and 11.3 tons fo.- 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 undersirable 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 as benzatine and procaine salts and feed grade forms) 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-aminocephalosporanic acid), which is the basic material of two important derivatives, Cephalexin and Cephradin.

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

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-Aminodesacetoxy cephalosporanic 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.

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(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, chlorotetracycline 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. Chloramphenicol 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.

Quantities involved are insufficient from the point of view of production feasibility.

3.4.3 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 latter 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 in the USA, there are talks to delist this product in the Philippines, despite its high therapheutic value in the treatment of typhoid fever.

Table 3.12

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 3.13

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	90-125
ERYTHROMYCIN ESTOLATE	1300	75-110

* FOB PRICES

Table 3.14

ARRIVAL BY SHIP OR PLANE IN 1987

FAMILY : PENICILLINS

ACTIVE INGREDIENT	QUANTITY (Kgs)	PRICE RANGE * ($ Per Kg.)
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)	1300	28-31
PENICILLIN V POTASSIUM	41400	30-60
PENICILLIN V ACID	1600	27- 30

Table 3.15

ARRIVAL BY SHIP OR PLANE IN 1987

FAMILY : RIFAMYCINS

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

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* FOB PRICES

Table 3.16

ARRIVAL BY SHIP OR PLANE IN 1987

FAMILY : STREPTOMYCINS

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

Table 3.17

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

* FOB PRICES

Table 3.18

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

Table 3.19

ARRIVAL BY SHIP OR PLANE IN 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

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* FOB PRICES

Table 3.20

ARRIVAL BY SHIP OR PLANE IN 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

Table 3.21

ARRIVAL BY SHIP OR PLANE IN 1988

FAMILY : PENICILLINS

ACTIVE INGREDIENT	QUANTITY (Kgs)	PRICE RANGE * ($ Per Kg.)
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

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* FOB PRICES

Table 3.22

ARRIVAL BY SHIP OR PLANE IN 1988

FAMILY : RIFAMYCINS

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

Table 3.23

ARRIVAL BY SHIP OR PLANE IN 1987

FAMILY : STREPTOMYCINS

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

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* FOB PRICES

Table 3.24

ARRIVAL BY SHIP OR PLANE IN 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 3.25

ARRIVAL BY SHIP OR PLANE IN 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 developed.

Rifamycins

Rifampicin is an important antituberculosis 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 3.4.2), 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 determine whether there is space for local production.(2)

3.4.4 Procurement from 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 Chlortetracycline 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)

3.4.5 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 :

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

3.4.6 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	-	0.500 T (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

(1) The TB incidence is estimated at 6.6%, the total number of TB patents in the country being in the vicinity of 375,000, not considering recurrent cases.

3.5 PROJECTIONS

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, we will discuss in detail the antibiotics which in the preceeding pages appeared to be of some 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 large scale fermentation plant, including 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 of the Philippines, reaching 68 millions in 1995
- the GNP growth projections and the distribution of wealth
- the family expenditure devoted to health care and purchase of medicines.
- the prescriptions and automedication habits (a more rational use of drugs and a better knowledge by the medical profession of the specificity of each antibiotic, as well as the use of generics)
- the DOH budgets devoted to the drug procurement
- the health programs for Tuberculosis and Leprosy, as well as other programs and measures, resulting in a possible improvement of the general health situation and the sanitary conditions of the population
- the increase of potential prescribers being about 6000 by 1995 (781 passed the board examination in 1988)

The estimates do not represent the total need of the country, but reflect only the market absorption capacity by the year 1995, including the private and public sector.

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

3.5.1 PENICILLINS

This family of antibiotics appears to be the most important in the Philippines market, both from the point of view of consumption volumes, as well as of value.

All the final products included in this family are manufactured starting from two fermentation antibiotics:

- Penicillin G Potassium
- Penicillin V Potassium

Penicillin G Potassium is the raw material for four classes of products·

a) Semi-synthetic Penicillins, as Ampicillin, Amoxycillin and Cloxacillin, produced from an intermediate called 6-APA (6-amino-penicillanic acid)

b) Semi-synthetic Cephalosporins, as Cephalexin and Cephradin, produced from the 7-ADCA (7-amino-desacetoxy-cephalosporanic acid)

c) Injectable Penicillins G, as Pen G Sodium, Pen G Procaine and Pen G Benzathine

d) Feed grade Penicillins G, as Pen G Procaine feed grade.

Penicillin V Potassium is utilized as it is or it is converted in Penicillin V Acid.

For the determination of the Penicillin G requirements in 1995, the following assumptions have been made:

a) Semi-synthetic Penicillins. This is the most important group of Penicillins. The detailed discussion on these products has been developed in the report of Dr. Sciaky concerning semi-synthetic antibiotics.

The estimated projected quantities in 1995 are:

Ampicillin	85 Tons/year
Amoxycillin	75 Tons/year
Cloxacillin	8 Tons/year

b) Semi-synthetic Cephalosporins. Though 6 Tons per year of Cephalexin have been foreseen for 1995 (see Dr. Sciaky's report on semi-synthetic antibiotics), this group of products has not been considered in evaluating the Pen G requirements,because their production from Pen G would involve the establishment of a plant for 7-ADCA production and such a plant, which is characterized by high complexity and high cost of investment, would not be viable for a Cephalexin production capacity of 6 Tons per year.

c) Injectable Penicillins G

About 21000 B.U. (Billion Units) (1) of injectable Penicillins G have been consumed in 1987 (Business Statistics Monitor).

The breakdown of this consumption among the different products is:

- Penicillin G Potassium	62 %
- Penicillin G Sodium	24 %
- Penicillin G Procaine	13 %
- Penicillin G Benzathine	1/2 %

(1) One B.U. is equivalent to 1.595 kg of activity of Pen G Potassium

Most of the consumption of these products is concentrated in the private sector.

Taking into consideration the foregoing elements, we estimate an increase of the market in volume of 6% per year, the total quantity of injectable Pen G reaching about 32000 B.U. in 1995.

d) Feed grade Penicillins G

Mostly Pen G Procaine feed grade is imported at present.

Quantities are in the range of 7500/8000 B.U. per year (Business Statistics Monitor, 1987).

The growth rate for this product having been rather low during the past few years, a reasonable increase of the market would be of 3/3.5 % per year, leading to a quantity of about 10,000 B.U. per year in 1995.

The Pen G Potassium estimated requirements for 1995 are therefore the following (considering the proper yields of conversion):

- Pen G K for Semisynthetic Penicillins : 352,000 B.U./year (through 6-APA)
- Pen G K for Injectable Penicillins G : 37,000 B.U./year
- Pen G K for Feed-grade Penicillins G : 11,000 B.U./year

In conclusion, the Pen G K quantity required to cover the overall local penicillin based antibiotics market necessities in 1995 (excluding Cephalexin) should be about 400,000 B.U. per year, corresponding to 250 Tons per year of Pen G K.

The Penicillin V consumption in 1987 was of about 45,000 B.U. (1) (43,000 B.U. being the requirement of the private sector and 2000 B.U. that of the public sector).

Assuming a growth rate of 6/7% per year, a requirement of 69,000 B.U. would be expected, corresponding to about 45 Tons of Pen V Potassium per year.

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(1) One B.U. is equivalent to 1.529 kg of activity of Pen V Potassium

3.5.2 ERYTHROMYCINS

The local projected production includes the preparation of the stearate and the ethylsuccinate from the Erythromycin Base, which is a fermentation antibiotic.

Erythromycin is an important broad spectrum antibiotic.

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 of DOH indicates about 4 tons in the form of stearate and ethylsuccinate.

In the projections up to 1995, we have considered a 6% growth of the private sector market up to 1991 and 4% up to 1995, thus reaching 17 tons in that year (for details see the report on semi-synthetic antibiotics prepared by Dr.Sciaky).

With a 6% increase in the DOH procurement giving a quantity of 6 tons in 1995, the total consumption could then reach 23 tons. Three tons per year of Erythromycin Thiocianate that is mainly used as a veterinary drug, could be added to this figure.

The total quantity of Erythromycin Base produced by fermentation, that would be necessary to cover the above mentioned consumption, is about 26 Ton per year (1995).

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 that the DOH could probably afford.

3.5.3 RIFAMYCINS

Rifampicin, which is the most widely used antibiotic of this family, is a product that plays an important role in the antituberculosis and antileprosy programs.

Imports for 1987 were of about 7 tons and the DOH procurement reached more than 13 tons.

The procurement program of the DOH for 1988 is of 11 tons in finished form, corresponding to the forecast for treatment of 40,000 cases of leprosy and 140,000 cases of tuberculosis.

For the coming year the projections of the DOH are (expressed in Kgs of Rifampicin):

Leprosy	1988	1989	1990	1991	1992
Paucibacillary	111	21	18	18	19
Multibacillary	416	405	92	92	88
Tuberculosis					
Short course chemotherapy	10,396	9,565	8,370	7,790	7,500
Total	10,923	9,991	8,480	7,900	7,607

Our projections reach a consumption of 9 tons in the private sector and 11 tons in the procurement programs of the DOH up to 1995, the total projected volume being of 20 tons annualy.

The corresponding quantity of Rifamycin B, that is the fermentation antibiotic commonly utilized to produce Rifampicin, is about 35 tons per year.

3.5.4 TETRACYCLINES

The main antibiotics of this family characterized by significant consumption in the Philippines are:

- Tetracyline Hydrochloride
- Oxytetracycline Hydrochloride
- Oxytetracycline feed grade
- Chlortetracycline feed grade

Tetracycline and Oxytetracycline Hydrochlorides are produced respectively from Tetracycline Base and Oxytetracycline Base, both fermentation products.

Chlortetracycline is produced by fermentation and it is not normally purified by extration from the broth.

For 1987, imports of Tetracycline Hydrochloride reached 16 tons. This product is a basic wide spectum antibiotic, having a relatively low price. The 1987 imports of Oxytetracycline hydrochloride were of 11.5 Tons.

For the projections up to 1995, the following additional considerations were kept in mind:

- Tetracyclines are old products with relatively limited market growth and with an annual increase which could be related only to the population growth.

- The DOH do not supply these antibiotics to the RHU's, except a very limited quantity of Oxytetracycline in the form of ophthalmic ointment (less than 1 kg).

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

- 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 of Tetracycline Hydrochloride and 15 tons of Oxytetracycline Hydrochloride.

As far as the Feed Grade Tetracyclines are concerned, about 35/40 Tons (expressed as 100% antibiotic) were imported into the Philippines in 1987. The orientative projection up to 1995 could reach 45/50 tons (corresponding to a growth rate of 3% per year). These feed grade products are characterized by a very small profit margin.

The overall quantities of fermentation antibiotics needed for the production of the above mentioned Tetracyclines in 1995 are:

- Tetracycline Base 20 Tons per year
- Oxytetracycline Base 16 Tons per year
- Chlortetracycline 50 Tons per year

It is to be underlined that some discrepancies could be noted between the above mentioned figures concerning imported quantities of Tetracyclines in 1987 and some data of the National Census Office that indicate a consumption of about 59 tons in 1986 and 109 tons in 1987. This discrepancy is probably due, in the opinion of the writer, to the fact that veterinary use Tetracyclines have probably been included in the calculation of the NCO not as 100% antibiotics but as total purchased qantities; it is to be noted that most of Chlortetracycline and Oxytetracycline feed grade are commonly sold as products with a 5 to 10 % content of antibiotics.

3.5.5 CEPHALOSPORINS

The consumption of Cephalosporins produced from Cephalosporin C, which is a fermentation product, did not exceed some hundreds of Kgs in 1987. Even if the market growth rate relevant to these products could be very high in the next years, the total local requirement shouldn't attain such values to guarantee the feasibility of a large scale fermentation plant.

For this reason no detailed projections have been made for these products, such as Cephalotin, Cephaloridin and Cephalotine produced from Cephalosporin C through 7-ACA (7-amino cephalosporanic acid).

3.5.6 AMINOGLYCOSIDES

The only fermentation products of this family of antibiotics important in the present local market, are Streptomycin and Neomycin.

Streptomycin consumptions reached a value of 12/15 Tons in 1987, but it has not been considered a realistic option for a future large scale fermentation plant for the following reasons:

- Streptomycin is generally considered an obsolete product and it has been eliminated from the Pharmacopeia of several countries due to its toxicity and its side effects on the hearing organs.

- Also in the Philippines, as in many other countries, Streptomycin is being replaced by other anti-tuberculosis drugs like Rifampicin

The local market size of Neomycin is in the range of one to two tons per year, which make it not interesting for an industrial production.

3.5.7 OTHER ANTIBIOTICS

The market size of all the other antibiotics not included in the preceeding paragraphs, is too low to allow the feasibility and viability of an industrial production, even in a multipurpose plant. This is the situation for Polyenes (Amphotericin and Nystatine), Peptides (Bacitracin and Colistin) and Lincosamides (Clindomycin and Lincomycin).

4.0 GENERAL ASSESSMENTS

4.1 RAW MATERIALS

The raw materials utilized for the production of fermentation antibiotics could be divided in 3 main categories :

a - Carbohydrates and proteins sources. These are mainly agricultural products.
b - Chemicals and fine chemicals
c - Organic Solvents

In the first category it is possible to identify several raw materials which are available locally and that have been therefore focused by the writer.

Practically all the fine chemicals should be imported, while, among the chemicals only a small number is locally produced, such as sulfuric acid (Chemphil Manufacturing Corp.) and some mineral salts, their incidence on the overall production cost of antibiotics considered negligible.

Organic solvents most commonly utilized for antibiotics production are at present imported in the Philippines. Only Ethanol is locally produced.

4.1.1 Corn based raw materials

There are presently thirteen registered starch mills in the country: eight Cassava starch mills and five corn starch mills. Some of the factories are not operative for the time being. Cassava starch and related products are at present scarcely utilized in the most known antibiotics technologies, though their use could be increased in the future by research and pilot-plant work.

Corn starch mills are distributed throughout the country with one operating in Metro Manila, two in the Visayas and two in Mindanao.

Corn Starch mills average capacity utilization is quite low: In the years from 1976 to 1981 it was estimated in the range 30/44% (1). Corn starch production was expected to be 80,000/90,000 MT in 1987 and it is not expected to increase rapidly due to shortage of cultivated land and market saturation. At present significant amount of corn are imported.

Main products from corn starch mills that could be utilized in fermentation plants are listed below, together with their main characteristics.

One large factory has been visited by the writer (Universal Rubina, Metro Manila) and some data have been collected from other factories in the Visayas (like General Milling Corporation-Cebu City).

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(1) From a paper presentated by Fortunato Jaime during the National Symposium on Root Crops Research and Development, 1982, VISCA, BAYBAY.

- Starch

Good quality starch seems to be available though it doesn't correspond to USP requirements.

A typical specification is the following:

Moisture	13 %
Protein	0.55%
Fat	0.2 %
Ashes	0.15%
Fiber	0.15%
Starch	98/99%

The actual price is about 6.5/7.5 P/Kg (in Metro Manila). Transportation costs could affect greatly the actual price (transportation cost within M. Manila area could reach 2 Pesos per bag).

- Dextrine

Available at Universal Rubina at 9/11 P/Kg (quantity produced : about 50 Tons/month).

- Modified Starches

Available at Universal Rubina. Production capacity and prices are equivalent to those of dextrine.

- Glucose solution

This raw material may be produced either by corn or by Cassava. It is sold at present mainly to food Industries. Price is in the range of 10/15 P/kg, which is to be considered rather high compared to European standards.

At Universal Rubina glucose is obtained from Cassava starch by acid hydrolysis, a rather obsolete method in western countries.

No purification is performed of the hydrolyzed glucose and the quality is the following:

Total solids : 82/87% (40/43 Be)
Dextrose equivalent : 35/45 (MAX.60)

This quality could be rather poor for utilization in high technology fermentation plants and therefore the utilization of local glucose solutions should be previously checked by laboratory and pilot-plant tests.

About 250 Tons per month of glucose solution are produced at Universal Rubina. This capacity would not be sufficient to supply a large fermentation plant, but it seems that it could be increased.

- Corn-steep liquor

This product seems to be scarcely marketed at present in the Philippines. It is mainly utilized as animal feed. Some factories, as is the case of Universal Rubina, do not concentrate the corn-steep liquor to 40/50% of total solids, as it is usual, and they dispose it a concentration of 6/7% of solids. The reason for this is the high cost of energy required for concentration, that make the operation uneconomic.

Concentration would be a necessity in the case local corn-steep should be utilized in fermentation plants, but this problem could be overcome, because concentration equipment by vaporization exists in some factories, equipment which could be utilized if the market requirements for corn-steep could justify it.

The writer has no data concerning the corn-steep quality, that could greatly affect fermentation yields. Therefore, only laboratory and pilot-plant tests could demonstrate the possibility of utilization of this important raw material.

Diluted corn-steep price at present is in the range of 1 to 2 Pesos per kg. Concentrated corn-steep price should not be less than 8 to 10 Pesos per kg.

Quantities available should be more than sufficient for the requirements of an Industrial fermentation plant.

- Dextrose mono-hydrate

On the basis of the information obtained by the writer, no solid dextrose is produced in the Philippines starting from corn. Importation figures for 1987 showed a cost of 0.29 $ per kg CIF Manila.

4.1.2 Soya based raw materials

Soya is imported at present in the Philippines from China and Brazil. Soya meal is produced in some wet milling factories. Market prices range between 6 and 8 pesos per kg. No high quality milled soya meal is availabe locally. Production capacity level at Universal Rubina is about 100 Ton per day of soya meal.

4.1.3 Cane sugar based raw materials

The sugar industry can be counted among the most important industrial activities in the Philippines.

Sugar cane production dropped down during the years 1982 to 1987, but seems to be relatively recovering, according to the Sugar Regulatory Administration contacted by the writer.

Some data concerning the sugar production in the last few years are given in the following tables as quantities, prices and distribution of sugar factories in the country. As apparent from Table 4.4 more than 40 sugar factories are distributed all over the different regions of the Philippines. In Table 4.5 a material balance showing the quantities of all the main products and by-products coming from the Philippines sugar industry is given. The following products have been considered from the point of view of their utilization in a fermentation plant:

- Raw sugar

Present prices have increased compared with the values indicated in Table 4.3. The 1988 price is about 8000/9000 Pesos per Ton but it is expected that, within 1989, the price of raw sugar supplied to local industries could be forecasted at about 6300/7500 P/Ton (source: Sugar Regulatory Administration).

Raw sugar is not commonly utilized in Western Countries for antibiotics production, due to its high cost compared to other sugar based raw materials, such as glucose syrup from corn. On the contrary, in the Philippines it seems to be more interesting than glucose syrup, both from an economical and quality point of view.

- Molasses

About 500,000 Tons per year of molasses are produced in the sugar factories of the Philippines. The quality of Filipino Molasses is considered quite high compared to cane molasses produced in other countries. In fact, the total fermentable sugars concentration is evaluated in the range of 55/65 %. Some data about the final molasses analysis are given in Table 4.8 for the different Filipino sugar factories. Actual prices of black-strap molasses is about 1200 Pesos per Ton, but could be highly affected by transportation costs; thus the opportunity of locating a fermentation plant close to a sugar mill is of utmost importance (this point shall be focused in the next paragraph by the writer).

The possibility of utilization of black-strap molasses should be demonstrated by laboratory and pilot plant test, since the high impurities content could affect the yield of the fermentation process.

It is however to be pointed out that some pharmaceutical companies have been utilizing molasses for Penicillin fermentation in South America. Higher quality molasses, i.e. molasses coming from earlier stages of sugar production process, could be a more attractive raw material for fermentation of antibiotics compared to the final black-strap molasses. Higher quality molasses, named also A Test molasses, have a market price of about 1500 Pesos per Ton. The bulk molasses consumed locally goes at present to alcohol production, which is a declining activity, while the rest find its way to the manufacture of animal feed, food seasoning and cosmetics. About 38% of all molasses produced were consumed locally in the period 1979/1982. Exports of molasses however declined in the last years at an average rate of 45% per year (1).

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(1) Data from the booklet on Molasses, Priority Export Commodities Series, National Book Store, Inc. 1987.

Molasses prices are to be considered rather high if compared to the actual price levels in other sugar cane producing countries.

- Cane juice

Cane juice could be a cheaper carbohydrate source compared to raw sugar and its quality should be more reliable than that of the molasses, in order to ensure acceptable fermentation yields. Qualities of clarified juices in the different Filipino sugar factories are given on Table 4.7. Available quantities are certainly adequate to satisfy the requirements of an industrial fermentation plant. Present market price could be estimated in about 6500 Pesos per kg of available sucrose, that is roughly 20/30% lower than the raw sugar prices.

It is to be pointed out, also for this product, that tranportation costs could greatly increase the actual price.

- Bagasse

The analysis of possible utilization of this by-product of sugar factories as fuel is developed under the paragraph relevant to Energy Requirements (4.2).

4.1.4 Vegetable oils

- Soybean oil

Soybean oil is produced locally in some wet milling factories starting from imported soybean.

Prices are ranging from 16 to 24 P/kg, higher than the European actual standards. The production capacity at Universal Rubina factory (Metro Manila) is of 120 MT per day at present.

- Coconut oil

Coconut oil could be utilized in fermentation plants as antifoam agent. The quality of locally produced coconut oil seems to be accetable (degree of saturation setup about 30%). Manila price for Coconut oil is 12 P/kg.

4.1.5 Coconut shells

The analysis of possible utilization of this waste product as fuel is developed under the paragraph relevant to Energy Requirements (4.2).

4.1.6 Lard oil

Though pork breeding is an important activity in the Philippines, lard oil is produced presently only in small quantities. Production capacity could be increased in the future, in case that the market requirement would stimulate new investments in this activity. The present market price for feed grade lard oil is ranging from 12 P/kg(first class) to 7 P/kg (third class).

TABLE 4.1

SUGARCANE PRODUCTION (PHILIPPINES

YEAR	TONS CANE (in million MT)
1983-84	23
1984-85	17
1985-86	15
1986-87	14

NOTE: The drop in sugarcane production was mainly due to crop diversification (due to drop in sugar export prices and termination of Laurel-Langley Agreement), limited crop losses (due to either delayed or non-payment of sugar quedans by NASUTRA) and high production input costs.

TABLE 4.2

RAW SUGAR PRODUCTION (PHILIPPINES)

YEAR	PRODUCTION (million MT)
1983-84	2.335
1984-85	1.719
1985-86	1.519
1986-87	1.41

SUGAR CLASSIFICATION AND ALLOCATION (1987)

CLASSIFICATION	ALLOCATION
"A" (US market)	11% (1.54 MMT)* (2.03 MMT in 1986)
"B" (Domestic market)	54% (7.56 MMT)
"C" (Reserve)	20% (2.80 MMT)
"D" (World market)	15% (2.10 MMT)

* The 1986 value was 2.03 MMT. The drop was due to reduced total sugar import of US resulting from discovery of sugar substitutes.

TABLE 4.3

SUGAR EX-FACTORY PRICES
(Canlubang Price Index as of March, 1987)

Raw Sugar	₱ 354.00/picul (63.25 kgs.)
DDD (washed sugar)	₱ 448.00/picul

EXPORT SUGAR PRICES (EX-FACTORY)

Year	Domestick Market (cents/lb.)	World Market (cents/lb.)	U.S. Market (cents/lb.)
1984	11-13	8	21-23
1985	11-13	6	21-23
1986	11-13	4-6	21-23
1987	12-14	4-6	21-23

NOTE: Production cost has an average of 11-14 cents/lb.

NUMBER OF OPERATING SUGAR FACTORIES

Year	Number	Total Capacity (TCD)	Capacity Utilization
1983-84	41	188,646	61%
1984-85	38	174,000	51%
1985-86	38	174,000	45%
1986-87	39	180,000	42%

TABLE 4.4

DIRECTORY OF RAW SUGAR FACTORY
(Millsite, Rated Capacity (TCD)

FACTORY	MILL SITE	RATED CAPACITY (TCD)	REGIONAL CAPACITY
NORTH & CENTRAL LUZON			
1. CASUCO	Sto. Domingo, Piat, Cagayan	4,000	
2. Hind	Baritao, Manaoag, Pangasinan	578	
3. Paniqui	Paniqui, Tarlac	1,500	
4. Tarlac	San Miguel, Tarlac	7,080	
5. Consolidated	San Juan, Botolan, Zambales	2,000	
6. NASUDECO	Del Carmen, Pampanga	6,000	
7. PASUDECO	Sto. Niño, San Fd., Pampanga	6,500	27,658 (14.50%)
SOUTHERN LUZON			
1. Canlubang	Canlubang, Laguna	5,190	
2. Don Pedro	Nasugbu, Batangas	7,000	
3. Batangas	Caloocan, Balayan, Batangas	4,000	
4. BISUDECO	Pili, Camarines Sur	4,000	20,190 (10.59%)
PANAY			
1. Pilar	Pres. Roxas City, Capiz	2,220	
2. Asturias	San Juan, Dumalag, Capiz	3,000	
3. Cal.-Lambunao	Calinog, Iloilo	4,000	
4. Passi	Ulang Juan, Sn. Enrique, Iloilo	5,000	
5. Allied	Bo. Man-it, Passi, Iloilo	3,500	
6. Santos-Lopez	Barotac Nuevo, Iloilo	2,678	20,398 (10.70%)
NORTH NEGROS			
1. Bacolod-Murcia	Bacolod City, Negros Occidental	4,400	
2. Talisay-Silay	Talisay, Negros Occidental	3,600	
3. First Farmers	Dos Hermanas, Talisay, Neg. Occ.	4,500	
4. Hawaiian-Phils.	Silay City, Negros Occidental	6,200	
5. AIDSISA	Kabankalan, Silay, Neg. Occ.	4,000	
6. VICMICO	Victorias, Negros Occidental	10,000	
7. Lopez	Fabrica, Negros Occidental	7,500	
8. Sagay	Bato, Sagay, Negros Occidental	3,000	
9. Danao	Toboso, Negros Occidental	3,000	
10. San Carlos	San Carlos City, Neg. Occ.	5,600	51,800 (27.17%)
SOUTH NEGROS			
1. Ma-ao	Ma-ao, Bago City, Neg. Occidental	5,000	
2. La Carlota	La Carlota, Negros Occidental	10,800	
3. BISCOM	Binalbagan, Negros Occidental	10,000	
4. SONEDCO	Kabankalan, Negros Occidental	4,000	
5. Dacongcogon	Tubogon, Kabankalan, Neg. Occ.	1,800	
6. UPSUMCO	Manjuyod, Negros Oriental	4,000	
7. Bais	Bais, Negros Oriental	8,000	
8. Tolong	Sta. Catalina, Negros Oriental	3,000	46,600 (24.44%)
EASTERN VISAYAS			
1. Bogo Medellin	Medellin, Cebu	2,500	
2. Durano	Dung-an, Danao City, Cebu	2,000	
3. HIDECO	Montebello, Kananga, Leyte	5,000	
4. Ormoc-Rosario	Ipil, Ormoc City, Leyte	2,500	12,000 (6.30%)
MINDANAO			
1. BUSCO	Quezon, Bukidnon	4,000	
2. DASUCECO	Guihing, Hagonoy, Davao del Sur	4,000	
3. NOCOSII	Mateo, Matalam, North Cotabato	4,000	12,000 (6.30%)
	Total:-	190,646	

MATERIAL BALANCE ON A NATIONAL LEVEL
(Weights in Metric Tons)

TABLE 4.5

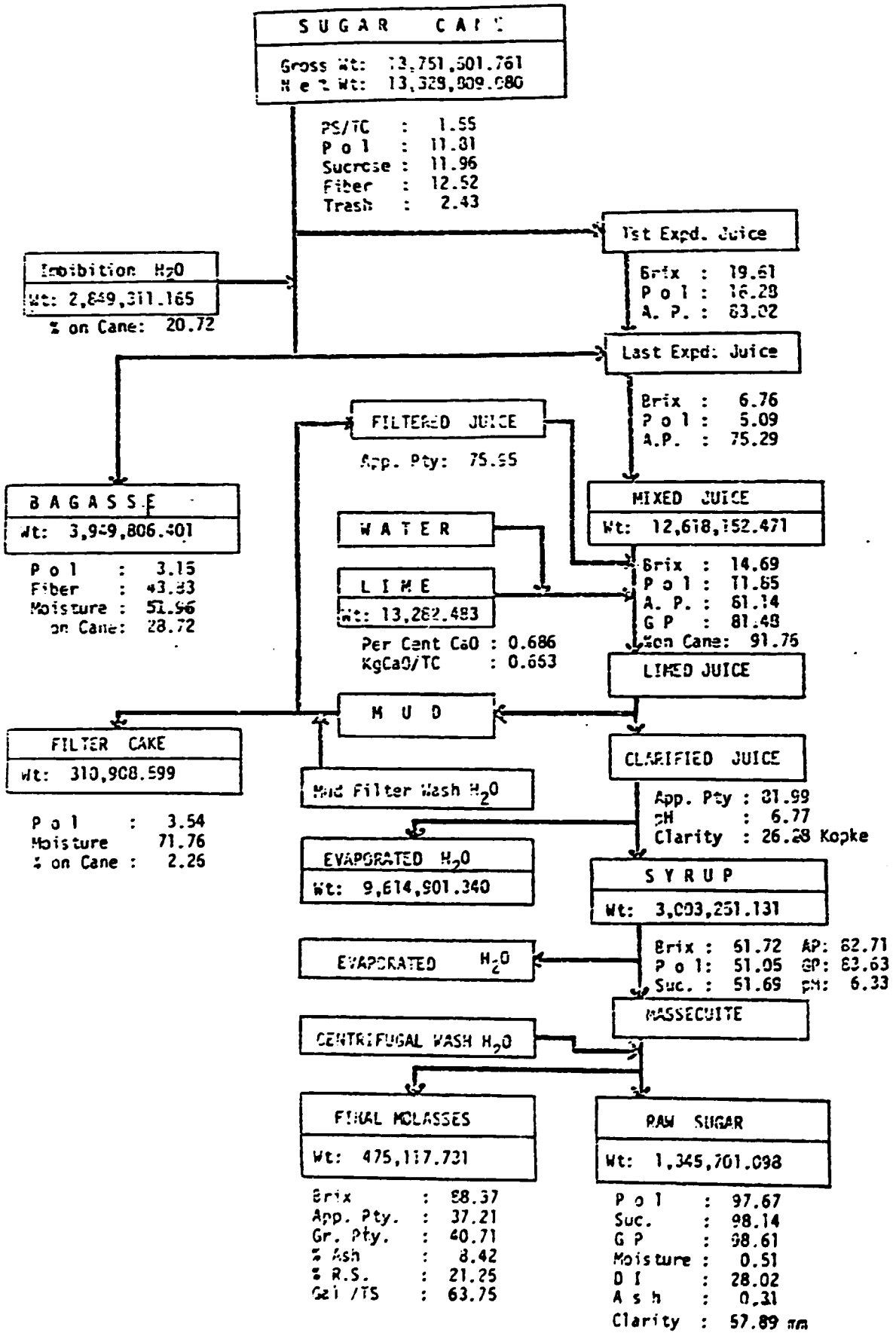

TABLE 4.6 RAW SUGAR PRODUCTION DATA

FACTORY	CANE	MANUFACTURED	
	Metric Tonnes	Metric Tonnes	50- kgs. Bags
I. LUZON	358,091.250	357,948.138	7,158,962.96
1. CASUCO	6,533.950	6,418.493	128,368.06
2. Hind	2,600.[illegible]	2,600.150	52,003.00
3. Paniqui	9,727.100	9,727.100	194,542.00
4. Tarlac	78,359.995	78,359.995	1,567,199.90
5. ARCAM (NASUDECO)	9,318.395	9,291.090	185,321.80
6. PASUDECO	43,499.850	43,499.850	869,997.20
7. Canlubang	66,118.211	66,118.211	1,322,364.22
8. Don Pedro	91,169.270	91,169.270	1,823,385.40
9. Batanges	45,728.105	45,728.105	914,562.10
10. BISUDECO	5,035.964	5,035.964	100,719.28
II. PANAY	56,203.718	56,086.521	1,121,732.42
1. Pilar	10,702.657	10,622.269	212,445.38
2. Asturias	6,760.730	6,724.021	134,480.42
3. Cal.-Lambunao		DID NOT MILL	
4. Passi	30,282.381	30,282.381	605,647.62
5. Allied		DID NOT MILL	
6. Santos-Lopez	8,457.950	8,457.950	169,159.00
III. NEGROS	757,985.646	750,412.093	15,008,241.86
1. Bac.-Murcia	5,665.077	5,354.745	107,094.90
2. Talisay-Silay		DID NOT MILL	
3. First Farmers	65,077.330	64,589.663	1,291,793.26
4. Hawaiian-Phil.	82,510.720	82,510.720	1,650,214.40
5. AIFSISA	42,373.887	42,162.449	843,248.98
6. VICMICO	154,735.119	149,112.650	2,982,253.80
7. Lopez	45,397.233	44,943.616	898,872.32
8. Sagay	24,617.282	24,569.901	491,398.02
9. Danao	8,070.517	8,039.170	160,783.40
10. San Carlos	35,829.417	35,829.417	716,588.34
11. Ma-ao	16,347.627	17,571.946	350,438.92
12. La Carlota	93,042.045	92,837.293	1,856,745.86
13. BISCOM	49,765.141	49,765.141	995,302.82
14. SONEDCO	36,191.492	36,100.493	722,009.86
15. Dacongcogon	4,505.485	4,095.176	81,903.52
16. Roosina (UPSUMCO)	42,368.639	42,368.639	847,372.78
17. Bais	44,430.784	44,430.784	888,615.68
18. Tolong	6,457.650	6,190.250	123,805.00
IV. EASTERN VISAYAS	93,434.724	93,401.035	1,868,020.70
1. Bogo-Medellin	42,862.711	42,862.711	857,254.22
2. Durano	10,558.481	10,560.889	211,217.78
3. HIDECO	22,868.094	22,865.435	457,308.70
4. Ormoc	17,145.438	17,112.000	342,240.00
V. MINDANAO	79,985.760	79,246.798	1,584,935.96
1. BUSCO	54,162.033	54,135.806	1,082,716.12
2. DASUCECO	19,491.250	18,941.080	378,821.60
3. NOCOSTI	6,332.477	6,169.912	123,398.24
PHILIPPINES	1,345,701.098	1,337,094.695	26,741,893.90

TABLE 4.7 CLARIFIED JUICE AND LIME ANALYSES

FACTORY	Apparent Purity	pH	Clarity (ICUMSA)	Kilos CaO Per TC
I. LUZON	83.56	6.79	23.51	0.703
1. CASUCO	80.46	6.68	28.47	0.730
2. Hind	85.88	6.40	20.10	0.460
3. Paniqui	84.20	6.80	20.00	0.730
4. Tarlac	83.29	7.17	27.14	0.668
5. ARCAM (NASUDECO)	82.51	6.50	21.02	-
6. PASUDECO	83.00	6.60	30.54	0.520
7. Canlubang	84.75	6.87	18.84	0.486
8. Don Pedro	83.34	6.61	23.00	1.080
9. Batangas	84.21	6.75	19.20	0.680
10. BISUDECO	80.65	6.02	18.62	0.490
II. PANAY	80.74	7.05	20.87	0.796
1. Pilar	79.82	7.00	21.00	0.770
2. Asturias	80.11	6.90	19.00	0.530
3. Cal.-Lambunao	D i d	n o t	m i l l	
4. Passi	80.96	7.15	21.21	0.850
5. Allied	D i d	n o t	m i l l	
6. Santos-Lopez	81.75	6.90	21.00	0.840
III. NEGROS	81.42	6.77	28.54	0.655
1. Bac.-Murcia	80.20	6.9	17.00	0.540
2. Talisay-Silay	D i d	n o t	m i l l	
3. First Farmers	82.33	6.31	28.13	0.530
4. Hawaiian-Phil.	82.23	6.60	25.58	0.590
5. AIDSISA	80.39	6.75	29.41	1.030
6. VICMICO	82.08	7.00	41.00	0.940
7. Lopez	79.93	7.06	25.43	0.560
8. Sagay	78.91	6.90	13.00	0.440
9. Danao	81.81	7.21	24.21	0.620
10. San Carlos	82.91	6.51	28.78	0.370
11. Ma-ao	82.38	6.63	23.95	0.508
12. La Carlota	80.78	6.70	40.00(b)	0.580
13. BISCOM	81.70	6.31	17.48	0.480
14. SONEDCO	80.12	6.63	26.24	0.830
15. Dacongcogon	85.70	6.86	26.17	0.630
16. Robina (UPSUMCO)	80.24	7.30	30.00	0.570
17. Bais	82.25	6.90	81.40(L)	0.390
18. Tolong	81.68	7.14	23.07	0.760
IV. EASTERN VISAYAS	82.60	6.42	24.14	0.484
1. Bogo-Medellin	84.71	6.56	26.70	0.360
2. Durano	82.69	6.90	24.00	0.850
3. BIDECO	79.93	6.62	18.87	0.740
4. Ormoc	81.60	5.50	26.07	0.180
V. MINDANAO	82.01	6.89	20.78	0.683
1. BUSCO	82.77	6.98	21.11	0.700
2. DASUCECO	80.79	6.71	20.04	0.570
3. NOCOSII	79.77	6.80	20.47	0.870
PHILIPPINES	81.99	6.77	26.28	0.663

TABLE 4.8 FINAL MOLASSES ANALYSES

Factory	Metric Tons	Brix	Apparent Purity	Gravity Purity	% Ash	Reducing Sugar	Gallons Per Tons Sugar
I. LUZON	123,361.981	89.02	38.30	42.46	9.03	21.97	62.02
1. CASUCO	2,528.372	85.90	39.48	42.74	6.74	25.04	69.65
2. Hind	706.526	86.20	40.79	-	-	-	49.56
3. Paniqui	2,449.100	89.50	37.98	42.69	6.70	26.22	45.22
4. Tarlac	26,496.748	83.22	38.43	44.84	6.36	20.62	61.10
5. ARCAM (NASUDECO)	3,144.505	94.28	38.89	41.93	-	-	62.31
6. PASUDECO	15,792.700	85.34	36.68	40.91	-	22.84	65.35
7. Canlubang	20,768.000	88.91	37.70	42.14	9.32	21.92	56.57
8. Don Pedro	34,524.430	91.00	37.98	40.96	11.85	21.73	67.24
9. Batangas	13,864.700	92.52	37.09	40.73	9.69	23.91	53.68
10. BISUDECO	3,066.000	85.41	56.83	-	6.68	16.87	112.21
II. PANAY	26,368.378	87.55	35.31	39.21	8.58	24.07	35.04
1. Pilar	4,533.804	86.14	35.57	41.34	8.15	26.74	77.35
2. Asturias	6,196.249	87.10	36.49	39.20	8.10	26.81	91.65
3. Cal.-Lambunao	Did not mill						
4. Passi	11,445.168	87.80	34.84	40.00	9.14	22.37	68.43
5. Allied	Did not mill						
6. Santos-Lopez	4,193.157	89.03	34.56	-	7.74	21.79	89.24
III. NEGROS	259,436.198	88.26	36.90	40.33	7.97	20.93	61.64
1. Bac.-Murcia	2,662.987	88.27	34.45	40.33	7.05	23.54	84.61
2. Talisay-Silay	Did not mill						
3. First Farmers	19,879.736	88.12	39.70	40.40	-	-	55.98
4. Hawaiian-Phil.	24,452.738	92.62	36.10	38.17	8.01	20.98	52.41
5. AIDSISA	13,710.000	91.13	34.47	39.49	-	19.98	52.66
6. VICMICO	51,791.100	88.41	35.66	40.61	8.82	20.28	60.92
7. Lopez	14,240.460	86.68	43.34	47.54	-	-	57.04
8. Sagay	7,361.000	86.76	33.06	-	-	24.55	54.41
9. Danao	3,399.905	87.51	35.27	41.50	-	21.89	76.37
10. San Carlos	10,408.000	89.15	34.19	36.84	7.97	24.07	52.29
11. Ma-ao	5,974.542	89.30	37.06	42.14	7.48	18.23	63.40
12. La Carlota	39,256.086	84.38	40.12	44.29	6.15	17.23	77.63
13. BISCOM	16,196.661	88.22	33.31	39.20	7.86	20.92	58.79
14. SONEDCO	14,846.86	90.38	36.39	-	9.82	24.61	73.42
15. Dacongcogon	1,442.777	85.50	-	38.42	-	-	58.62
16. Robina (UPSUMCO)	14,414.916	90.60	34.53	35.76	7.97	22.99	60.40
17. Bais	17,115.17	85.70	36.50	39.09	8.29	23.44	70.08
18. Tolong	2,233.26	87.72	40.43	42.03	-	17.87	53.64
IV. EASTERN VISAYAS	31,607.160	88.82	34.92	37.59	9.46	19.28	60.96
1. Bogo-Medellin	11,772.500	91.36	34.08	37.00	8.10	19.09	48.90
2. Durano	4,316.879	87.15	39.04	41.82	8.01	18.36	77.68
3. MIDECO	9,168.990	88.14	34.80	35.65	11.09	19.54	72.48
4. Ormoc	6,348.391	86.21	33.84	39.34	9.57	19.90	67.55
V. MINDANAO	34,344.914	87.09	39.15	41.32	-	20.78	78.01
1. BUSCO	23,651.240	86.43	39.35	42.00	-	20.05	79.58
2. DASUCECO	8,391.163	87.94	39.84	-	-	22.55	77.90
3. NOCOSII	2,302.511	89.69	34.60	39.68	-	21.77	64.94
PHILIPPINES	475,117.731	88.37	37.21	40.71	8.42	21.25	63.75

TABLE 4.9 . BAGASSE ANALYSES

FACTORY	Metric Tons	% Pol	%Moisture	% Fiber	% Cane
I. LUZON	935,971.765	3.34	51.67	43.98	27.74
1. CASUCO	19,483.739	3.06	49.85	46.10	27.57
2. Hind	8,391.924	4.76	50.92	43.34	29.30
3. Paniqui	25,798.638	3.70	50.73	44.52	27.29
4. Tarlac	202,229.051	2.77	50.56	45.88	25.59
5. ARCAM (NASUDECO)	27,268.054	3.42	51.29	44.21	27.30
6. PASUDECO	116,922.885	3.58	49.93	45.43	24.97
7. Canlubang	159,718.411	3.65	49.49	45.94	25.23
8. Don Pedro	230,767.354	2.79	54.19	41.94	30.69
9. Batangas	128,412.831	4.35	53.90	40.53	31.43
10. BISUDECO	16,973.878	4.36	50.95	43.19	29.38
II. PANAY	175,046.228	3.48	50.68	44.54	26.10
1. Pilar	34,491.293	3.61	51.07	44.07	26.93
2. Asturias	21,040.460	3.33	52.24	43.28	27.27
3. Cal.-Lambunao	D I D N O T M I L L				
4. Passi	89,336.047	3.24	49.90	45.57	25.70
5. Allied	D I D N O T M I L L				
6. Santos-Lopez	30,178.428	4.15	51.47	42.88	26.96
III. NEGROS	2,317,899.381	2.97	52.25	43.75	29.10
1. Bac.-Murcia	17,918.013	2.99	49.81	46.23	27.53
2. Talisay-Silay	D I D N O T M I L L				
3. First Farmers	191,421.101	3.08	52.89	43.09	28.34
4. Hawaiian-Phil.	196,046.386	2.47	48.58	48.22	23.13
5. AIDSISA	124,835.796	2.55	54.61	41.98	27.25
6. VICMICO	561,321.672	2.99	52.42	43.44	34.76
7. Lopez	135,351.869	2.68	51.95	44.32	27.38
8. Sagay	87,362.107	3.21	56.11	39.47	31.95
9. Danao	24,373.697	3.61	52.18	42.89	27.96
10. San Carlos	86,642.242	3.30	50.38	45.25	25.95
11. Ma-ao	48,643.202	3.19	49.55	46.27	25.76
12. La Carlota	256,463.759	3.61	50.91	44.25	25.99
13. BISCOM	143,054.538	3.04	51.30	44.66	27.02
14. SONEDCO	104,083.127	3.17	49.45	46.39	25.04
15. Dacongcogon	16,149.781	3.38	50.53	45.11	27.92
16. Robina (UPSUMCO)	156,733.893	2.10	57.86	39.26	36.16
17. Bais	156,165.934	3.01	53.17	42.83	33.06
18. Tolong	19,332.264	3.45	51.77	43.61	29.35
IV. EASTERN VISAYAS	261,877.958	2.90	51.10	45.09	27.27
1. Bogo-Medellin	110,515.243	3.08	49.91	46.13	26.84
2. Durano	31,281.264	3.42	52.13	43.40	27.81
3. HIDECO	69,886.986	2.01	52.53	44.70	27.52
4. Ormoc	50,194.465	3.41	51.11	44.39	27.55
V. MINDANAO	259,011.069	4.15	52.26	42.20	33.12
1. BUSCO	171,437.152	3.60	53.03	42.15	33.10
2. DASUCECO	68,417.099	5.30	51.10	41.33	35.10
3. NOCOSII	19,156.818	3.18	49.49	45.80	27.74
PHILIPPINES	3,949,806.401	3.15	47.31	43.83	28.72

4.2 ENERGY AND WATER REQUIREMENTS

4.2.1 Energy

Fermentation facilities are characterized by high energy requirements, an important part of these requirements being due to the refrigeration necessity. The average air and water temperature in the Philippines make it very problematic the utilization of once through well or river water for refrigeration. According to data collected by the writer in several factories, available water temperature is ranging in the hottest season from 25 to more than 30 degrees Celsius. In some localities like Los Baños well water reaches a temperature of 40 ^{o}C. Furthermore, utilization of once through well water would require very large continuous flow rates, that could not be available in several Filipino localities. On the other hand, utilization of river water would require important treatment units due to the high amount of solids in suspension, that would greatly increase the fouling factor of heat exchanges. For these reasons, large refrigeration units should be installed in an industrial fermentation plant.

Another factor increasing energy consumption of a large fermentation plant, is the considerable amount of compressed air that must be fed to the culture media as well as the mixing required by the fermentors, obtained by the installation of high power agitators.

The cost of electric energy in the Philippines is rather high compared to other South East Asian countries,ranging from 1.8 to 2.1 Pesos per Kwh for facilities equipped with their own electrical substation, including all additional expenses, such as taxes etc. In Mindanao, the cost of electric energy is about 20% less than other regions. The price of fuel oils utilized for boilers ranges from 2.6 to 3.8 Pesos per liter, depending on the type (Diesel oil, Bunker C,etc). It is to be pointed out that antibiotics fermentation, as is the case of any other biological process, is very sensitive to the maintenance of the vital conditions in the culture media. Interruptions of these conditions, for only a short period (say 15 minutes), inevitably entails negative and irrreversible effects and eventually the death of the microorganisms. To avoid this risk, the first condition is to guarantee the absolute continuity of the electrical power supply.

On this purpose it seems that the national electric network reliability is not very high in all the regions of the country and most of the existing industrial plants are equipped with their own back-up generators.

For all the reasons listed above, it is highly recommended to provide the fermentation plant with self-generation of electric power.

Due to the high cost of fuel oil, the utilization of local materials as Bagasse would be very important to increase the profitability of the plant operations. Bagasse is already extensively utilized in the Philippines as fuel in most of the existing sugar factories. In table 4.9 are given some characteristics of the Bagasse produced in the different sugar factories.

About 4 million tons of Bagasse are produced per year (see table 5) but most of it is consumed in the same factories for steam production. A total surplus of about 500,000 tons per year is available and this quantity should largely satisfy the total energy requirement of a large fermentation plant.

The surplus bagasse being scarcely marketable, its cost is practically negligible, if not affected by the transportation costs. For this reason, it would be quite reasonable to install a fermentation plant adjacent to an existing sugar factory that could supply not only the Bagasse necessary for energy and steam production, but also a carbohydrate fermentation substrate such as raw sugar, cane juice or molasses.

This suggestion made by the writer to some officials of the Sugar Regulatory Administration, has been considered by them with interest.

In order to ensure the total self sufficiency of the plant as far as electric power and steam requirements are concerned, high pressure boilers should be provided utilizing bagasse as fuel. In this case, high pressure steam will be produced at 40-50 ATE and fed to the steam turbine generators, where all the electric energy required by the plant is produced.

A part of the steam is extracted from the turbines at 5-6 ATE to fulfil all the steam requirements of the plant. The rest is extracted at very low pressure to maximize electric power production and then it is condensed under

vacuum conditions. The outlined system could provide electric power at very low costs, while the cost of steam would be practically negligible.

On the other hand, sophisticated boilers should be provided, but their higher cost should be payed out in a very short period. The high flow rates of cooling water required by the steam condensers could be easily provided if the plant is located close to the sea or to a river.

Coconut shells could be considered as an alternative to Bagasse as local fuel source, but, coconut shells collecting points being spread-out all over the country, transportation costs could increase the cost of energy production, compared with bagasse utilization.

4.2.2 Water

Refrigeration requirements of process equipments should be covered by closed-loop systems of chilled water at about $10^{o}C$, produced by mechanically refrigerated units and of cooling water at about $30-35^{o}C$, produced in cooling towers. The make-up of this system would constitute the main consumption of fresh water. Quality of raw water is quite different in the various localities where the plant could be installed, but it results that well water quality utilized in some facilities visited by the writer (as Chemfields Inc. in Sta Rosa Laguna) is quite acceptable from the point of view of hardness and total dissolved solids and consequently shouldn't require very sophisticated and expensive treatment units. Water utilized for fermentation culture media preparation could require only softening treatment, while water for boilers and extraction or synthesis operations should require a demineralization unit.

4.3 MANPOWER

In order to evaluate the skilled manpower that could be utilized in a large scale fermentation plant, some University Institutions, some Government R & D Institutes, as well as some pharmaceutical companies have been contacted.

Investigations have been done in the following Universities:

-University of the Philippines (Diliman)

-Dela Salle Univesity

-Ateneo University

At the University of the Philippines, the College of Science is the most important source of qualified technical personnel and in three departments should be considered in particular:

- Biophysics Group. A special program on Molecular Biology and Biotechnology is being developed in this Group coordinated by Prof. A. Nazarea. Several PhD's are supposed to be graduated from this group in the next few years.

- Department of Chemistry (Chairman Prof. C. Llaguno). This department trains 10 to 15 B.S. and 5 to 8 M.S. each year. From 3 to 6 PhD's are expected to be graduate each year in the foreseeable future. Some research on microbiology has also been done and the teaching laboratories seem to be well equipped. Much of the research work is concentrated on plants products.

- Department of Chemical Engineering (Chairman Prof. W. Jose). Some significant research studies have been done in the pilot-plant installed in this department, as far as Ethanol fermentation and Biogas processes are concerned. A course of Biochemical Engineering is held in the department.

In the Dela Salle University, one should mention the Biology Department, the Chemistry Department and the Chemical Engineering Department. Several PhD's in these specialization are trained abroad every year. The graduates in Chemistry are 10 to 15 per year. The work in this University is mainly centered on medicinal plants, only a small emphasis being given to organic synthesis and biotechnology.

In close association with the Department of Chemistry of the Ateneo University, the PIPAC (Philippine Institute of Pure and Applied Chemistry) is a private and independent entity directed by Prof. M.T. Chua. It is a new institute with modern equipment both for chemistry and microbiology (a pilot fermentor is also installed and from time to time utilized). In this Institute 10 to 15 B.S., 3 to 4 M.S. and and average of 3 PhD's graduate every year.

In the Department of Chemistry of U.P. Los Baños, a pilot-fermentor is installed and some works have been done in the past on Butanol and Acetone fermentation.

In the field of Biotechnology, one should mention particularly the BIOTECH Institute (National Institute of Biotechnology and Applied Microbiology) in Los Baños directed by Prof. W. Padolina. Major research activity of BIOTECH concerned so far the following fields:

-Nitrogen fixation and Mycorrhiza
-Biofuels production (Ethanol)
-Food and feed production

This Institute could supply some graduates with certain skills in the fermentation process. 6 PhD's are working at present in the Institute , as well as 50 M.S. A very well equipped fermentation pilot-plant is installed in BIOTECH which could be utilized for works on antibiotics and for training of technical personnel in fermentation techniques (see chapter 6.0 devoted to the Fermentation Pilot-Plant).

The ITDI (Industrial Technology Development Institute) is one of the few local Institutes where some research has been done in the past years in the field of fermentation. The Microbiology and Genetics Division, directed by Dr. L. Joson, has developed in particular some studies on Ethanol and Citric Acid Fermentationas well as some researches on antibiotics such as Rifampicin.

Some pilot equipment is installed in the Bicutan center (see chapter 6.0 devoted to the fermentation pilot plant). It seems that five to ten specialized graduates could be available for a proposed project of a new antibiotic fermentation pilot plant.

Some pharmaceutical Companies were contacted to get informations on problems related to manpower.

Chemfields Inc., which is the only bulk antibiotic production company in the Philippines, has a staff of about 100 persons, most of them technicians. The writer visited the plant and got an impression of efficiency in plant operating. A large amount of graduates, mainly engineers and chemists, are involved in the production facility. It seems that a short period of training was required for the key personnel at the start-up of the plant. Only high level supervisors were trained abroad (Italy).

The visit of pharmaceutical Companies involved in formulation and packaging as Ciba-Geigy, Bayer, Astra, etc. confirmed the impression that not very important training problems were encountered at the start-up of these plants(1). Most of the technical specialists were locally selected and the percentage of graduates is higher than in similar Companies in the west.

Summarizing the impressions received during the above mentioned visits, it is our opinion that a basic technical manpower could be easily recruited among the graduates from Filipino Universities, with an educational level, probably higher than in other developing countries, but with rather limited practical experience. This fact points to the necessity of proper training programs that should be developed in case of implementation of industrial scale facilities. Training requirements are specified for the proposed plants.

Part of the skilled technicians required by a fermentation plant could be selected among specialists or workers who had a previous working experience in some of the several Ethanol fermentation plants or the breweries operating in the Philippines many years. In fact, some of the operations held in these plants have several points in common with antibiotic fermentation processes.

The relatively low cost of manpower could be one of the reasons which might attract new investors in the Philippines. Some data concerning manpower costs were collected during the above mentioned visits of the local production Companies, in order to estimate the incidence of this factor in the manufacturing cost. The following figures have been utilized as far as salaries are concerned in the calculation of the profitability of the proposed projects (see chapters 7.0 and 8.0):

-Supervisors	:6,000 - 6,500 Pesos per month
-Senior Production Technicians	:4,000 - 4,500 Pesos per month
-Production Technicians	:3,000 - 3,500 Pesos per month
-Unskilled workers	:2,000 - 2,500 Pesos per month

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(1) To be noted that packaging plant require much lower technical skill compared with a fermentation plant.

4.4 LOCAL CAPABILITIES IN PLANT CONSTRUCTING

4.4.1 Equipment

The capability in equipment manufacturing of several Filipino companies has been investigated by the writer. Vessels and tanks could be manufactured locally both in carbon steel and in stainless steel. Stainless steel sheets are normally imported while equipment construction is done locally. Stainless steel AISI 304 is very easily available, while AISI 316 requires longer supply times. For vessels and tanks characterized by particular internals(1) or special devices, the basic design of the equipment should be supplied to the local manufacturer by a foreign engineering company.

Reactors with external half-coils and, in general, vessels whose construction is characterized by delicate welding procedures would be better imported, to ensure an acceptable quality.

In fact, not all of the local manufacturing workshops are equipped with advanced machinery,like fully computerized welding machines or welding testing devices, as ultrasonic or radiography apparatuses. Some companies manufacturing tanks and vessels, in their own workshops, both atmospheric and pressure types, were contacted by the writer:

- APV BELL BRYANT MFC. CORPORATION. This company can supply also small size reactors.
- STAINLESS STEEL INDUSTRIES INC. Mainly specialized in architectural products, but could supply also simple vessels to the food and pharmaceutical industries.
- ATLANTIC, GULF & PACIFIC COMPANY. This is one of the largest local Engineering Companies.(2) They have a workshop in Batangas where tanks, columns and other equipment could be manufactured.
- CONSTRUCTION & ENGINEERING EQUIPMENT. Also this is an Engineering Company that can manufacture in its own facility tanks, columns etc.
- SPP CORPORATION. This enterprise is capable to develop its own design of sophisticated vessels.

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(1) such as distributors, trays, etc -

(2) Some rumours of financial problems of this company have been reported in the local press.

Most of these companies are in a condition to manufacture also tube and sheet heat exchangers, as well as distillation columns. Internals of distillation columns (like trays and distributors) should be imported.

The cost of all the above mentioned locally manufactured pieces of equipment should be cheaper, when compared with the average European standard. A saving ranging from 35% to 50% could be expected.

Delicate and important equipment like fermentors should be imported, if a high quality assurance is required, even though it is to be pointed out that similar equipment have already been locally fabricated on the basis of foreign design (e.g.some Beer Storage Tanks with external jacket having a capacity of 850 and 960 cubic meter supplied by AG & P to the San Miguel Corporation).

AG & P Company as well as other enterprises are capable of manufacturing small size boilers, while medium and large size ones are imported.

For the time being, all other equipment and machinery like pumps, agitators, centrifuges, extrators, dryers and compressors should be imported. It is to be underlined however that most of these equipments could be imported from Asian countries like Korea, Singapore, Taiwan, or India at lower prices than European ones.

Also instrumentation and electric systems including motors should be imported. Only low design pressure, carbon steel and welded piping could be locally supplied, while seamless and stainless steel piping (mostly utilized in fermentation plants) are to be imported.

4.4.2 Civil works

All civil works of industrial plants including design, engineering and building could be performed by local Companies. Architectural basic design should probably be done by foreign companies but it could be possible to entrust also this part of a project to local enterprises.

The most important Companies which could be involved in such a job are:
- AG & P, that has erected both industrial and residential buildings.

- PROJECT MANAGEMENT CONSULTANTS INC. This company is specialized in the design and construction of pharmaceutical plants (packaging) including the supply of architectural services.

- ENGINEERING EQUIPMENT, INC. This company operates also abroad and in particular in the Middle East.

Some orientative prices of civil work have been collected, in order to evaluate the investment cost of the suggested plants:

-Industrial buildings	
Steel structure frame	7000/8000 Pesos per square meter
Reinforced concrete frame	5000/7000 Pesos per square (bare structure) meter
Reinforced concrete frame (Including Ventilation and aircon)	10000/12000 Pesos per square meter
- Warehouses	
Steel structure	5000/6000 Pesos per square meter

Execution time for engineering and construction seems to be of the same order of magnitude of western countries standards.

4.4.3 Plant installation

Plant erection including equipment, piping, instrumentation and electric system installation could be performed by local Companies.

Some of these, such as AG & P and Engineering Equipment Inc., are actually competing with major Korean, Taiwanese and Singaporian Companies in getting important contracts for plant installations all over the world and in particular in the Middle East and in Libya.

Due to low cost of local manpower, the costs of installation are lower than those in the western countries.They can be evaluated as 15 to 30 % of the cost of equipment and material to be installed.

4.4.4 Engineering

Local Engineering Companies are capable of performing the detailed engineering of industrial plants, once the basic engineering has been defined by foreign main contractors. Some of these companies like Engineering Equipment Inc., Project Man. Consultants Inc. (1) or AG & P have completed in recent years the engineering of several multimillion dollar projects.

Besides the front-end engineering including the basic specification of all equipment, piping and instrumentation, the foreign main contractors normally supply the local engineering Companies with a general supervision of the detailed engineering activities. Purchasing and procurement of important equipment and of instrumentation are often undertaken by the main contractor instead of the domestic Companies. It is however the impression of the writer that at least 60-70% of the total engineering activities could be performed by local enterprises.

5.0 RECOMMENDATIONS

5.1 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

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(1) This company has engineered and built some pharmceutical plants owned by well known multinational Corporations like ASTRA, PFIZER AND SQUIBB

- Availability of domestic raw materials (in particular agricultural products)
- Existence of down-stream facilities (e.g. Chemfields Inc. products are all obtained starting from 6-APA and Penicillin)
- Presence of adequate and qualified human resources.

5.2 PROPOSED OPTIONS

On the basis of the analysis of the present status of the antibiotic market in the Philippines developed in chapter 3.0 it appears that the only fermentation antibiotic for which a single line production could be feasible are Penicillins (more specifically Penicillin G and Penicillin V) with projected consumptions in 1995 reaching about 3. tons per year.

Other antibiotics such as Erythromycins (26 Tons/year), Tetracyclines (86 Tons/year) and Rifampicin (20 Ton/year) could be the object of a multipurpose industrial Plant, since the quantities of each of these 3 antibiotics alone are too low to justify the viability of an industrial plant. Penicillin production should not be included in this hypothetical multipurpose plant because the GOOD MANUFACTING PRACTICES for pharmaceutical plants as well as the regulations of most countries concerning penicillin based drugs manufacture advise against the production, in the same facility, of beta-lactam and non beta-lactam antibiotics, due to possible problems connected with cross contamination. Fermentation antibiotics are not to be taken in serious consideration for industrial production.

In order to get an indication of the historic growth and forecasted demand for bulk antibiotics it is helpful to examine these same parameters for the finished products on a world wide basis. Historic growth for the five major antibiotic categories are given for the United States, Western Europe, Japan, Latin America and the rest of the world in Tables 5.1-5.5 (sales volumes are given for 1980 and 1985). Forecasted sales for the Rest of world market excluding U.S., Europe, Japan and Latin America, are given in Table 5.6 (sales volumes are given for 1990 and 1995). Growth rates have not been reported by volume since antibiotics are sold in many different forms and concentrations.

The following observations can be done about these data:

- A higher growth in demand is forecasted for Penicillins and Cephalosporins compared with other antibiotics.
- The Cephalosporins market is expected to grow much more in the Western countries than in the developing countries.
- Tetracyclines and Erythromycins are charaterized by a limited growth due also to price constraints. (More recent data on Tetracyclines advise to expect a lower growth rate in the future that the one indicated in the above mentioned Tables).

Another factor that makes the fermentation of Penicillins interesting for an industrial scale production is the high variety of products that could be manufactured starting for Penicillin G. Table 5.8 shows some of the main products which could be obtained from this fermentation antibiotic.

Furthermore, it is to be pointed-out that a semisynthetic production plant already exists in the Philippines (Chemfields Inc.) producing semi-synthetic Penicillins starting from imported 6-APA. The production of Penicillin G and its conversion into 6-APA would allow the Philippines to cover with national products all the line of Penicillins, eliminating the import of 6-APA. In fact, the bulk of the 6-APA manufactured in the world is done by major Penicillin producers, using this material as feed stock for semi-synthetic Penicillin manufacture. Open market quantities of 6-APA vary, but usually only constitute 10 to 15 % of production. The open market for 6-APA was estimated to have a value of 60 to 70 million dollars in 1985.

Table 5.7 describes the historic and forecasted Worldwide production of 6-APA from 1980 to 1995.

For all the foregoing reasons it seems to the writer that 2 main options should be examined in order to reach a reasonable degree of self-reliance in the antibiotics production of the Philippines. These options could be materialized in 2 projects to be developed , according to a long term schedule:

a) establishment of a fermentation pilot plant for antibiotics
b) implementation of a large scale fermentation plant for Penicillin G and Penicillin V production

To be noted that project a) and b) should not necessarily be successive in time, but on the contrary they could overlap or even be developed simultaneously.

A third option has also been examined, consisting in the implementation of a multipurpose fermentation plant for Erythromycin, Rifampicin and Tetracyclines production.

This third option seems to be, on the basis of the present situation, the less attractive one from a profitability point of view (see chapter 8) and it would require a bigger effort in terms of plant complexity, investment costs and number of technologies to be acquired. But it could be still considered a second step in the achievement of self-sufficiency in the antibiotics production, in the case that some changes occur in the International Market conditions and in the local situation concerning regulatory policies for the pharmaceutical industry.

TABLE 5.1

GROWTH OF U.S. ANTIBIOTIC SALES BY MAJOR CATEGORY

Sales in $ Million
1985 Dollars

	1980	1985	Percent Growth
Penicillins	285	300	1
Cephalosporins	550	770	7
Tetracyclines	140	150	1
Erythromycins	170	180	1
Aminoglycosides	110	120	2
Other	375	460	4
T o t a l	1,630	1,980	4

Private Sources

TABLE 5.2

GROWTH OF WESTERN EUROPE ANTIBIOTIC
SALES BY MAJOR CATEGORY

	Sales in $ Million 1985 Dollars		Percent
	1980	1985	Growth
Penicillins	1,980	2,400	4
Cephalosporins	660	1,060	10
Tetracyclines	350	370	1
Erythromycins	290	360	4
Aminoglycosides	290	320	2
Other	780	790	-
T o t a l	4,350	5,300	4

Private Sources

TABLE 5.3

GROWTH OF JAPANESE ANTIBIOTIC SALES BY MAJOR CATEGORY

Sales in $ Million
1985 Dollars

	1980	1985	Percent Growth
Penicillins	330	400	4
Cephalosporins	930	1,500	11
Tetracyclines	105	125	3
Erythromycins	75	80	2
Aminoglycosides	185	235	5
Other	95	160	11
T o t a l	1,720	2,500	8

Private Sources

TABLE 5.4

GROWTH OF LATIN AMERICA
ANTIBIOTIC SALES BY MAJOR CATEGORY

Sales in $ Million
1985 Dollars

	1980	1985	Percent Growth
Penicillins	290	430	8
Cephalosporins	100	140	7
Tetracyclines	95	115	4
Erythromycins	120	160	6
Aminoglycosides	45	55	4
Other	130	160	4
T o t a l	780	1,060	6

Private Sources

TABLE 5.5

ROWTH OF REST OF WORLD
ANTIBIOTIC SALES BY MAJOR CATEGORY

	Sales in $ Million 1985 Dollars		
	1980	1985	Percent Growth
Penicillins	700	1,240	12
Cephalosporins	560	830	8
Tetracyclines	515	690	6
Erythromycins	260	330	5
Aminoglycosides	105	140	6
Other	370	570	9
T o t a l	2,510	3,800	9

Private Sources

TABLE 5.6

FORECASTED REST OF WORLD
ANTIBIOTIC SALES BY MAJOR CATEGORY

Sales in $ Million
1985 Dollars

	1985	1990	1995	Percent Growth 1985-1990	Percent Growth 1990-1995
Penicillins	1,240	2,380	3,850	14	10
Cephalosporins	830	1,220	1,965	8	10
Tetracyclines	690	920	1,235	6	6
Erythromycins	330	440	535	6	4
Aminoglycosides	140	180	250	5	5
Other	570	840	1,350	8	10
T o t a l	3,800	5,980	9,185	10	9

Private Sources

TABLE 5.7

HISTORIC AND FORECASTED WORLDWIDE PRODUCTION OF 6-AMINOPENICILLANIC ACID (6-APA)

Metric Tons				Growth Percent		
1980	1985	1990	1995	1980-1985	1985-1990	1990-1995
5,400	9,800	14,400	19,300	13	8	6

Private Sources

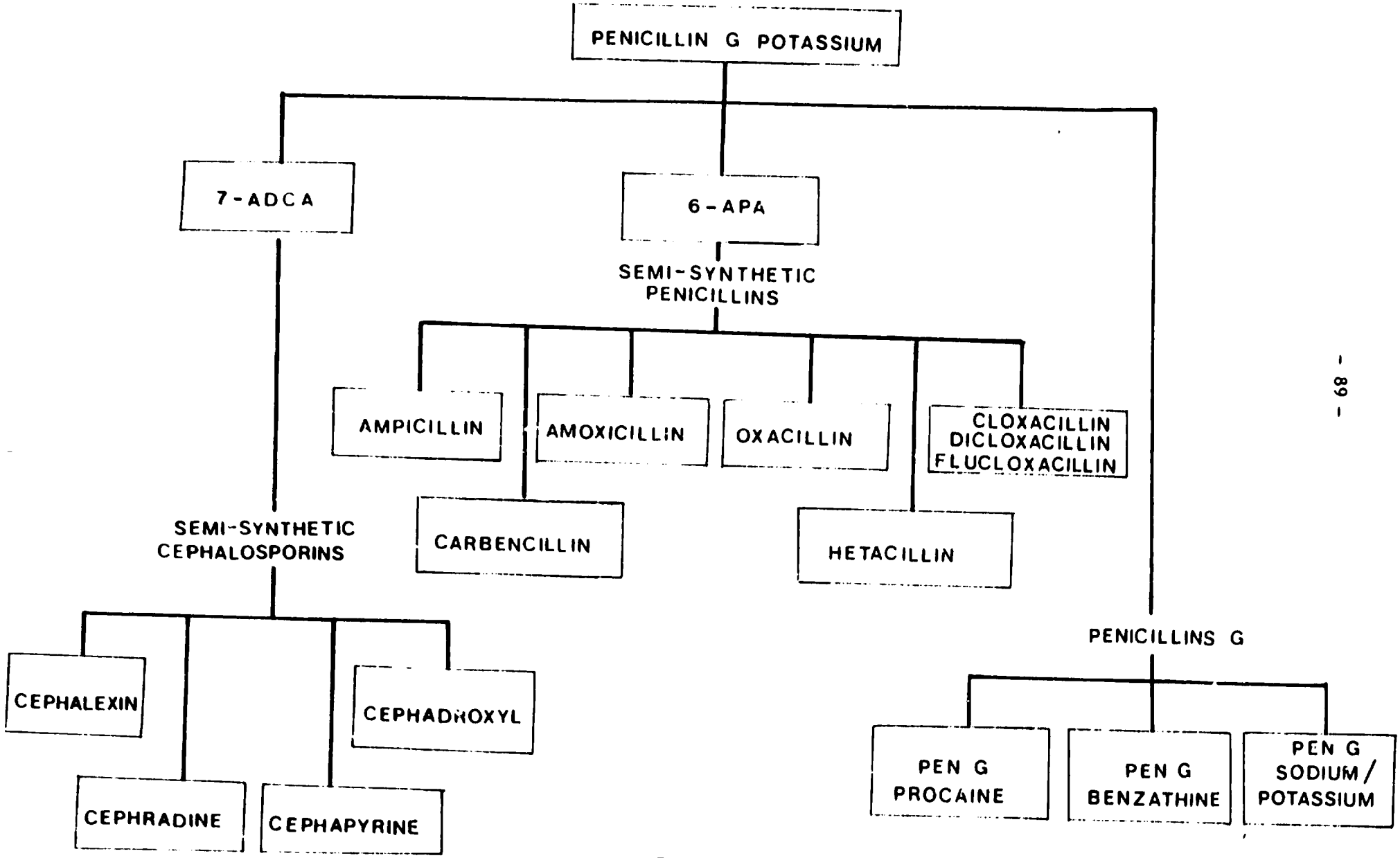

TABLE 5.8

MANILA- AUGUST 1988

6.0 FERMENTATION PILOT PLANT FOR ANTIBIOTICS

6.1 GENERAL EVALUATION

The establishment of a Fermentation Pilot Plant for Antibiotics fits with one of the main objectives of the National Drug Policy of the DOH, that is to create a reliable and affordable supply of basic drugs for the people's health programs by installing a National Drug Industry, including fermentation-based production facilities.

Main objective of such a pilot plant should be, in the opinion of the writer:

1) To investigate the local availability of raw materials for antibiotics fermentation, the main condition for the implementation of large scale production plants. Mostly raw materials of agricultural origin such as corn, soybean, sucrose and vegetable oil should be investigated (see paragraph 4.1)

2) To train technical personnel with special skills and expertise in the production of antibiotics. In fact a Manpower Development Program would be the first milestone on the road to Biotechnology development. From this point of view, a modern fermentation pilot-plant would be a formidable source of researchers, industrial microbiologists, engineers and operators, who could be perfectly utilized in the development of a large scale fermentation plant.

It is the firm impression of the writer that such a Fermentation Pilot-plant should be Development Oriented and not mainly Research Oriented. It wouldn't be realistic, at least in a first phase, to undertake microorganisms strain improvement programs that would require a quite long period of time and the utilization of a considerable team of skilled researchers and microbiologists who are probably not available at present (both from the point of view of technical expertise and of number). In one word, it would not be worthwhile to compete with R & D centers of big International Companies equipped with thousands of researchers who have already improved high yield strains after working for many years, while the same strains and the related technologies are available on the market at very reasonable prices. Development of new technologies could be the objective of the work of the Pilot-plant in a second phase, after having fulfilled points 1 and 2 mentioned above. Another point to be

underlined is that a very detailed program of activities should be formulated when preparing the project document. Some classes of antibiotics should be identified by updating all information relevant to the current consumptions and projected requirements of pharmaceuticals. It is not advisable to focus on the most advanced antibiotic fermentations. Most probably, Penicillin should be one of the main objectives of the Pilot-plant. Non Beta-lactam antibiotics that should be probably investigated are:

- Erythromycins
- Rifampicins
- Tetracyclines

Vague and generalized programs envisioned to include many types of antibiotics might not be the proper approach to the problem, as a lack of manpower and local resources as well as a dilution of efforts on too many products, would mean a loss of time and energy.

Furthermore, a well conceived proposal for a fermentation pilot-plant should not be based on the massive assistance of foreign consultants, but on the contrary, it should underline the necessity of involving the maximum number of available local technical personnel. The former approach would probably make it difficult to reach the main goal of development of new skills and specialized manpower and it will only increase the cost of the project. The assignment of international experts who are required for the preliminary operation of the plant should be therefore in proportion to the size of the national experts team assigned to the plant.

The local Institutions engaged at present in fermentation technology are:

- ITDI, Industrial Technology Development Institute (Department of Science and Technology) and in particular the Microbiology & Genetics Division, supervised by Dr. Lydia Joson, who performed some studies on antibiotics fermentation, as well as on ethanol and citric acid fermentation.
- BIOTEC. U.P. LOS BANOS. In this center, directed by Dr. William Padolina, researches have been conducted on Ethanol fermentation, nitrogen fixation technologies, and biofuels, as well as on vaccines and antibiotics (mainly Tylosine).
- NSRI U.P., National Science Research Technology. Enzyme immobilization studies.

- USTRC U.P., University of Santo Tomas Research Center-Fermentation studies on antifungals and antibiotics.

- College of Science U.P., Molecular Biology and Biotechnology Program, coordinated by Dr. Apolinario Nazarea.

Only the first two mentioned intitutions could be taken in consideration for the coordination of a project having as objective the development of a fermentation pilot-plant for antibiotics. Present manpower resources of ITDI Microbiology and Genetics Division, as well that of BIOTECH seems to be severely lacking both in quantity and quality, to be able to handle the above mentioned project (see following paragraph 6.3 relevant to manpower) and both of them should increase significantly the number of technical experts to fullfill the objectives of the pilot-plant.

However, a solution to the problem of limited human resources could be envisaged if an interdepartmental national project could be launched involving the cooperation of these two intitutions (and possibly other ones), thus allowing an optimization in the utilization of human resources, as well as of existing facilities (see for this purpose the paragraph 6.2 relevant to equipment and infrastructures).

It is however realized that there could be complications and difficulties from a logistic, management and financial point of view.

The establishment of a well integrated pilot-plant would require from 2 to 3 years while at least three additional years should be expected before obtaining the first solid outputs of the plant operation.

A proposal concerning a fermentation pilot-plant for antibiontics has been already submitted by ITDI to UNIDO in 1987. Though it could be taken as reference for a further study of this subject, it is the opinion of the writer that it should be reconsidered on the basis of the general evaluations explained above (see also paragraph 6.3).

6.2 PLANT FEATURES

A list is given hereafter of the main equipment the pilot-plant should be equipped with in order to fulfil the requirements set-up in paragraph 6.1.

It has been assumed that one or maximum two antibiotics are processed at the same time in the pilot facilities. Small amounts of antibiotics produced in the plant could be marketed in the future and sold in the local drug market.

a) Process Equipment

- Pilot fermenters (including inoculation and seed fermentors):
- No. 6 glass fermenters of 2 liters each (to perform laboratory scale tests)
- No. 6 glass fermenters of 10 liters each
- No. 3 stainless steel fermenters of 100 liters each
- No. 2 stainless steel fermenters of 800/1000 liters each

This number of fermenters should allow performing of duplicate tests.

The fermenters should be highly instrumented: temperature control, air flow control, pH and dissolved oxygen analyzers, agitators, power and speed indicators should be provided. At least one computer system must be included to collect data from all the fermentors. 100 and 1000 liters fermentors must be equipped with a proper number of sterile additives vessels and with air sterilization filters. A steam sterilizer should also be provided.

Extration Equipment:

- No. 1 Rotary vacuum filter (1 M2 surface)
- No. 1 Disk-stack type extractor (Westphalia or Alfa-Laval)
- No. 1 Liquid-liquid centrifugal extractor (Podbielniak)
- No. 3 Jacketed vessels of 100 leters each (stainless steel) equipped with agitators
- No. 3 Jacketed vessels of 1000 liters each (stainless steel) equipped with agitators
- No. 3 Vessels of 500 liters (fiber glass)
- No. 3 Heat exchangers, double pipe type, stainless steel

- No. 1 set of ion exhange resins columns, rubber lined
- No. 1 falling film evaporator
- No. 1 crystallizer, 100-200 liters, stainless steel
- No. 1 Vacuum dryer
- No. 1 Basket type centrifuge
- No. 1 Filterpress
- No. 1 Mill
- No. 1 Distillation column, stainless steel
- No. 5 Portable pumps

b)Engineering

Infrastructure Equipment

Quantity	Description of equipment
1	Deep well pump (if necessary)
1	Storage tank
2	Pressure pumps
1	Fire pump (preferably diesel)
1	Hot water generator, steam-heated (if necessary)

STEAM

Quantity	Description of equipment
1	Boiler, 2 T/h capacity + water-softening equipment
1	Oil storage tank (size depends on delivery terms)
1	Condensate return tank
2	Fuel pumps
2	Feed-water pumps

CHILLED WATER UNIT

Quantity	Description of equipment
1	Chiller unit with compressor and air-cooled condensing coils
	Chilled water pumps
	Electric control panel for AC plant

COMPRESSED AIR

Quantity	Description of equipment
1	Oil-free compressor 200 N m3/h
1	Air dehydrator
1	Compressed air storage tank, 3 cu.m capacity

Electricity

Quantity	Description of equipment
1	Transformer
1	Emergency generator
1	Switchboard for low tension
1	Transformer

Water treatment plant

Depends on local requirements.

c)Laboratories

Master Culture Preservation Lab

Laboratory (air conditioned) equipped with:

- -Minus 80°C Deep Freeze refrigerator
- -37°C Incubator
- -Autoanalyzer
- -Centrifuges
- -Label maker
- -Analytical balances
- -Miroscope
- -pH meters
- -Refrigerator
- -Glassware and chemicals storage cabinets

Sterile box, 4 M^2, equipped with:

- -Vial filling unit
- -Laminar flow hood

No. 2 Incubators, 4/6 M^2 temperature 25/30°C, equipped with:

-Rotary shaker

-Shelving

Inoculum Development Lab

Laboratory (air conditioned) equipped with:

-Microscope

-37°C Incubator

-Cabinets for raw materials, glassware

-Refrigerators

No 2 Incubators, 4/6 M^2, temperature 25/30°C, equipped with:

-Reciprocating shaker

-Shelving

-Sterile box for sterility testing, 5 M^2, with laminar hood

-Sterile box for Inoculum transfer, 4 M^2, with laminar hood

Glassware Cleaning and Media Preparation Area

-Autoclave (steam sterilizer)

-Laminar hood

-Cabinets for raw materials, glassware

-Hot air sterilizer

In-process laboratory Equipped with:

-Autoanalyzer

-Vacuum oven

-Gas chromatography unit

-Analytical balances

-pH meters

-Refrigerator

-Viscosimeter

-Refractometer

-Spectrophotometer

The total space requirement is about 800/1000 M^2.

The investment cost including equipment, materials, intrumentation and Installation, but excluding civil works, should be in the range of U.S $ 1.5-2.0 million

6.3 PLANT LOCATION

Two approaches are possible in developing the fermentation pilot-plant:
-setting up a completely new facility
-strengthening of existing facilities

The two most probable places where the plant could be installed are:
- The ITDI in the Bicutan center
- The BIOTECH in Los Banos, UP.

The installation of the plant in the ITDI Complex of Bicutan would require the setting up of new facilities, the existing equipment of the Microbiology and Genetics division being very limited, as it appears from the list of existing NIST equipment included in the proposal presented to UNIDO (1 fermenter 2 lt, 1 fermenter 14 lt, Shakers, Autoclaves, Drying oven, Refrigerators, Vacuum Oven and Centrifuge).

Furthermore a new building with related infrastructures would be required, unless the existing building housing the Citric Acid Pilot Plant could be adapted at this scope, thus utilizing also the relevant equipment, (but this would imply the elimination of the possibility of going on with tests concerning citric acid).

On the contrary an existing fermentation pilot plant is already installed at BIOTECH , Los Banos that could be expanded in order to cover the requirements listed in paragraph 6.2.

The BIOTECH plant consists mainly of the following equipment:

-No. 6 glass fermenters of 2 liters each
-No. 1 glass fermenter of 20 liters
-No. 1 stainless steel fermenter of 30 liters
-No. 1 stainless steel fermenter of 100 liters
-No. 1 stainless steel fermenter of 130 liters
-No. 1 stainless steel fermenter of 200 liters
-No. 1 stainless steel fermenter of 1000 liters
-No. 1 Autoclave and No. 2 hot air sterilizers.

Most of the fermentors are highly instrumented and one computer system is provided.

Some extration equipment is also installed as:

-No. 1 Ultrafiltration set
-No. 3 Stainless steel vessel of about 1 M^3
-No. 1 Westphalia centrifuge
-No. 1 Rotary drum dryer
-No. 1 Vacuum dryer (Buflovac)
-No. 1 Filter press
-No. 1 Blender (V type)
-No. 1 Hammer mill
-No. 1 Tube type centrifuge
-No. 1 complete plant for the Fermentation and distillation of Ethanol.

The BIOTECH plant is equipped with a water treatment unit, two boilers, one air compressor, one chilled water unit.

The laboratories operating at BIOTECH are equipped with some of the equipment that have been listed in paragraph 6.2 such as laminar flow hoods, shakers, incubators, refrigerator, computers and bench instruments.

It appears from this description that an important part of the materials indicated at paragraph 6.2, as necessary for the development of a well integrated pilot plant, are already existing at BIOTECH, Los Baños.

The expansion of the BIOTECH plant could be performed by:

- providing a second floor at about 4.0 meters level in the existing building whose total height is at present 8.0 meters. On this floor the microbiology laboratory could be installed.

- erecting a new local of about 300/400 M^2, adjacent to the existing building. In this local the new equipment for antibiotics extration should be installed.

- installing in the existing building some new fermenters in addition to the existing ones

- improving the capacity of some of the utilities generation systems, in particular of the chilled water one.

It is to be expected that the investment cost would be, in this case, from 40 to 50% lower than in the case of the construction of a totaily new facility.

For these reasons, it appears that one option that should probably be considered for the fermentation plant is to install it at BIOTECH, to be eventually operated jointly by ITDI and BIOTECH personnel, in order to maximize the utilization of existing local skills in the field of fermentation(1) and in the same time to minimize the investment costs.

It is obvious that this cooperation could be implemented only if political inter-departmental decisions are made on this subject.

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(1) It seems that a maximum number of 5 part-time researcher could be provided from the ITDI, a number insufficient by any standards to run a fermentation pilot plant.

6.4 MANPOWER

The required operating personnel is outlined hereafter.

6.4.1 Microbiology laboratory personnel

- No.1 Team leader
- No.2 Senior microbiologists
- No.2 Microbiologists
- No.3 Workers

- The team leader should preferably be a PhD in biology with an experience of at least two years in the technique of strains selection, mutagenesis, inoculum development, etc. A proper training period in an industrial facility as well as in a University highly specialized in this field is very important.

- Senior microbiologist. A master degree in biology should be required with some practical experience in the fields already mentioned for the team leader. Also in this case a training period abroad should be planned.

- Microbiologist - A bachelor degree in biology should be required.

The above mentioned staff should be involved fulltime in the activity of the antibiotic project. A part time involvement of other technical personnel such as analysts and chemists is to be foreseen.

6.4.2 Pilot-plant personnel

- No. 1 Team leader
- No. 2 Senior microbiologists
- No. 3 Microbiologists or Chemists
- No. 5 Workers
- No. 1 Chemical Engineer

- The team leader should have a Master degree in biology or chemistry and some experience in running of antibiotics fermentation processes and in scaling-up techniques. He should have a basic training as far as equipment, instrumentation and maintenance are concerned. A training period in an industrial facility or in a pilot-plant should be foreseen.

- Senior microbiologist - A master degree in biology should be required even though also Chemical Engineers with some experience in microbiology and biochemical engineering could be accepted to fill this post. An experience in running of fermentation process should be required. A training period in a pilot-plant would be desirable.

- Microbiologists or Chemists. A bachelor degree is required

- Chemical Engineer. A master degree is accetable, provided the candidate has some basic training in biochemical engineering and some knowledge of fermentation equipment and maintenance problems. He should be responsible for the technical maintenance of the plant.

7.0 PENICILLINS PLANT

7.1 PLANT CAPACITY

The proposed plant capacity is:

250 tons per year of Penicillin G Potassium plus

45 tons per year of Penicillin V Potassium

As outlined in paragraph 3.5.1, these quantities correspond to the projected domestic market requirements of Penicillins in 1995, without considering the possibilities of export. In case this possibility could materialize (in particular to the ASEAN countries), the design capacity should be increased, thus improving the plant profitability. Main data of the following paragraphs refer to the most conservative alternative excluding exports.

In the proposed complex, 88% of the produced Penicillin G should be converted into 110 Tons per year of 6-APA (6-amino-penicillanic acid), while the remaining 12 % is converted into injectable Penicillins (such as Pen G Potassium, Pen G Sodium, Pen G Procaine) and into feed grade Pen G Procaine (see attached flow chart). Such an integrated complex would be characterized by a higher profitablity, compared to a plant producing only Penicillin G and Penicillin V.

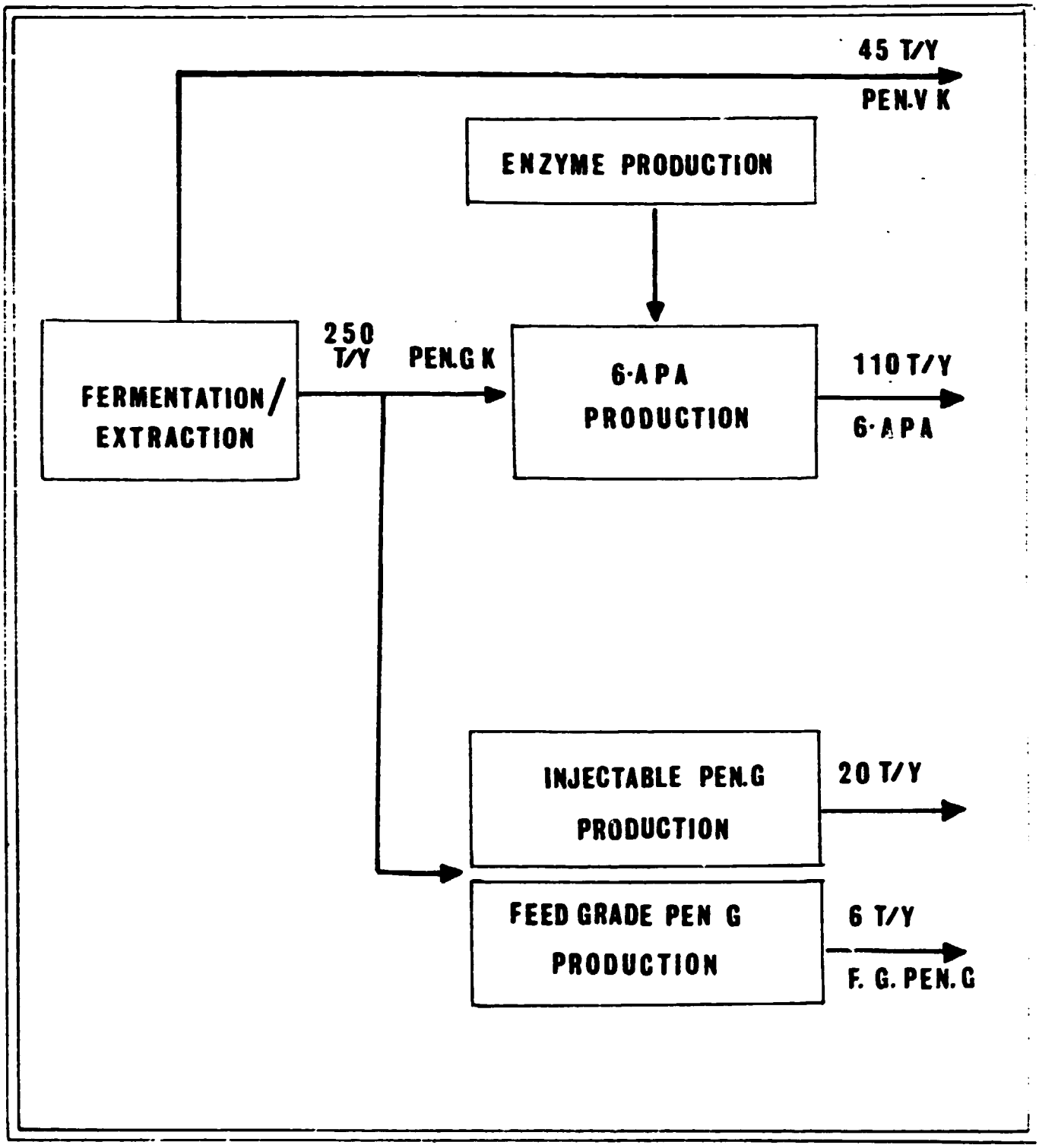
For the 6-APA production process, phenylacetate is recovered and is then reutilized in the fermentation process, thus decreasing raw materials costs.

In order to improve the self-sufficiency of the complex, the enzyme necessary for the 6-APA production is also manufactured in the plant by fermentation.

This option allows a decrease of the production costs of 6-APA.

Furthermore, it is to be pointed out that the possibility of producing both Penicillin G and 6-APA provides a high commercial flexibility to the project allowing it to face the variations of the market requirements for these two products.

PENICILLIN PLANT



FLOW CHART

7.2 PLANT LOCATION

As it will be highlighted in the next paragraphs, there are two very important factors to be considered in this case:

The carbohydrate source, that could be raw sugar, cane juice or molasses and the energy source, that could be bagasse. From this point of view, an optimization of the plant location would consist in installing the new complex adjacent to an existing sugar factory, thus providing a cheap source of energy and eliminating high transportation costs, both increasing the project profitability.

7.3 PLANT DESCRIPTION

The plant is subdivided into the following sections:

- Penicillin Fermentation and Extraction
- Solvent Recovery
- 6-APA Production (including Enzyme fermentation)
- Injectable and feed grade Penicillins production
- Utilities Generation Units
- Laboratories
- Waste Treatment
- Auxiliary Services (workshops, administration, canteen, etc.)

A description of the different sections is given in the following pages.

7.3.1 Penicillin Manufacture

Fermentation and Extraction [1] (see attached flow chart and process diagrams included in the annexes).

The microbiological laboratory takes care of the production of the spore suspension required as inoculum for the seed fermenters.

---

(1) This is one of several possibilities in the manufacture of Penicillins.

Three seed fermenters should be provided.

The culture medium for the seed fermenters is prepared in an agitated vessel and is then transferred to the seed fermenter for sterilization.

After adjusting the pH of the culture medium is inoculated with the spore suspension. Sterile process air is fed to the culture system and an overpressure is maintained during the whole cultivation time in the vessel, while pH values are adjusted as appropriate.

In this phase of the process, the aim is to achieve optimal mycelium growth. In about 40 hours, the mycelium growth phase is completed and the seed fermenter contents are ready to be transfered to the main fermenter. Six fermenters of 85 cubic meters each should be provided to cover the production capacity mentioned in paragraph 7.1. A typical fermenter drawing is given in the Annexes. The culture medium for the main fermentation is prepared in a vessel with stirring and then fed to the fermenter. The fermenter culture medium after adjustment of its pH, is heated up to 121°C and held for 20 minutes at this temperature, before it is cooled to fermentation temperature.

The contents of the seed fermenter are fed into the main fermentation vessel as the inoculum for Penicillin production.

At the begininning of the fermentation, antibiotic production is very low because further mycelium growth is required; fermentation conditions are then slightly changed and the addition of the precursor initiated to begin the production of Penicillin. In the case of Penicillin G fermentation, Phenylacetate is added as presursor, while for Penicillin V fermentation Phenoxyacetate must be added.

Parameters such as temperature, overpressure, process air, pH (by adding ammonia gas) foam level (by adding a sterile antifoam agent) are automatically controlled. Moreover, dissolved oxygen, viscosity, total sedimented material, sterility, mycelium form and quality, non - metabolized materials and Penicillin content should be recorded or checked by sampling.

Several sterile additions, other than those already mentioned, are made during fermentation such as precursor, lard oil, sugar and mineral salts solution. Normally during the fermentation, some drainages of broth are carried out and the volume withdrawn is replaced with culture medium, if this is needed to supplement the sterile additions.

Drainages are added to the harvested broth to be extracted.

At the end of the fermentative process, the broth is cooled down and then filtered to eliminate mycelium on a rotary vacuum filter.

Mycelium is thoroughly washed with water to limit Penicillin losses and then discharged. This washing water, mixed with broth, is sent to extraction. Diluted sulphuric acid is added to the filtered broth that is then fed into centrifugal continuous countercurrent extractor. In this equipment filtered broth is intimately mixed with chilled solvent (butyl-acetate, amylacetate or metyl - isobutylketone). At low pH values, Penicillin solubility in the aqueous phase is negligible, compared to its solubility in the solvent, and it transfers into the solvent together with part of the pigments present.

At the extractor outlet, the mixture is seperated: spent broth is sent to storage and then fed to a distillation column for solvent recovery, while rich butyl acetate is decolorized by treatment with decolorizing charcoal and after filtration, is fed to the second extraction stage with an aqueous potassium bicarbonate buffer solution.

Penicillin G transfers to the aqueous solution together with a part of the remaining pigments.

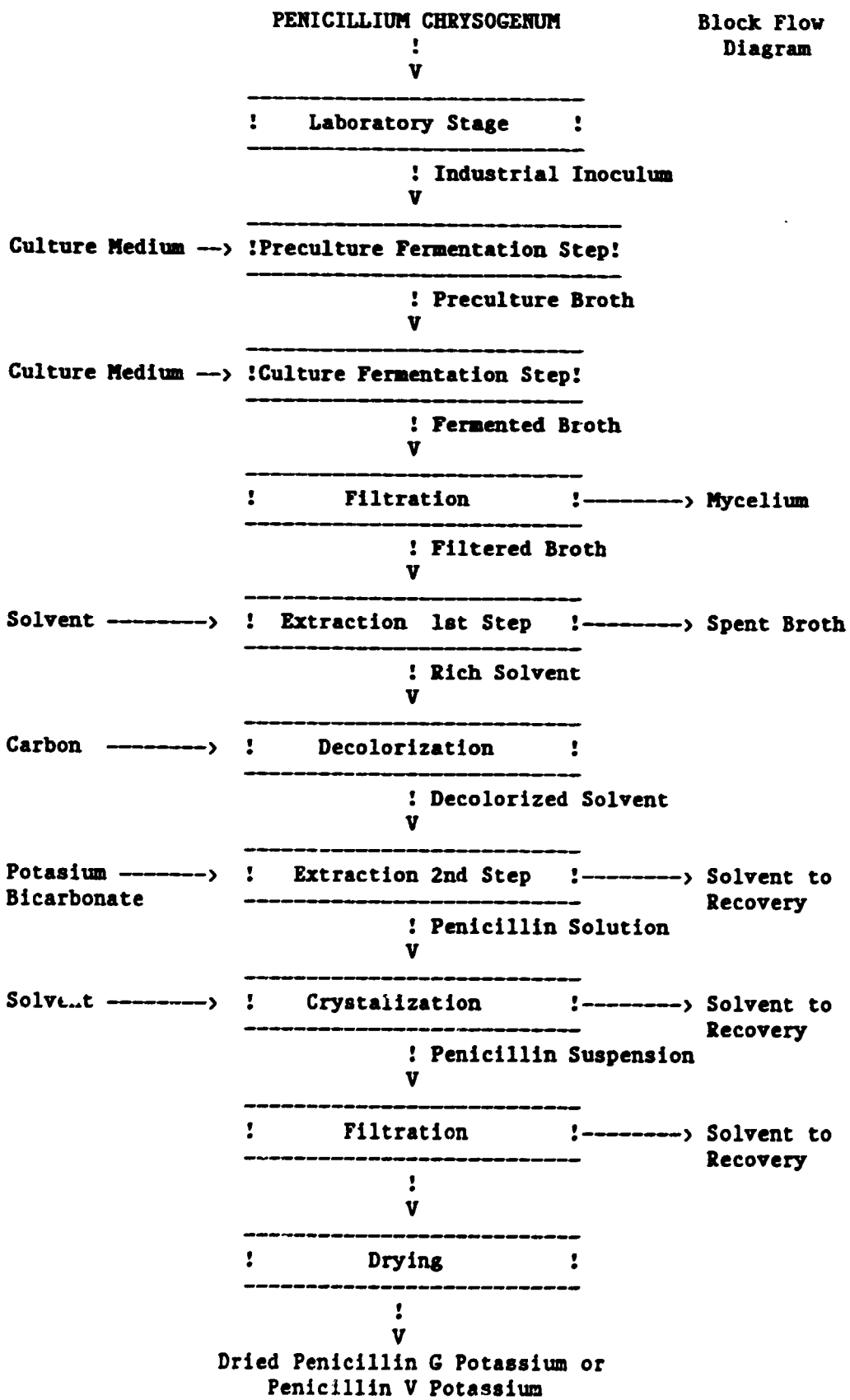
The mixture is then fed to a liquid-liquid separator from which the rich aqueous solution is sent to a vacuum cristallizer.

The rich aqueous phase is collected in the crystallizer where it is mixed with butanol to remove water by vacuum azeotropic distillation.

After removing all water, the Penicillin salt, not soluble in butanol, crystallizes.

The suspension of the crystals is fed to a pressure filter or to a centrifuge.

Penicillin crystals are thoroughly washed, inside the filter, with anhydrous butanol and then dried in a rotary-vacuum-drier with a hot-water circulation in the jacket.


PENICILLIUM CHRYSOGENUM
Block Flow Diagram
Laboratory Stage
Industrial Inoculum
Culture Medium
Preculture Fermentation Step
Preculture Broth
Culture Medium
Culture Fermentation Step
Fermented Broth
Filtration
Mycelium
Filtered Broth
Solvent
Extraction 1st Step
Spent Broth
Rich Solvent
Carbon
Decolorization
Decolorized Solvent
Potasium Bicarbonate
Extraction 2nd Step
Solvent to Recovery
Penicillin Solution
Solvent
Crystalization
Solvent to Recovery
Penicillin Suspension
Filtration
Solvent to Recovery
Drying
Dried Penicillin G Potassium or
Penicillin V Potassium

7.3.2 Solvent Recovery

Solvents are recovered in a standard distillation unit. Two main sections ,may be distinguished in this unit; one for butyl acetate and the other for butanol recovery Butyl acetate is recovered from spent broth by steam stripping and butanol - by azeotropic distillation in a two-distillation column system.

7.3.3 6-APA Manufacture (see attached flow chart)

The process consists of the hydrolysis of Potassium Penicillin G by the immobilized acylase enzyme to form 6-Aminopenicillanic Acid (6-APA), and Phenylacetic acid (PAA). The 6-APA is separated from PAA by extraction and is isolated by crystallization, centrifugation, drying and blending. The enzyme is reused.

Enzyme Production

Penicillin acylase enzyme is produced by a strain of Bacillus Megaterius using conventional fermentation techniques. Mycelia is removed by centrifugation and the broth concentrated using ultrafiltration. The enzyme is immobilized either with the aid of a carrier of by crosslinking.

The potency of harvested broth could be about 300 units per ml in 45-55 hours. The activity of the enzyme is about 30,000 units/gm.

Penicillin Dissolution

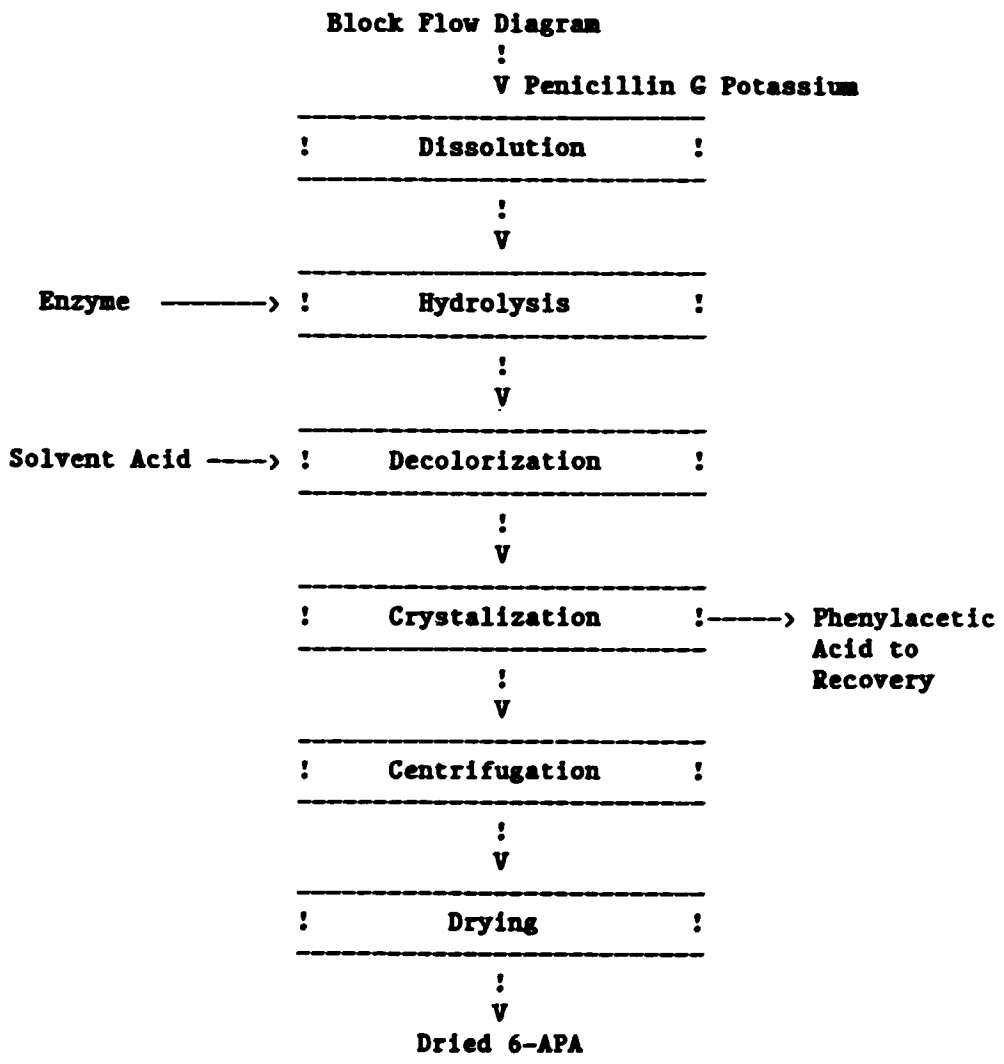
Potassium Penicillin G is dissolved in deionized water, under agitation, in a dissolving tank.

Hydrolysis

Into the hydrolysis reactor are introduced prescribed quantities of deionized water and resin containing the acylase enzyme. The pH of the contents of the hydrolysis reactor is adjusted to a defined level. The Penicillin solution is then transferred into the reactor. Hydrolysis takes place by maintaining careful control of the pH at a prescribed temperature. After the hydrolysis is finished, as determined by an in-process assay, the mixture is filtered through integral screens in the vessel into the crystallizer; the filtrate is polish-filtered enroute.

The hydrolysis is subsequently repeated with a fresh solution of potassium Penicillin G. Additional enzyme may be added at any time during the series of hydrolyses to improve the ratio of enzyme to Penicillin and reduce the hydrolysis time.

Many batches could be run on a given charge of enzyme (periodically fortified).



Extraction and Crystallization

The combined hydrolysate from the hydrolysis reactors is mixed with a proper solvent in the crystallizer and is cooled while being rapidly agitated. The pH is then adjusted; this causes 6-APA to crystallize and extract phenylactic acid into the solvent phase. The contents are then cooled, with agitation applied. Agitation is stopped to allow the phase to separate; 6-APA will be suspended at the aqueous-solvent interface.

Centrifugation

The mixture is separated by centrifugation; the crystalsare washed with solvent, then with chilled deionized water.

Drying

The wet cake is dried at prescribed conditions of air temperature in a fluid bed air dryer until the moisture content meets specifications.

7.3.4 Injectable Pen G and Feed-grade Pen G Manufacture

Injectable Penicillins G such as Pen G Potassium, Sodium, Procaine and Benzathine are produced in a sterile room. A special air conditioning system is provided to ensure the sterility of this area and air filtered in absolute HEPA filters before entering the sterile area.

Preparation of the solution is made in 2 reators outside the sterile room, while one crystallizer is installed inside it, together with a centrifuge, a dryer, a blender and a mill.(1)

Feed grade Pen G Procaine is produced in a separate area.A small unit consisting of one crystallizer, one centrifuge and dryer is provided for this purpose.

(1) This unit is installed in the Extraction and 6-APA Building. The building lay-out attached in the annexes shows only the orientative area requirement for the sterile unit, while all special devices required by sterility (such as entrance gowning room) are not shown.

7.3.5 Utilities and Off-site Facilities

- Electric Power and Steam

In order to guarantee the selfsufficiency of the plant concerning energy requirement,as well as to minimize the energy costs, it is suggested to produce all the needed electric energy in a bagasse-fed power plant (see paragraph 4.2). For this purpose two boilers operating at 40 - 50 ATE should be installed with a design capacity of 20 Ton/Hr each. High pressure steam is fed to a turbine generator which supplies up to 7000 Kw. (An average output of 5000-6000 Kw. could be expected). Electric Power is distributed to the users at two voltage levels : 6000 V and 400 V.

Steam is partly (20 - 25%) extracted at 8-10 ATE to face the steam requirements of the production units and partly (75-80 %) condensed under vacuum to maximize the electric power production. The power plant cooling requirement could be covered by sea or river treated water (once through circuits).

- Water Treatment

Raw water is delivered to the plant on a continuous basis. An average consumption of 30-40 cubic meters per hour is expected. Raw water, depending on its source and characteristics, should possibly be softened to be suitable for fermentation uses. Part of the water must be demineralized (about 5-6 cubic meters per hour) both for the supply of boilers feed water make-up and to fit with the process requirements. Demineralization is performed by ion exchange resins.

- Refrigeration

Three closed circuit systems are foreseen to cover the refrigeration needs of the plant :

a) Cooling water system - A cooling tower system could be provided with a capacity of 1500 cubic meters per hour. Cooling water supply temperature would be about 30 ^{o}C. Return temperature to cooling towers would be 40 ^{o}C

b) Chilled water system - Two refrigeration units, mechanical type, are installed. The capacity of each unit should be 3 - 4 millions of Kcal/Hr. Chilled water supply temperature is 10 °C.

c) Brine system. Two units with a capacity of 200,000 Kcal /Hr each should be installed. Glycol type brine is utilized. Brine temperature is minus 10 °C.

- Compressed Air

Three centrifugal compressors having a capacity of 12000 NM3/ Hr. each are installed to supply compressed air to the fermentation unit. Air is compressed at 2.5 ATE. One compressor is stand-by. Other two compressors are foreseen having a capacity of 500 Nm3/Hr. each at 7 ATE to feed the plant with instrument air and service air.

- Off-site Facilities

Storage tanks should be installed for all the raw materials supplied in bulk as glucose solution, or molasses, or raw sugar, corn-steep, ammonia, sulfuric acid, caustic soda, solvents and liquid nitrogen (used mainly for blanketing purposes). An outdoor storage for Bagasse should also be provided.

- Fire Fighting Protection

The protection of the plant is ensured with water, foam and powder.

The fire water system is constituted by an underground network looped all around the plant.

The solvent area shall be protected by foam-water monitors. Dry chemical powder estingushers will be provided all over the plant.

7.3.6 Laboratories

The following laboratories should be foreseen for the Penicillin Plant:

a)Industrial Microbiology Laboratory.

This laboratory is located in the Fermentation building and its scope is to supply the Inoculum to be fed to the industrial fermenters. It consists of the following sections:

- Master Culture preparation and preservation
- Inoculum Development
- Glassware cleaning and Media Preparation Area
- In process laboratory

b)Quality Control Laboratory.

This laboratory is located in a centrtal building, seperated from the production areas. It could be subdivided as follows :

- Chemical Analysis Laboratory
- Microbiological Laboratory
- Sterility Control Laboratory
- Biological Laboratory and Animal House (mainly for pyrogen-free tests).

7.3.7 Waste Treatment

Waste water is treated in a biological type system, in order to comply with the local quality standards for final effluent discharge. The waste water treatment plant consist of the following main sections:

- Equalization and Balancing
- Neutralization, Flocculation and Flotation
- Biological Oxidation (one or two stage activated sludge treatment, depending on required water quality).
- Sludge Thickening and inceneration.

The mycelium coming from the Penicillin fermentation is first thickened to reduce handled volumes and then either utilized as animal feed or fertilizer (if this is permitted by local regulations) or incinerated.

7.4 EQUIPMENT

A list of the main equipment to be installed in the plant is given hereunder:

7.4.1 Fermentation

Item	No.	Capacity	Material
Fermenters (1)	6	85 m^3	s.s.
Seeds fermenters (1)	3	10 m^3	s.s.
Culture media vessels	3	10 m^3	s.s.
Sugar sterilizers (1)	2	20 m^3	s.s.
Precursor sterilizers(1)	2	6 m^3	s.s.
Ammonium Sulfate sterilizers (1)	2	6 m^3	s.s.
Oil sterilizers (1)	2	2 m^3	s.s.
Caustic solut. sterilizers (1)	2	1 m^3	s.s.

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(1) Equipped with external cooling coil, turbine agitator, and air sterilization filter and prefilter (cartridge type)

7.4.2 Penicillin Extraction

Item	No.	Capacity	Material
Harvest Vessels (1)	2	85 m^3	s.s.
Treating vessels (1)	2	20 m^3	s.s.
Vacuum filters	2	20 m^2	s.s.
Filtered broth vessel	1	20 m^3	s.s.
Podbielniak centrifugal extractors (1st stage)	2	D36 model	s.s.
Podbielniak or Alfaloval centrifugal extractor (2nd stage)	1	-	s.s.
Sulfuric acid dilution vessel (1)	1	2 m^3	glass lined
Sulfuric acid storage vessel	1	10 m^3	fiberglass
Solvent vessels	6	8 m^3	s.s.
Spent broth vessel	1	4 m^3	s.s.
Buffer vessels (1)	3	4 m^3	s.s.
Rich Pen G vessels (1)	3	5 m^3	s.s.
Pressure filters	4	Sparkler type	s.s.
Crystalizers (1)	2	10m^3 (with condensers)	s.s.
Penicillin filters	2	Pressure filter 3m^3	s.s.
Dryers	2	Rotating Vacuum dryer 3m^3	s.s.
Pumps	30	Centrifugal type	s.s.

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(1) Equipped with agitator and external jacket

7.4.3 Solvent Recovery

Item	No.	Capacity	Material
Broth Stripper	1	Distillation Column (20 Trays)	s.s.
Solvent vaporizers	1	Distillation column (5 trays)	s.s.
Butanol stripper	1	Distillation Column (20 trays)	s.s.
Aqueous phase stripper	1	Packed tower	s.s.
Vent scrubber	1	Disc & Donut Column	s.s.
Spent broth tank	1	200 m^3	s.s.
Solvent storage vessels	6	25 m^3	Carbon steel
Pumps	20	Centrifugal type	s.s. and c.s.
Heat exchange	12	Shell and Tube	s.s.

7.4.4 Enzyme Production

Item	No.	Capacity	Material
Enzyme prefermenters (1)	2	0.3 m^3	s.s.
Enzyme fermenters (1)	2	3 m^3	s.s.
Centrifugal extractor	1	Disk-stack type	s.s.
Ultrafiltration system	1	-	-
Reactor (1)	1	2 m^3	s.s.
Filter	1	Pressure type	s.s.

(1) Equipped with agitator and external half-pipe coil

7.4.5 6-APA Production

Item	No.	Capacity	Material
Dissolver (1)	1	2 m^3	s.s.
Hydrolysis reactor (1)	1	3 m^3	s.s.
Crystallizers (1)	2	8 m^3	s.s.
Surge vessels	2	15 m^3	s.s.
Centrifuge	1	Basket type diameter:1200 mm	s.s.
Dryer	1	Fluid bed type volume:500 liters	s.s.

7.4.6 Injectable Penicillins Production

Item	No.	Capacity	Material
Reactors (1)	3	2 m^3	s.s.
Sterile reactors (1)	1	3 m^3	s.s.
Sterilization filter	2	Cartridge type	-
Centrifuge	1	Basket type Diameter: 1200 mm	s.s.
Dryer	1	Vacuum type (1.5 m3)	s.s.
Blender	1	Double cone (1.5 m3)	s.s.
Mill	1	Fitz Mill	s.s.
Autoclave	1	1000 liters	s.s.
Hot air oven	1	1000 liters	s.s.

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(1)Equipped with agitator and external half pipe coil

7.4.7 Feed Grade Penicillin Production

Item	No.	Capacity	Material
Reactors (1)	3	2 m^3	s.s
Centrifuge	1	Basket type (diameter 1200 mm)	s.s.
Dryer	1	Vacuum type (0.5 m^3)	s.s.

7.4.8. Utilities

Item	No.	Capacity	Material
Boilers	2	20 T/Hr	-
Steam Turbine generator	1	7000 Kw	-
Water treatment (2)	1	Filtering, softening and demineralizing unit	
Raw Water Tank (2)	1	2000 m^3	Carbon Steel
Cooling tower (2)	3	Total Flow rate: 1500 m^3/hr	
Refrigeration Units (2)	2	Capacity: 3.5 million Kcal/hr. (each)	
Brine Units (2)	2	Capacity 200,000 units each	
Fermentation air compressor	3	12,00 Nm^3/hr (each)	
Instrument air compressors	2	500 Nm^3/hr each	

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(1) Equipped with agitator and external half pipe coil

(2) Including distribution pumps

7.4.9 Tank Farm

Item	No.	Capacity	Material
Corn steep tanks	2	30 m^3	Fiber glass
Sugar solution tanks	2	50 m^3	s.s.
Precursor tanks	2	30 m^3	s.s.
Lard oil tanks	2	30 m^3	s.s.
Ammonia tank	1	30 m^3	Carbon steel
Liquid nitrogen tanks	2	20 m^3	Dewar type
Sulfuric acid tank	1	50 m^3	Carbon steel
Caustic solution tank	1	50 m^3	Carbon steel

7.4.10 Waste Treatment

Item	No.	Capacity	Material
Equalization tanks	2	300 m^3	Carbon steel
Floculation and flotation basin	1	-	Concrete
Oxidation basins	2	With surface aerators	Concrete
Sludge thickening basin	1	-	Concrete
Mycelium tank	1	50 m^3	Carbon steel
Sludge centrifuge	1	Decanter type	-
Sludge incinerator	1	Tray type	-

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(1) Including distribution pumps

7.5 PLANT LAYOUT AND BUILDINGS

A preliminary layout is attached in the Annexes. A total surface of about 5.0 hectares is required.

The following buildings are foreseen:

a. Fermentation building (see attached drawing)-1500m^2 covered surface

The fermentation area is a multi-level building that houses the germinators (prefermenters), the fermenters, the sterile feed solution vessels, as well as the harvested broth vessels.

In addition, the industrial microbiological laboratory (see paragraph 7.3.6) is installed. Space is also provided for storage, control room, electrical rooms, social facilities, area maintenance, offices, etc.

A reinforced building could be foreseen or, as an alternative, a steel structure one with simple steel sandwich deck used as roofing and no external walls.

b. Penicillin extraction and 6-APA production building. (see attached drawing) - 2000 m2 covered surface.

This two-level-building houses the extraction area of Penicillin, including crystaillization, filtration, and drying, as well as the Enzyme production unit, the 6-APA production unit and the sterile room for injectable Penicillin manufacture. A storage area for the different products is also provided. The bulk products (Penicillin, 6-APA, etc.) are handled in a highly controlled environment, once the product is on a wet cake or dry powder stage. This helps assure the highest possible product quality.

A reinforced concrete type building is recommended.

c. Warehouse

This one level building is devoted to store all the raw materials supplied in bags and drums

d. Compressor House

Compressors and refrigeration units are installed under a shelter, without external walls.

e. Offices and central laboratories building. A three or four levels air conditioned building is to be forseen

f. Social Building

This building houses mainly the central locker room and the canteen.

g. Electrical Substation (ventilated building).

h. Workshop

This building houses the spare parts warehouse, as well as the workshop.

7.6 RAW MATERIALS

7.6.1 Penicillin G and V

The main raw materials utilized in the manufacture of Penicillin G or Penicillin V are as follows:

Fermentation

- Corn-steep Liquor
- Glucose solution that can be substituted either by raw cane sugar, or by molasses or cane juice.
- Lard oil or soybean oil
- Potassium Phenylacetate (for Pen G) or Sodium Phenoxy Acetate (For Pen V). These products act as precursors of the Penicillin biosynthesis.
- Calcium carbonate, Ammonium sulphate, Calcium hydroxide
- Anhydrous Ammonia and Sodium Hydroxide

Extraction:

- Sulfuric Acid
- Potassium Bicarbonate

- Solvents such as butylacetate (that can be substituted by amylacetate or methylisobutylketone) and butanol
- Demulsifier and dispersing agents
- Formyldehyde
- Activated charcoal and filter aid

The carbohydrate source (glucose solution, or sugar, or molasses) is the most cost effective raw material in European Conditions and it represents about 45-50 % of the total raw material cost in the Pen G production in Europe.

The raw materials which could be locally manufactured are corn-steep liquor, raw sugar (or glucose solution, or molases, etc), lard oil, or soybean oil and sulfuric acid (for a detailed discussion on local raw materials see paragraph 4.1). Raw materials consumption greatly varies with the different technologies for Penicillin production and depends on the fermentation yields.

For Penicillin GK, the glucose solution consumption is ranging from 8 to 10 Kgs. per B.U. of Penicillin(1). If molasses areutilized, the consumption would be 10-15 Kgs. per B.U.

In the case of raw sugar utilization, the consumption would be of 5 - 6 Kgs. per B.U. It should be pointed out that most of the glucose solution available in the Philippines seems to be of much lower quality than the one utilized in European factories and the relevant consumption could be accordingly higher (the above mentioned consumption data refer to European high quality glucose from corn). The cost of the domestic carbohydrate sources could be summarized as follows:

(1) 1 B.U. is equivalent to 1.595 kg of activity of Pen G K.

- Glucose solution : 4 to 6 U.S $ per B.U.
- Raw sugar : 2 U.S. $ per B.U.
- Molasses[1] : 0.9 to 1.1 U.S. $ per B. U.

From these figures, it appears that raw sugar and molasses are more attractive raw materials, compared with glucose solution. Molasses utilization should be in any case checked with fermentation tests, since its quality could greatly affect the fermentatin yields.

All the other raw materials should be imported, the most cost effective imported raw material being the phenylacetate (or Phenoxyacetate)

The cost of all the other raw materials for Penicillin G K,excluding the carbohydrate source is expected to be 5-7 $ per B.U., including transport costs.

7.6.2 6-APA

The most important raw material in the 6-APA production is the immobilized enzyme, with prices on the European market reaching US$ 3000 - 5000 per Kg. It is therefore convenient to produce the enzyme by fermentation in the same plant, as it has been suggested in this study. In these conditions, the total raw materials cost of 6-APA would be much lower, expected to reach 1 to 2 $ per Kg. of 6-APA.

The other raw materials are ammonia solution, sulfuric acid, caustic soda and solvents, as butylacetate or acetone.

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(1) Sugar cane juice could also be envisaged (see paragraph 4.1)

7.6.3 Injectable and Feed Grade Penicillins

The cost of raw materials for this production can be considered as negligeble, if compared with the fermentation raw materials. The most significant raw materials are:

- Procaine Hydrochloride (for Pen G Procaine production)
- N-N-dibenzyl-ethylendiamine-diacetate (for Pen G Benzathine)

These products are to be imported.

7.7 UTILITIES CONSUMPTION

The basic average utilities requirements of the plant are:

Electric Power	5000-6000 Kw
Steam	5-6 Ton/Hr.
Raw Water	30 - 40 m^3/Hr

On the basis of the hypothesis described under paragraph 7.3.5, i. e. all the required energy produced in a power plant supplied with bagasse, the only cost for utilities generation would consist in the transportation cost of Bagasse.

The consumption of Bagasse is about 90,000- 100,000 Ton per year. Assuming a cost of bagasse (mainly transportation) of 100 - 150 Pesos per ton, the total cost for utilities would be about 500,000-700,000 $ per year.

In case that fuel oil would be utilized instead of Bagasse, the above mentioned costs would increase to US $ 2.5-3.5 millions per year.

7.8 MANPOWER REQUIREMENTS

7.8.1 Organization

The operations are carried out 24 hours per day during 330 days per year.

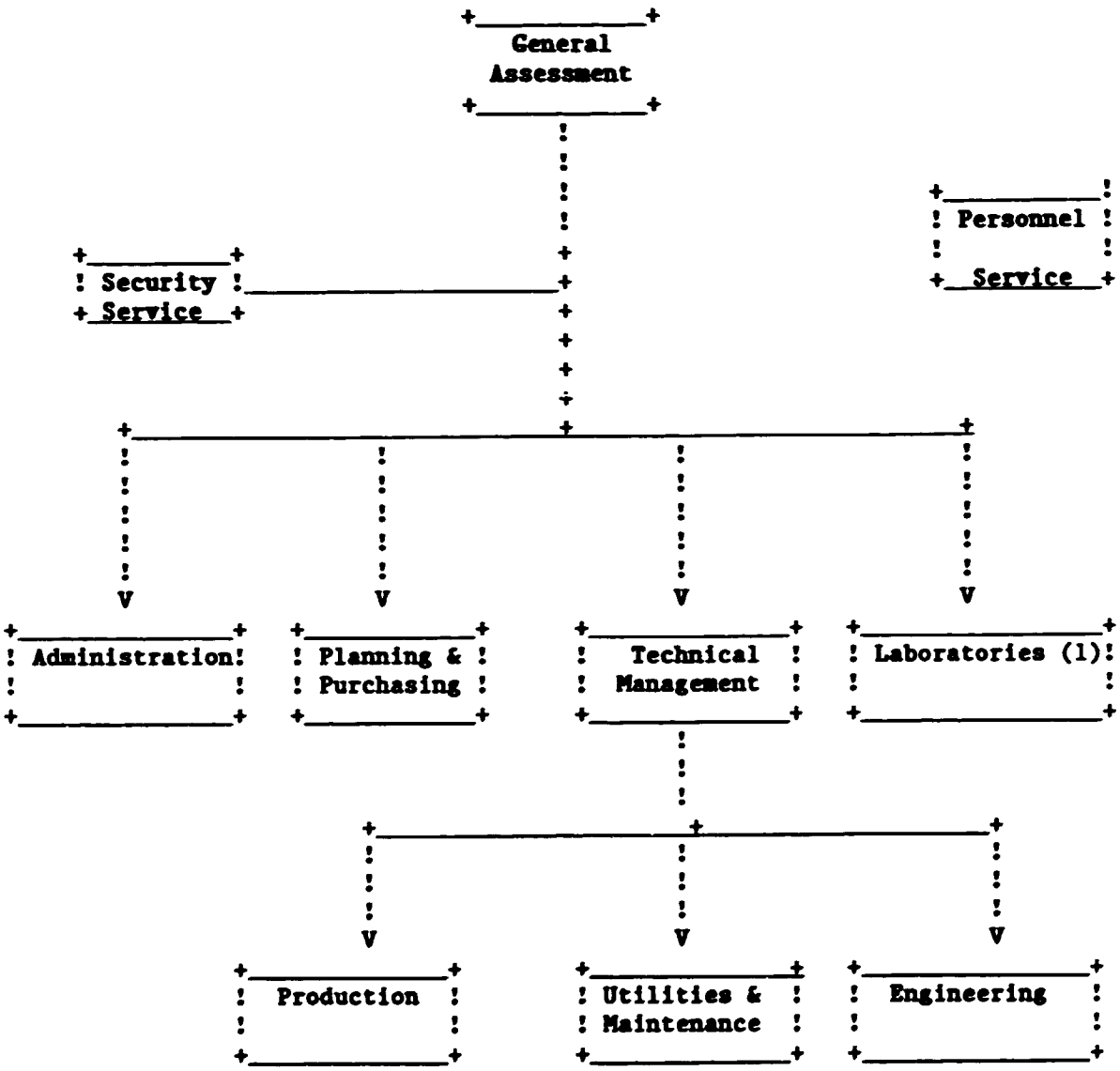
An organization flow chart of the complex is given on the next page.

The personnel requirement for the plant is as follows:

	Production	Utilities, Eng. & Maintenance	Laboratories	Administration	Planning & Purchasing
Plant Manager & Supervisory Personnel	8	4	3	2	2
Operators, Technicians, Clerks, and Laboratory specialists	25	15	12	5	5
Skilled workers	30	15	5	1	1
Unskilled workers	37	20	-	-	-
	100	54	20	8	8

Total need : 190 persons

Organization Chart



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(1) The laboratories should not report to the technical management, but directly to the Top Management, for obvious reasons.

7.8.2 Qualifications

Heads of Departments such as Fermentation, Extraction, Utilities etc, should be persons with University degrees in Chemistry, Biology, Chemical Engineering or in any other related scientific field. If possible, some subordinate levels for fermentation and extraction of Penicillin (supervisors) should also be filled by staff with University degrees, such as Chemical Engineers, for instance.

The responsible for the laboratories should be a PhD. in Microbiology with at least 2 years of experience in strains development. The laboratory technicians team should include at least two other Senior Microbiologists (Master Degree), two Bachelors in Biology and two Bachelor in Chemistry, with a specialization in Analytical Chemistry and experience in the use of modern equipment such as HPLC and gascromatography. Operators and first level supervisors of production units are usually persons with a high school equivalent education. Proficient and dependable operators are usually promoted to first level supervision. Occasionally, second level supervision might be filled by such individuals.

Whenever possible other workers such as packers, storekeepers and cleaners etc, those involved in production, should be able to read and write properly.

Part of the technical personnel and in particular mechanical and electrical maintenance workers, could be recruited among skilled personnel having a working experience in domestic industries such as Chemfields Inc. (Semisynthetic Penicillins Production), brewery factories as San Miguel Corporation, etc.

7.8.3 Training

A selected group of supervisors and technicians should be probably trained in an existing industrial fermentation facility. This training program should therefore be performed abroad.

At least the heads of Fermentation, Extraction and Injectable Penicilins units should be trained for a minimum of 3-4 months.

Also three of the graduated laboratory technicians should be trained for 3-4 months in a modern microbiological laboratory abroad.

On the spot training in Good Manufacturing Practices (GMP), especially on "problem oriented teaching", e.g. personal hygiene, health habits, basics of quality assurance, etc. is important. Key personnel in injectable Penicillin production could be given periodical specific training programs, concerning injectables.

Other specific training programs should be undertaken for quality control key personnel.

Furthermore, it is suggested that at the initial stage, for two years at least, to have the support of some foreign Experts. Three experts could be employed as:

- Plant and Production Manager
- Quality Control Manager
- Engineering and Maintenance Manager

During their stay on the spot, the three Experts will cooperate with the national staff and will continue their training program in order to complete, as soon as possible, the transfer of management and technical responsibilities of the plant to Nationals.

A management based on a secondment agreement with foreign Companies, participating or not in this venture, could also be considered.

7.9 ECONOMIC EVALUATIONS

A preliminary evaluation of the project profitability is given hereafter

7.9.1 MANUFACTURING COSTS

a) Raw Materials Costs

The raw material costs can be subdivided as follows:

- Carbohydrates source (locally manufactured).
  Considering raw sugar as carbohydrate source the relevant yearly cost would be about 1,000,000/year US $ (1988). In case that molasses could be util_zed,this cost might be lowered by 40-60%. For the profitability calculations, the most conservative hypothesis shall be made i.e. utilizing raw sugar.

- All other raw materials relevant to the Penicillin G and Penicillin V production. Their costs would be about 2,500,000 US$ per year at 1988 price levels, with the assumption of import duties and tax exemption on imported raw materials. Transportation and other expenses have been included.

- Raw materials for 6-APA, Injectable Penicillins G and Feedgrade Penicillins. Their cost would be about 500,000 US$ per year (1988) with the abovementioned assumption for imported raw materials.

The total raw material cost would therefore be about 4,000,000 US$ per year at 1988 price levels.

b) Manpower Costs

On the basis of the manpower requirements mentioned in paragraph 7.8, a total cost for personnel of US $ 800,000 per year has been estimated.

c) Energy and Utilities Costs

On the basis of a Bagasse consumption of 90,000 to 100,000 per year, an annual cost of US$ 600,000 has been estimated.

d) Depreciation

A ten years straight line depreciation of machinery and equipment and a fifteen years one for civil works has been considered.

7.9.2 Other costs

Operating expenses, including administration maintenance and marketing[1], as well as all other expenses not pertaining to production, should be in the range of US$ 1,200,000 per year.

7.9.3 Income Taxes

In accordance to the incentives offered by the Board of Investments a tax holiday for 4 years, for non-pioneer firms, has been foreseen.[2]

7.9.4 Investment Costs

When considering the investment costs, it was assumed that the enterprises will be granted for 5 years tax and duty exemption on imported capital equipment, as well as tax credit on the domestic one, as well as exemption from contractor's tax.

The overall estimated investment cost of the complex would be in the range between 26 and 30 millions US $. The latter shall be taken as basis for profitability calculations. The breakdown of this cost is 50% for production units, 33% for utilities units and 17% for civil works. The following items are included in the abovementioned estimate:

- Machinery and Equipment
- Bulk materials (piping, instrumentation and electric system)
- Spare parts
- Transportation
- Erection
- Civil Works (including land preparation)
- Engineering
- Know-how (Penicillin and 6-APA technologies)
- Personnel training
- Construction and start-up assistance

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(1) In this case, marketing expenses for a very limited number products in Bulk from under BOI promotion, should be relatively low.

(2) In case of a pioneer firms, a 6 years period should be considered.

7.9.5 Sales

For the sales estimates, the international market prices of the different products have been increased by about 10%, to take into account the transportation cost, and other expenses related to the fact that at present these products are imported.

- 6-APA (110 tons per year)	:US $ 7,260,000
- Penicillin V (45 tons per year)	:US $ 2,270,000
- Injectable Penicillin G (20 tons per year)	:US $ 1,800,000
- Feedgrade Penicillin	:US $ 300,000
Total Sales estimates	:US$ 11,630,000 per annum

7.9.6 PROFITABILITY ESTIMATION

Sales	11,630,000 $/year
Production Costs	5,400,000 $/year
Other costs	1,200,000 $/year
Industrial Profit	5,030,000 $/year
Depreciation	2,800,000 $/year
Profit before provision for Income Tax	2,230,000 $/year
Provision for Income Taxes (after the 4th year)(1)	780,000 $/year
Profit after taxes	1,450,000 $/year

(1) Or the 6th year in case of a pioneer industry.

-Return on sales= 19.0% (for the first 4 years) and 12.5% (after the 4th year)

-Pay-back time = about 6.5 years

-Annual rate of return on investment = 11 %. The calculation has been made on the basis of the well-known discounted cash flow rate of return method, assuming a period of life of the plant of 15 years and a salvage value recovered at the end of the project equal to zero (a conservative hypothesis)(2).

The abovementioned figures were based on the fact of incentives foreseen in the " Omnibus investment code of 1987"(executive order No. 226) mentioning income tax holiday, tax and duty exemption on imported capital equipment, tax credit on domestic Capital equipment, exemption from contract tax, etc.

Additional incentives, such as tariff protection, long-term guaranteed government contracts for purchasing a part of the production, soft-loans for project financing etc., should be considered in order to nurture and foster the growth of such a natant industry.

In order to check the impact of such possible incentives on the project economics, an alternative calculation of profitability has been made, considering that product prices would be increased by 10%, as a consequence of price regulatory policy.

In these conditions the economic evaluation indexes should become:

- Return on sales: 26% (for the first 4 years) and 17% after the 4th year
- Pay-back time: about 5 years
- Rate of return on investment: 14%

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(2) For the calculation method see "Grant and Ireson" - PRINCIPLE OF ENGINEERING ECONOMY, Ronal Press, New York, 1960".

Another factor that would allow an increase of the project profitability consists in the possibility of exporting part of the produced Penicillin or 6-APA. In this case, the production capacity should be increased, thus obtaining an economy of scale that would improve the annual rate of return on investment. In particular, it could be interesting to check the possibility of export to some countries of the ASEAN area, where Penicillin production has not yet been implemented. For the time being, however, this possibility seems to be rather remote, since it would involve a strong competition with multinational Corporations controlling the market at present.

It is finally to be focused that all the above mentioned profitability indexes were calculated on the basis of the main assumption that local raw sugar is utilized as carbohydrate source(1) and Bagasse is utilized as energy source. In the case that a traditional carbohydrate source as glucose solution, should be selected and fuel oil should be utilized to supply the required amounts of energy, the project would no more be viable, being the total cost of production (including administration, marketing, maintenance, etc.) increased, in this case, of at least 45%. All the profitability indexes would then drop dramatically; pay-back time, for instance, would be about 15 year.

7.9.7 CONCLUSIONS AND RECOMMENDATIONS

On the basis of the previous data on profitability, it appears that the implementation of a Penicillin Plant could be the first important step in the way of reaching a relative self-reliance in the antibiotics production in the Philippines.

It would therefore be essential, to initiate and execute a detailed feasibility study which would enable the Authorities to make the proper decisions.

(1) If Molasses are used the profitability is even improved.

8. MULTI-PURPOSE PLANT FOR ERYTHROMYCIN, TETRACYCLINES AND RIFAMPICIN

8.1 PLANT CAPACITY

The proposed capacity of the multi-purpose fermentation plant is:

26 Tons per year of Erythromycin Base
35 Tons per year of Rifamycin B
20 Tons per year of Tetracycline Base
16 Tons per year of Oxytetracycline Base
50 Tons per year of Chlortetracycline

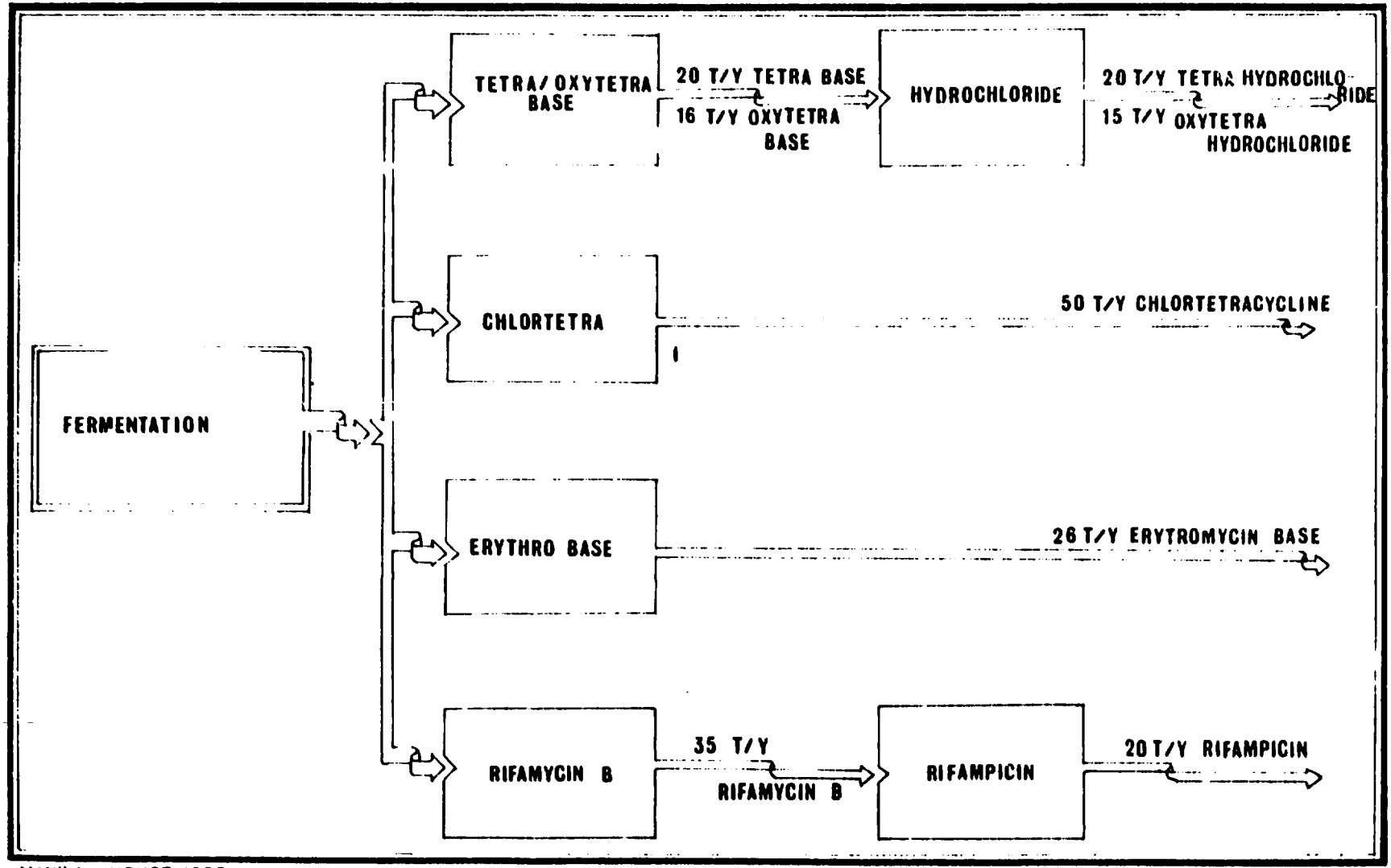
As outlined in paragraph 3.5.1., these quantities correspond to the projected domestic market requirements of these families of antibiotics in 1955. Therefore, as in the case of the Penicillins Plant, the possibility of exports has not been considered.

In the proposed Complex, Tetracycline Base and Oxytetra cycline Base are transformed into the relevant Tetracycline and Oxytetracycline Hydrochlorides, products required the market. The technical informations relevant to this last step of the production process are supplied in the report of Dr. Sciaky concerning the semi-synthetic antibiotics.

Rifamycin B, which is produced by fermentation, is further transformed into Rifampicin, via production of an intermediate, named 8-formyl-Rifamycin SV. In the case that the last step of the process, consisting in the conversion of 8-formyl-Rifamycin SV into Rifapicin, is already performed in a separated synthesis plant, as it is proposed in the report of Dr. Sciaky, only Rifamycin SV would obviously be produced in the fermentation plant.

As far as Erythromycin is concerned, it has been assumed that only the base is produced in the fermentation plant, the transformation of the Base into the final products (Stearate, Ethylsuccinate and Thiocyanate) being the object of an option suggested in the report relevant to the semi-synthetis antibiotics. This option concerns the possibility of performing the transformation in a new unit to be installed in the existing plant of Chemfields Inc. As an alternative, also this unit could be installed in the fermentation plant that would be in a condition, in this case, to supply also the final products. A flow-chart showing the subdivision of the plant in its different sections, is given in the following page.

MULTI-PURPOSE PLANT



MANILA AUGUST 1988

FLOW CHART

Chlortetracycline, which is a veterinary or feedgrade antibiotic, has been included in the production program in order to achieve a total self-reliance in the Tetracyclines supply, though the added value relevant to this product is rather low. One additional option to be examined on the basis of a detailed market study on this product, could therefore consist in the eliminating it from the production program of the plant, thus reducing the investment costs.

Five fermenters of 85 cubic meters each should be provided to cover the above mentioned production capacity. The different antibiotics are produced by campaigns (blocked-out operations). 330 operating days per year are assumed as basis of design and three shifts operations are required. The breakdown of the plant utilization is the following:

- Erythromycin : 150 days per year
- Rifampicin : 70 days per year
- Tetracyclines : 110 days per year

8.2 PLANT LOCATION

As far as plant location is concerned, the same recommendation that has been done for the Penicillins plant is stressed again for the multi-purpose plant, i.e. to install it adjacent to an existing sugar factory (in paragraph 7.2 the reasons of this recommendation are highlighted).

8.3 PLANT DESCRIPTION

The plant is subdivided into the following sections:

- Fermentation
- Tetracyclines Base,
  Erythromycin Base and
  Rifamycin B Extraction

- Hydrochlorides Production
- Rifampicin Production
- Solvent Recovery
- Utilities Generation Units
- Laboratories
- Waste Treatment
- Auxiliary Services (workshop, administration, canteen, etc.)

A description of the different sections is given in the following pages

8.3.1 Erythromycin Base Manufacture (see attached flow chart)

The Microorganism used for production of Erythromycin is Streptomyces erythreus.

Two stages of fermentation are required and a batch type fermentation is normally performed.

The operations of seeding and fermentation are similar to what has already been described for Penicillin, except for the fact that neither drainages, nor sterile additions are commonly provided.

The medium is mainly formed by starch, soya flour and salts.

The fermentation broth is fed to disk type centrifuges for the seperation of mycelium.

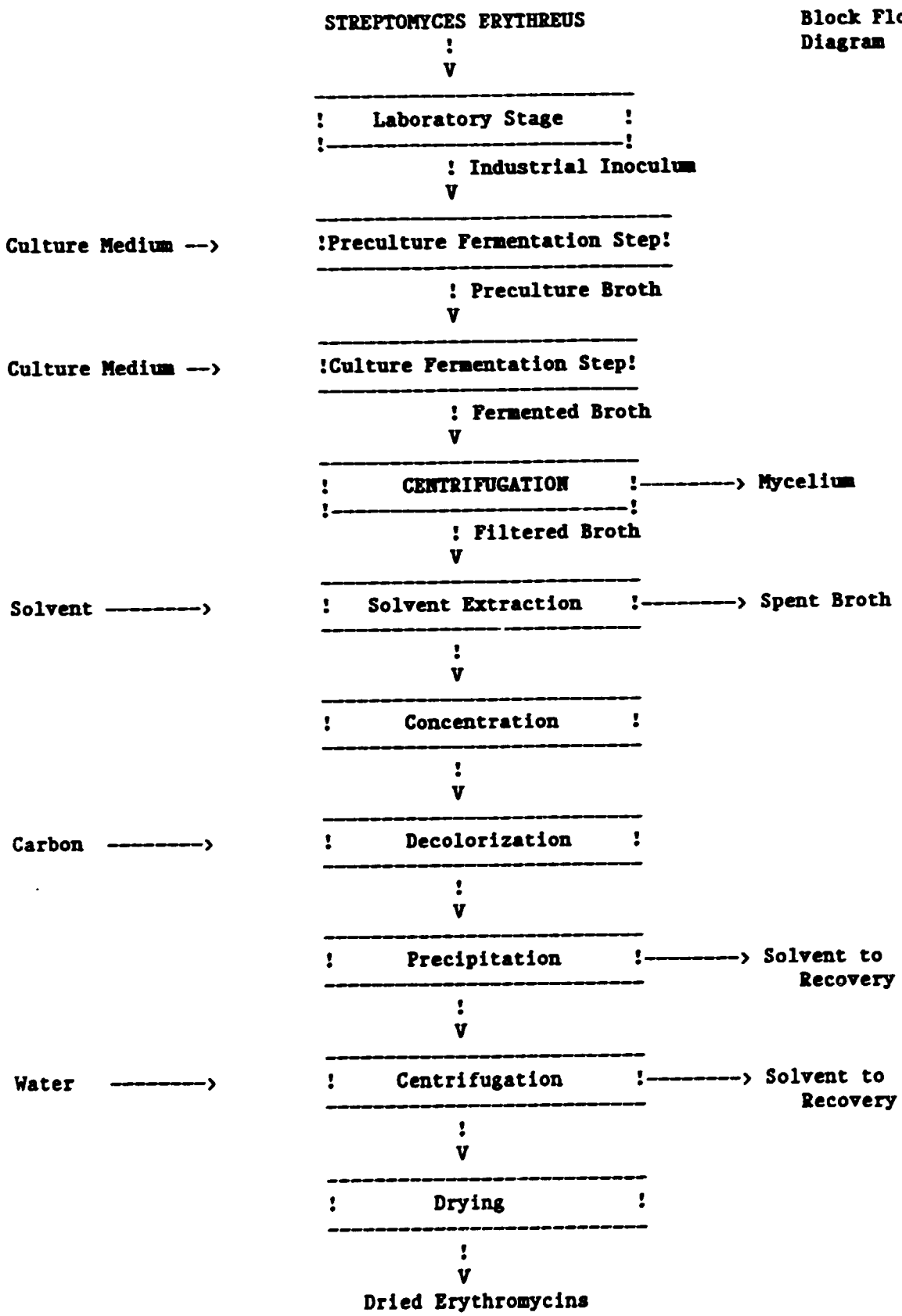
The centrifuged broth, after a pH adjustment, is sent to a centrifugal separator where the Erytromycin is extracted by means of a solvent. For this purpose Butyl - acetate, as well as a Chlorinated solvent could be utilized as solvents.

The rich solvent is concentrated in a vacuum falling film evaporator and it is then sent to a reactor where, after a decolorization treatment, it is precipitated by means of addition of some proper additives.

The precipitated product could be redissolved and precipitated again in another crystallizer in order to obtain a higher degree of purity.
Erythromycin Base is then centrifuged and washed with water and finally dried in a fluid-bed drier or in a vacuum dryer.
Erythromycin Thiocianate could be obtained as a by-product of the Base extraction process.

8.3.2 Tetracyclines Manufacture

Tetracycline and Oxytetracycline Base are obtained by selected strains of Streptomyces.
Two stages of batch fermentation are commonly foreseen. The seeding and fermentation operations are performed in a similar way to the Erythromycin ones.


STREPTOMYCES ERYTHREUS
Block Flow Diagram
Laboratory Stage
Industrial Inoculum
Culture Medium
Preculture Fermentation Step
Preculture Broth
Culture Medium
Culture Fermentation Step
Fermented Broth
CENTRIFUGATION
Mycelium
Filtered Broth
Solvent
Solvent Extraction
Spent Broth
Concentration
Carbon
Decolorization
Precipitation
Solvent to Recovery
Water
Centrifugation
Solvent to Recovery
Drying
Dried Erythromycins

The fermented broth coming from the fermenters is collected in the harvest vessel, diluted with water, acidified and fed to the rotary vacuum filters to separate the mycelium. Precoat type filter are used for this service. The mycelium so separated is collected into a bin and transferred to the waste treatment.

An intermediate product is precipitated from the filtered broth by alcalinization. This intermediate is then filtered and redissolved in water by addition of sulfuric acid. Another intermediate complex is then precipitated by proper pH variation and it is then centrifuged and redissolved. From this solution, Tetracycline or Oxytetracycline Base are obtained by precipitation with ammonia solution. Some other technologies relevant to Oxytetracycline provide a solvent extraction of the antibiotic from the broth, with the use of disk type centrifugal extractors. The antibiotic is then precipitated as an intermediate complex in the rich organic phase while the successive phases of the process are similar to what was previously described.

Tetracycline and Oxytetracycline Base are separated by centrifugation and dryed in a fluid bed dryer.

As far as Hydrochlorides production is concerned, the Bases are dissolved in a solvent mixture by addition of Hydrochloric Acid. The antibiotic solution, after filtration, is fed to a crystallizer, where it is heated up to precipitate the hydrochloride. For details relevant to the Hydrochlorides Production, reference should be made to the Report on Semi-Synthetic Antibiotics.

Chlortetracycline, commonly utilized as a feed-grade product or a veterinary drug, is not separated from the fermented broth. A concentration of the broth is first performed by vaporization and then the whole broth is dried in a drum dryer, heated with steam. A product with an antibiotic content ranging from 5% to 12% is normally obtained.

8.3.3 Rifampicin Manufacture

Rifamycin B is obtained from a fermentation broth utilizing a proper mutant of "Streptomyces Mediterranei". The fermentation process is similar to what was already described for Erythromycin and Tetracyclines.

After the separation of the biomass from the fermented broth, Rifamycin B is extracted with a proper solvent utilizing Podbielniak centrifugal separators.

Rifamycin B is oxidized to the more active Rifamycin O upon standing in solution. This reaction occurs by treating Rifamycin B with a variety of oxidizing agents. Rifamycin O in turn can be hydrolized to the even more active Rifamycin S, with the expulsion of glycolic acid. Rifamycin S is then reduced with Ascorbic Acid to Rifamycin SV. For the conversion of Rifamycin SV to Rifampicin, reference should be made to the Report on Semi-Synthetic Antibiotics. Main raw materials utilized in the Rifamycin B fermentation are Saccarose (raw sugar), Corn-steep liquor, Soyameal and Soja oil. The transformation of Rifamycin B into Rifampicin involves the utilization of lead tetracetate, manganese dioxide, pirrolidine, formaldehyde, as well as proper organic solvents. For the conversion of Rifamycin SV to Rifampicin (last step), commonly 1-Methyl-4-Aminopiperazine is utilized and an Acetone/Ethylacetate mixture.

8.3.4 Solvent Recovery

Solvents are recovered in a standard out-door distillation unit.

Two main sections may be distinguished in this unit:

- Stripping of spent broth coming from Erythromycin or Rifamycin B extraction process. This distillation is performed continuously

- Distillation of other solvent mixtures, distillation performed batch-wise.

8 .5 Utilities and Off-Sites Facilities

For the description of the utilities generation units, reference should be made to paragraph 7.3.5 relevant to the Penicillins Plant. In fact, the Utilities Facilities of the two plants are very similar, the only difference being the consumptions of some basic utilities. The design capacities of the different systems are specified in the following paragraph 8.4 devoted to equipment description.

8.3.6 Laboratories

The following laboratories should be foreseen for the Multi-purpose Plant:

a) Industrial Microbiology Laboratory

This laboratory is located in the Fermentation building and its objective is to supply the inoculum to be fed to the industrial fermenters. It consists of the following sections:

- Master Culture Preparation and Preservation
- Inoculum Development
- Glassware Cleaning and Media Preparation Area
- In Process Laboratory

b) Quality Control Laboratory

This laboratories is located in a central building, separated from the production areas. It can be subdivided as follows:

- Chemical Analysis Laboratory
- Microbiological Laboratory
- Sterility Control Laboratory

8.3.7 Waste Treatment

Waste water is treated in a biological type system in order to comply with the local quality standards for final effluent discharge. The waste water treatment plant consists of the following main sections:

- Equalization and balancing
- Neutralization, flocculation and flotation
- Biological oxidation (one or two stage activated sludge treatment depending on required final water quality).
- Sludge tickening and incineration.

The mycelium coming from the Tetracylcine/Oxytetracycline fermentation is incinerated. The mycelium coming from the Erythromycin or Rifamycin B fermentation might be either incinerated or utilized as animal feed or fertilizer (if this is permitted by local regulations).

8.4 EQUIPMENT

A list of the main equipment to be installed in the plant is given below:

8.4.1 Fermentation

Item	No.	Capecity	Material
Fermenters (1)	5	85 M^3	s.s.
Seeds Fermenters (1)	3	10 "	s.s.
Culture Media Vessels	3	10 "	s.s.
Additives Sterilizers (1)	2	20 "	s.s.
Ammonium Sulfate Sterilizers(1)	2	6 "	s.s.
Oil Sterilizers (1)	2	2 "	s.s.
Caustic Sol. Sterilizers (1)	2	1 "	s.s.

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(1) Equipped with external cooling coil, turbine agitator and air sterilization filters and prefilters (cartridge type)

8.4.2 Extraction

Item	No.	Capacity	Material
Harvest Vessels	2	85 M3	s.s.
Vacuum Filters	2	20 M2	s.s.
Centrifugal Extractors	2	Disk Stack Type	s.s.
Filtered Broth Vessel	1	30 M3	s.s.
Podbielniak Centrifugal Extractors	2	D36 Model	s.s.
Podbieliniak Centrifugal Extractors	2	D18 Model	s.s.
Sulfuric Acid Dilution Vessel (1)	1	2 M3	Glass Lined
Sulfuric Acid storage Vessel	1	10 "	Fiber Glass
Filter aid Silo	1	10 "	Carbon Steel
Filter aid suspension Vessel	1	10 "	s.s.
Tetracycline Complex	2	20 "	s.s.
Precipitation Vessels (1)			
Tetracycline Reactors (1)	8	6 "	s.s.
Filter Press	2	50 M2	Polypropilene
Filter Press	2	10 "	Polypropilene
Solvent Vessels	6	8 M3	s.s.
Spent Broth Vessels	1	4 "	s.s.

Buffer Vessels (1)	3	4 "	s.s.
Rich Solution Vessels (1)	3	5 "	s.s.
Rifampicin Reactors (1)	4	4 "	s.s.
Pressure Filters	6	Sparkler Type	s.s.
Cristallizers (1)	2	10 "	s.s.
Centrifuges	4	Basket Type dia. : 1500 mm	s.s.
Dryers	2	Rotating Vacuum dryer - 3M3	s.s.
Dryers	2	Fluid Bed Type	s.s.
Dryer	1	Drum Dryer	s.s.
Mills	2	Fritzpatrick	s.s.
Blenders	2	Double cone	s.s.
Evaporator	1	Falling Film Type	s.s.
Heat Exchangers	15	Shell and Tube	s.s.
Pumps	50	Centrifugal Type	s.s.

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(1) Equipped with agitator and external jacket.

8.4.3 Solvent Recovery

Item	No.	Capacity	Material
Broth Stripper	1	Distillation Column (20 trays)	s.s.
Solvent Vaporizer	1	Distillation Column (15 Trays)	s.s.
Solvent Stripper	1	Distillation Column (20 Trays)	s.s.
Solvent aporizer	1	Packed Column	s.s.
Vent Scrubber	1	Disc & Donut column	Carbon Steel
Spent Broth Tank	1	200 M3	s.s.
Solvent storage Vessels	8	35 "	Carbon
Pumps	24	Centrifugal Type	s.s. & c.s.
Heat Exchangers	12	Shell and Tube	s.s.

8.4.4 Tetracycline and Oxytetracycline Hydrochloride

Item	No.	Capacity	Material
Reactors (1)	2	2 M3	Glass Lined
Dosing Vessels	2	100 lt	Fiber Glass
Centrifuge	1	Basket Type Dia. : 1500 mm	s.s.
Dryer	1	Fluid Bed type 700 lt capacity	s.s.
Pressure Filter	1	Sparkler Type	s.s.

(1) With external jacket and agitator.

8.4.5 Utilities

Item	No.	Capacity	Material
Boilers	2	18 T/Hr.	-
Steam Turbine Generator	1	6000 Kw	-
Water Treatment (1)	1	Filtration softening and demineralization unit	
Raw Water Tank	1	2000 M3	Carbon Steel
Cooling Tower (1)	3	Total Flowgate 1200 M3/Hr.	
Refrigiration units(1)	2	Capacity:3. million Kcal/Hr. (each)	
Brine Units	2	Capacity 300,000 Kcal/Hr. (each)	
Fermentation Air Compressors	3	10000 NM3/Hr. (each)	
Instrument Air Compressors	2	500 NM3/Hr. (each)	

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(1) Including Distribution Pumps

8.4.6 Tank Farm

Item	No.	Capacity	Material
Corn Steep Tanks	2	30 M3	Fiber glass
Sugar Solution Tanks	2	50 M3	s.s.
Sojameal Silos	2	100 M3	Carbon Steel
Starch Silos	2	100 M3	Carbon Steel
Maize or Dextrine Silos	2	100 M3	Carbon Steel
Tank	1	30 M3	s.s.
Ammonia Tank	1	30 M3	Carbon Steel
Ammonia Solution Tank	1	30 M3	Dewar type
Liquid Nitrogen tanks	2	20 M3	Dewar Type
Sulfuric Acid Tank	1	50 M3	Carbon steel
Caustic Solution Tank	1	50 M3	Carbon Steel

8.4.7 Waste Treatment

Item	No.	Capacity	Material
Equalization Tanks	2	300 M3	Carbon Steel
Floculation and Flotation Basin	1	-	Concrete
Oxidation Basins	2	With surface aeration	Concrete
Sludge Thickening Basin	1	-	Concrete
Mycelium Tank	1	50 M3	Carbon Steel
Sludge Centrifuge	1	Decanter Type	-
Sludge Incinerator	1	Tray type	-

8.4.8 Laboratories

The laboratories subdivision is described under paragraph 8.3.6. Besides all the analytical instrumentation, they should be equipped with the proper furniture consisiting of benches, work tables, wash basins, fume hoods, etc.

8.5 PLANT LAY-OUT AND BUILDINGS

The plant lay-out could be quite similar to the one proposed for the Penicillin Plant. A total surface of about 5.0 hectares is required.

The following buildings are forseen:

a.Fermentation Building

1300 M2 covered surface

The fermentation area is a multi-level building housing the germinators (prefermenters), the fermenters, the sterile feed solution vessels, as well as the harvested broth vessels. In addition, an industrial microbiological laboratory (see Paragraph 8.3.6) is installed. Space is also provided for storage, control room, electrical rooms, social facilities, area maintenance, offices, etc.

A reinforced concrete building could be foreseen or, as in alternative, a steel structure with no external walls.

b.Extraction Building

3500 M2 covered surface

This two level building houses the extraction area of Erythromycin, Tetracyclines and Rifamycin, as well as thearea for Tetracycline and Oxytetracycline Hydrochlorides, and Chlortetracycline production. A multipurpose extraction unit is provided for the three families of antibiotics.

A storage area for the different products is also provided. The bulk products (Erythromycin, Rifampicin, etc.) are handled in a highly controlled environment, once the product is in a wet cake or in a dry powder stage. This helps to assure the highest possible product quality.

A reinforced concrete type building is recommended.

c.Warehouse

This one level building is devoted to store all the raw materials supplied in bags or drums.

d. Compressor house

Compressors and refrigeration units are installed under a shelter, without external walls.

e. Offices and Central laboratories building. A three or four levels air conditioned building is to be foreseen.

f.Social building. This building house mainly the control locker room and the canteen.

g.Electrical Substation (Ventilated Building)

h.Workshop. This building houses the spare parts warehouse, as well as the workshop.

8.6 RAW MATERIALS

8.6.1 Erythromycin

The main raw materials utilized in the manufacture of Erythromycin Base are:

- Soya meal
- Corn starch
- Glucose solution, which could be substituted by raw cane sugar or by molasses, or cane juice.
- Corn-steep liquor
- Dextrine
- Soya oil
- Mineral salts as Calcium Carbonate, Ammonium Sulfate, Sodium Chloride, etc.
- Sulfuric Acid, Caustic Soda, and Ammonia
- Organic solvents such as Butyl-acetate, Amylacetate, Methylene Chloride, Ethanol and Methanol.

Corn starch, Glucose or raw sugar (or molasses), Dextrine, Soya oil and Corn-steep are locally manufactured raw materials for fermentation. Also Sulfuric Acid and Ethanol are locally produced. All the other raw materials should be imported.

On this basis, the total raw materials cost for Erythromycin Base manufacture would be about US $ 40 per Kg.

8.6.2 Tetracyclines

The main raw materials utilized in the manufacture of Tetracyclines (Tetracycline, Oxytetracycline and Chlortetracycline) are :

- Corn starch
- Dextrine
- Maize meal
- Corn-steep liquor
- Saccarose (raw sugar)
- Soya oil
- Soya meal
- Mineral Oils as Calcium Carbonate, Ammonium Sulfate, Ammonium Chloride, etc.
- Sulfuric Acid, Caustic Soda and Ammonia
- Organic compounds, such as Oxalic Acid, Urea or Acquad
- Organic solvents, such as Butanol and Ethylcellosolve (for the hydrochlorides production), or Acetone.

Corn starch, Dextrine, Maize meal, Corn-steep liquor, saccarose and soya oil, as well as Sulfuric Acid, are locally manufactured, while all other raw materials should be imported.

Utilizing the above mentioned local products, the raw materials cost for the Tetracycline Hydrochloride would amount to about US $ 18-20/Kg., while for Oxytetracycline Hydrochloride, it would be of US $ 16-18 /Kg.

8.6.3 Rifampicin

The essential raw materials utilized in the manufacture of Rifampicin passing through Rifamycin B are :

- Saccarose (raw sugar)
- Corn Steep Liquor
- Soja meal
- Soya Oil
- Mineral salts like Calcium carbonate and Ammonium
- Sulfate
- Sulfuric Acid, Caustic Soda and Ammonia

- Organic solvents, such as Ethylacetate and Acetone
- Lead Tetracetate
- Manganese Dioxide
- Pirrolidine
- Formaldehyde
- 1 - Methyl - 4 - Amino Piperazine

Saccarose, Corn-steep, Soya oil, and Sulfuric Acid are locally manufactured, while all the other raw materials should be imported.

Total raw materials costs or Rifampicin manufacture should be in the range from US $70 to 80 per Kg.

8.7 UTILITIES CONSUMPTION

The basic average utilities requirements of the plant are:

- Electric power 4200-5000 Kw
- Steam 5-6 Ton/Hr.
- Raw Water 30 M3/Hr.

On the basis of the hyphotesis described under paragraph 7.3.5, i.e. all the required energy will be generated in a power plant supplied with Bagasse, practically the only cost for utilities would consist in the transportation cost of Bagasse. The consumption of Bagasse would be about 75,000-85,000 Tons per year. Assuming a cost of Bagasse (mainly transportation) of 100 : 150 Pesos per ton, the total cost for utilities would be of about US $ 400,000 - 600,000 per year.

In the case that fuel oil would be utilized instead of Bagasse, the above mentioned cost would increase to US $ 2-3 millions per year.

8.8 MANPOWER REQUIREMENTS

8.8.1 Organization

The operations are carried out 24 hours per day during 330 days per year. The organization chart of the complex is identical to the one given in paragraph 7.8 for the Penicillin Plant.

The personal requirements for the plant is the following:

	Production	Utilities, Eng. & Maintenance	Labora-tories	Administra-tion	Planning & Purchasing
Plant Manager & supervisory Personnel	10	4	3	2	2
Operators, Technicians, Clerk, and Laboratory specialists	32	15	15	7	7
Skilled Workers	36	15	7	1	1
Unskilled workers	43	20	-	-	-
	121	54	25	10	10

Total Need: 220 persons

8.8.1 Qualifications

The qualifications of the above mentioned personnel are identical to those described in paragraph 7.8.2 for the Penicillin Plant

8.8.2 Training

A selected group of supervisors and technicians should be properly trained in existing industrial fermentation facilities. This training program should therefore be performed abroad. At least, the Head of the fermentation unit and the one Responsible for the Erythromycin, Tetracycline and Rifampicin extraction unit should undergo a practical training for a minimum of 3 months.

Also four of the graduated laboratory technicians should be trained for 3-4 months in a modern microbiological laboratory abroad.

On the spot training in Good Manufacturing Practices (GMP), especially on "problem oriented teaching", e.g. personal hygiene, health habits, basics of quality assurance, etc, is important.

Other specific training programs should be undertaken for quality for control key personnel.

Also in this case, as for the Penicillin Plant, it is suggested, at the initial stage, for two years at least, to have the support of some experts. Three or four experts could be employed as :

- Plant and Production Manager
- Quality Control Manager
- Engineering and Maintenance Manager

The function of these Experts should be the same to the one described in paragraph 7.8.2 for the Penicillin Plant.

8.9 ECONOMIC EVALUATIONS

A preliminary evaluation of the project profitabiliy is given hereafter

8.9.1 Manufacturing Costs

a.) Raw Materials

- Erythromycin base
  US $ 40/Kg. x 26,000 Kg/Y = US $ 1,040,000 per year
- Tetracycline Hydrochloride
  US $ 18/Kg. x 20,000 Kg/Y = US $ 360,000 per year
- Oxytetracycline Hydrochloride
  US $ 16/Kg. x 15,000 Kg/Y = US $ 240,000 per year
- Chlortetracycline
  US $ 12/Kg. x 50,000 Kg/y = US $ 600,000 per year
- Rifampicin
  US $ 80/Kg. x 20,000 Kg/y = US $ 1,600,000 per year

The total raw materials cost could therefore be of US $ 3,840,000 per year. The percentage of locally manufactured raw materials could be estimated as 20 : 30 % of the above mentioned value.

b) Manpower costs

On the basis of the manpower requirements reported in paragraph 8.8, a total cost of personnel of US $ 900,000 per year has been estimated

c.) Energy and Utility costs

On the basis of a Bagasse consumption of 75,000-85,000 tons per year, an annual cost of US $ 500,000 has been estimated.

d) Depreciation

The same assumption as for the Penicillin plant have been made (see paragraph 7.9.2)

8.9.2 Other Costs

General Expenses, including administration, maintenance, marketing, as well as all other expenses not pertaining to production should be about US $ 1,000,000 per year.

8.9.3 Income Taxes

See paragraph 7.9.3

8.9.4 Investment Costs

The overall estimated investment cost of the complex in the range between US $ 30 to US $ 33 million. The latter figure shall be taken as basis for profitability calculations. The following items are included in the above mentioned estimate:

- Machinery and Equipment
- Bulk materials (piping, instrumentation and electric system)
- Spare parts

- Transportation
- Erection
- Civil works (including load preparation)
- Engineering
- Know how (Erythromycin base, Rifampicin and Tetracycline Technology)
- Personnel training
- Construction and start-up assistance

8.9.5 Sales

For the sales estimates, the international market prices of the different products have been increased of about 10 % to take into account the transportation costs and the other expenses related to the fact that at present these products are imported.

- Erythromycin base sales (26 Tons/y)	= US$ 2,860,000/year
- Tetracycline Hydrochloride sales (20 Tons/y)	= US$ 750,000/year
- Oxytetracycline Hydrochloride sales (15 Tons/y)	= US$ 490,000/year
- Chlortetracycline sales (50 Tons/y)	= US$ 1,400,000/year
- Rifampicin sales (20 Tons/y)	= US$ 4,830,000/year
Total sales estimates :	US $ 10,330,000/annum

8.9.6 Profitability estimation

- Sales	10,330,000 US$ per year
- Production costs	5,240,000 "
- Other costs	1,000,000 "
- Industrial profit	4,090,000 "
- Depreciation	3,000,000 "
- Profit before provision for income taxes	1,090,000 "
- Provision for income taxes (after the 4th year)	380,000 "
- Profit after tax	710,000 "

- Return on sales = 10.5 % (for the first 4 years) and 7% (after the 4th year)

- Annual rate of return f investment = 7% The calculation has been done on the same basis described in paragraph 7.9.6 (Penicillin Plant)

- Pay-back time = about 8.5 years

It appears from the preceding figures that the multipurpose plant is less profitable, at least at the present situation, compared with the Penicillin Plant

Also in this case, as for the Penicillin Plant, an alternative calculation of profitability has been made, considering the case that all the product prices would be icreased by 10 %, as a consequence of price regulatory policy. In these conditions, the economic evaluation indexes should become:

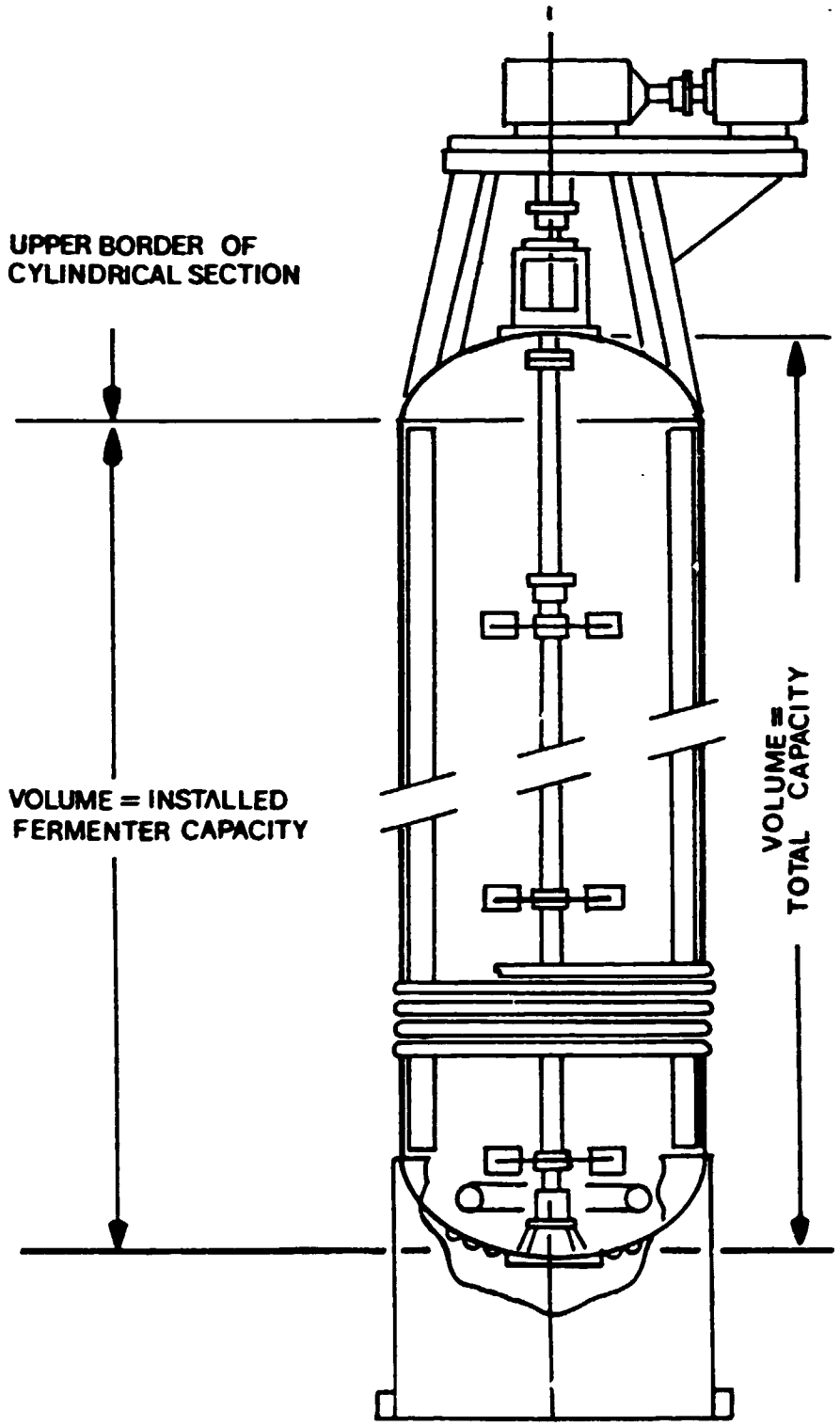
- Return on sales : 19 % (for the first 4 years) and 12 % (after the 4th year)
- Rate of return on investment : 10 %
- Pay-back time : about 7 years

Another factor that would increase the project profitability would be the possibility of exporting part of the products, especially to the ASEAN countries. In this case, the production capacity should be increased, thus obtaining an economy of scale. For the time being, however, this possibility seems to be rather remote.

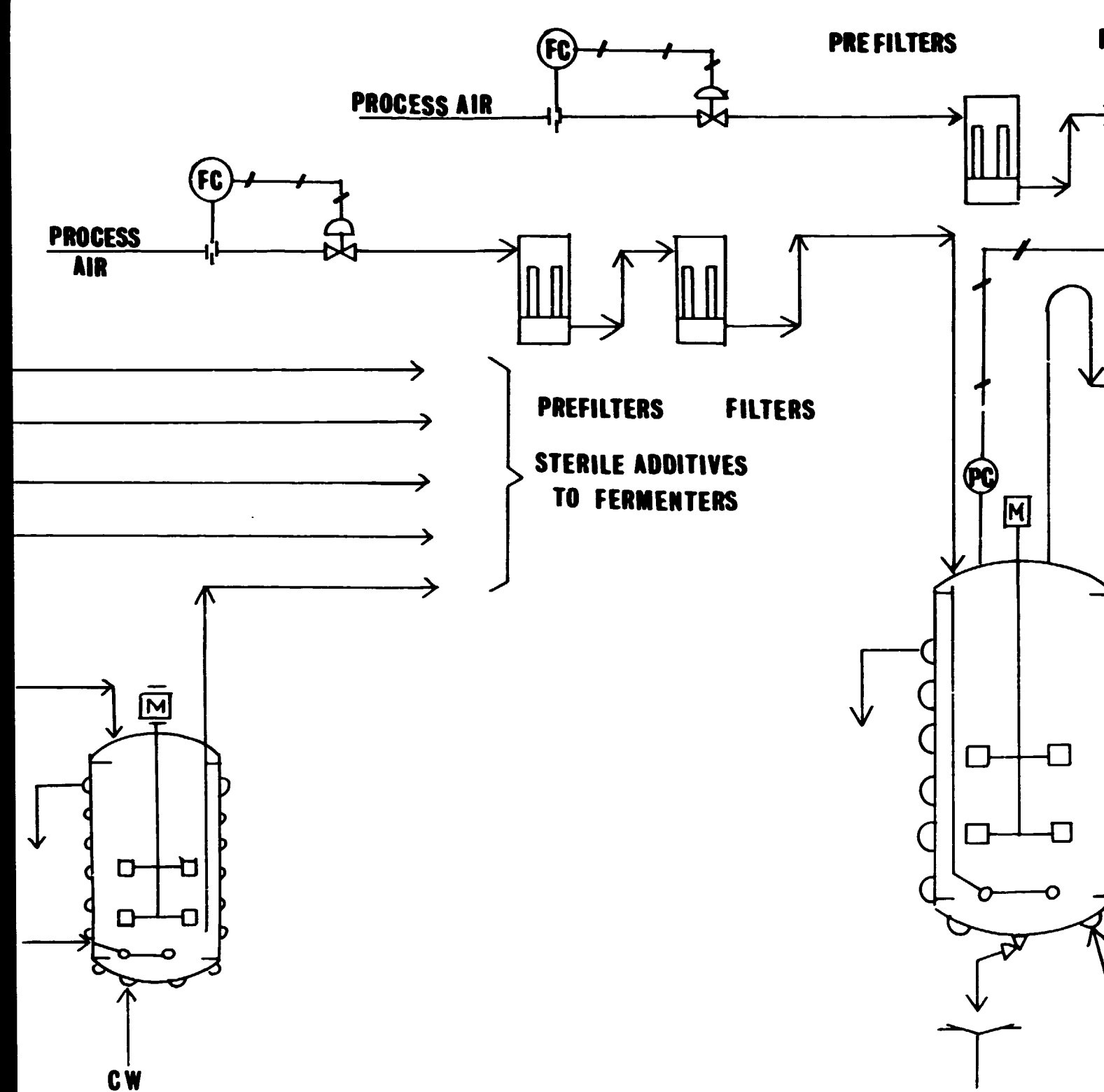
8.9.7 Conclusions

On the basis of the previous data on profitability, it appears that the above defined Multipurpose Plant cannot be considered at present as the object of a feasible project, but could be kept in mind as a long-term objective in the achievement of self-reliance in the antibiotics production, in case that in the future some changes could occur, either in the international market conditions, or in the local situation concerning incentives for the Pharmaceutical Industry.

TYPICAL FERMENTER

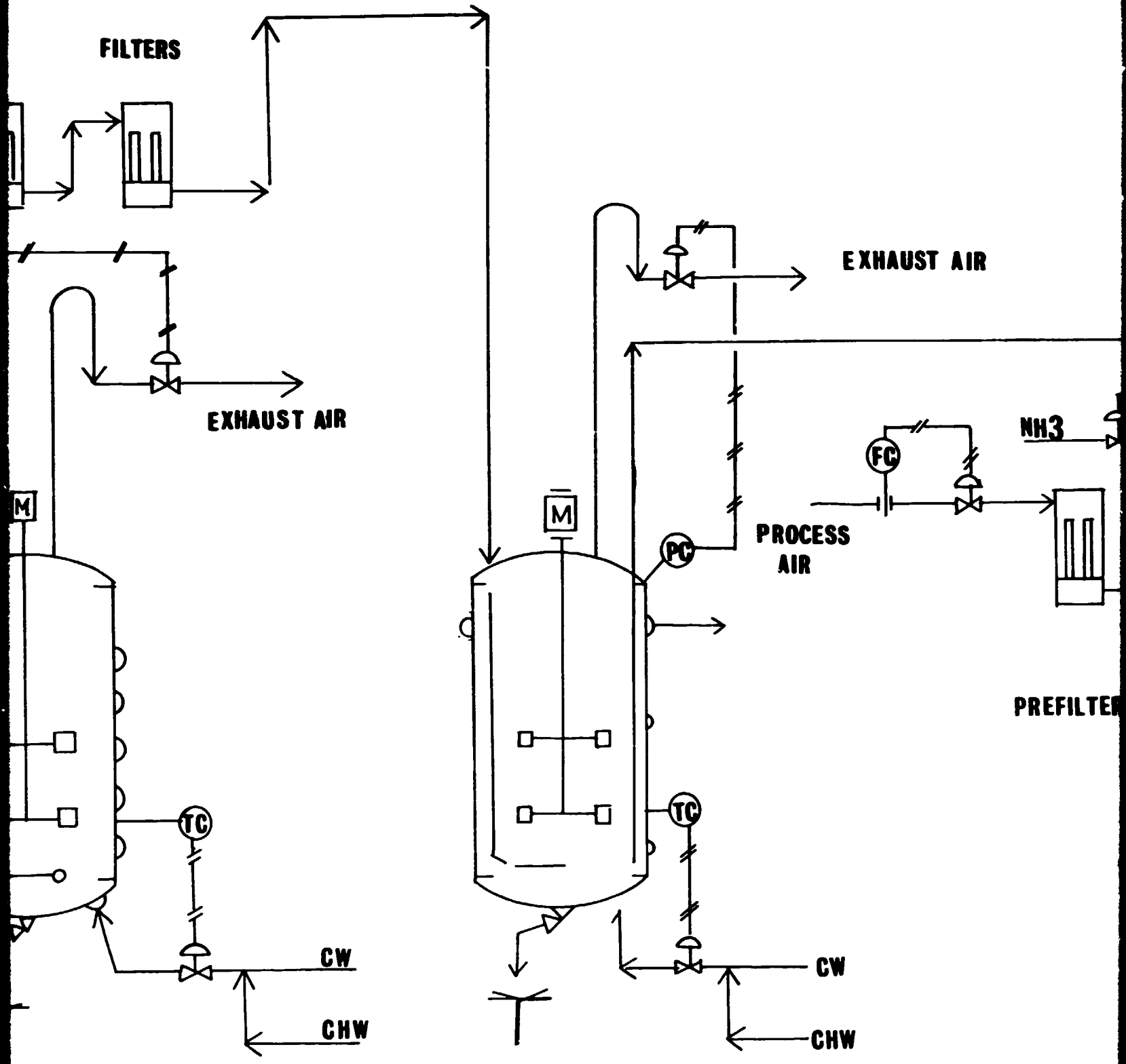


MANILA- AUGUST 1988



CAUSTIC SOLUTION
STERILIZERS

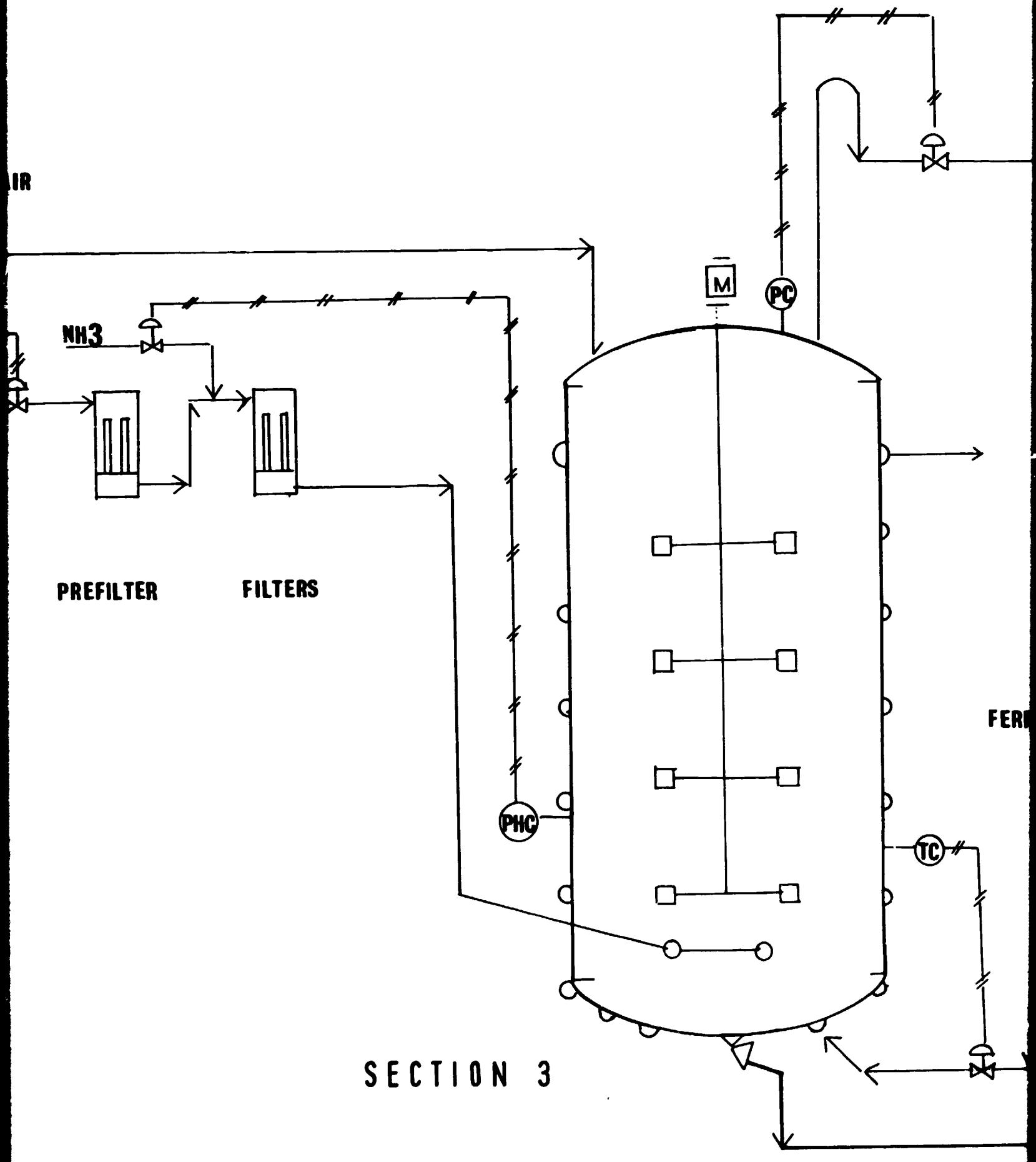
PILOT FERMEN



SECTION .2

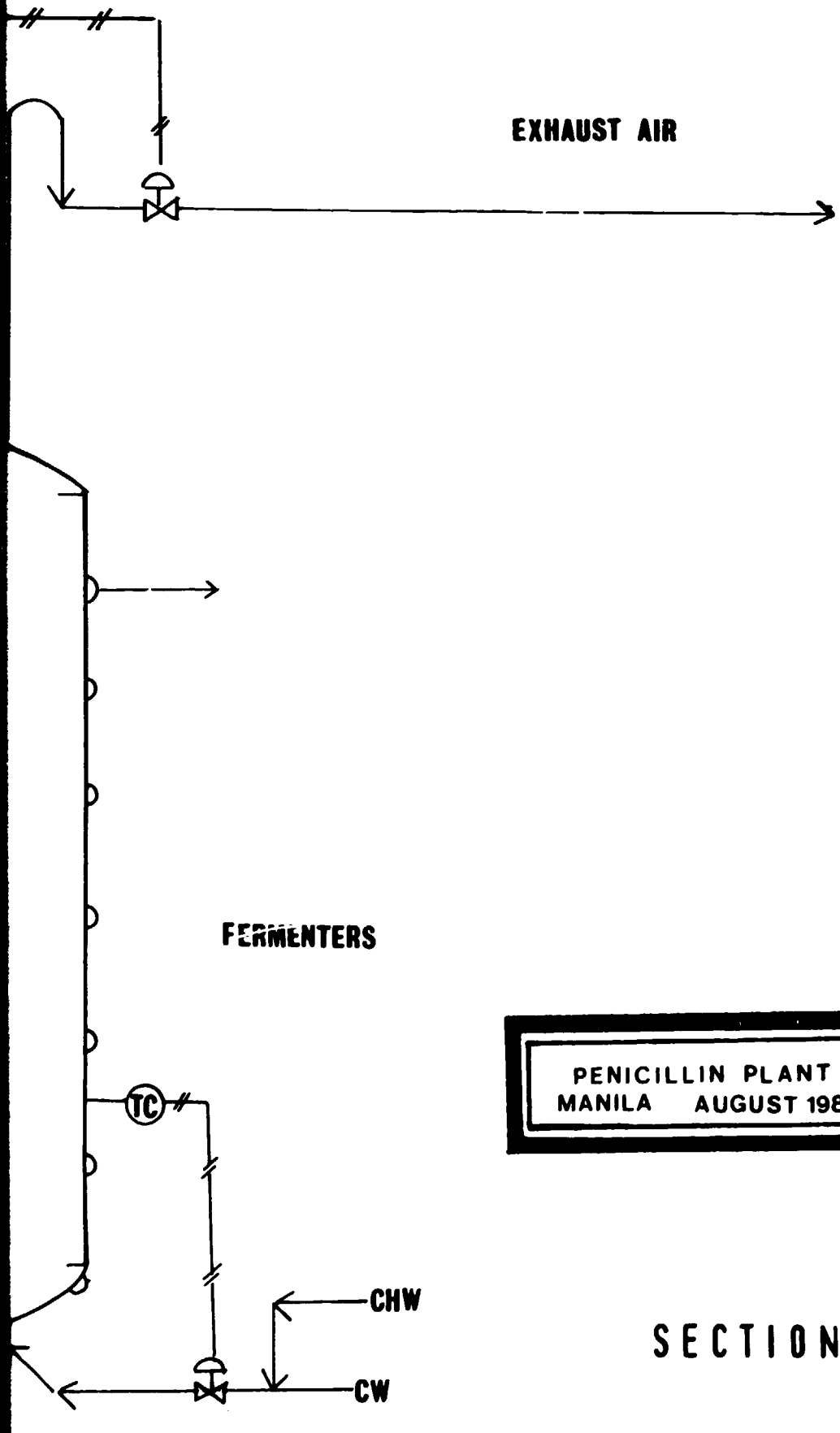
FERMENTERS

PREFERMENTERS



SECTION 3

CW COO
CHW CHI
STM STE



PENICILLIN PLANT MANILA AUGUST 1988	PENICILLIN FERMENTATION PROCESS FLOW DIAGRAM

SECTION 4

CW COOLING WATER
CHW CHILLED WATER
STM STEAM

EXHAUST AIR

FERMENTERS

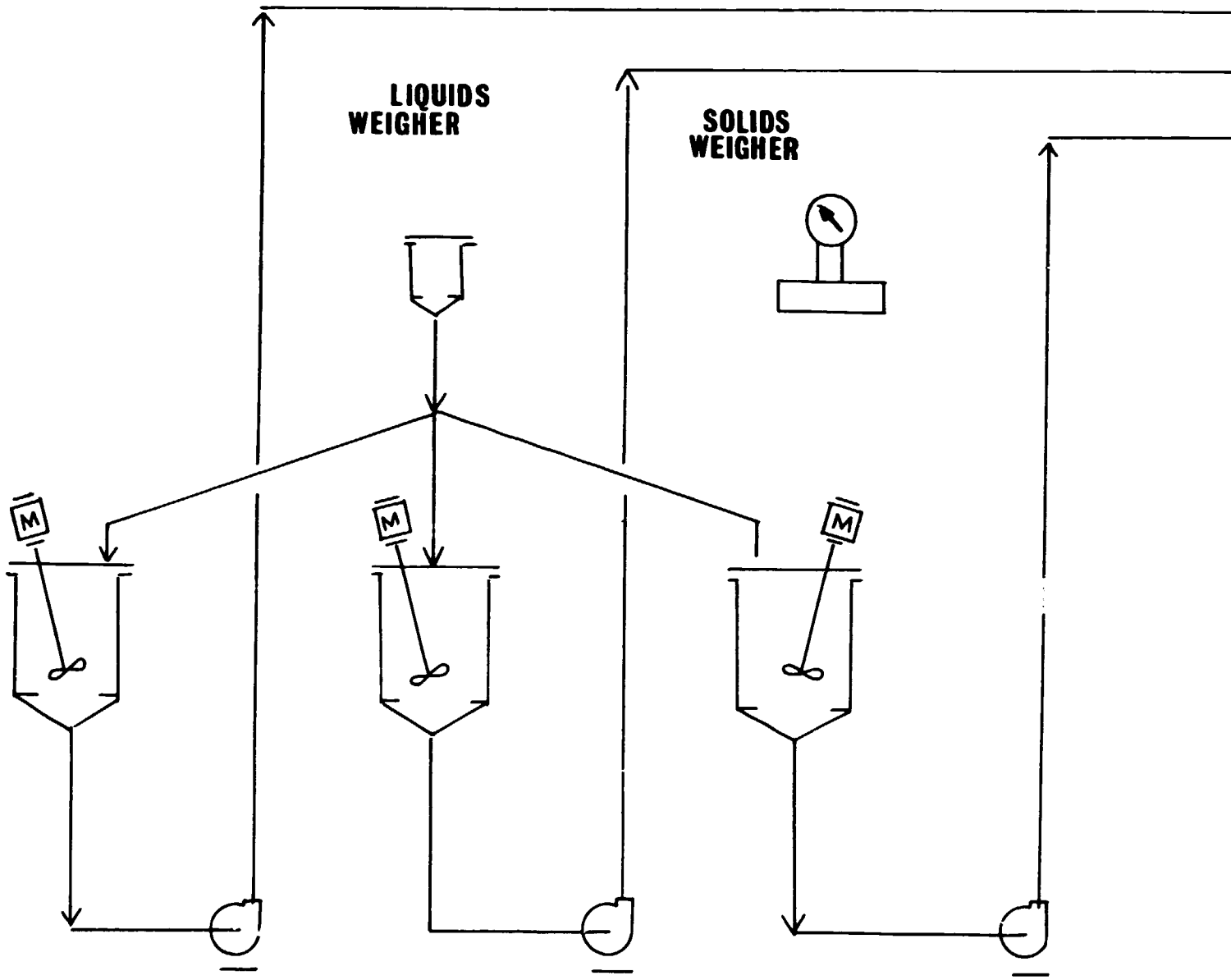
PENICILLIN PLANT MANILA AUGUST 1988	PENICILLIN FERMENTATION PROCESS FLOW DIAGRAM

CHW

CW

FERMENTED BROTH
TO THE HARVEST
VESSELS

SECTION 5



CULTURE MEDIUM VESSEL

CULTURE MEDIUM PUMP

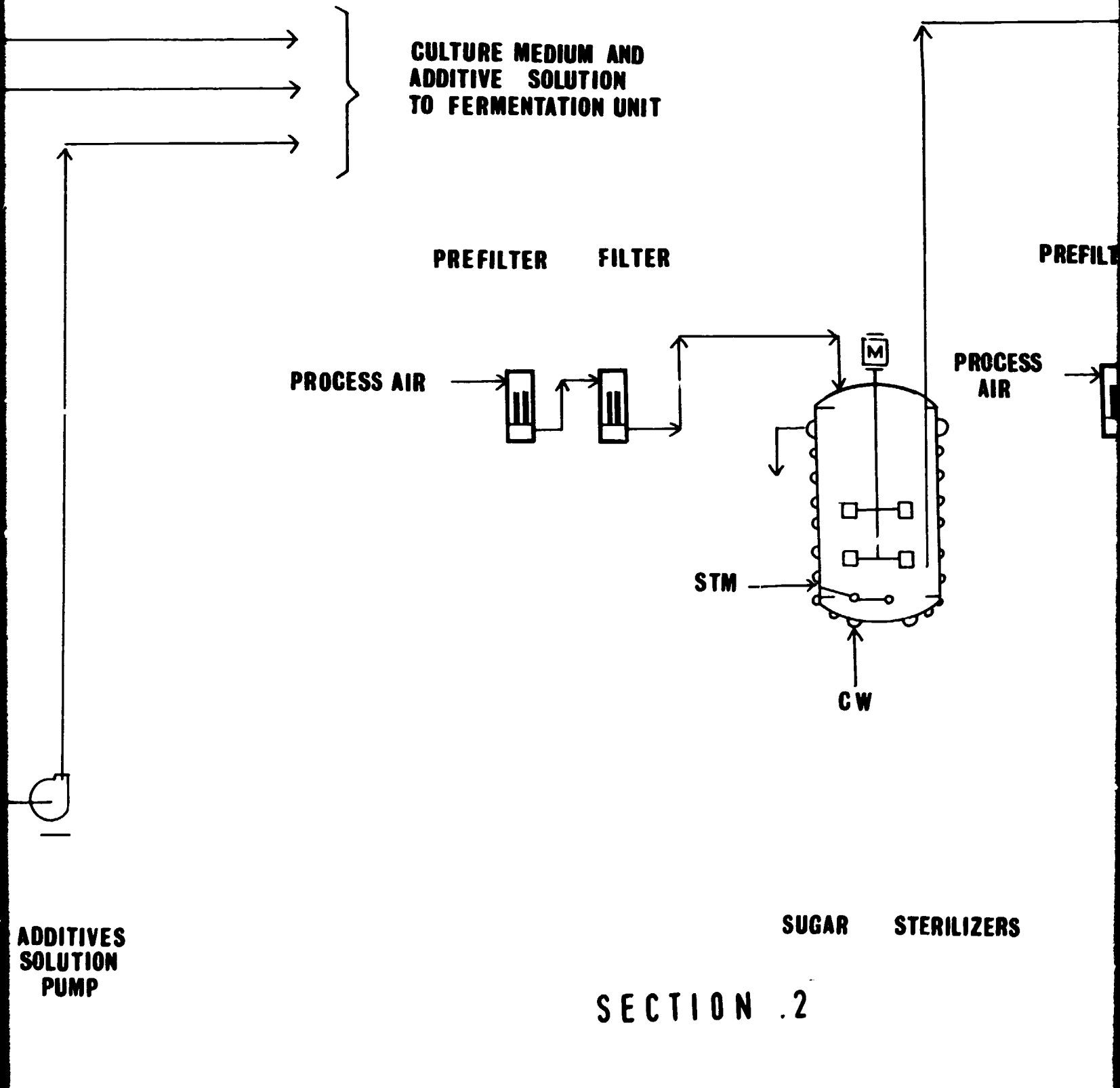
CULTURE MEDIUM VESSEL

CULTURE MEDIUM PUMP

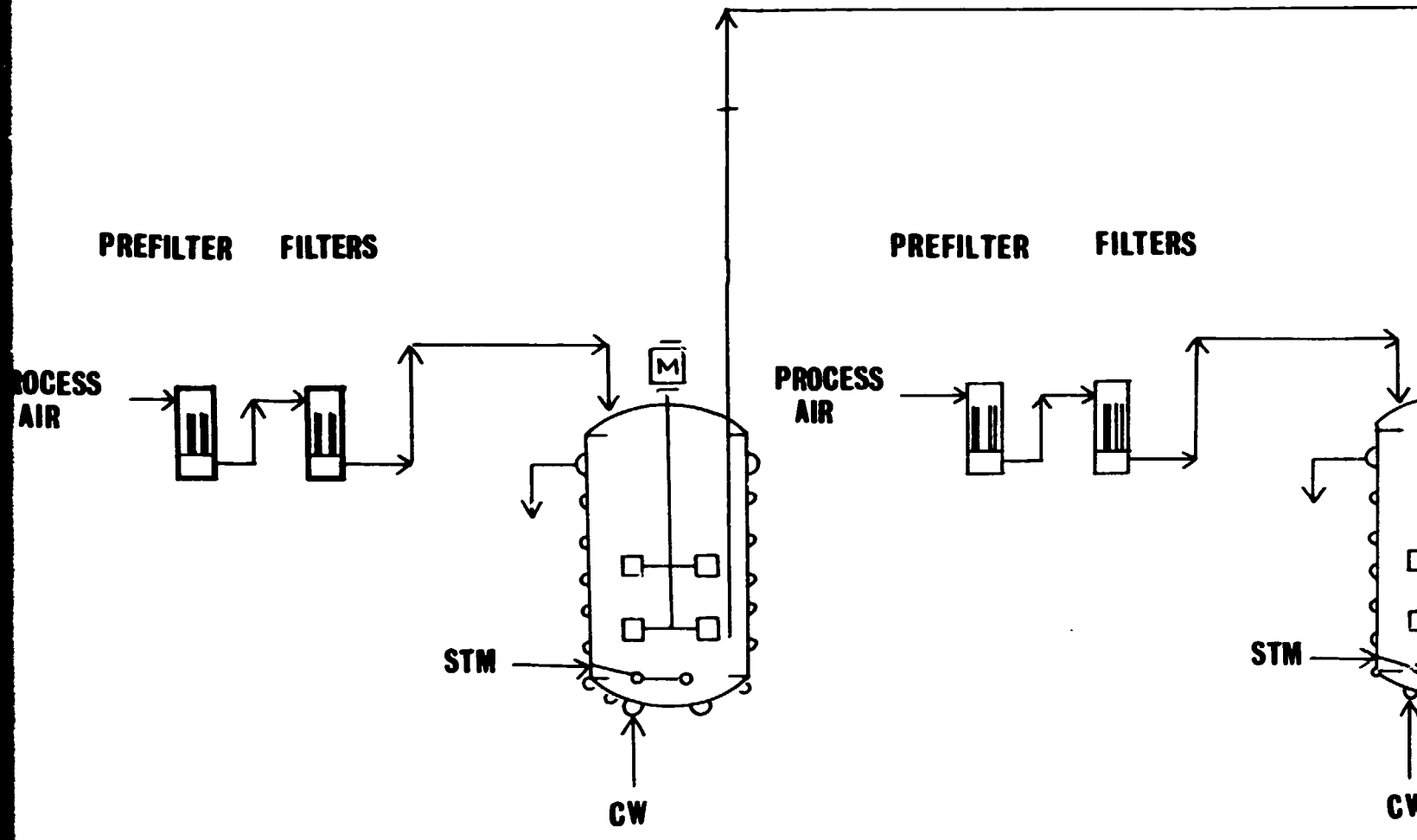
ADDITIVES SOLUTION VESSEL

ADDITIVES SOLUTION PUMP

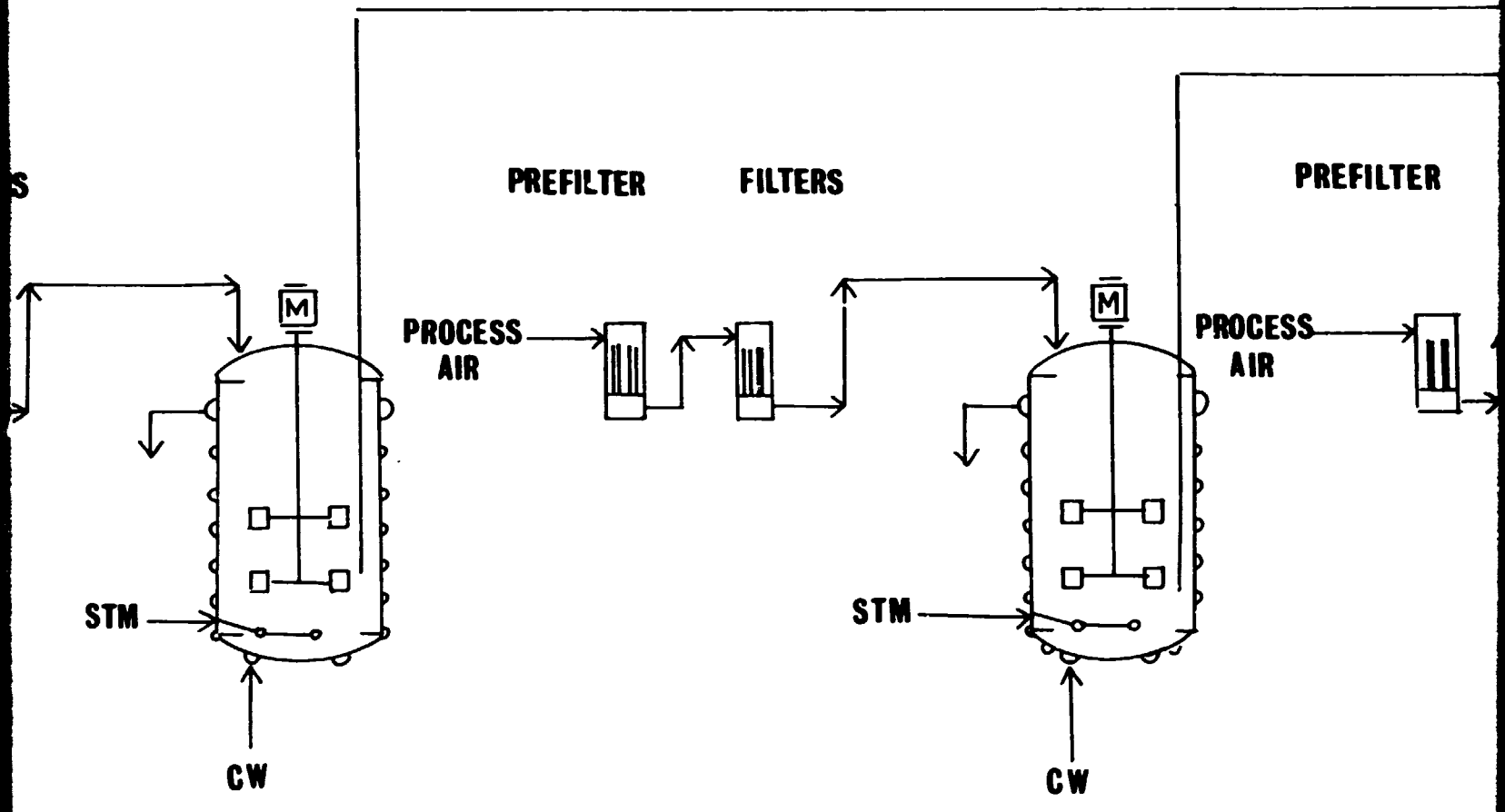
SECTION 1


CULTURE MEDIUM AND
ADDITIVE SOLUTION
TO FERMENTATION UNIT
PREFILTER
FILTER
PREFILT
PROCESS AIR
PROCESS
AIR
M
STM
CW
ADDITIVES
SOLUTION
PUMP
SUGAR
STERILIZERS

SECTION .2


PREFILTER
FILTERS
PROCESS AIR
M
STM
CW
PREFILTER
FILTERS
PROCESS AIR
STM
CW
PHENYL ACETATE STERILIZERS

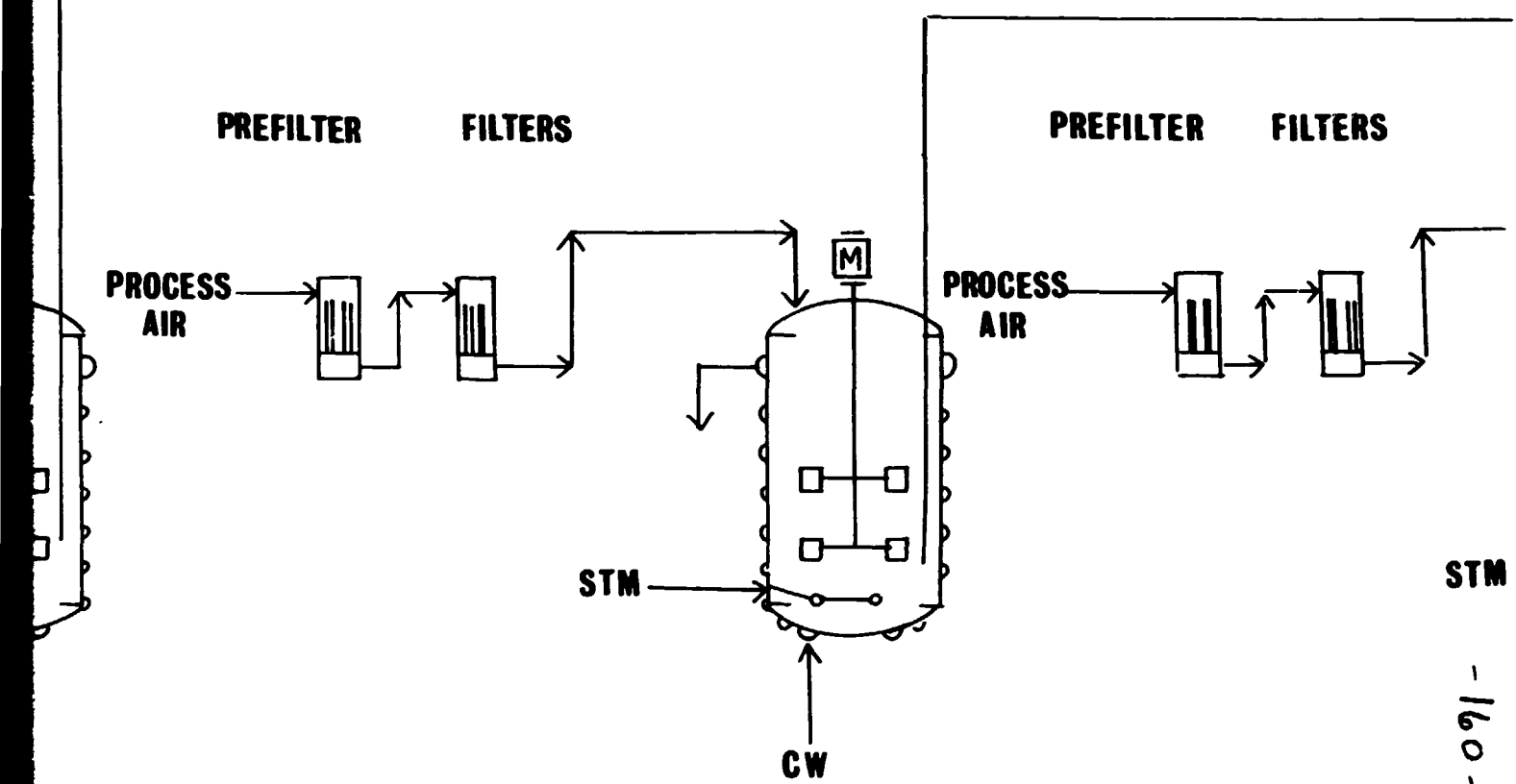
SECTION 3



AMMONIUM SULPHATE STERILIZERS

OIL STERILIZERS

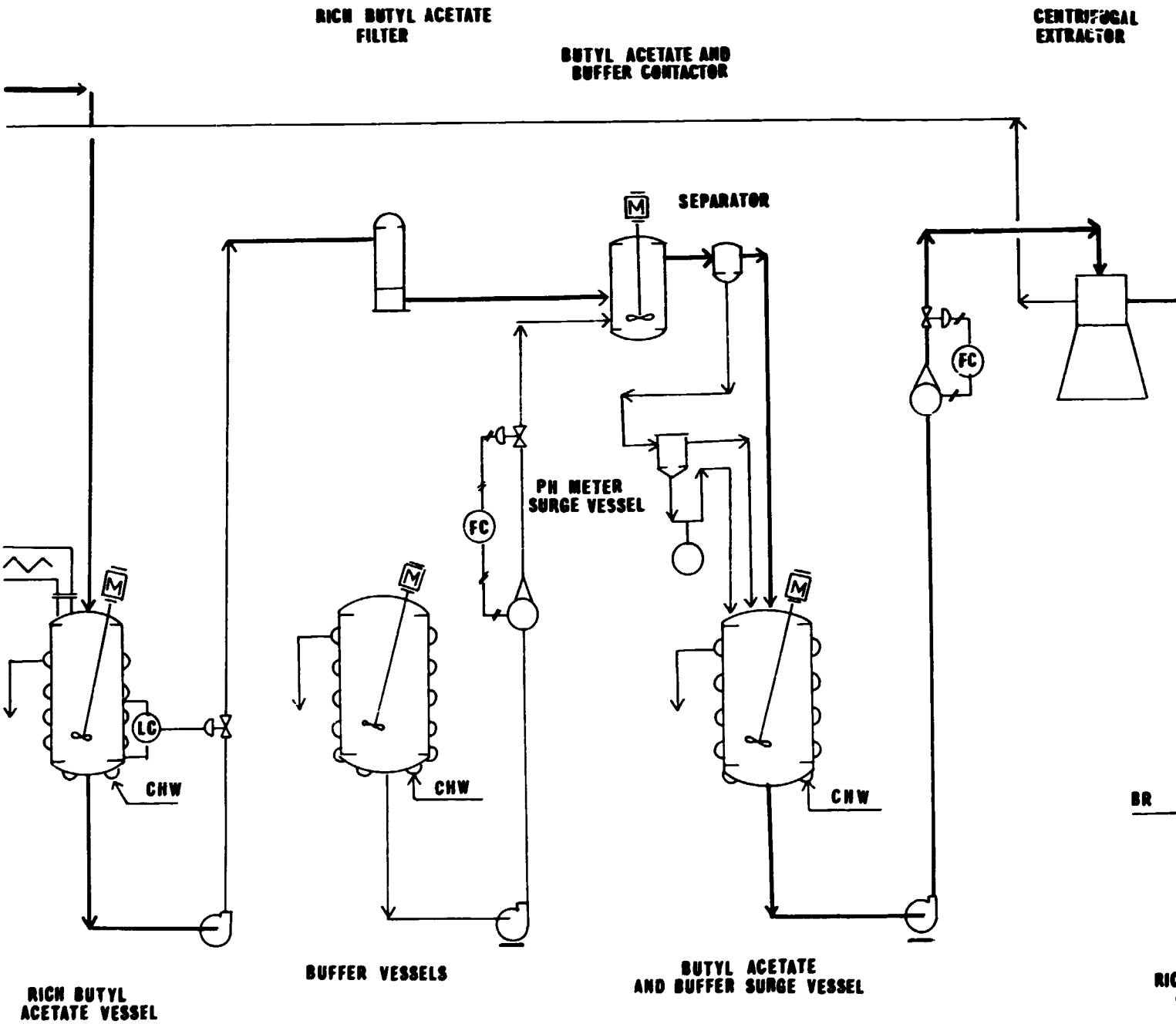
SECTION 4



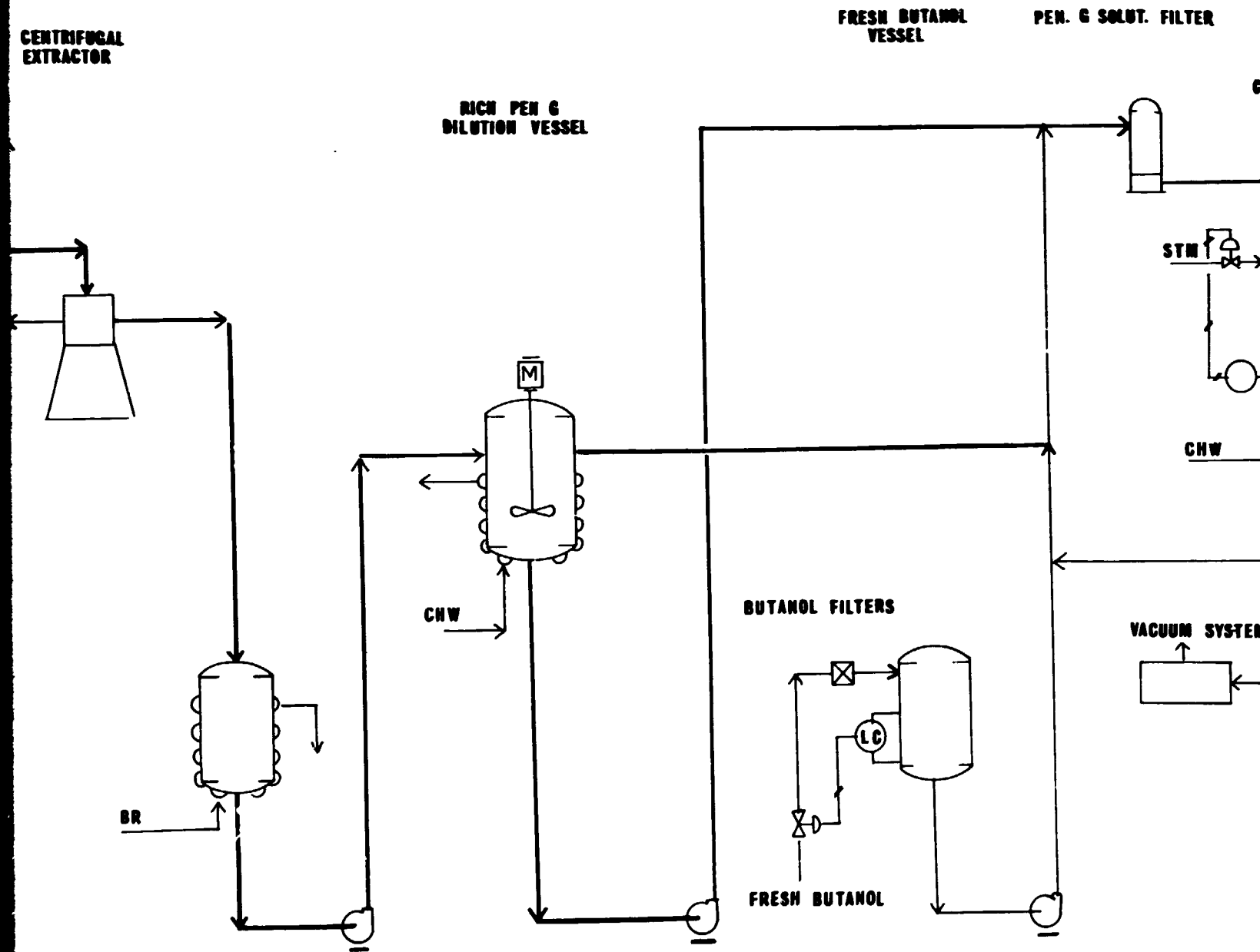
SULPHATE
ERS

OIL STERILIZERS

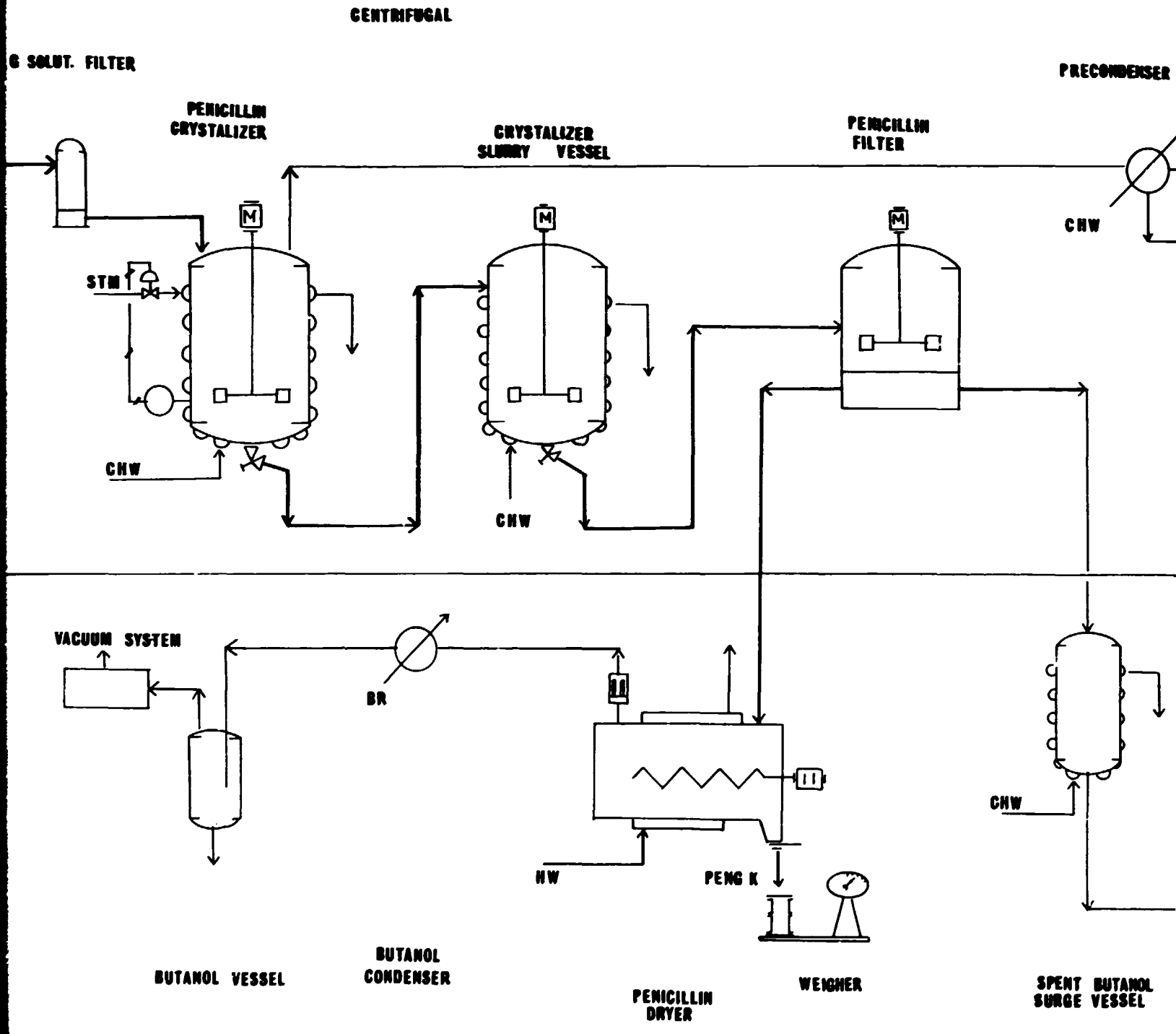
SECTION 5


RICH BUTYL ACETATE FILTER
BUTYL ACETATE AND BUFFER CONTACTOR
CENTRIFUGAL EXTRACTOR
SEPARATOR
PH METER SURGE VESSEL
FC
LC
CHW
RICH BUTYL ACETATE VESSEL
BUFFER VESSELS
BUTYL ACETATE AND BUFFER SURGE VESSEL
BR

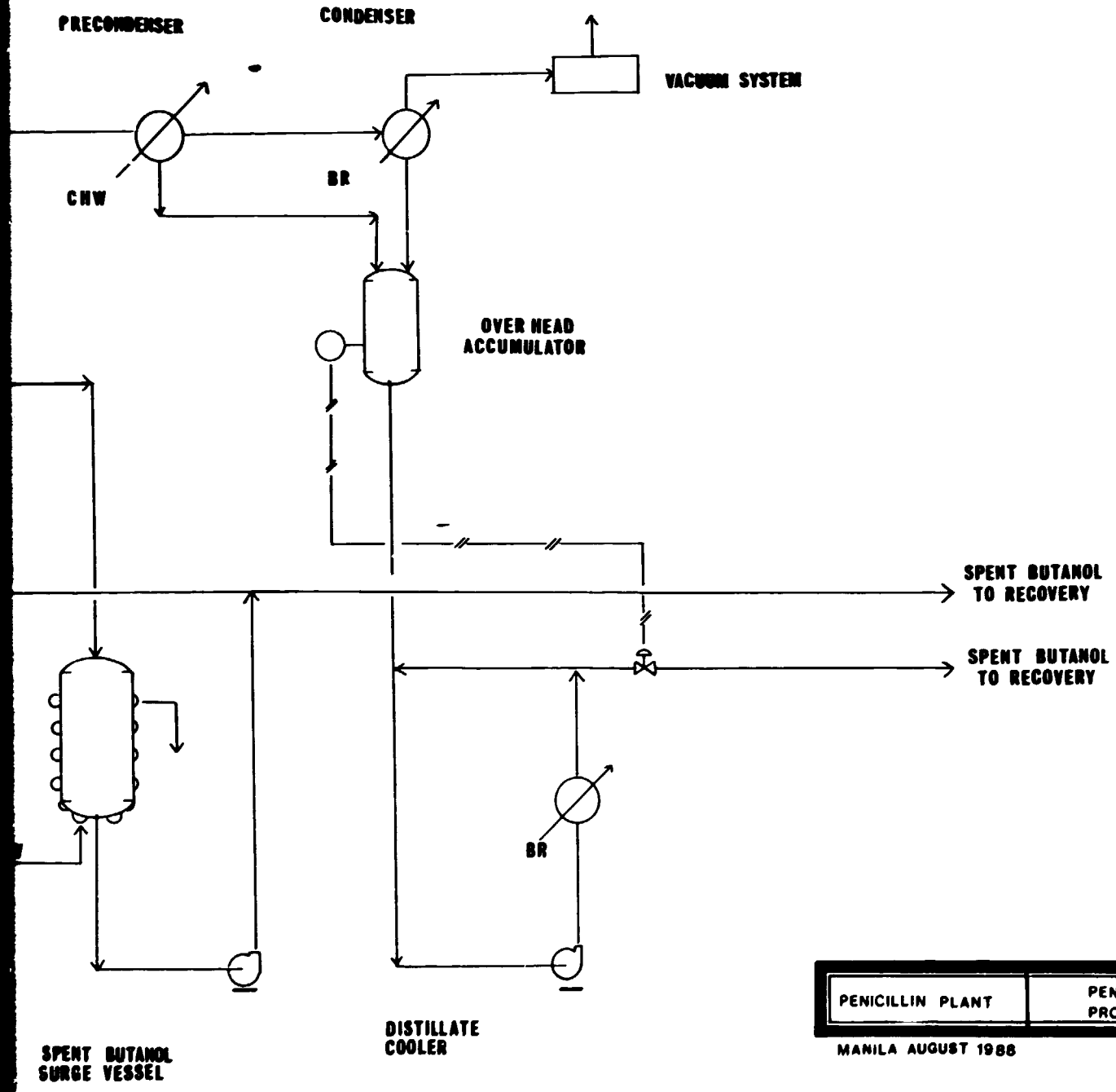
SECTION 1


CENTRIFUGAL EXTRACTOR
FRESH BUTANOL VESSEL
PEN. G SOLUT. FILTER
RICH PEN G DILUTION VESSEL
STM
M
CHW
CHW
BUTANOL FILTERS
VACUUM SYSTEM
LC
BR
FRESH BUTANOL
RICH PEN G VESSELS

SECTION .2


CENTRIFUGAL
6 SOLUT. FILTER
PRECONDENSER
PENICILLIN CRYSTALIZER
CRYSTALIZER SLURRY VESSEL
PENICILLIN FILTER
CHW
STM
CHW
CHW
VACUUM SYSTEM
BR
HW
PENG K
CHW
BUTANOL VESSEL
BUTANOL CONDENSER
PENICILLIN DRYER
WEIGHER
SPENT BUTANOL SURGE VESSEL

SECTION 3

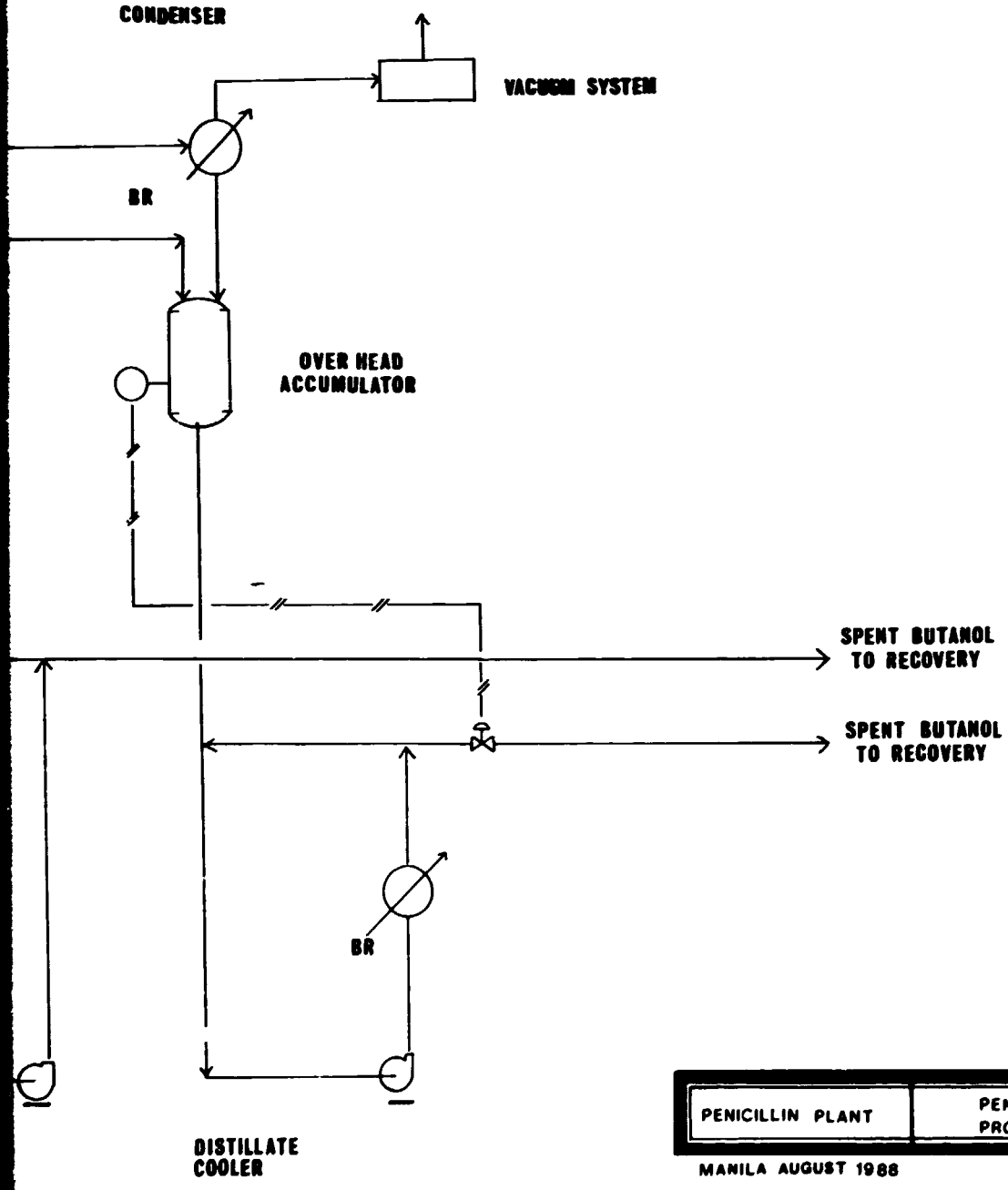


CHW CHILLED WAT
CW COOLING WAT
BR BRINE
STM STEAM
DW DEMINERALIZ
RW RAW WATER
HW HOT WATER

PENICILLIN PLANT	PENICILLIN EXTRACTION PROCESS FLOW DIAGRAM

MANILA AUGUST 1988

SECTION 4

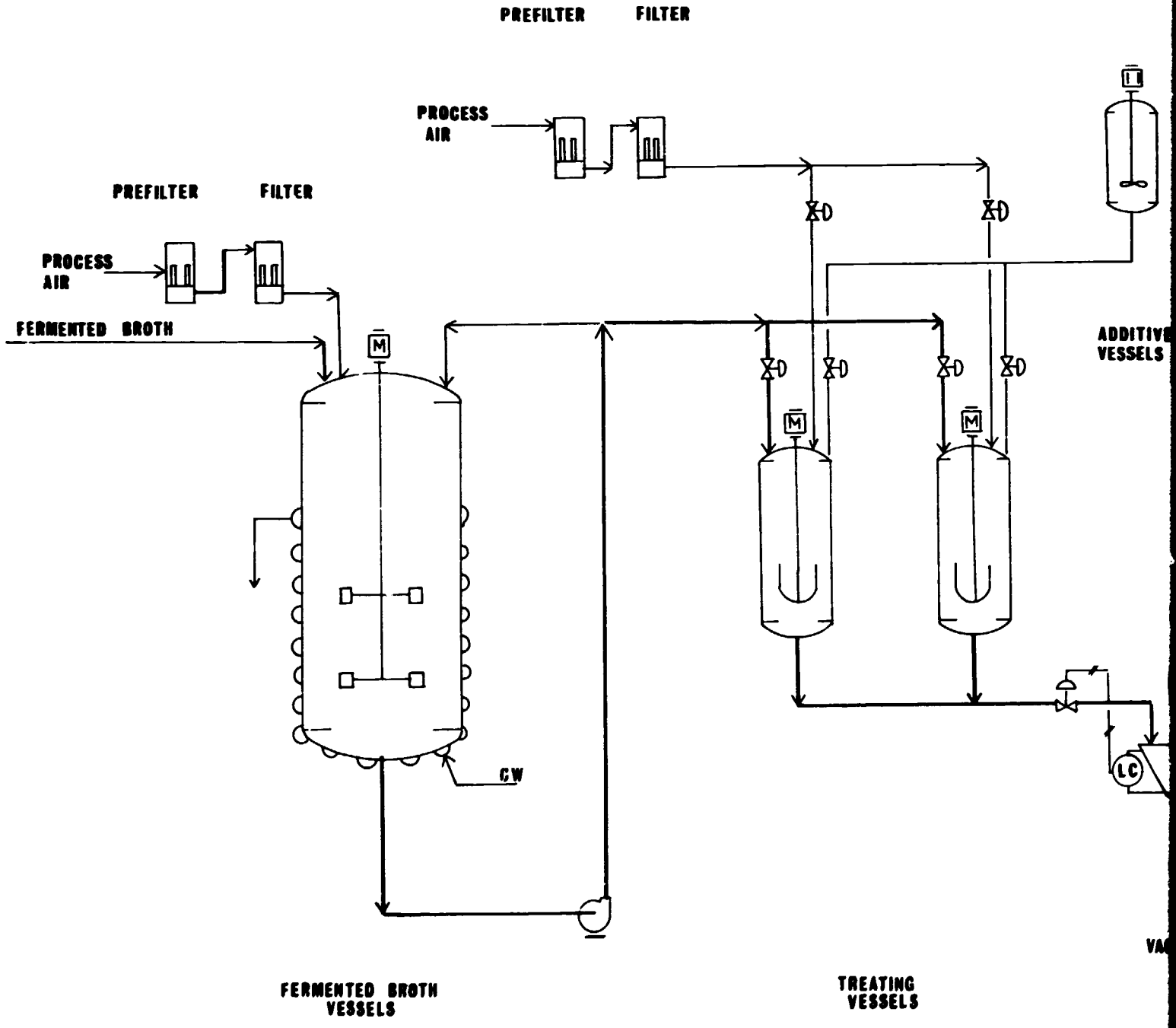


CHW	CHILLED WATER
CW	COOLING WATER
BR	BRINE
STM	STEAM
DW	DEMINERALIZED WATER
RW	RAW WATER
HW	HOT WATER

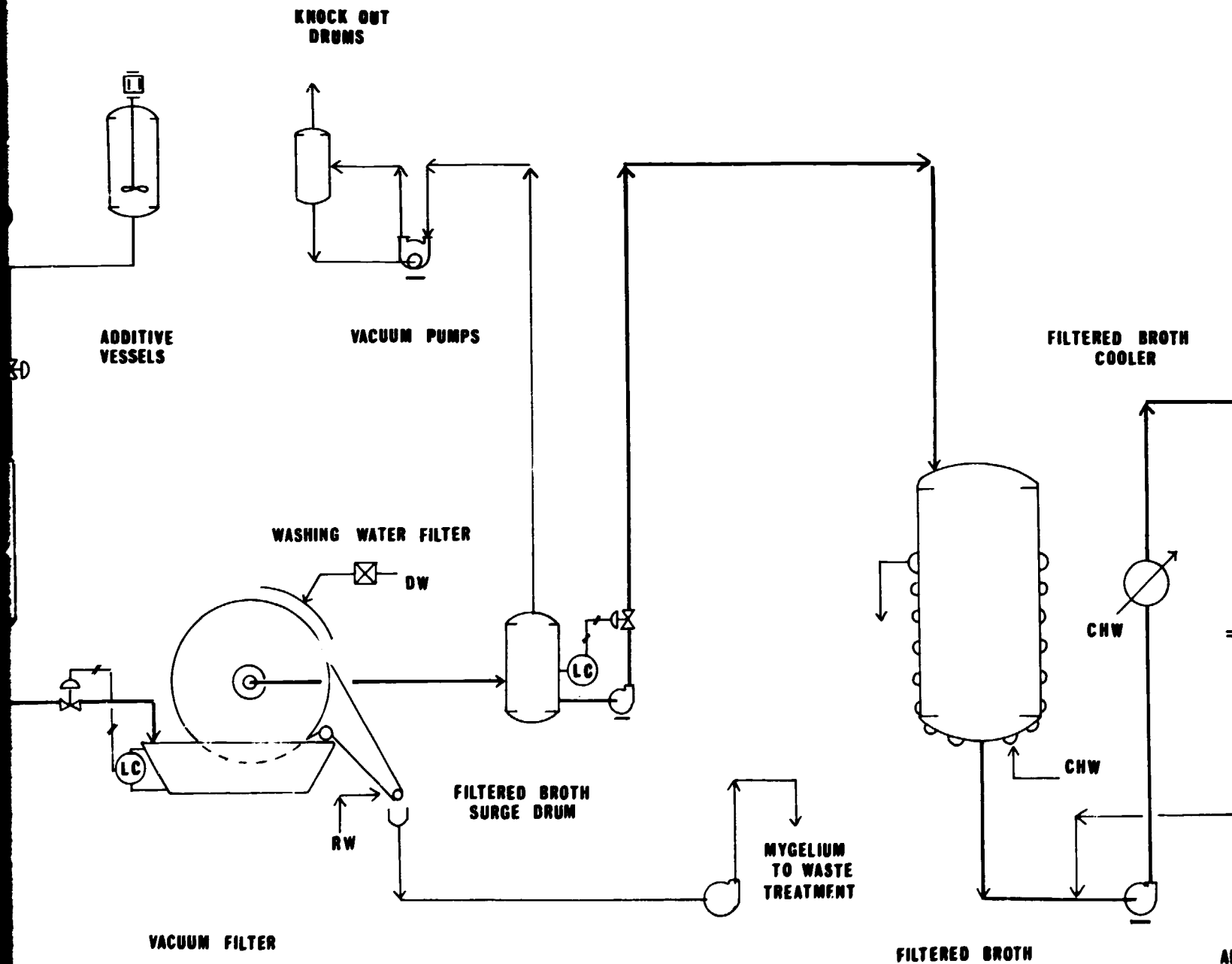
PENICILLIN PLANT	PENICILLIN EXTRACTION PROCESS FLOW DIAGRAM

MANILA AUGUST 1988

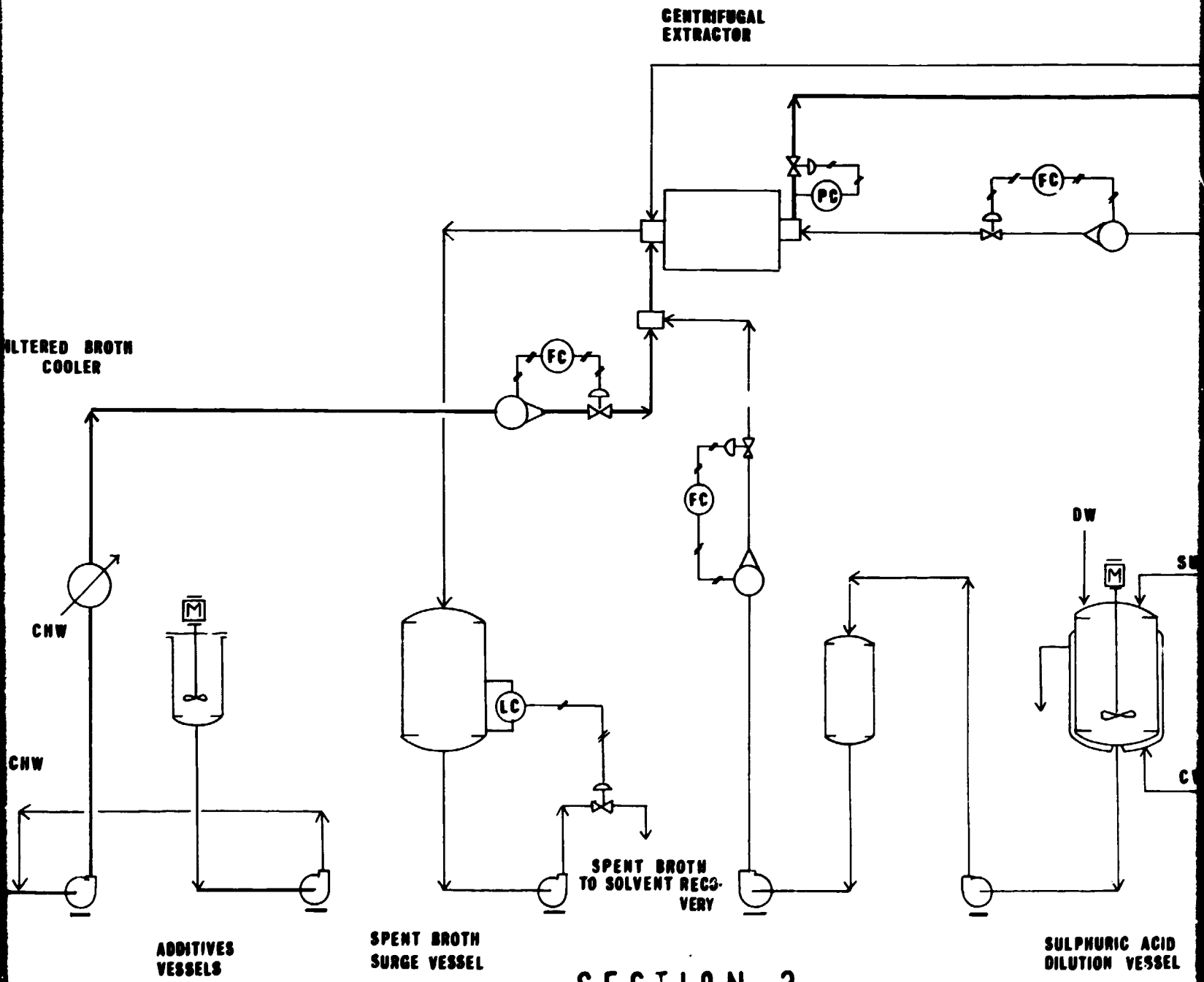
SECTION 5


PREFILTER
FILTER
PROCESS AIR
PREFILTER
FILTER
PROCESS AIR
FERMENTED BROTH
M
CW
ADDITIVE VESSELS
LC
FERMENTED BROTH VESSELS
TREATING VESSELS

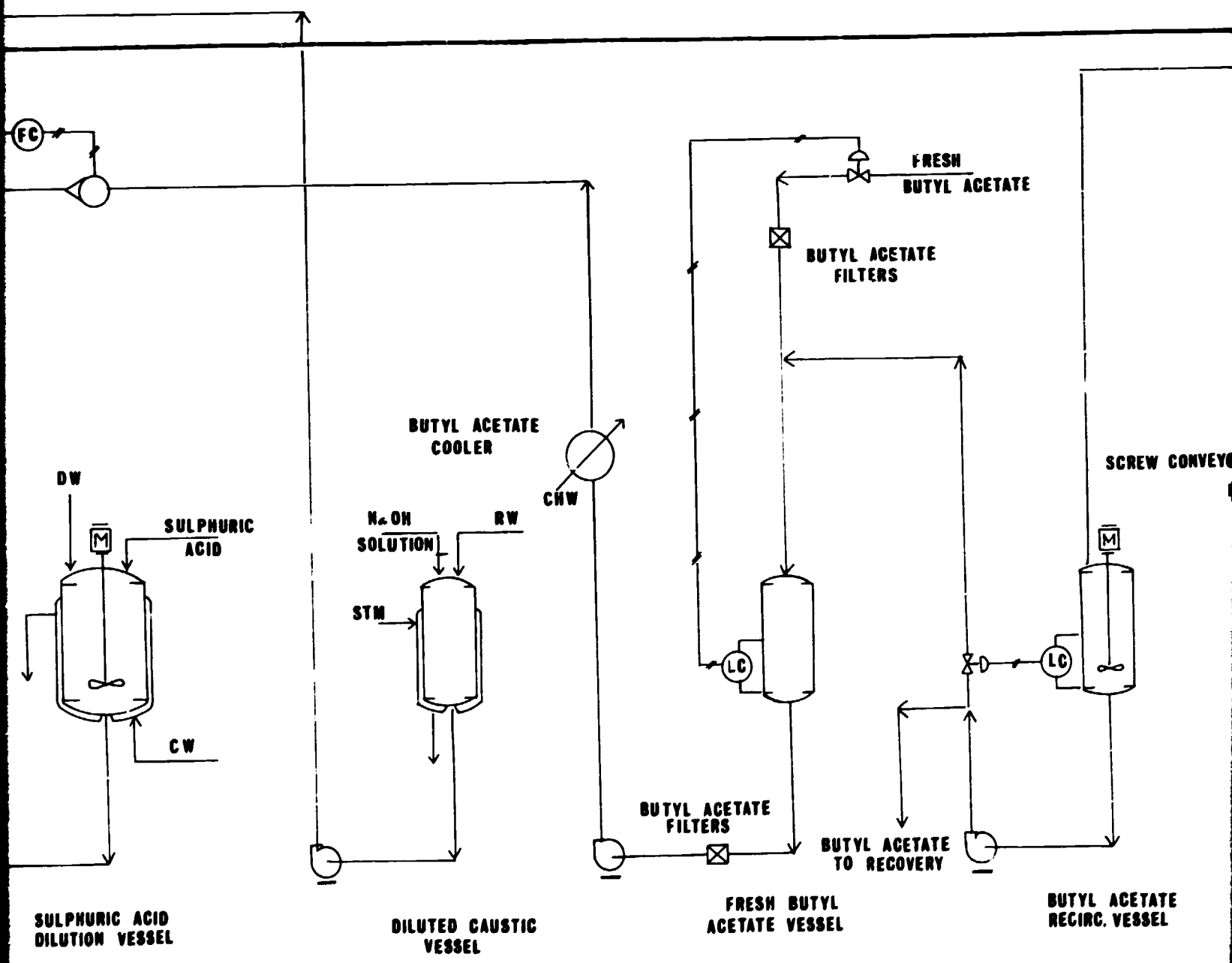
SECTION 1


KNOCK OUT DRUMS
ADDITIVE VESSELS
VACUUM PUMPS
FILTERED BROTH COOLER
WASHING WATER FILTER
DW
LC
CHW
CHW
LC
FILTERED BROTH SURGE DRUM
RW
MYCELIUM TO WASTE TREATMENT
VACUUM FILTER
FILTERED BROTH VESSEL

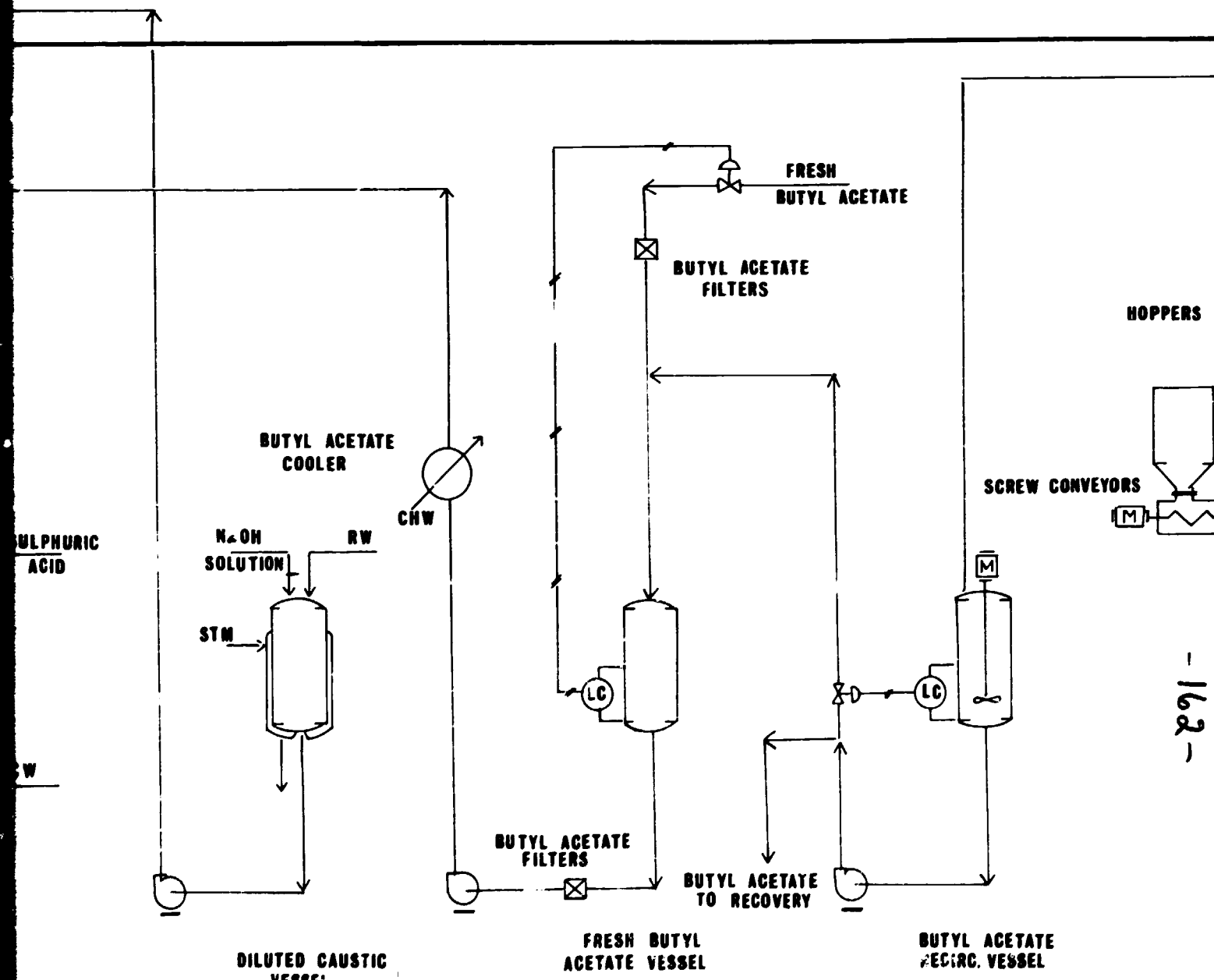
SECTION .2

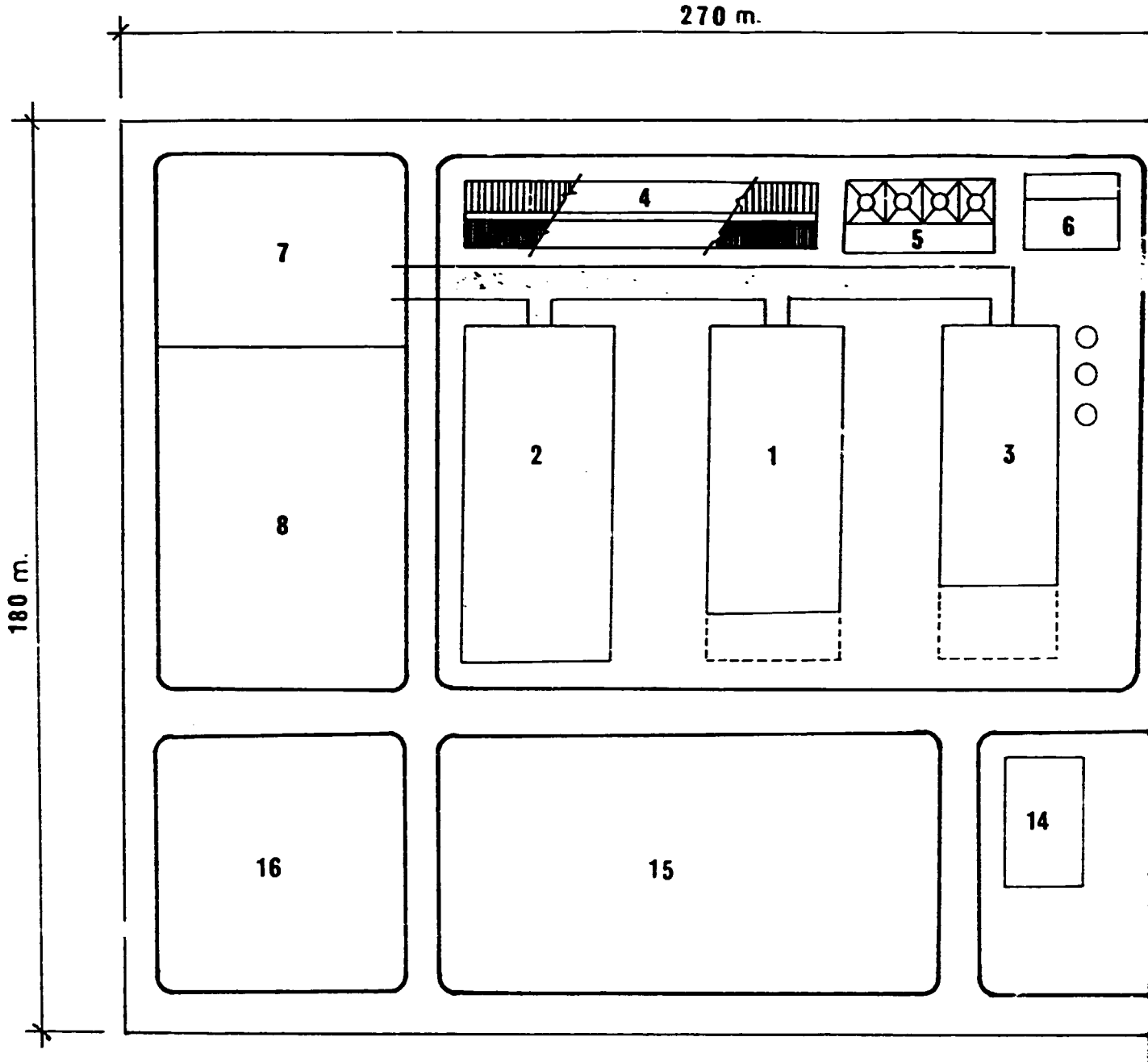

CENTRIFUGAL EXTRACTOR
PC
FC
FC
FC
LTERED BROTH COOLER
CHW
CHW
LC
DW
M
M
SPENT BROTH TO SOLVENT RECO- VERY
ADDITIVES VESSELS
SPENT BROTH SURGE VESSEL
SULPHURIC ACID DILUTION VESSEL

SECTION 3


FC
FRESH
BUTYL ACETATE
BUTYL ACETATE
FILTERS
BUTYL ACETATE
COOLER
CHW
SCREW CONVEYO
DW
SULPHURIC
ACID
M
NaOH
SOLUTION
RW
STM
LC
LC
CW
BUTYL ACETATE
FILTERS
BUTYL ACETATE
TO RECOVERY
SULPHURIC ACID
DILUTION VESSEL
DILUTED CAUSTIC
VESSEL
FRESH BUTYL
ACETATE VESSEL
BUTYL ACETATE
RECIRC. VESSEL

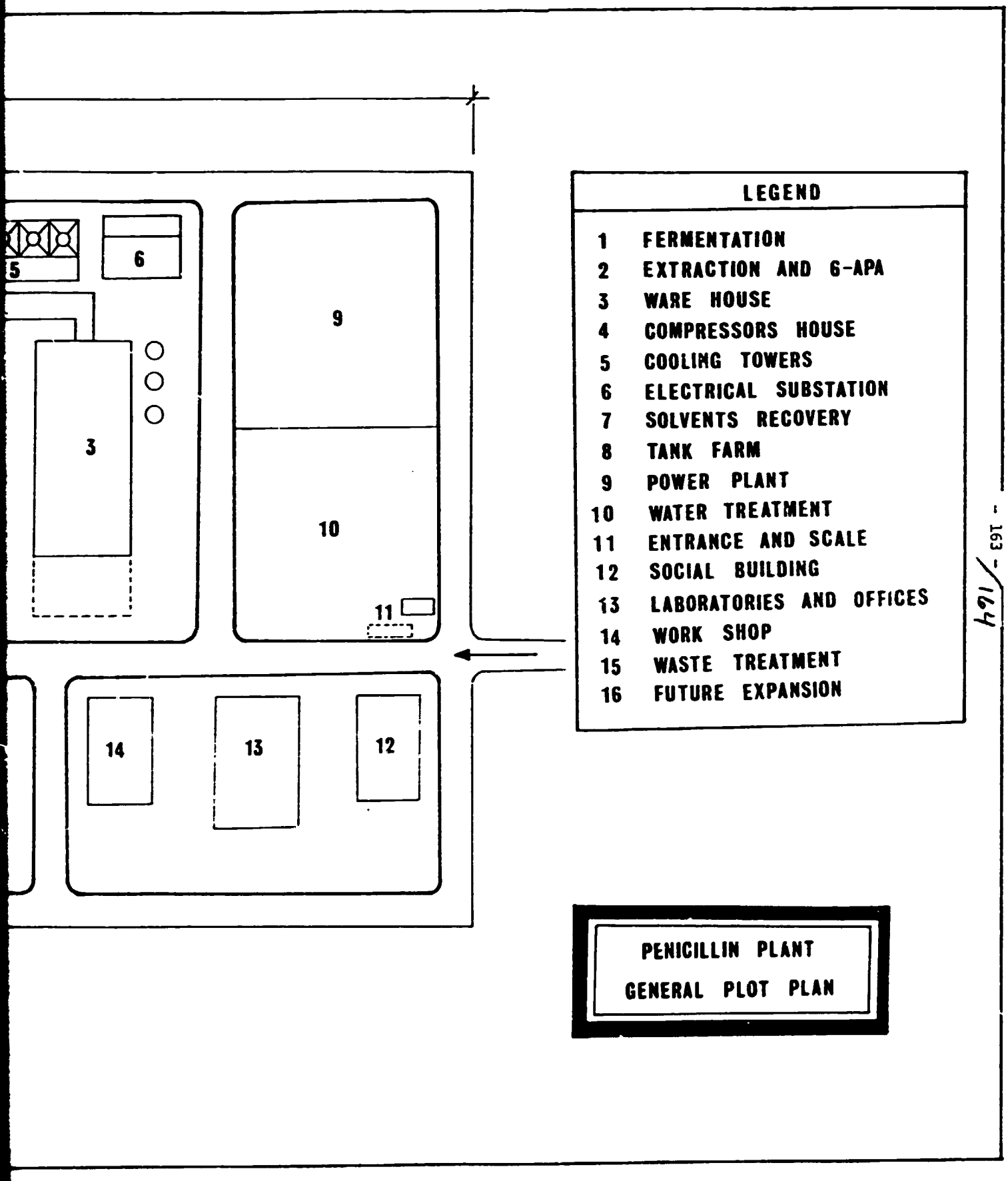
SECTION 4


FRESH
BUTYL ACETATE
BUTYL ACETATE
FILTERS
HOPPERS
BUTYL ACETATE
COOLER
CHW
SCREW CONVEYORS
ULPHURIC
ACID
NaOH
SOLUTION
RW
STM
LC
LC
W
BUTYL ACETATE
FILTERS
BUTYL ACETATE
TO RECOVERY
DILUTED CAUSTIC
VESSEL
FRESH BUTYL
ACETATE VESSEL
BUTYL ACETATE
RECIRC. VESSEL

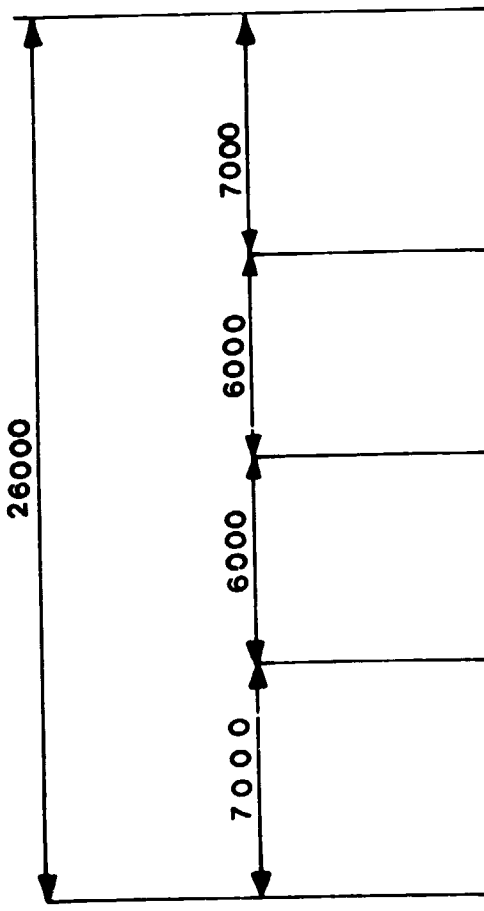


MANILA - AUGUST 1988

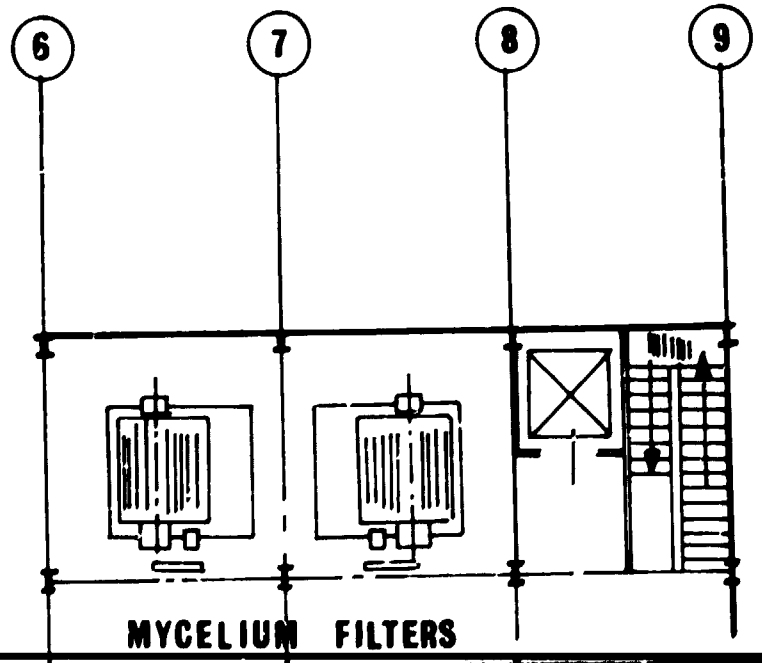
SECTION 1

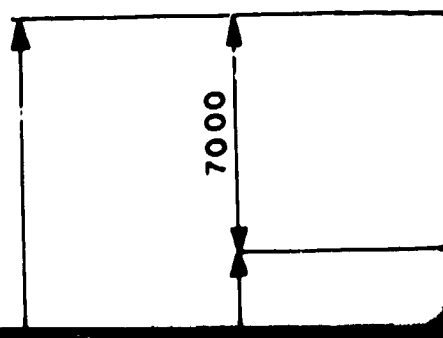

LEGEND
1 FERMENTATION
2 EXTRACTION AND 6-APA
3 WARE HOUSE
4 COMPRESSORS HOUSE
5 COOLING TOWERS
6 ELECTRICAL SUBSTATION
7 SOLVENTS RECOVERY
8 TANK FARM
9 POWER PLANT
10 WATER TREATMENT
11 ENTRANCE AND SCALE
12 SOCIAL BUILDING
13 LABORATORIES AND OFFICES
14 WORK SHOP
15 WASTE TREATMENT
16 FUTURE EXPANSION
PENICILLIN PLANT
GENERAL PLOT PLAN

SECTION .2



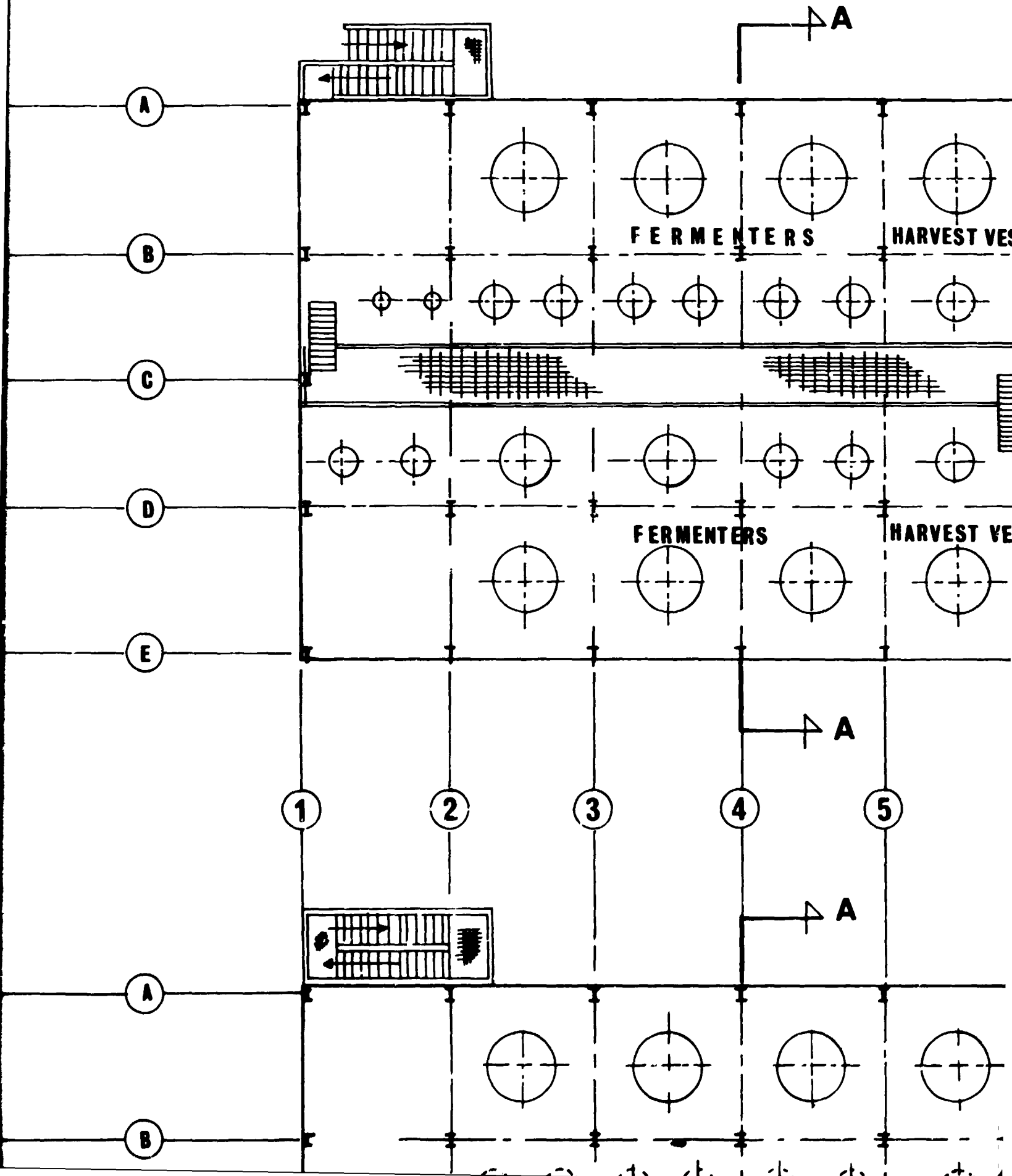
SECTION 1





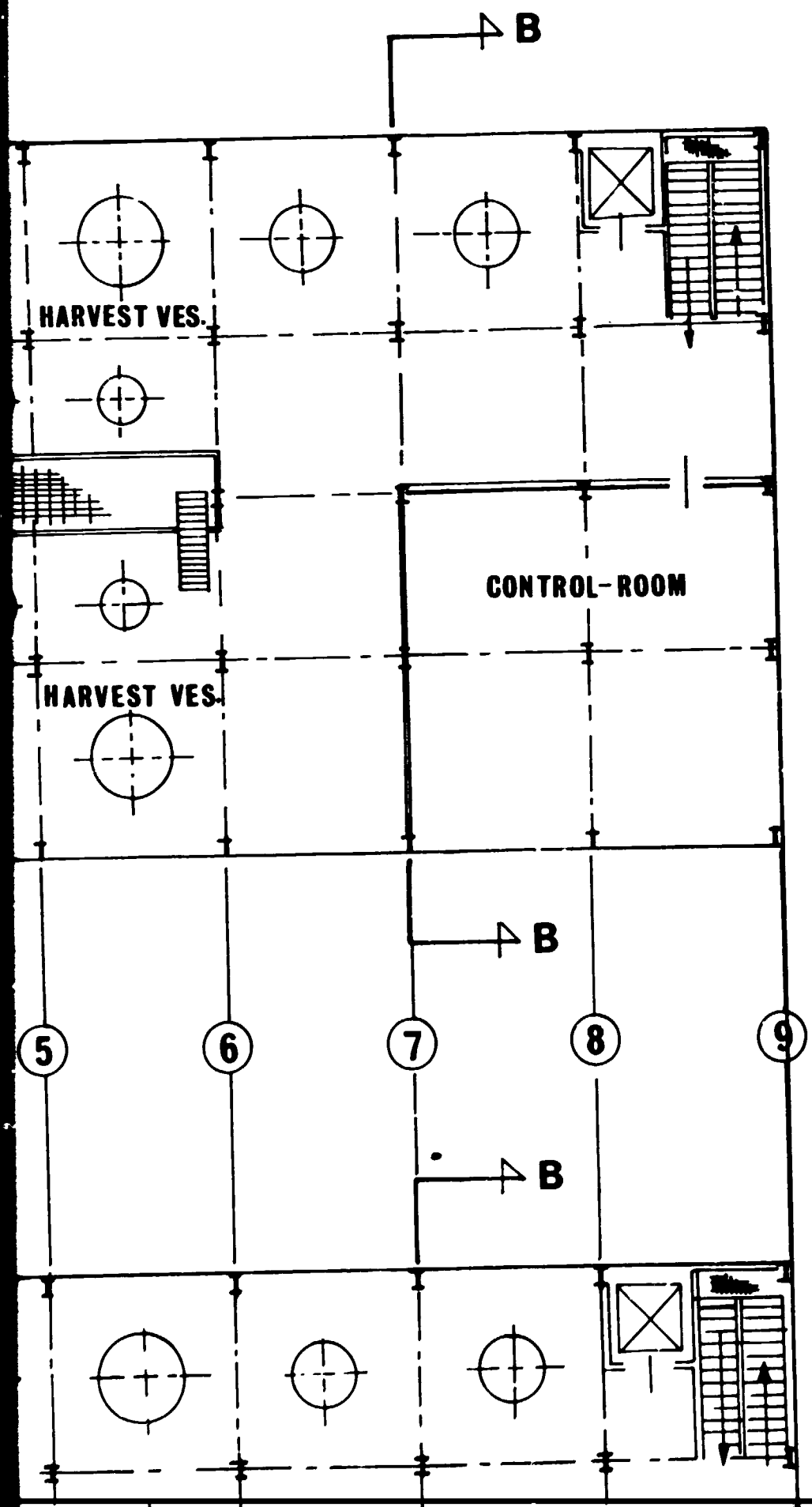
SECTION .2

PLAN AT ELEV. 12000



12000

SECTION 3



▽ 20000

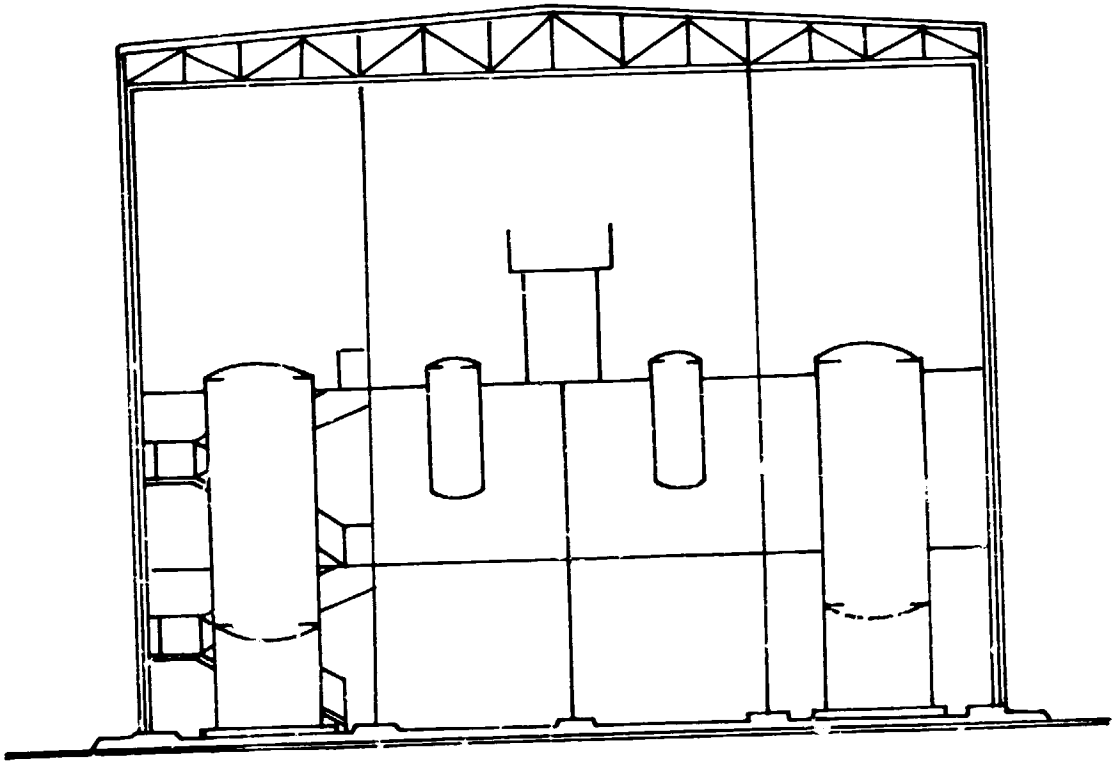
▽ 12000

▽ 6000

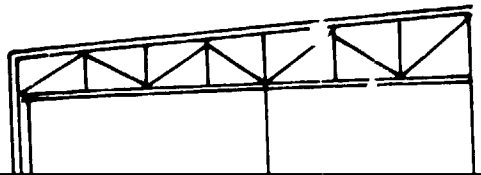
▽ 000

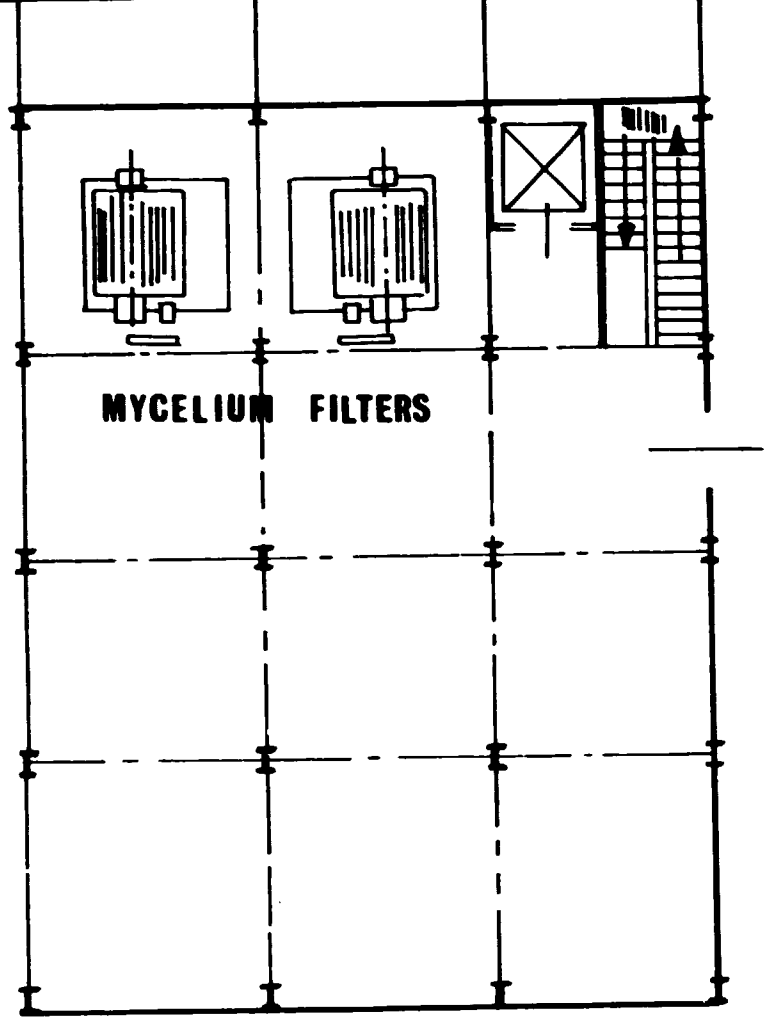
▽ 20000

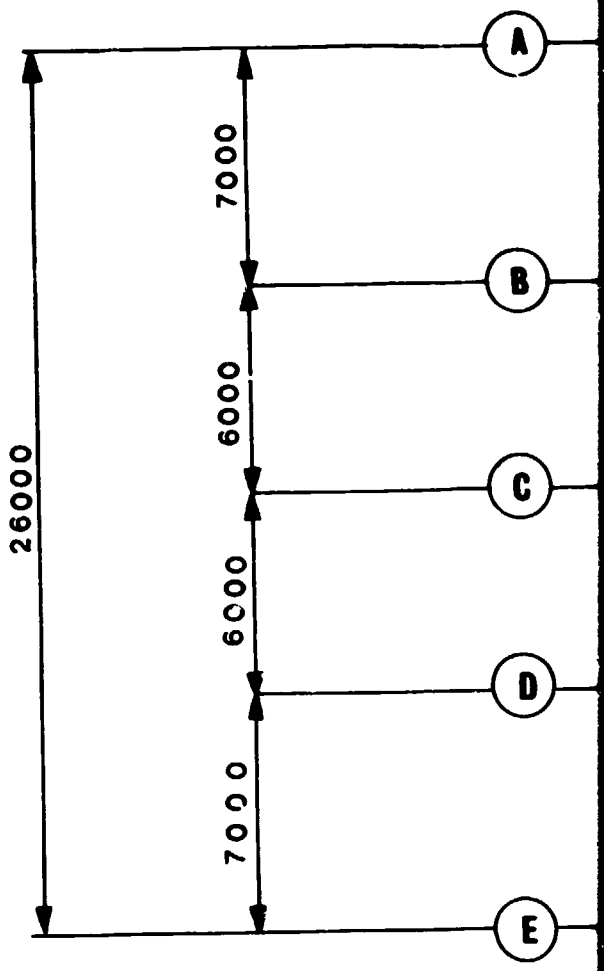
SECTION 4



SECTION A-A

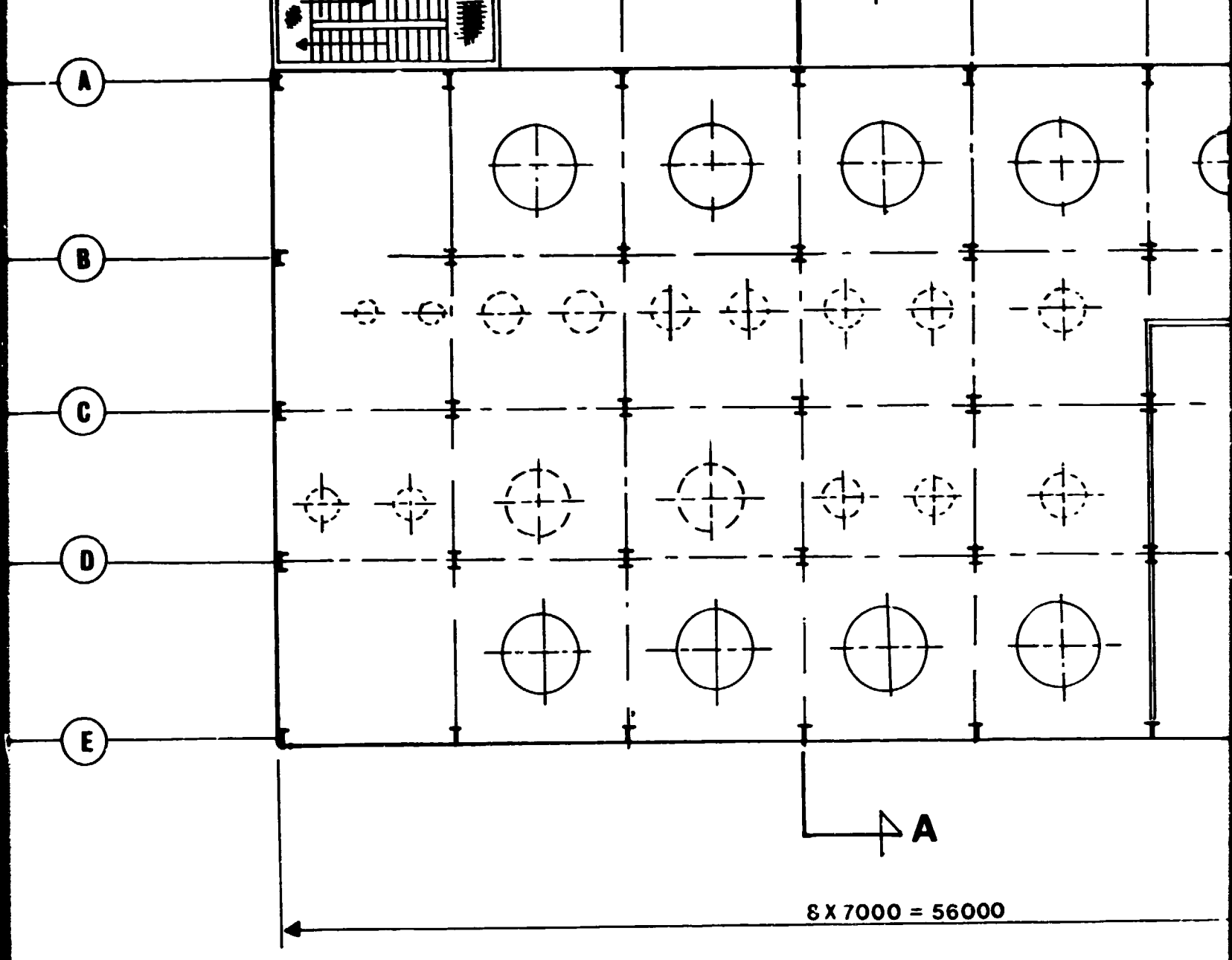






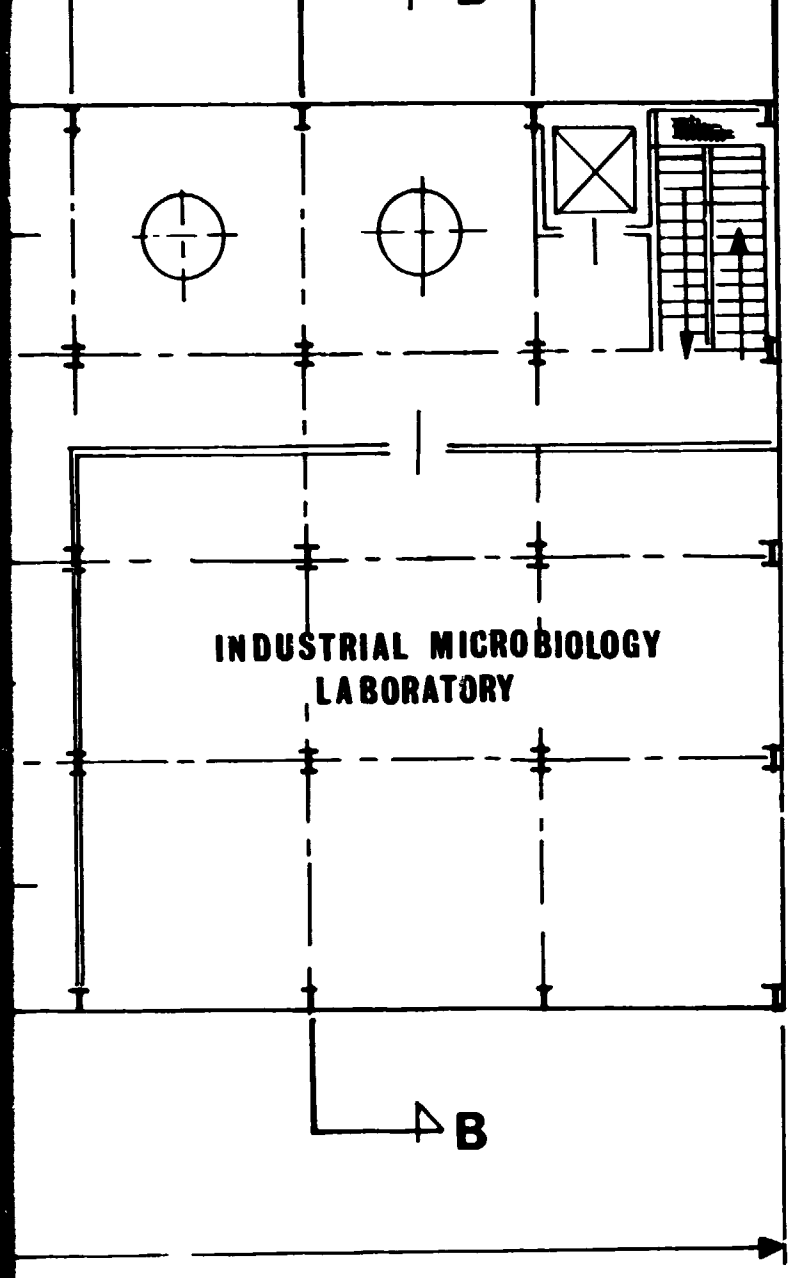
PLAN AT ELEV. 150

SECTION 5

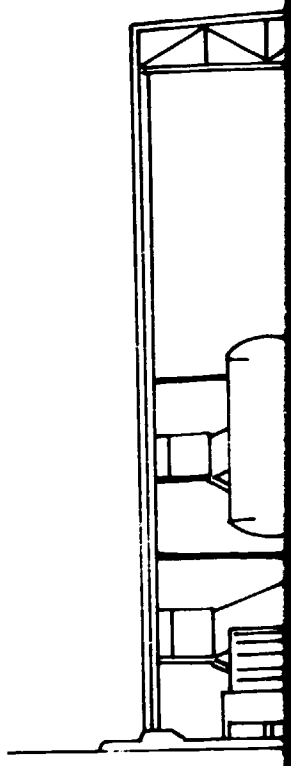


PLAN AT ELEV. 5000

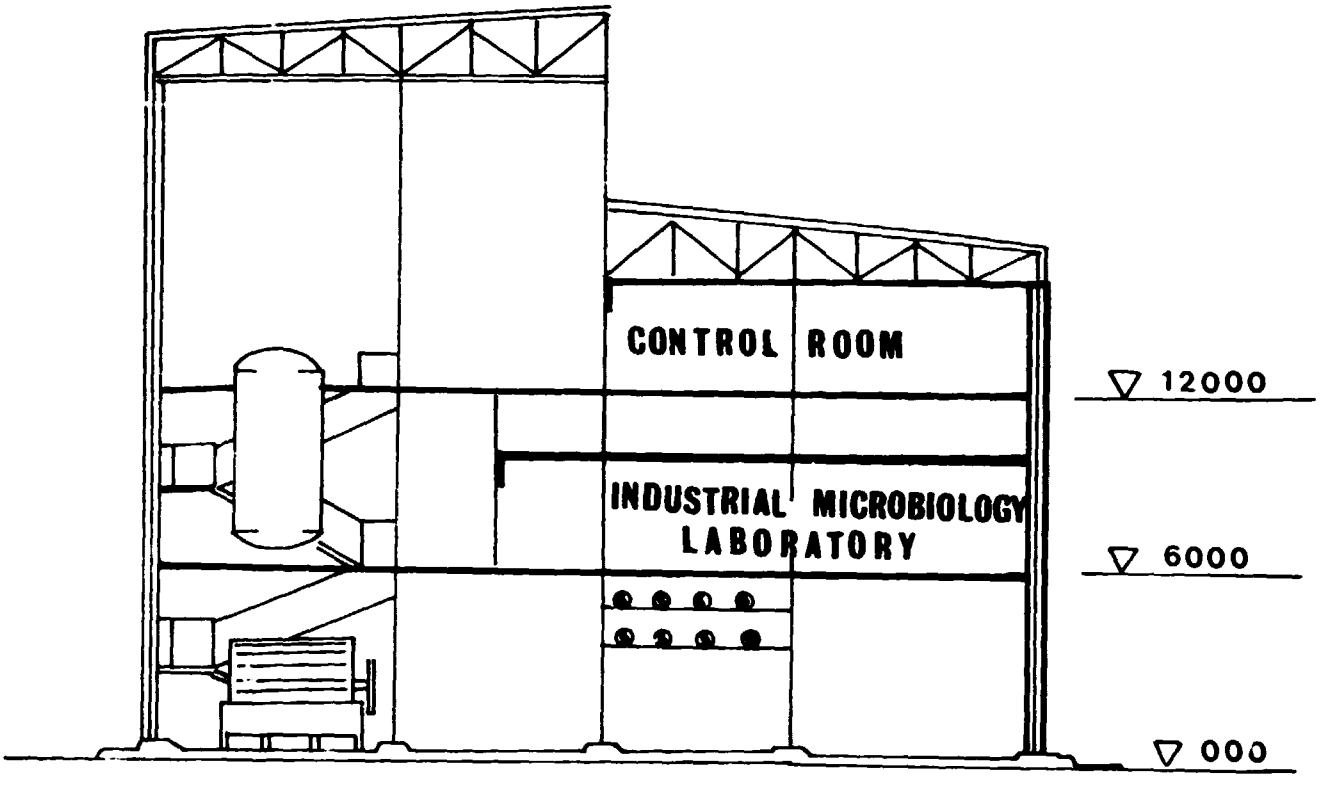
SECTION 6



▽ 20000



SECTION 7



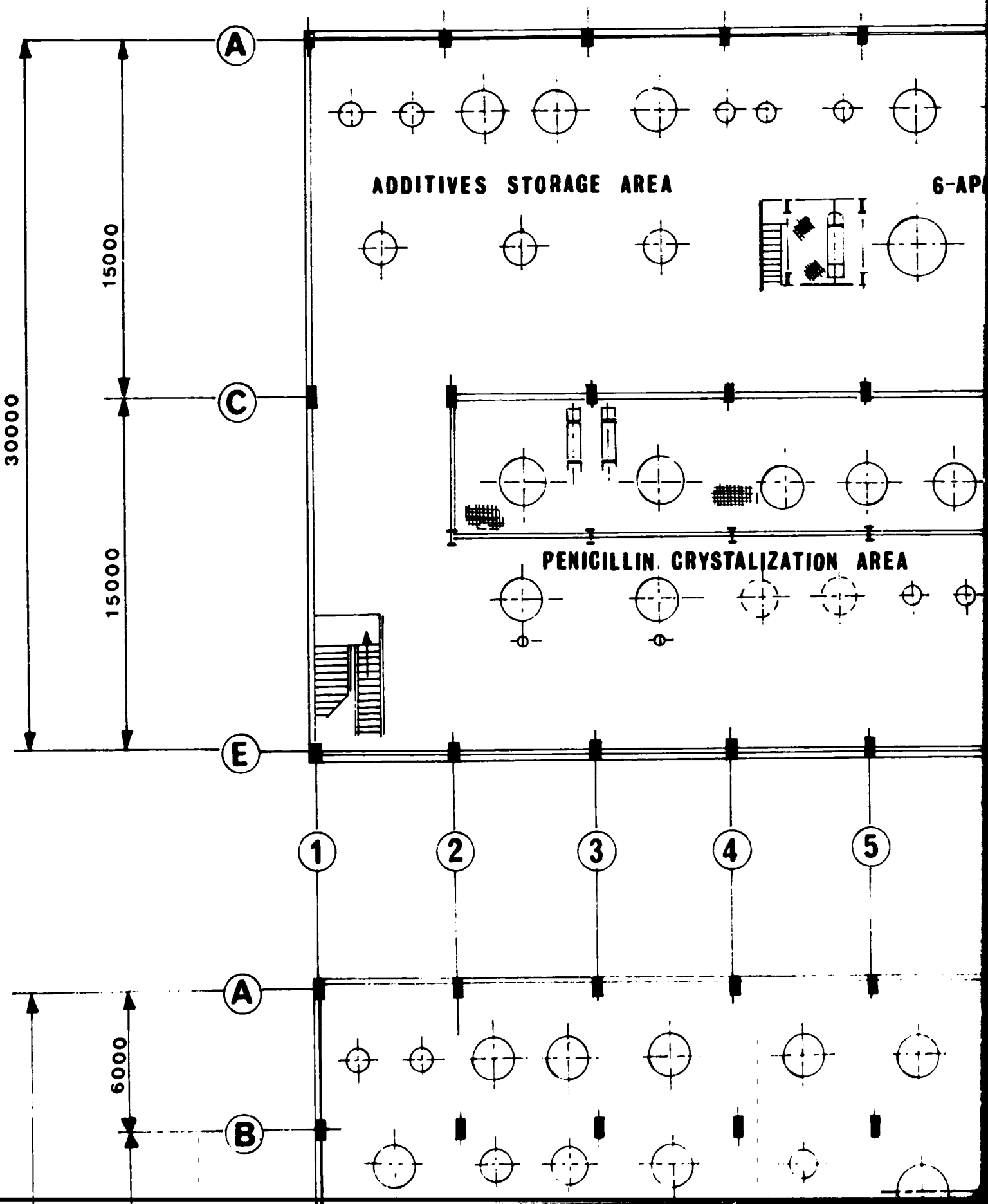
SECTION B-B

FERMENTATION BUILDING
EQUIPMENT LAY-OUT

SECTION 8

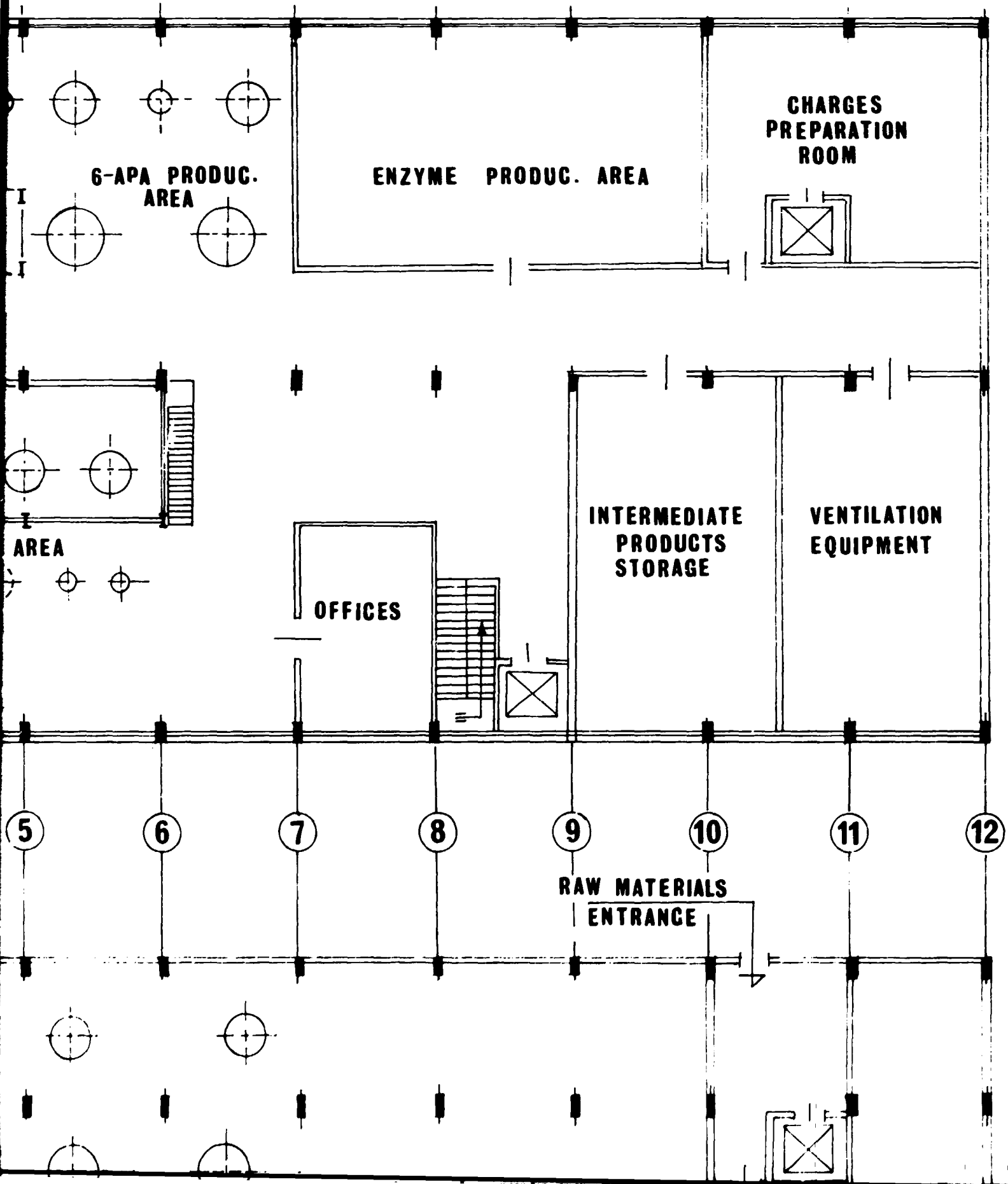
PLAN

SECTION 1

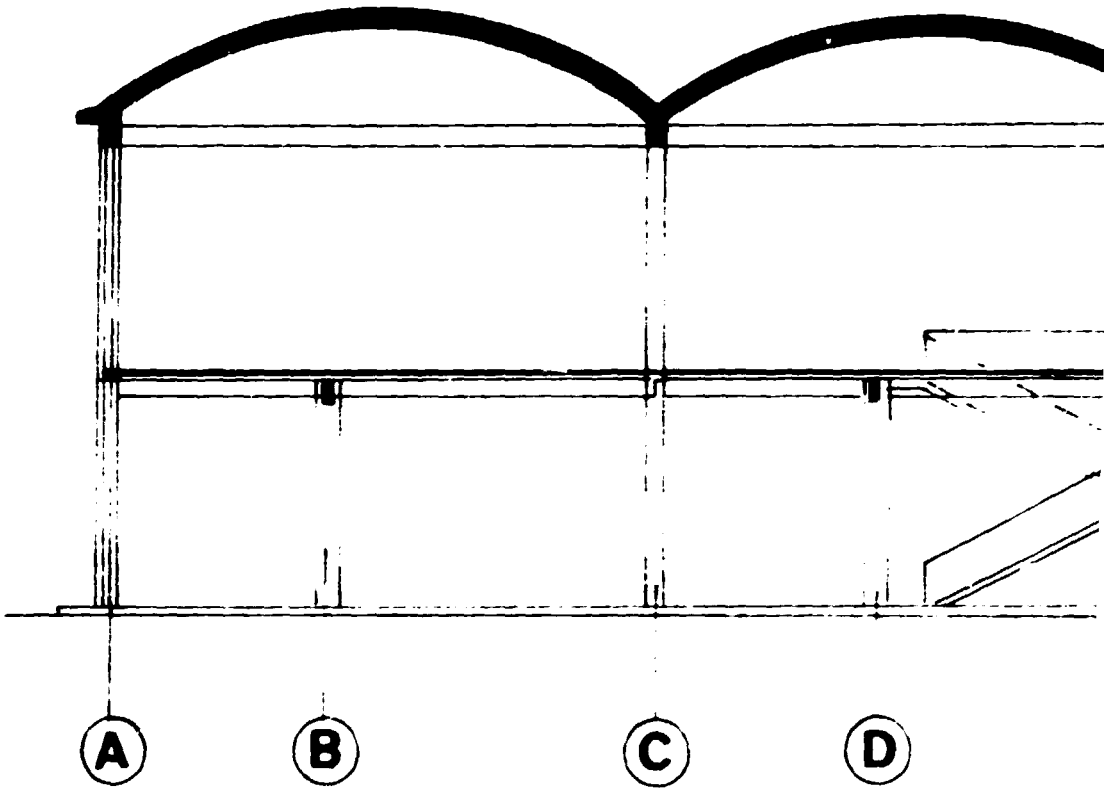


PLAN AT ELEV. 7000

SECTION .2

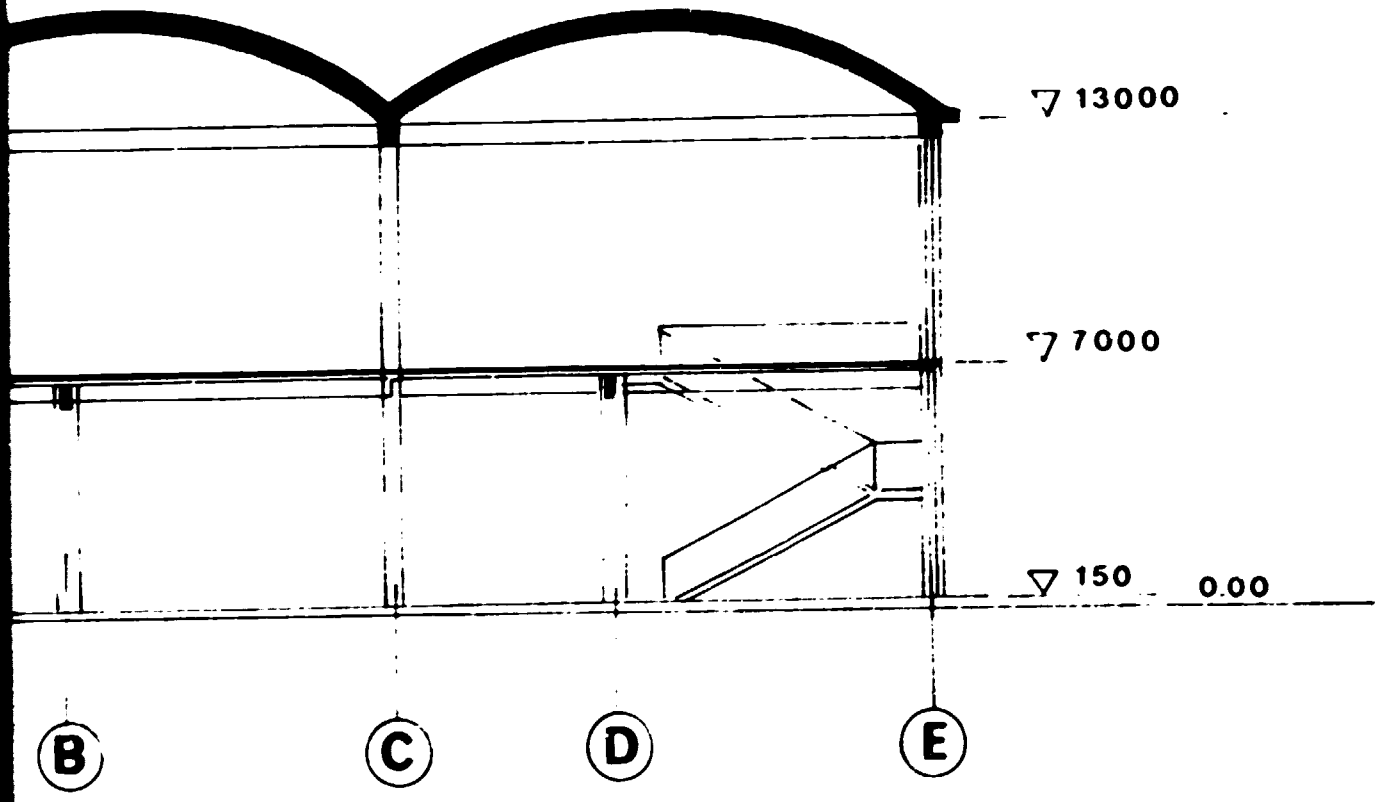


SECTION 3

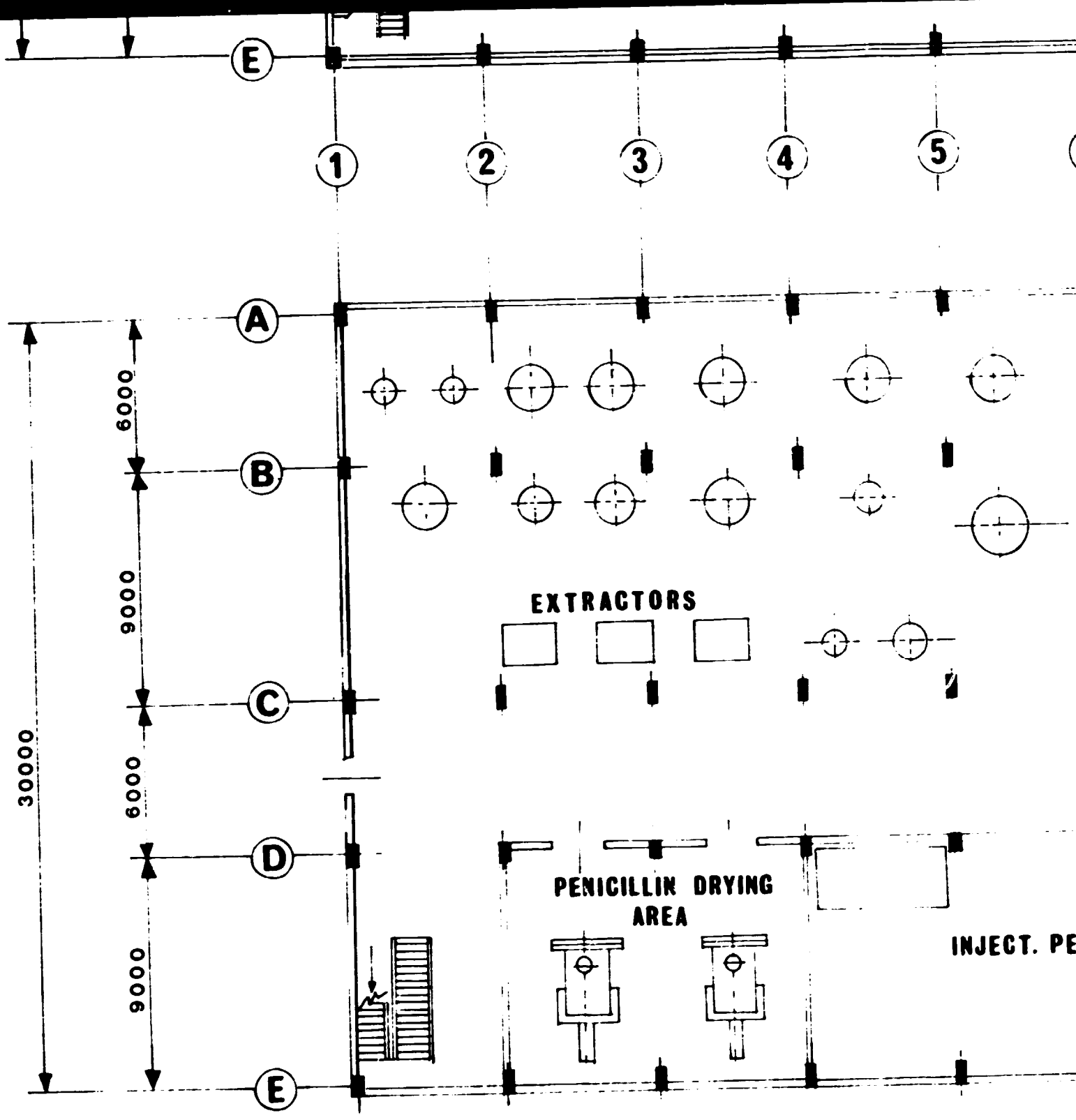


BUILDING SECTION

SECTION 4

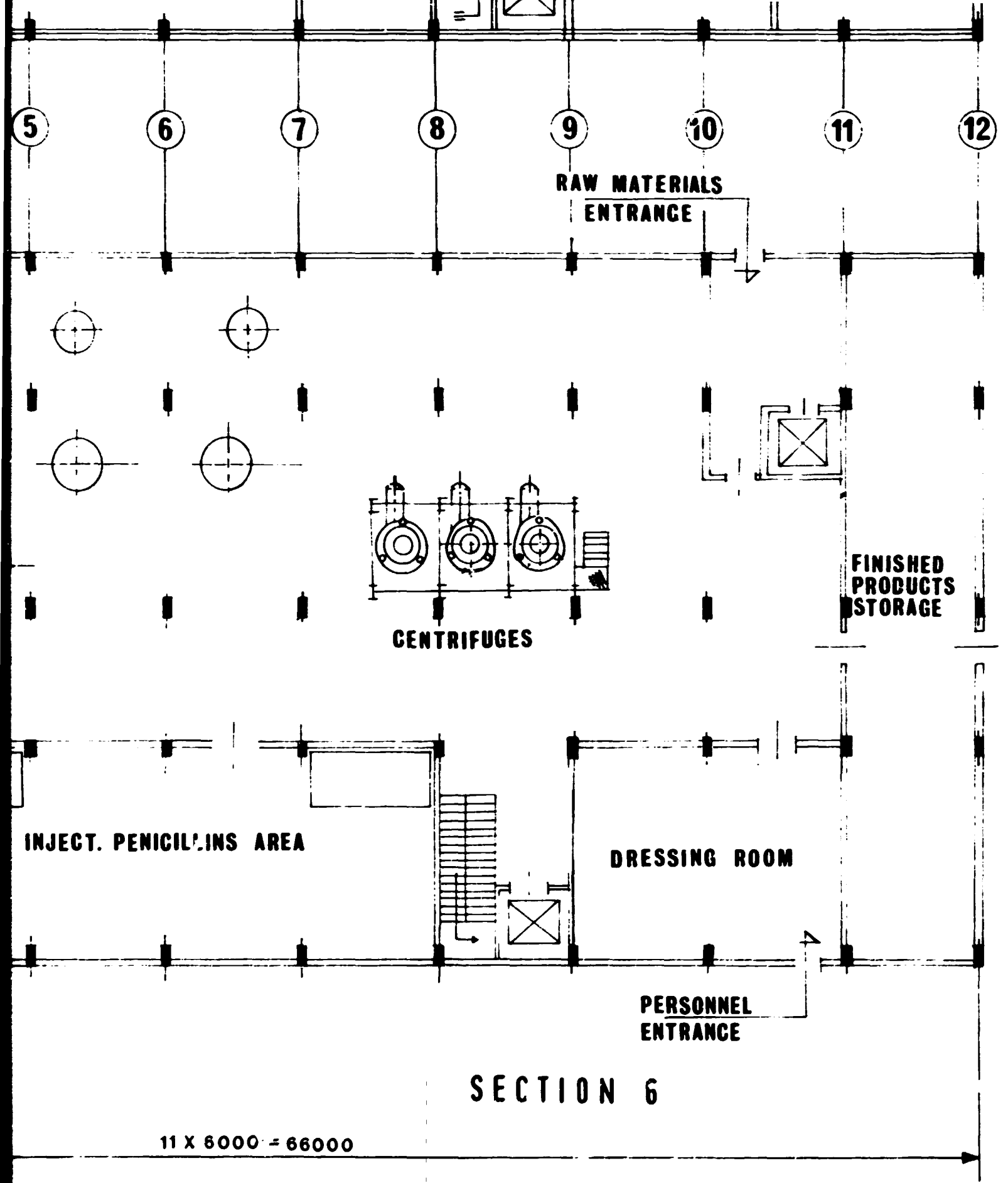


BUILDING SECTION



SECTION 5

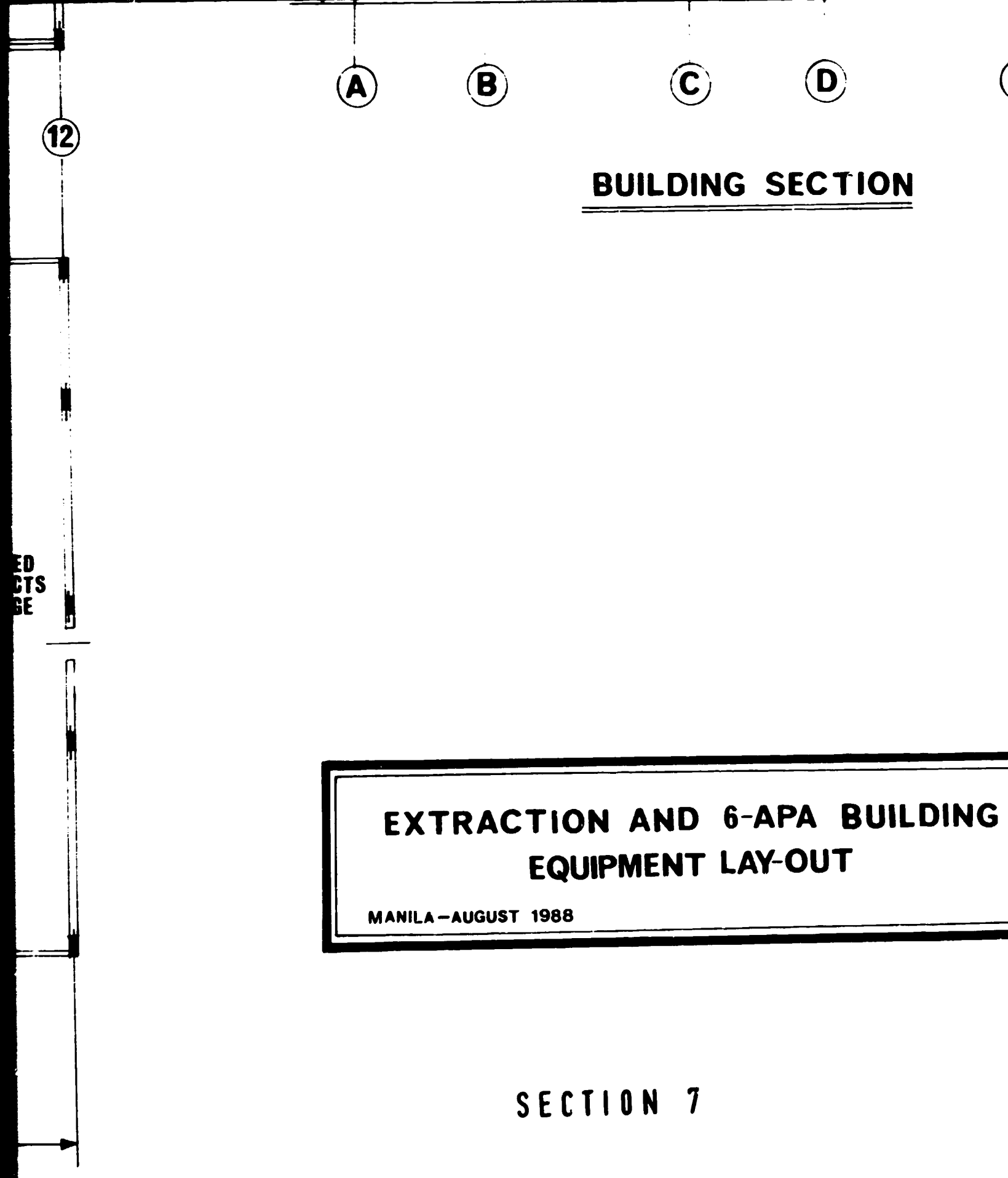
PLA



SECTION 6

11 X 6000 = 66000

PLAN AT ELEV. 150



BUILDING SECTION

EXTRACTION AND 6-APA BUILDING EQUIPMENT LAY-OUT

MANILA—AUGUST 1988

SECTION 7

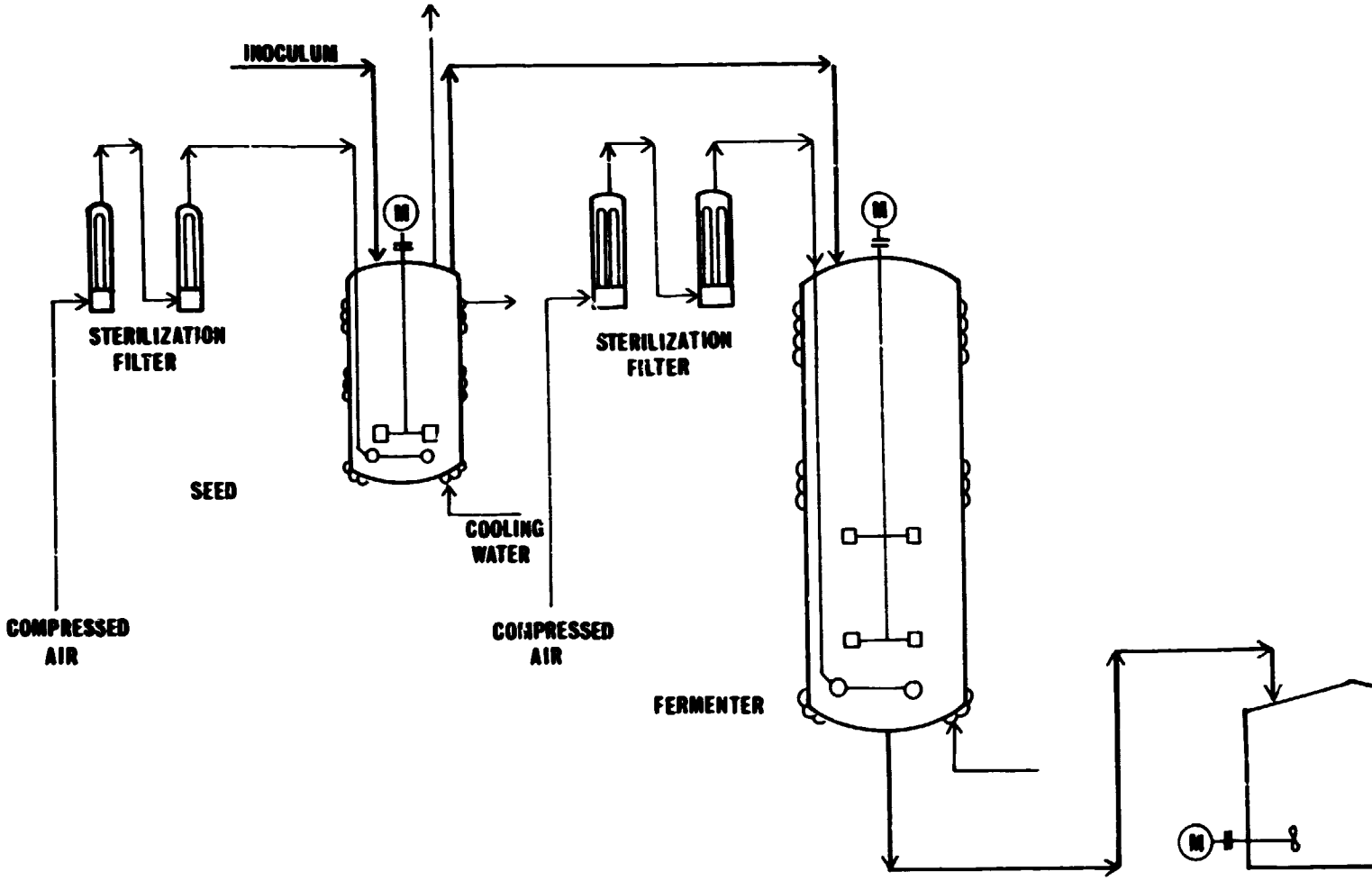
B C D E

BUILDING SECTION

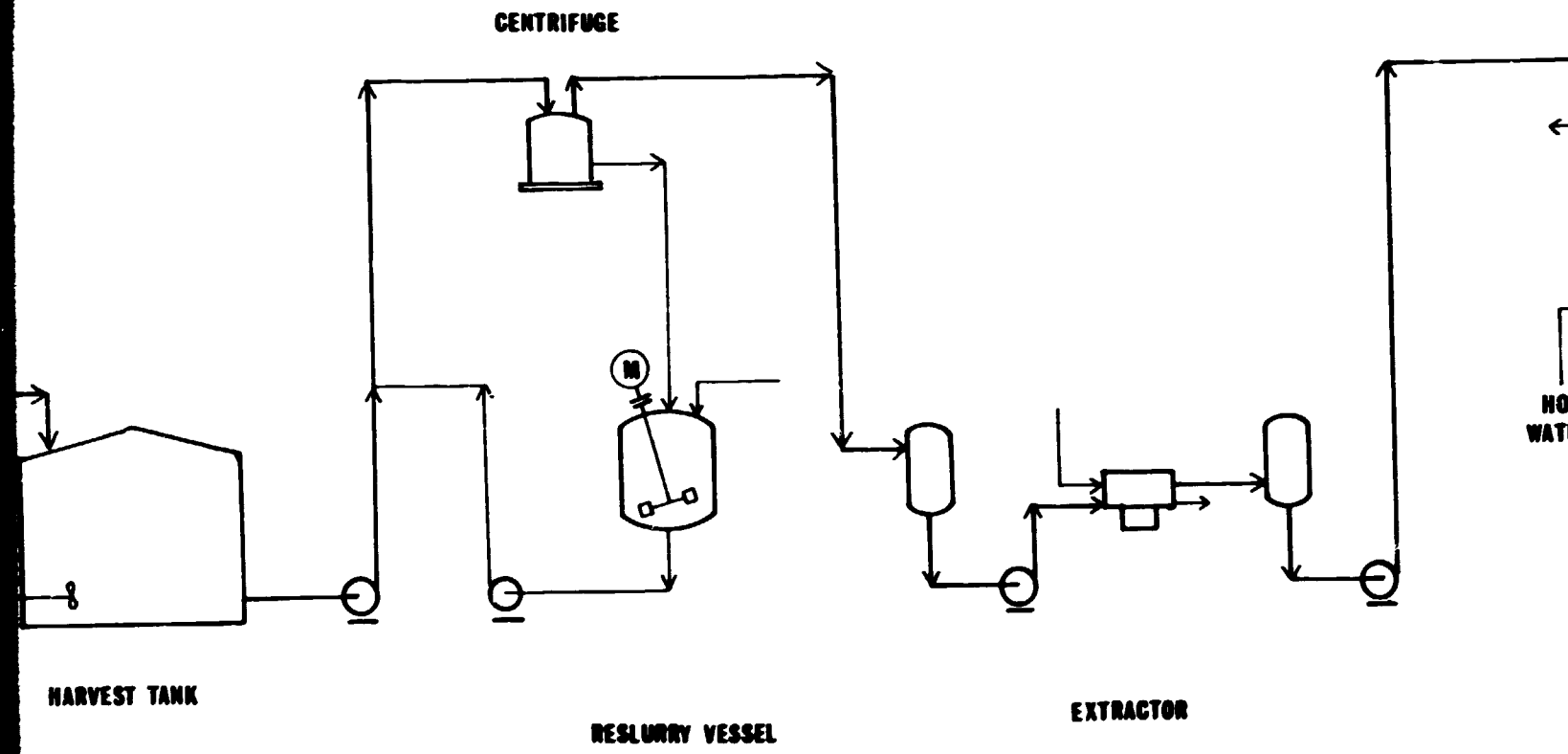
TRACTION AND 6-APA BUILDING
EQUIPMENT LAY-OUT

AUGUST 1988

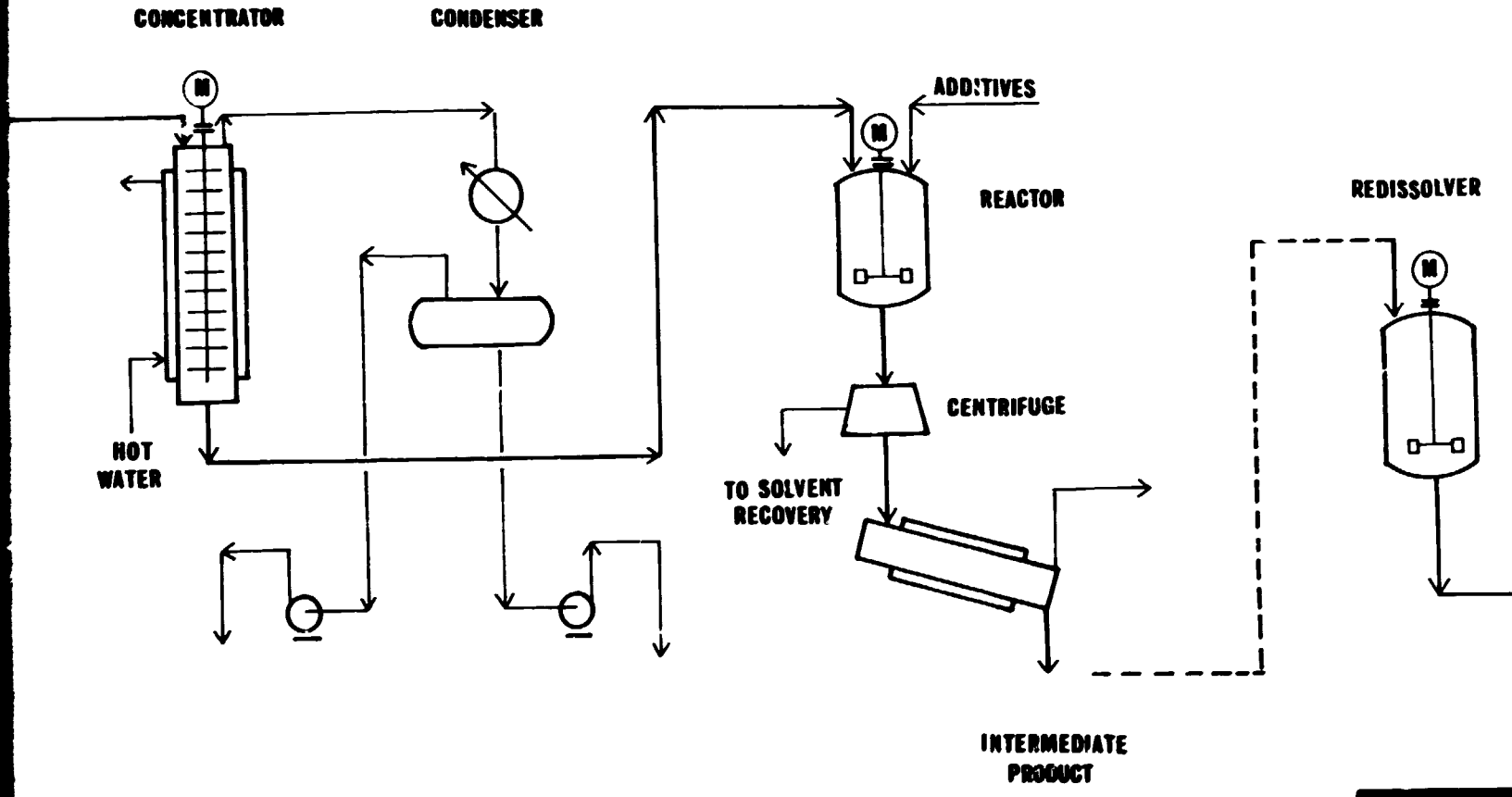
SECTION 8


INOCULUM
STERILIZATION FILTER
SEED
COOLING WATER
COMPRESSED AIR
STERILIZATION FILTER
COMPRESSED AIR
FERMENTER
HARVEST T

SECTION 1

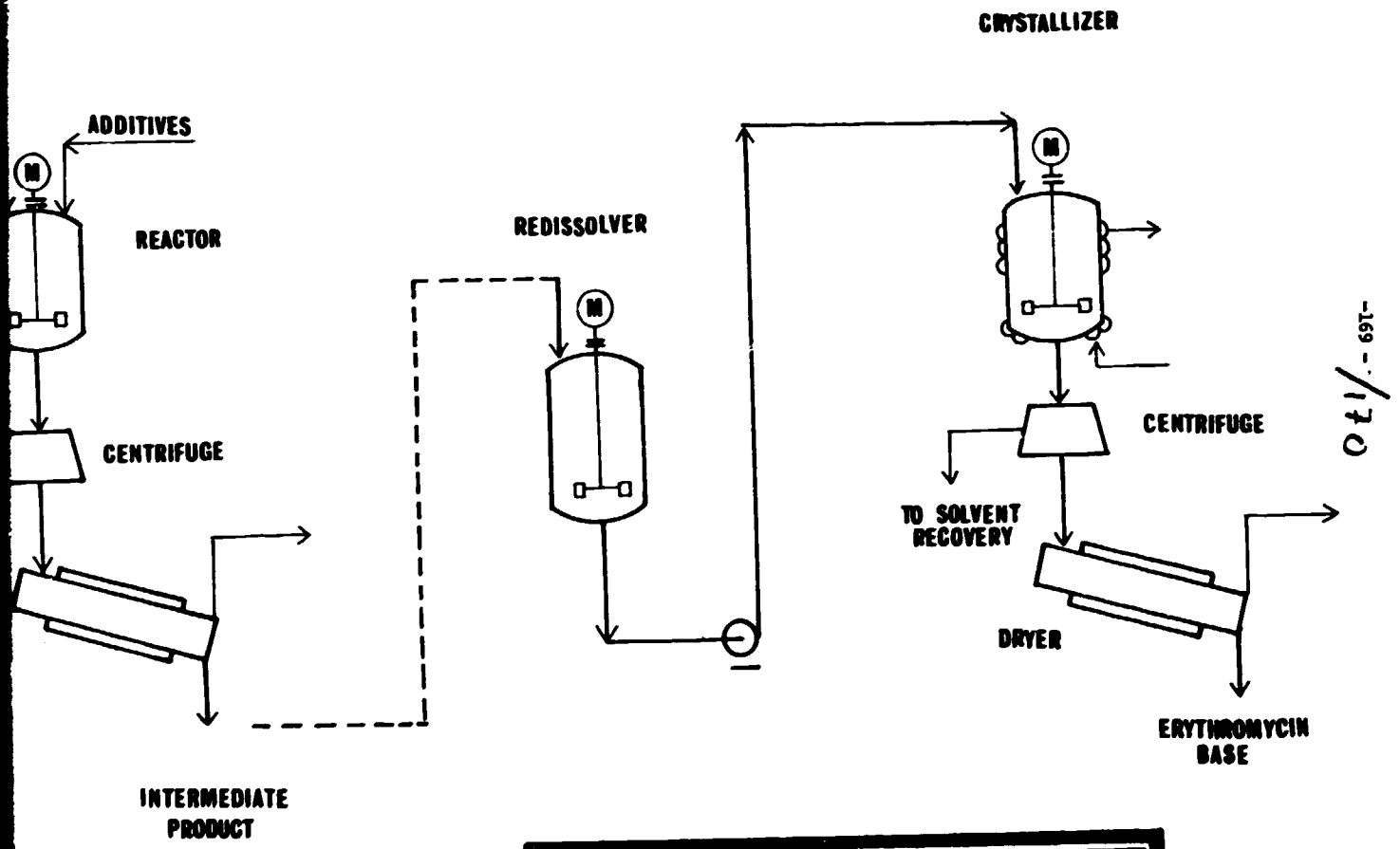


SECTION .2



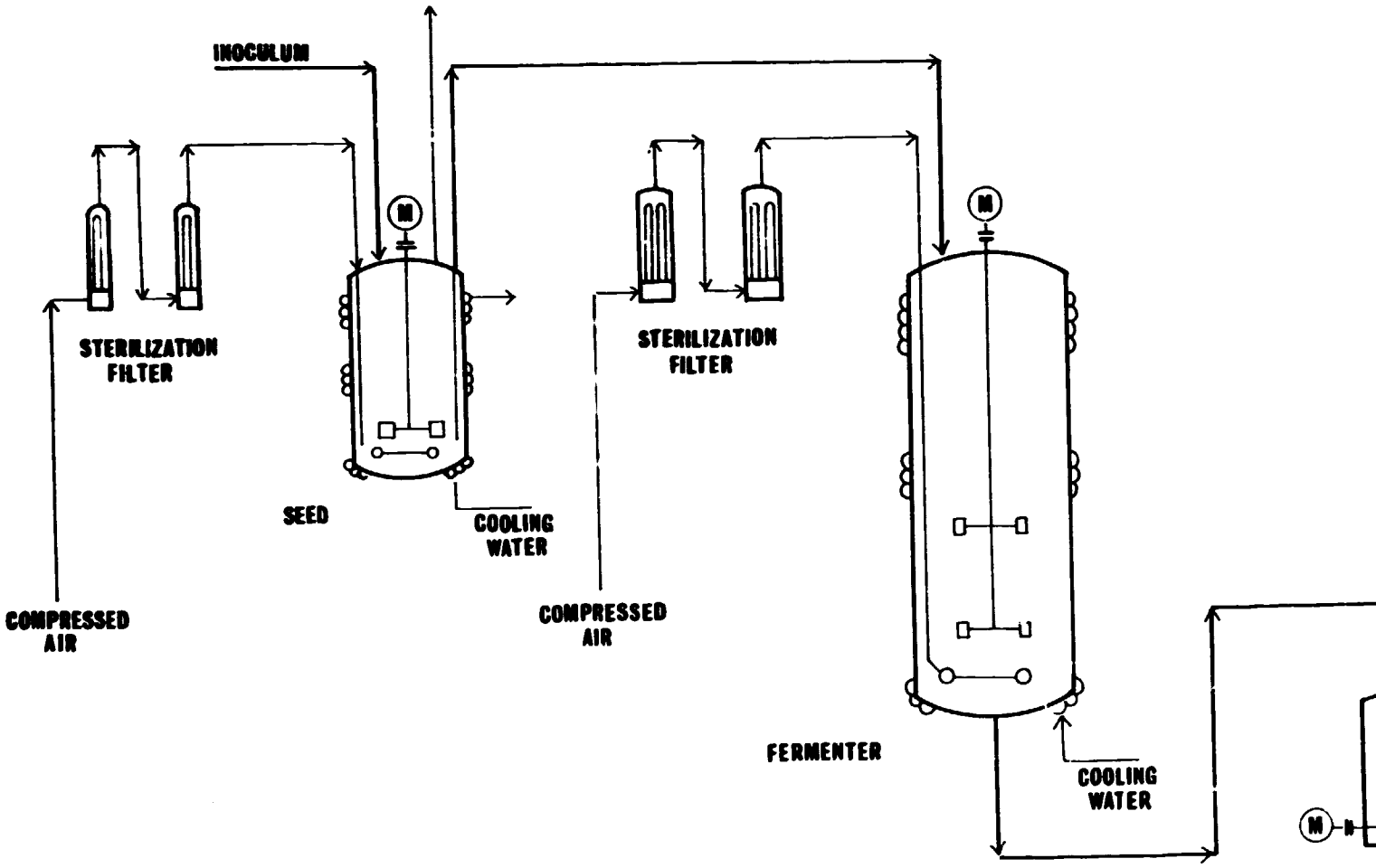
MULTI-PU
MANILA - A

SECTION 3

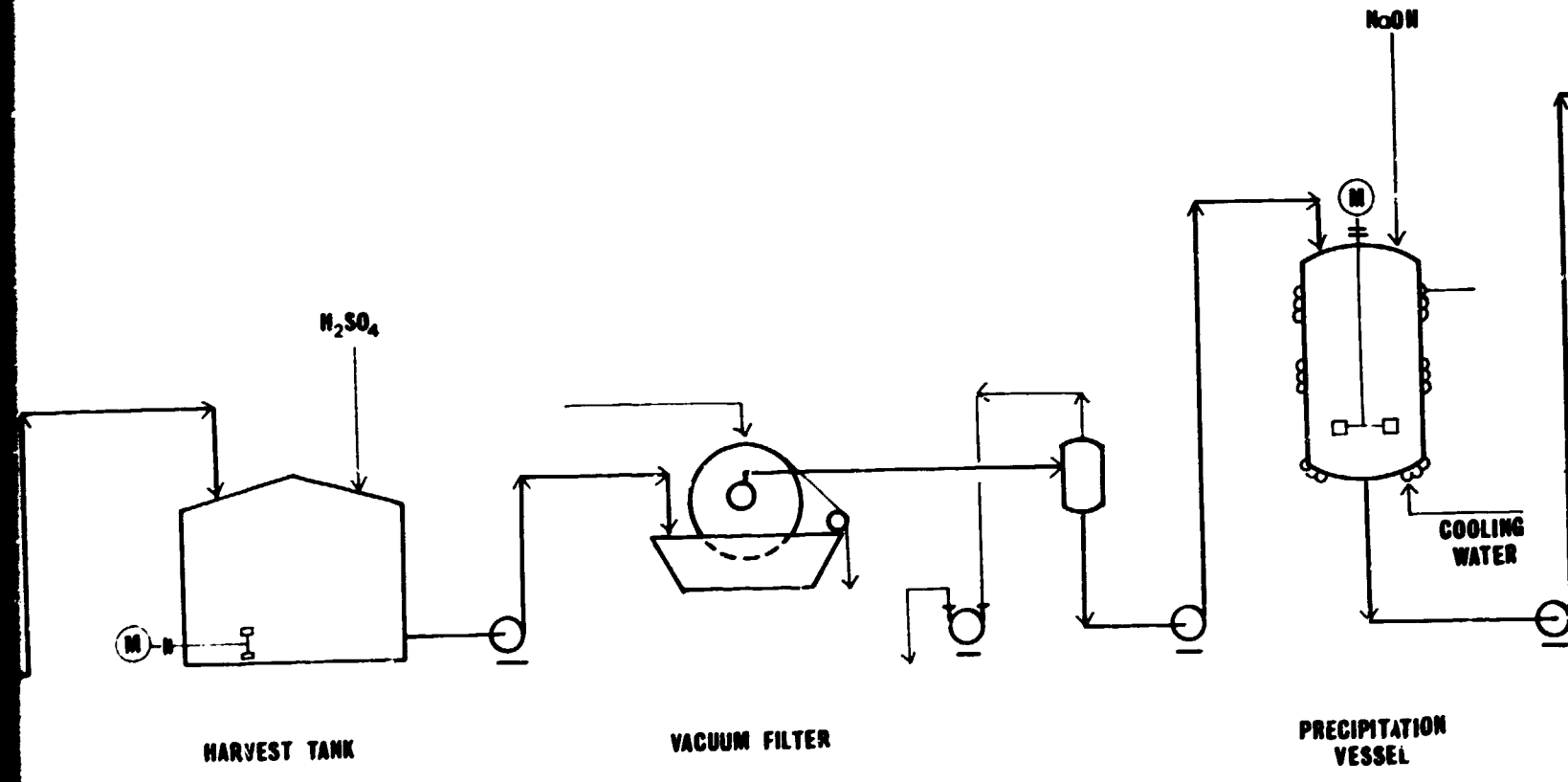


MULTI-PURPOSE PLANT MANILA - AUGUST 1968	ERYTHROMYCIN BASE PROCESS FLOW DIAGRAM

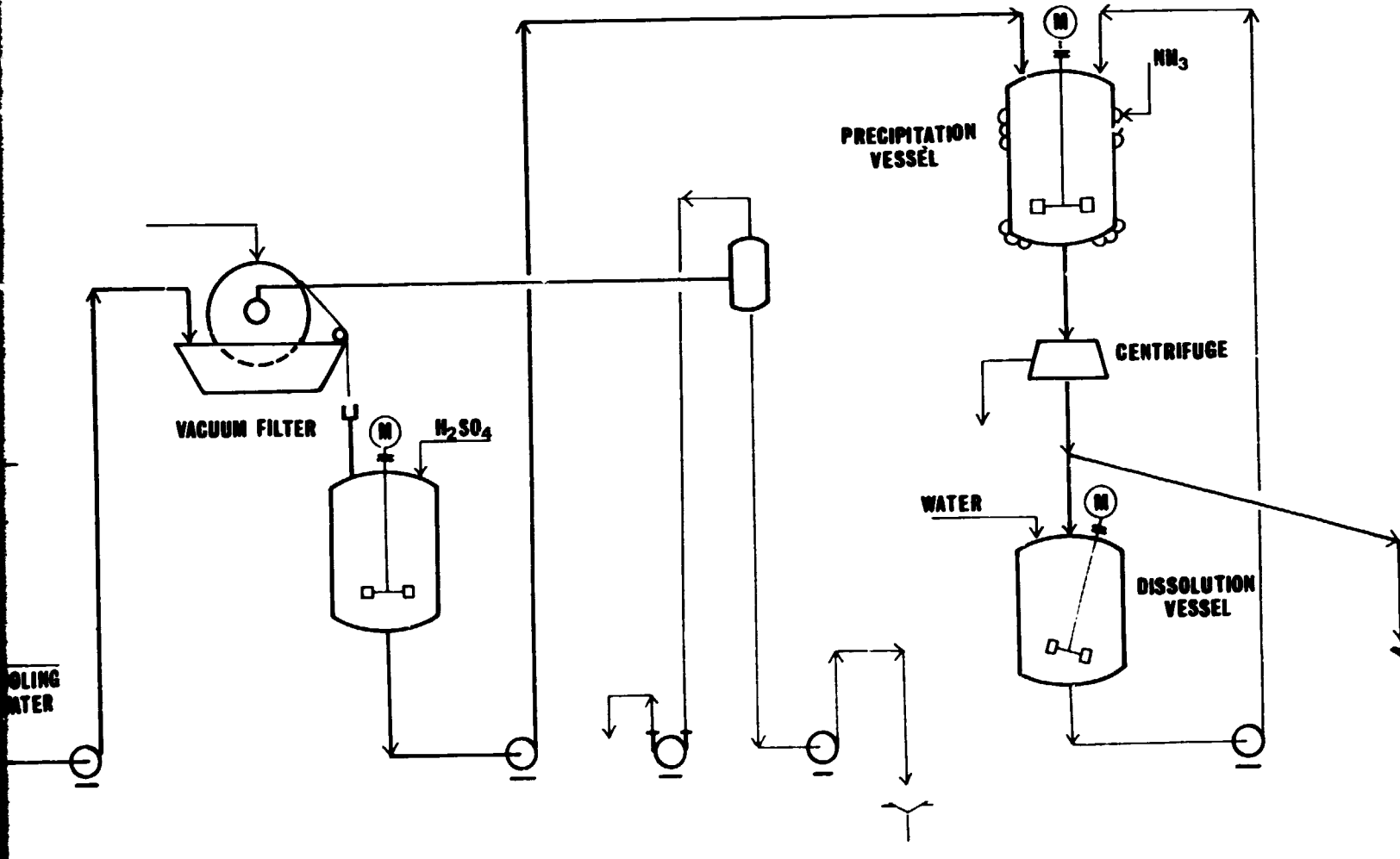
SECTION 4


INOCULUM
STERILIZATION FILTER
SEED
COOLING WATER
COMPRESSED AIR
STERILIZATION FILTER
COMPRESSED AIR
FERMENTER
COOLING WATER
M

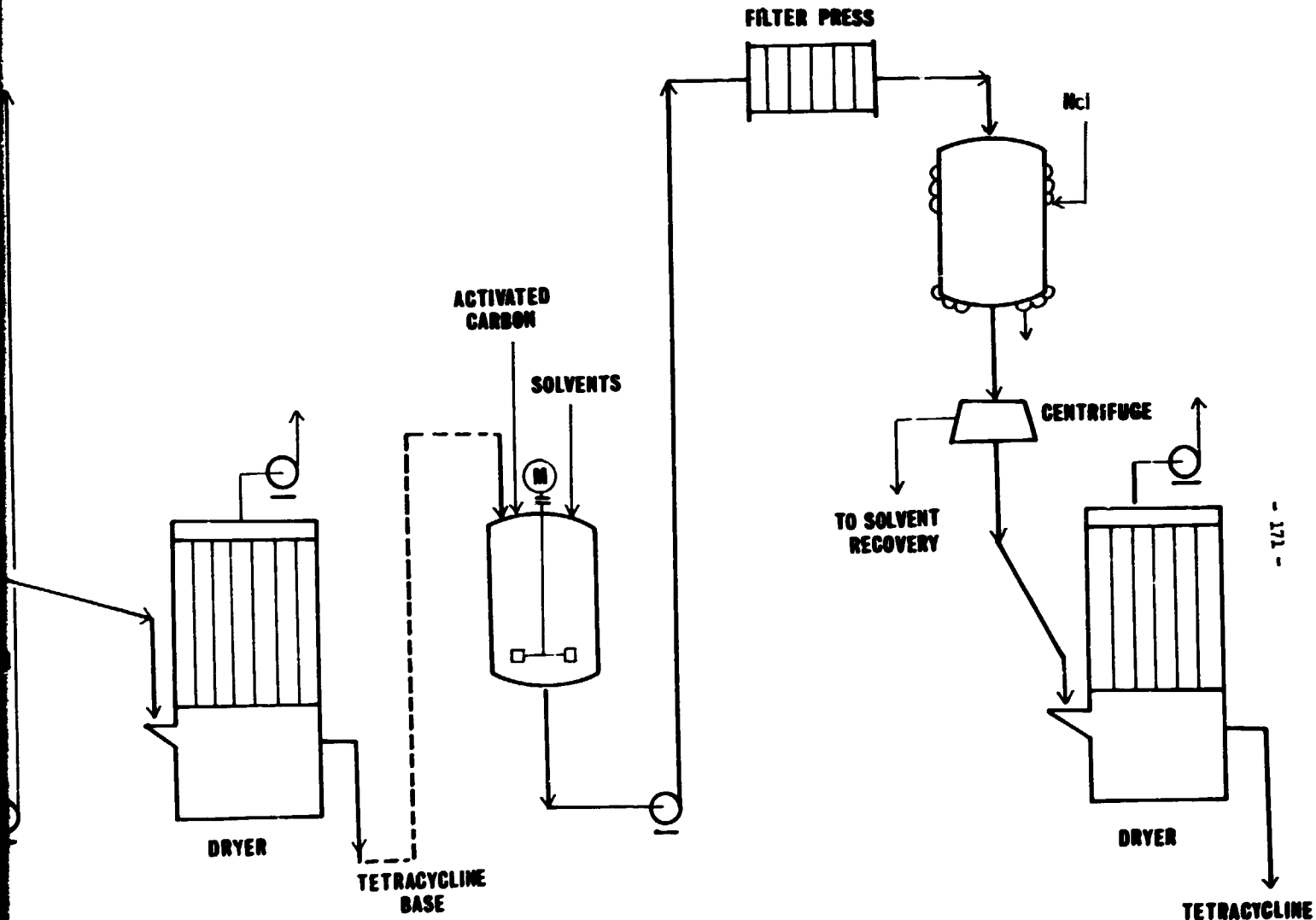
SECTION 1


NaOH
M
H_2SO_4
M
COOLING WATER
HARVEST TANK
VACUUM FILTER
PRECIPITATION VESSEL

SECTION .2


M
NH_3
PRECIPITATION VESSEL
CENTRIFUGE
VACUUM FILTER
M
H_2SO_4
WATER
M
DISSOLUTION VESSEL

SECTION 3



MULTI-PURPOSE PLANT MANILA-AUGUST 1988	TETRACYCLINE AND OXYTETRACYCLINE PROCESS FLOW DIAGRAM

SECTION 4