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27-28 October 1988

VALIDATION OF TECHNICAL ASPECTS OF THE INDUSTRIAL PROFILES AND RECOMMENDATIONS OF PHILIPPINE PHARMACEUTICAL INDUSTRY DEVELOPMENT STUDY*

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* This document has not been edited.

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BRIEF ON THE PHILIPPINE PHARMACEUTICAL INDUSTRY DEVELOPMENT STUDY

1. Background

The Philippine pharmaceutical industry can be characterized as essentially a formulating and a packaging industry. Except for ampicillin, amoxycillin and cloxacillin, all the raw material requirements for pharmaceutical production are imported.

In order to have quality pharmaceutical products more affordable and accessible, a national drug policy (NDP) was enunciated. One of the pillars of the NDP is to achieve relative self-reliance in the manufacture of strategic pharmaceutical products. The objective is to develop the capability to manufacture the pharmaceutical chemicals (i.e. intermediates and basic) so that the Philippines is not totally reliant on foreign sources and avoid the detrimental effects and vagaries of such dependence.

In this regard, the Philippine Government tapped the financial assistance of UNDP and the technical expertise of UNIDO to undertake a study that would identify areas where possible upstream integration of existing production capabilities can be done.

2. Status of the Study

The study utilized the expertise of both international and national experts whose individual reports have all been submitted to date.

To ensure that the premises of the technical recommendations of the international experts are valid, an independent group of experts was convened in Vienna on 27-28 October 1988. As a result of the meeting, there is now more confidence in the technical recommendations of the study and further socio-economic analyses can be undertaken. It is estimated that the final draft of the report can be submitted by UNIDO to the Philippine Government by the end of January 1989.

At this stage of the study, there has emerged a consensus that the main thrust of the country's efforts in the field of pharmaceutical manufacture should be initially focused towards the development of antibiotics, with particular attention towards optimizing the use of indigenous available raw materials and energy sources. To this end, specific projects have been identified and initial market, technical and socio-economic evaluation is being done. These projects include:

a) multi-purpose fermentation pilot-plant for antibiotics
b) penicillin and 6-APA plant
c) plant for semi-synthesis of ampicillin, amoxycillin, cloxacillin and cephalexin
d) erythromycin derivatives and rifampicin production plant
e) multi-purpose pilot-plant for chemical synthesis
f) production of sera and vaccines

3. Indicated Follow-Up Projects

While the final report of the study is being prepared, the Vienna meeting of the technical experts has resulted in a consensus that the following projects may already be pursued, subject to Philippine Government approval:

a) establishment of a multipurpose fermentation pilot-plant on the premises of Biotech at Los Baños.
   Building on the existing facilities at Biotech, the additional investment would be about US$ 1 million. This pilot-plant would immediately test the suitability of local raw materials in antibiotics production and provide training opportunities to local people.

b) Pre-feasibility studies in the following areas:
   (i) Establishment of an industrial scale fermentation plant for Penicillin, including enzymatic conversion of Penicillin G into 6-APA . This industrial plant must have its own pilot-plant for process development.

(ii) In terms of backward integration, Chemfields can itself consider manufacturing the Penicillin G or importing the Penicillin G and converting it to 6-APA. For forward integration, Chemfields can consider going into formulation of final dosage forms.
The undertaking of this feasibility study is dependent on Chemfields' decision, it being recognized that Chemfields is a private entity.

iii) Establishment of an Erythromycin derivatives and Rifampicin synthetic production plant at the site of Chemfields.

iv) Establishment of a multipurpose pilot-plant for chemical synthesis with particular reference to:
- the product mix covering the widest possible range of therapeutic groups;
- the economic viability of the operation taking into account that synthesis of pharmaceutical chemicals is not an acceptable proposition if it does not have forward integration from active ingredient production all the way to formulation and packaging of final dosage forms. This forward integration may utilize existing access production capacity;
- the optimal use and handling of solvents.

v) Cultivation and processing of Cinchona and its utilization in the manufacture of Quinine and its derivatives. Other medicinal plants to be indicated by the Philippines Government may also be included in this study.

The above proposed pre-feasibility studies are intended to provide better grounds for potential investors to evaluate the projects. However, it is to be emphasized that interested investors need not wait for the results of such studies but that they could on their own conduct their own feasibility studies if they so decide.

c) Upgrading of production facilities of the Alabang Vaccine Plant. In this area, the following activities need to be addressed or looked into:

(i) Upgrading of the Quality Control Laboratory for biologicals at the Biological Production Services, Alabang

(ii) Obtaining the views of UNIDO "Advisory Panel on Preventive Medicine" on the "Intercare Study on the Alabang Vaccine Complex" in order to validate the technical premises of said study.

SUMMARY OF DISCUSSIONS

While reviewing the first drafts of the technical reports of the international experts assigned to the project DP/PHI/87/019 entitled "Philippines Pharmaceutical Industry Development Study" in Manila from 3 to 6 October 1988, it was agreed that an ad hoc panel meeting of independent international experts validate the recommendations of this study. The ad hoc panel meeting held in Vienna on 27-28 October 1988 discussed the following industrial profiles :

1. Multipurpose fermentation pilot-plant for antibiotics
2. Penicillin and 6-Amino-Penicillanic Acid production plant
3. Semi-synthesis of Ampicillin, Amoxycillin, Cloxacillin and Cephalexin (expansion of existing facilities)
4. Tetracycline and Oxytetracycline Hydrochlorides production plant
5. Erythromycin derivatives and Rifampicin production plant
6. Multipurpose fermentation plant for the manufacture of Erythromycin, Tetracyclines and Rifamycin
7. Multipurpose pilot-plant for chemical synthesis

In addition to the industrial profiles, a document entitled "Manufacture of antibiotics in the Philippines, General considerations" was made available as background material. A study on vaccine production was discussed as well. The list of participants (members of the panel, representatives of the Philippines Government, international experts of the project and UNIDO Secretariat) is given in Annex I.

After opening of the meeting, the Head of the Philippines Delegation emphasized the importance of the Pharmaceutical Industry Development Study as a contribution to one of the 4 pillars of the National Drug Policy. Recognizing that no country could be totally self-reliant in the manufacture of pharmaceuticals,the main criteria of the projects are reasonable economic viability and their impact on the socio-economic and public health status of the country. He also emphasized that the

Philippines delegation members were attending as individual experts. Hence, they are not in a position to make any commitments, the recommendations of the study being subject to the Philippines Government approval, once the final report of UNIDO is submitted.

The summary presentation and discussion on the study findings on each subsector of the pharmaceutical industry covered by the Philippines Pharmaceutical Industry Development Study followed the industrial profiles.

Industrial profile No. 1: Multi-purpose fermentation pilot-plant for antibiotics

The summary presentation was followed by an in-depth discussion on the utilization of indigenous raw materials, the role of pilot-plants, the importance of fermentation strains and technological know-how, the manpower development, the pre-feasibility studies and the modalities of implementation of the indicated follow-up projects.

The meeting reached a concensus on the establishment of a multi-purpose fermentation pilot-plant on the premises of Biotech at Los Baños to be carried out. The arguments in favour of this recommendation were the on-going research programmes on fermentation and the readily available facilities. If the pilot-plant was installed at Biotech, the total investment costs could be reduced by 40-50%. On-hand experience with the multi-purpose fermentation pilot-plant could also provide stronger indications of the techno-economic feasibility for pursuing the establishment of an industrial-scale fermentation plant.

The main activities of the multi-purpose fermentation pilot-plant for antibiotics would be:

- Comparative testing of indigenous raw materials, such as raw sugar and molasses;
- Training;

- Development-oriented work, such as testing, maintaining and improving of Penicillin fermentation strains. This type of work could be started with a strain of 30,000-35,000 U/ml yield.

It was agreed that the main criteria for the locally available raw materials were :

- quality,
- quantity,
- continuity of supply,
- economic advantage,
- alternative sources.

It was agreed that a pre-feasibility study on the Pencillin and 6-Amino-Penicillanic Acid production plant as discussed under Industrial profile No. 2 should be carried out in parallel with the establishment of the multi-purpose fermentation pilot plant. Furthermore this pilot-plant would always remain as a research and development tool for the Government to provide preliminary data in case of developing any other fermentation project in the future.

In the meeting the necessity of the establishment of a second fermentation pilot-plant as an integral part of the proposed Penicillin and 6-Amino-Penicillanic Acid production plant was also discussed. It should be noted that the main activities and the location of these pilot-plants would be different.

The summary of technical discussions on the multi-purpose fermentation pilot-plant for antibiotics held in a separate session of the meeting is given in Annex II.

Industrial profile No. 2: Penicillin and 6-Amino-Penicillanic Acid (6-APA) production plant

The establishment of a Penicillin and 6-Amino-Penicillanic Acid production plant seems to be an economically viable project, based on

the assumptions that indigenous raw materials would be used as source of energy and that of the carbohydrates in the culture media. However, with respect to the use of indigenous raw materials as ingredients of the culture medium, particularly as far as molasses were concerned, the opinion of the panel members differed. While raw sugar which is abundant in the Philippines is being utilized in several countries as adequate carbohydrate source, molasses may pose difficulty due to variability in quality.

It was agreed, however, that the experience gained with the multi-purpose fermentation pilot-plant at Biotech, Los Baños, particularly the results of the comparative testing of molasses and those of the pre-feasibility study on the Penicillin and 6-Amino-Penicillanic Acid production plant with the options of utilizing raw sugar and molasses would provide better grounds for the Government to present the project to prospective investors. In addition to the above-mentioned 2 options several other alternatives should be considered in the suggested pre-feasibility study. According to the Philippines Pharmaceutical Industry Development Study 70% and 30% of the Penicillin G would be used for biological transformation into 6-APA and for formulation into final dosage forms of injectable Penicillins, respectively. The study concluded, that 6-APA production by enzymatic transformation would not be viable from imported Penicillin G, however further down-stream processing and other formulation were not reviewed. Several factors being influential on the economic viability of the project and therefore be included the pre-feasibility study were also discussed as follows:

- utilization of indigenous energy source such as bagasse;
- site of the fermentation plant and logistics required for the operation;
- functions and size of the pilot plant to be set up on the premises of the fermentation plant;
- utilization of locally produced Penicillin amidase enzyme for biological transformation of Penicillin G into 6-APA.

To create a healthy environment for private investment in the pharmaceutical industry, the Government should consider different incentive measures. An expert expressed the view that the major incentives must be adequate patent protection, free and fair competition in the market place and absence of initiatives to nationalize the industry or reduce foreign equity in pharmaceutical companies.

The meeting noted that all recommendations in the Industrial profiles No. 3 and 5 pertaining to the expansion of existing facilities, or the installation of new ones at Chemfields, were based on technical and economic considerations only, the majority Government equity and the shareholding of United Laboratories in Chemfields being purely incidental. As a conclusion all pre-feasibility studies indicated as follow-up projects may consider alternative options depending on Chemfields' decision recognizing that Chemfields is a private entity.

Industrial profile No. 3: Semi-synthesis of Ampicillin, Amoxycillin, Cloxacillin and Cephalexin (Expansion of existing facilities)

As the result of a lengthy discussion, the expansion of existing facilities at Chemfields was suggested by the international consultants. The meeting, however, agreed that if a pre-feasibility study decided to be carried out by Chemfields, both up-stream and down-stream integration should be considered as options.

For up-stream integration the purchase of locally-produced or imported Penicillin G as starting raw material for biological transformation into 6-APA, while in terms of down-stream integration the formulation of final dosage forms of semi-synthetic Penicillins could be considered as options and the analysis of production costs could also be carried out.

Industrial Profile No. 4: Tetracycline and Oxytetracycline Hydrochlorides production plant

The project concept for a Tetracycline and Oxytetracycline Hydrochlorides production plant, in line with the recommendation of the Philippines Pharmaceutical Industry Development Plan study, was withdrawn, hence the multi-purpose fermentation pilot-plant for the manufacture of Erythromycin,Tetracyclines and Rifamycin (Industrial profile No. 6), not being an economically viable proposition.

Industrial Profile No. 5: Erythromycin derivatives and Rifampicin production plant

Based on the Philippines Pharmaceutical Industry Development Study the establishment of an Erythromycin derivatives and Rifampicin production plant on the premises of Chemfields seemed to be an economically viable project, therefore the ad-hoc panel of experts agreed that it would be an area what Chemfields could further explore. It was also agreed that even if the consumption of Rifampicin decreased within a period of 5-8 years, the enlarged capacity of Chemfields could be utilized for other existing or new products.

Industrial Profile No. 6: Multi-purpose fermentation pilot-plant for the manufacture of Erythromycin, Tetracyclines and Rifamycin

The meeting agreed that due to the small size of the market, the proposal for a multi-purpose fermentation plant for the manufacture of Erythromycin, Tetracycline, Oxytetracycline and Rifamycin was not economically viable and therefore, the project concept was withdrawn.

Industrial Profile No. 7: Multipurpose pilot-plant for chemical synthesis

The meeting discussed in-depth the project concept of the establishment of a multi-purpose pilot-plant for chemical synthesis and it came to the conclusion that it would not be an acceptable proposition unless it was extended to forward integration for formulation of final dosage forms. The meeting also agreed that prior to a pre-feasibility study to be carried out the main features of the pilot-plant should be determined. In the discussions the following options were mentioned:

- An industrial project designed primarily to fit existing and planned formulations of dosage forms. While it was recognized that an excess formulation and packaging capacity of about 50% existed in the Philippines at present, it was deemed appropriate to invite the industry to consider the purchase and utilization of locally-produced pharmaceutical chemicals;
- A development project designed to utilize indigenous raw materials only;
- A mixed project incorporating both alternatives. In this respect it was mentioned that one could also envisage the possibility of importing some intermediates and performing one or more steps of the synthesis, or of utilizing some locally available raw materials for that purpose.

The experts reached a consensus that a pre-feasibility study on the establishment of a multi-purpose pilot-plant for chemical synthesis should address at least the following:

- The identification of a product mix covering the widest possible range of therapeutic groups;
- The economic viability of the operation taking into account that due to the small size of the market the manufacture of pharmaceutical chemicals by chemical synthesis is not an acceptable proposition unless extending to forward integration for formulation of final dosage forms;

- The optimal use and handling of solvents;
- Environmental aspects and the Good Manufacturing Practices (GMP).

The ad-hoc Panel agreed that a pre-feasibility study concerning the Cinchona plantation at Mindanao for the cultivation and processing of Cinchona and its utilization for manufacture of Quinine and its derivatives should separately be undertaken. Other medicinal plants to be indicated by the Philippines Government may also be included in this study.

The meeting also discussed the schedule and modalities of the preparation of the above proposed pre-feasibility studies and hence it was agreed that they would provide better grounds for potential investors to evaluate the projects, the interested investors need not wait for the results of these studies but they could on their own conduct feasibility studies if they so decide.

Vaccine production

Due to the complexity of the problem as well as to the recommendations of prior studies in this field, the following actions were suggested by the panel:

- To upgrade the Quality Control Laboratory for biologicals at the Biological Production Services, Alabang irrespectively from the decision which might be taken with regard to the upgrading of the vaccine production facilities.
- To obtain the views of the UNIDO "Advisory Panel on Preventive Medicine" on the "Intercare Study on the Alabang Vaccine Complex" in order to validate the technical premises of this study, should the Philippines Government decide so.

RECOMMENDATIONS

At the end of the ad-hoc Panel meeting the following recommendations were unanimously made by the technical experts:

Industrial profile No. 1: Multipurpose fermentation pilot-plant for antibiotics

Immediate action was recommended to establish the pilot-plant at the premises of Biotech. It was noted that a Penicillin fermentation strain of 30,000-35,000 U/ml would be an adequate initial choice for the development-oriented works in the pilot-plant.

Industrial profile No. 2: Penicillin and 6-Amino-Penicillanic Acid Production plant

A pre-feasibility study was recommended to be carried out on the establishment of an industrial scale fermentation plant for Penicillin and 6-APA including a pilot-plant. It was noted however that the prospective investors could directly undertake their own feasibility study.

Industrial profile No. 3: Semi-synthesis of Ampicillin, Amoxycillin, Cloxacillin and Cephalexin

A pre-feasibility study on the expansion of the existing facilities at Chemfields was recommended.

It was also recommended that if imported materials were used the starting raw material should be 6-APA and not Penicillin G hence using the latter the operation would not be economically viable unless a forward integration for formulation of final dosage forms of semi-synthetic Penicillins was taken into account.

Industrial Profile No. 4: Tetracycline and Oxytetracycline Hydrochlorides production plant

Withdrawn.

Industrial Profile No. 5: Erythromycin derivatives and Rifampicin production plant

A new production plant at Chemfields was recommended to be established. In order to implement this programme, a feasibility study as a first step was recommended to be carried out.

Industrial Profile No. 6: Multipurpose fermentation pilot plant for the manufacture of Erythromycin, Tetracyclines and Rifamycin

Withdrawn.

Industrial Profile No. 7: Multipurpose pilot-plant for chemical synthesis

A pre-feasibility study on the establishment of a multipurpose pilot-plant for chemical synthesis of pharmaceutical chemicals was recommended with the following considerations:

- The economic viability of the operation should be analysed for the synthesis of pharmaceutical chemicals only and inclusive the formulation and packaging into final dosage forms;
- The produc mix covering the widest possible range of therapeutic groups should be identified;
- The availability of domestic raw materials should be assessed;
- The optimal use and handling of solvents should be examined.

A separate prefeasibility study was recommended to be carried out for the cultivation and processing of Cinchona and its utilization as raw material for synthesis of Quinine derivatives at Mindanao.

Vaccine production

The upgrading of the quality control facility at the Biological Production Services, Alabang strictly meeting the requirements of WHO, was recommended. For the further expansion of the biological industry the Government may consider to present the "Intercare study on the Alabang Vaccine Complex", to the UNIDO Advisory Panel on Preventive Medicine in order to validate the technical premises of this study.

INDUSTRIAL PROFILE No. 1

MULTIPURPOSE FERMENTATION PILOT-PLANT FOR ANTIBIOTICS

1 General considerations

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 developing the domestic drug industry, including fermentation-based production facilities.

1.1 Objectives

The main objective of such a pilot plant should be:

1.1.1 To investigate the locally available raw materials and their quality and suitability for antibiotics fermentation, the main condition for the implementation of large scale production plants. Mostly raw materials from agricultural origin are investigated.

1.1.2 To train technical personnel with special skills and expertise in the production of antibiotics. In fact, a Manpower Development Program would be the first step 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 utilized in the development of a large scale fermentation plant.

1.1.3 Such a fermentation pilot-plant should be development oriented and not research oriented. It would not be realistic, at least in a first phase, to undertake microorganisms strain

improvement programs, or reproducing already achieved results,that would require long periods of time and the utilization of a large team of skilled microbiologists, who are not available in the Philippines at present (both from the point of view of technical expertise and of numbers). In other words, it would not be worthwhile to compete with R & D centers of large International companies staffed 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 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. For obvious reasons, it is not advisable to focus on the most advanced antibiotic fermentations. The development of Penicillin should be one of the main objectives of the pilot-plant. Non beta-lactam antibiotics that should be investigated are:

1.1.3.1 - Erythromycins
1.1.3.2 - Rifampicin
1.1.3.3 - 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 latter.

1.2 Local Institutions

The local institutions engaged at present in fermentation related activities are:

1.2.1 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 as well as on ethanol and citric acid fermentation.

1.2.2 Biotech U.P., Los Baños. In this center, directed by Dr. William Padolina, research conducted on ethanol fermentation, nitrogen fixation technologies and biofuels, as well as on vaccines and antibiotics is taking place.

1.2.3 NSRI (National Science Research Institute), U.P. The institute supports projects in biology, chemistry, physics. earth science and mathematics.

1.2.4 USTRC (University of Santo Tomas Research Center),U.P. Fermentation studies on antifungals and antibiotics have been undertaken.

1.2.5 College of Science, U.P. A Molecular Biology and Biotechnology Program, coordinated by Dr. Apolinario Nazarea, has started recently.

Due to the nature of the research activities, the expertise of the staff and the presence of modern equipment, especially at Biotech in Los Baños, only the first two intitutions could be taken into consideration for the coordination of a project having as objective the development of a fermentation pilot-plant for antibiotics. However, present manpower resources of ITDI Microbioloby and Genetics Division(1), as well as that of Biotech seem to be severely lacking both in quantity and quality, to be able to handle the above mentioned project and both of them should increase significantly the number of technical experts to fulfil the objectives of the pilot-plant.

' solution to the problem of limited human resources could envisaged in the case, that an inter-departmental national project could be launched involving the cooperation of these two intitutions, allowing an optimization in the utilization of human resources, as well as of existing facilities. (It is 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 valid outputs.

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

A proposal concerning a fermentation pilot-plant for antibiotics 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 should be reconsidered on the basis of the abovementioned general considerations.

2. Investment costs

The total investment costs, including equipment materials, instrumentation and installation, but excluding civil works, have been estimated at about US$ 1.5-2.0 million (1988).

However, if the pilot-plant is installed as an extension of the the existing facilities at Biotech, Los Baños, the abovementioned costs could be reduced by 40%-50%, e.g. to approximately US $ 900,000-1,200,000.

3. Manpower requirements

The total manpower requirements of the microbiology laboratory and the pilot-plant itself would be 20 persons, as follows:

3.1 Microbiology laboratory personnel

3.1.1	Team leader	1
3.1.2	Senior microbiologists	2
3.1.3	Microbiologists	2
3.1.4	Workers	3
	T o t a l	8

3.2 Pilot-plant personnel

3.2.1	Team leader	1
3.2.2	Senior microbiologists	2
3.2.3	Microbiologists or Chemists	3
3.2.4	Workers	5
3.2.5	Chemical Engineer	1
	T o t a l	12

3.3 Qualifications

3.3.1 Microbiology laboratory personnel

3.3.1.1 Team leader. Preferably with 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.

3.3.1.2 Senior microbiologist. A Master's 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.

3.3.1.1 Microbiologist - A Bachelor's 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.

3.3.2Pilot-plant personnel

3.3.2.1 Team leader. A Master's degree in Biology or Chemistry and some experience in running of antibiotics fermentation processes and in scaling-up techniques is required. 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.

3.3.2.2 Senior Microbiologist. A Master's degree in Biology should be required eventhough chemical engineers with some experience in microbiology and biochemical engineering could be accepted. An experience in running of fermentation processes should be required. A training period in a pilot-plant would be desirable.

3.3.2.3 Microbiologists or Chemists. A Bachelor's degree is required

3.3.2.4 Chemical Engineer. A Master's degree is acceptable, provided that the candidate has some basic training in biochemical engineering and some knowledge of fermentation equipment and maintenance problems, his responsibilities being the technical maintenance of the plant.

4. Pilot-plant location

The pilot-plant should be located in the premises of Biotech at Los-Baños, as an expansion of the existing facilities, as follows:

4.1 Erecting a second floor at about a 4.0-meter level in the existing building with a total height of 8.0 meters. The microbiology laboratory should be installed on this floor.

4.2 Erecting a new local of about 300/400 m^2, adjacent to the existing building. The new equipment for antibiotics extraction should be installed there.

4.3 Installing, in the existing building, some new fermentors in addition to the existing ones.

4.4 Improving the capacity of some of the utilities generation systems, in particular the one of chilled water.

INDUSTRIAL PROFILE No. 2

PENICILLIN AND 6-AMINO-PENICILLANIC ACID PRODUCTION PLANT

Investment	:	US $ 30,000,000
Annual Output	:	295 tons
Sales Estimates	:	US $ 11,630,000
Manufacturing Costs:		US $ 6,600,000
Manpower	:	190

1. Plant description

The plant is subdivided into the following sections

1.1 Penicillin fermentation and extraction
1.2 Solvent recovery
1.3 6-APA production (including enzyme fermentation)
1.4 Injectable and feed grade Penicillins production
1.5 Utilities generation units
1.6 Laboratories
1.7 Waste treatment
1.8 Auxilliary services (workshops, administration, canteen, etc.)

2 Annual manufacturing output

The annual output of the plant could be summarized as follows:

		Tons
2.1	Penicillin G	250
2.2	Penicillin V	45
2.3	6-APA	110
2.4	Injectable Penicillins G	20
2.5	Feedgrade Penicillins G	6

The manufacturing capacity calculation was based on a fermentation yield of 100 B.U./m^3/month corresponding to 40,000 Units/ml.[1/]

The 6-APA, the Injectable Penicillin G and the Feedgrade Penicillin G, will be produced out of the 250 Tons Penicillin G (see Flowchart).

The annual capacity was calculated on the basis of a 24 hours operation during 330 days per year.

The importance of Penicillin as a strategic product has been illustrated on Table .

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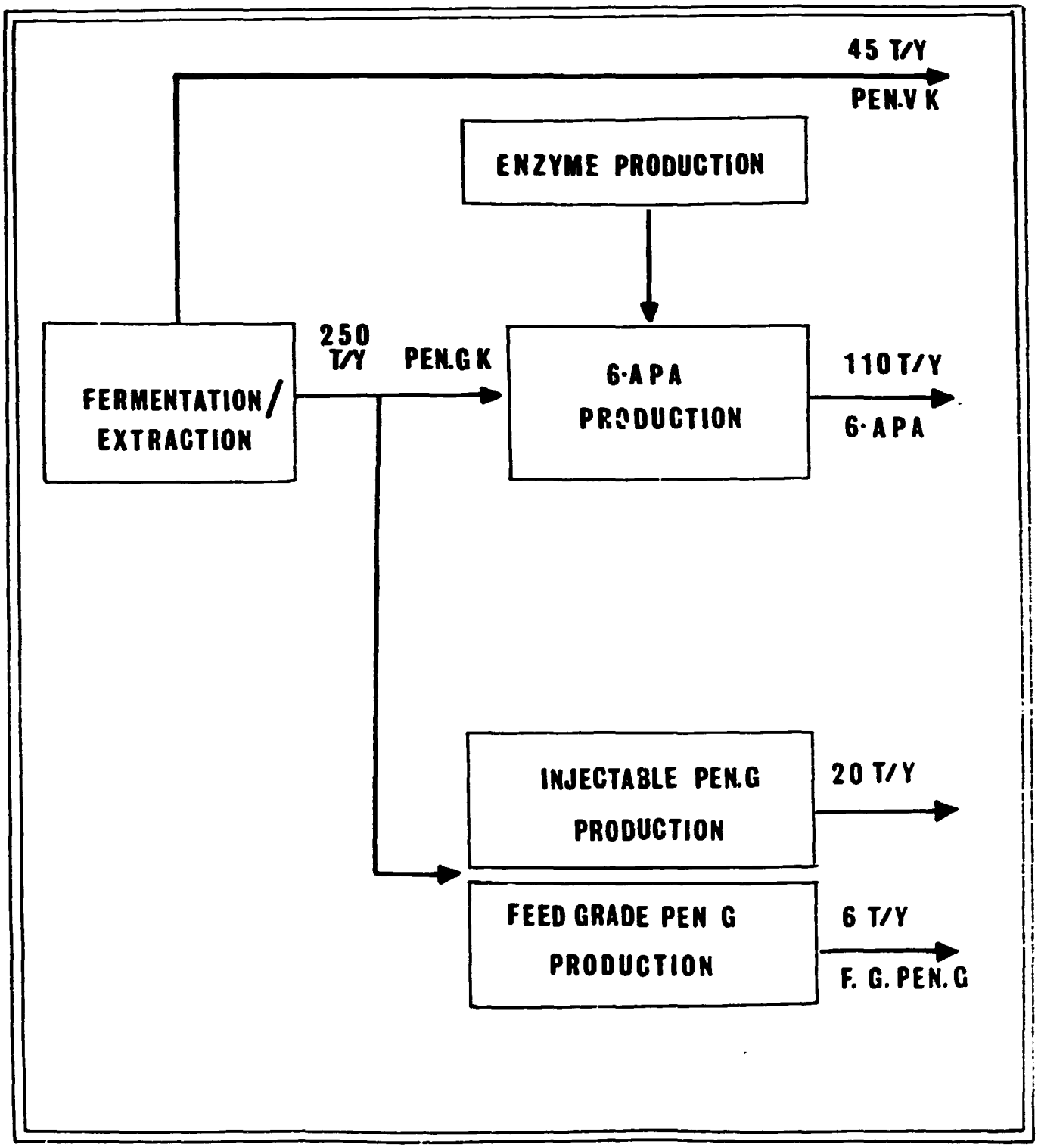
1) One B.U. is equivalent to 1,595 kg of activity of Pen G Potassium

PENICILLIN PLANT



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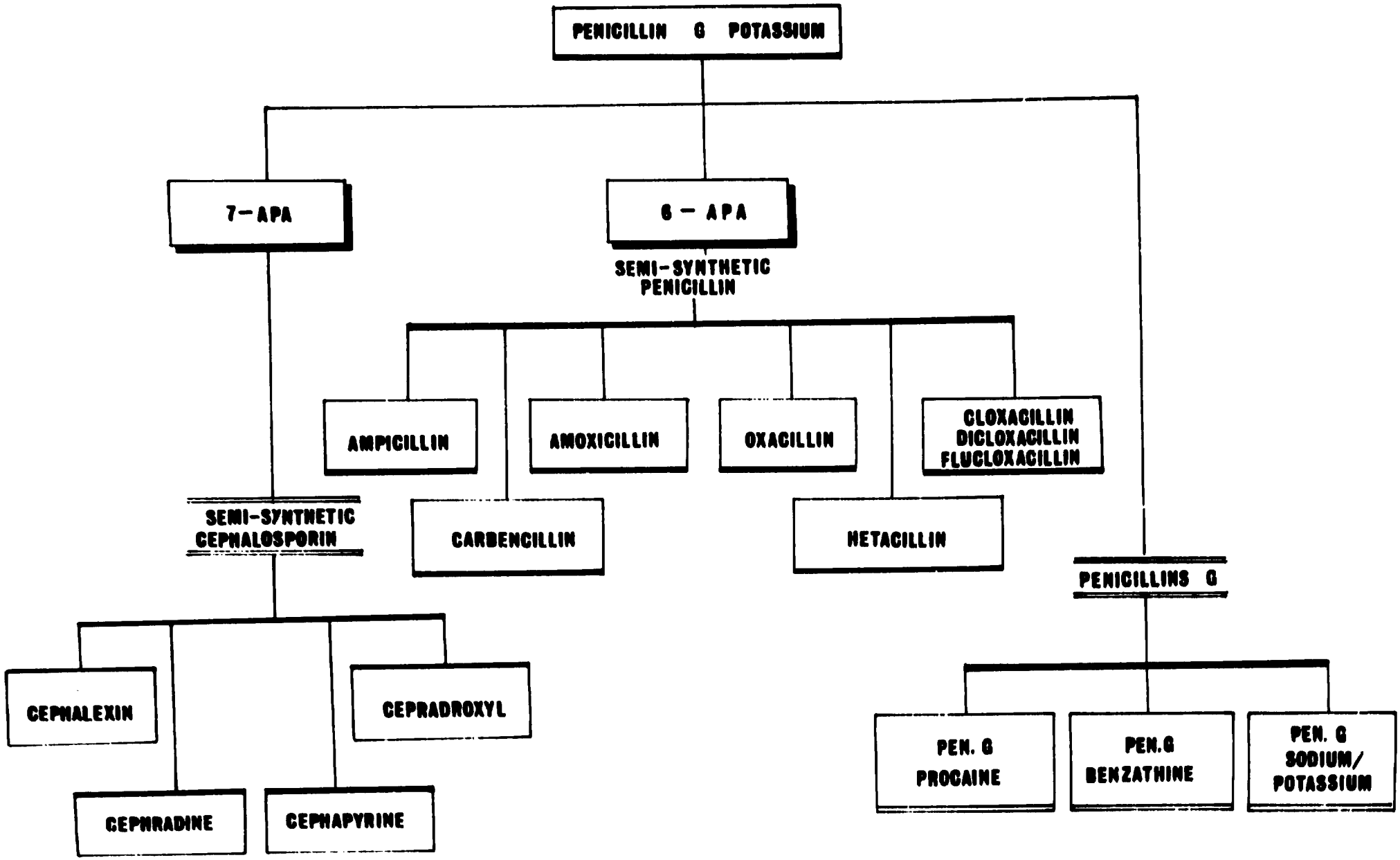

MANILA - AUGUST, 1988

TABLE

3. Investment costs

The total estimated investment costs of the complex would be on the range of US$ 26-30 millions (1988), the latter taken as a basis for calculation. The break-down of this cost is 50% for production units, 33% for utilities units and 17% for civil works. The estimated investment costs include:

3.1 Machinery and equipment
3.2 Bulk materials (piping, instrumentation and electric systems
3.3 Spare parts
3.4 Transportation
3.5 Erection
3.6 Civil works (including land preparation)
3.7 Engineering
3.8 Know-how (Penicillin and 6-APA) including strains and technology
3.9 Personnel Training
3.10 Construction and start-up assistance

4. Annual sales estimates (1988 base)

The annual sales were estimated as follows:

			US $
4.1	6-APA	(110 tons)	7,260,000
4.2	Penicillin V	(45 tons)	2,270,000
4.3	Injectable Penicillin G	(20 tons)	1,800,000
4.4	Feedgrade Penicillin G	(6 tons)	300,000
	Total sales		11,630,000

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.

The abovementioned amounts are based on a projected 1995 consumption on the Philippines only without taking into account possible exports.

5. Manufacturing costs

5.1 The total manufacturing costs could be summarized as follows:

		US $
5.1.1	Raw materials	4,000,000
5.1.2	Manpower	800,000
5.1.3	Energy and utilities	600,000
5.1.4	Other expenses (1)	1,200,000
5.1.5	Total	6,600,000

Provided that the same yields could be reached, the following figures could serve as a very rough comparison of Penicillin manufacturing costs in Europe, utilizing traditional raw materials and energy and in the Philippines locally available raw materials and bagasse as energy source:

	US $ per B.U.	
	EUROPE	PHILIPPINES
Raw materials		
Carbohydrates	3.5 (raw sugar)	1-2 (molasses)
all the rest	4.5	5 - 5.5
Energy/Utilities	6 - 6.5	1 - 1.5
Manpower	2	1 - 1.5
Other expenses	2 - 3	2
Total	17.50 - 19.50(2)	10.00 - 12.50

(1) All other expenses not directly connected to manufacturing

(2) This manufacturing cost is relevant to a Penicillin broth potency in the range of 40,000 U/ml.

6. Raw materials

6.1 Penicillin G and V

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

6.1.1 Fermentation

- 6.1.1.1 - Corn-steep liquor
- 6.1.1.2 - Glucose solution that can be substituted either by raw cane sugar, or by molasses or cane juice.
- 6.1.1.3 - Lard oil or coconut oil
- 6.1.1.4 - Potassium Phenylacetate (for Pen G) or Sodium Phenoxy Acetate (For Pen V). These products act as precursors of the Penicillin biosynthesis.
- 6.1.1.5 - Calcium Carbonate, Ammonium Sulphate, Calcium Hydroxide
- 6.1.1.6 - Anhydrous Ammonia and Sodium Hydroxide

6.1.2 Extraction:

- 6.1.2.1 - Sulfuric Acid
- 6.1.2.2 - Potassium Bicarbonate
- 6.1.2.3- Solvents such as Butylacetate (could be substituted by Amylacetate or Methylisobutylketone) and Butanol
- 6.1.2.4 - Demulsifier and dispersing agents
- 6.1.2.5 - Formaldehyde
- 6.1.2.6 - 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 represents about 45-50 of the total raw materials cost in the Penicillin G production .

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

For Penicillin G K, the glucose solution consumption is ranging from 8 to 10 Kgs per B.U. of Penicillin (1). If molasses are utilized, 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 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).

6.1.3 Cost of domestic carbohydrates

The cost of the domestic carbohydrate sources could be summarized as follows:

6.1.3.1 - Glucose solution : U.S $ 4 to 6 per B.U.

6.1.3.2 - Raw sugar : U.S.$ 2 per B.U.

6.1.3.3 - Molasses(2): U.S. $ 0.9 to 1.1 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 checked with fermentation tests, since its quality could greatly affect the yields.

All the other raw materials should be imported, the most cost effective imported 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 US $5-7 per B.U., including transport costs.

6.1.4 Supply of domestic carbohydrates.

As mentioned before, some of the raw materials and their quantities necessary for Penicillin production are as follows:

6.1.4.1 Corn-steep liquor (from wet millings of corn)
4 Kgs/kg Penicillin produced

6.1.4.2 Glucose solution (70% glucose equivalent)
16kgs/kg Penicillin produced

Around 0.77-088m^3 of corn-steep liquor (CSL) is recovered during the wet milling process (May, 1987). This material (CSL) contains 5% total solids, thus having around 0.04-0.05mt solids/mt corn. On the basis of the assumption that 4 kg CSL of 50% total solids is needed in combination with other ingredients to give one kg of penicillin, the recovered CSL which May (1987) considers has to be further concentrated to 50% solids. One then gets an equivalence of 22 kg penicillin that can be manufactured out of one mt of corn. Since the estimated 1988 penicillin demand is 175 mt/year, the total amount of corn needed to supply enough CSL for fermentation is 7,945.5 mt/year coming from about 7,192 hectares of corn planted land.

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

(2) Sugar cane juice could also be considered, butitis very perishable

As for glucose solution requirements, the local source would be glucose syrup produced from cassava starch. Glucose syrup from Philippine sources contains 360 grams glucose obtained from one kg of tubers. Thus, based on the requirement of 16 kg of glucose solution containing 70% reducing sugars to produce one kg of Penicillin, 29.8 kg of glucose syrup is necessary. This means an annual requirement of 5,215 mt of glucose syrup or 125,000 mt of cassava tubers from 15,822.8
hectares of land.

In 1986, the Philippines produced 3,922,000 mt of shelled corn from a land area of 3,544,700 hectares (Agricultural Policy and Strategy Team, 1987) and 1,726,587 mt of cassava from 218,000 hectares of land (Villamayor, 1987). To produce the local requirement of 175 mt ofpenicillin/year, 0.20% of the total shelled corn, or of the corn land area in 1986 and 7.2% of the total cassava tubers produced, or of the cassava area in the same year have to be directed for penicillin production. This clearly indicates that the Philippines are capable of supplying the corn-steep liquor and glucose solution requirements of the penicillin plant, provided that the supply of corn and cassava products to other end-users is not jeopardized.

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. Under these conditions, the total raw materials cost of 6-APA would be much lower, expected to reach US$1 to 2 per Kg of 6-APA.

The other raw materials are:

6.2.1 Ammonia solution,

6.2.2 Sulfuric Acid,

6.2.3 Caustic Soda

6.2.4 Solvents (Butylacetate or Acetone).

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 are:

6.3.1 - Procaine Hydrochloride (for Pen G Procaine production)

6.3.2 - N-N-dibenzyl-ethylendiamine-diacetate (for Pen G Benzathine)

These products are to be imported.

7. Manpower requirement

7.1 The manpower 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

7.2 The personnel qualifications and skills could be summarized as follows:

Head of Departments - University Degrees in Chemistry Biology or Chemical Engineering

Head of Laboratories - PhD in Microbiology with at least 2 years experience in strains development

Laboratory Technicians- Masters Degree in Microbiology
Bachelor's Degree in Biology or Chemistry with experience on analytical chemistry and the use of modern equipment

7.3 Laboratories(1)

The following laboratories are foreseen for the Penicillin plant:

7.3.1 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:

7.3.1.1 - Master culture preparation and preservation
7.3.1.2 - Inoculum development
7.3.1.3 - Glassware cleaning and media preparation area
7.3.1.4 - In process laboratory

7.3.2 Quality Control Laboratory.

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

7.4 Training

A selected group of supervisors and technicians should be 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.

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(1) In view of the nature of the process and the special importance of the preparation and preservation of strains, this subject has been singled out.

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 foreign Experts. Three experts could be employed as:

7.4.1 Plant and Production Manager

7.4.2 Quality Control Manager

7.4.3 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 and a secondment agreement with foreign companies, participating or not in this venture, could also be considered, the management team, being part of it.

8. Plant location

The plant should be installed adjacent to an existing sugar factory, for securing a cheap source of energy like bagasse, as well as carbohydrates, such as raw sugar, molasses or cane juice, minimizing the high transportation costs.

INDUSTRIAL PROFILE No. 3

SEMI-SYNTHESIS OF AMPICILLIN, AMOXYCILLIN, CLOXACILLIN AND CEPHALEXIN (EXPANSION OF EXISTING FACILITIES)

Investment	:	US $ 5,900,000
Annual Output	:	74 tons
Sales Estimates	:	US $ 7,620,000
Manufacturing Costs	:	US $ 6,461,000
Manpower	:	45

1. Plant description

The plant for the production of semi-synthetic Penicillins is composed of 8 stainless steel reactors ranging from 1 to 5 m^3. capacity, one press and one plate filter, some tanks for mother liquors, two stainless steel centrifuges and two driers. Minor equipment (centrifugal pumps, grinder, sieve etc.,) are also provided. Solvents come from external tanks through metering pumps. The following units will be required:

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

1.2 One refrigeration unit for production of brine at 30 ^{o}C, with 40 tons capacity

1.3 One unit for demineralized water production

1.4 One boiler for steam production

1.5 One cooling tower for cooling water.

2. Annual manufacturing output and plant utilization

2.1 Manufacturing output

The annual plant output will be as follows:

2.1.1	Ampicillin	35 tons
2.1.2	Amoxicillin	30 tons (1)
2.1.3	Cloxacillin	3 tons
2.1.4	Cephalexin	6 tons
	Total	74 tons

An additional capacity of 28 tons for the manufacture of an intermediate (Dane-Salt) in the Amoxicillin Semi-synthesis is also provided.

2.2 Plant utilization

The data concerning the duration of the operation for each product, the number of batches required and the total time of utilization of the plant, are as follows:

Product	Output per batch (kg)	Duration of each batch	Number of batches (hours)	Total working days
2.2.1 Ampicillin Trihydrate	300	36	117	117
2.2.2 Amoxycillin Trihydrate	300	36	100	100
2.2.3 Cloxacillin Sodium Monohydrate	150	36	20	20
2.2.4 Cephalexin Monohydrate	150	36	40	40
2.2.5 Dane salt for Amoxycillin	500	36	56	56

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

When the plant will reach the full production capacity, it will be occupied for the entire year, additional capacity being obtained with an increase of the number of batches by working on three shifts. There will be 284 working days a year since Dane salt will be prepared at the same time with other products using additional equipments.

3. Investment cost

The estimated investment cost could be summarized follows:

		US $
3.1	Plant	2,350,000
3.2	Equipment (transportation included)	
3.3	Erection (piping, mounting, electrical parts,	
3.4	Instrumentation, insulation, painting etc.)	2,350,000
3.5	Engineering 7%	330,000
3.6	Construction assistance 7%	330,000
3.7	Cost of technology (Cephalexin)	165,000
3.8	Training of personnel	100,000
3.9	Laboratory equipment (additional)	120,000
3.10	Buildings	
3.11	Main build'ng	70,000
3.12	Warehouse (air conditioned)	85,000
	T o t a l	5,900,000

The figures do not include the land cost. The investment for the utilities (refrigeration unit, cooling tower, boiler, demineralizer, distillation columns) take into account also the utilities needed for the Erythromycin derivatives and Rifampicin, which will be located in the same factory. Some spare capacity being already available in the Chemfields plant, the capacity to be installed for some utilities will be lower than the total capacity required.

Since satisfactory technologies for Ampicillin, Amoxycillin and Cloxacillin are already available in the country, the cost of the technology includes only Cephalexin.

4. Annual sales estimates

The annual sales estimates could be summarized as follows:

		US $
4.1	Ampicillin	2,940,000
4.2	Amoxycillin	3,060,000
4.3	Cloxacillin	324,000
4.4	Cephalexin	1,296,000
	Total	7,620,000

The above-mentioned figures have been based on prevailing international prices augmented by 20%, deemed to cover freight, insurance, import duties and taxes.

5. Manufacturing costs

The manufacturing costs have been calculated to reflect two possibilities, namely manufacturing with imported 6-Amino-Penicillanic Acid (6-APA) and with a locally produced one.

They are as follows:

		Imported (US $)	Domestic
5.1	Ampicillin	2,765,000	2,450,000
5.2	Amoxycillin	2,520,000	2,220,000
5.3	Cloxacillin	234,000	210,000
5.4	Cephalexin (1)	942,000	942,000
5.5	Total	6,461,000	5,822,000

6. Raw materials

The required raw materials could be summarized as follows:

6.1 Ampicillin Trihydrate

Hereunder is the list of the main raw materials needed for one batch of 300 Kg and the corresponding quantities for one Kg. of Ampicillin trihydrate.

The amounts of solvents in brackets are the quantities used, the other figures being the consumptions, considering a 70% recovery for Dichloromethane and Acetone.

6.1.1	6-APA		194 Kg		0.647 Kg
6.1.2	Phenylglycine chloride hydrochloride		185 Kg		0.62 Kg
6.1.3	Trimethylchlorosylane		94 Kg		0.31 Kg
6.1.4	Dimethylaniline		180 Kg		0.61 Kg
6.1.5	Dichloromethane	(3800 Kg)	1140 Kg	(12.6 Kg)	3.8 Kg
6.1.6	Triethylamine		105 Kg		0.35 Kg
6.1.7	Acetone	(200 Kg)	60 Kg	(0.66kg)	0.2 Kg
6.1.8	Diethylamine		105 Kg		0.35 Kg

6.2 Amoxycillin Trihydrate

The main raw materials needed for one batch of 300 Kg. and the corresponding quantities for one Kg of Amoxycillin trihydrate are indicated hereunder. The amounts of the solvents in brackets are the quantities used, the other figure being the consumptions, considering the following percentage of recovery:

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(1) Cephalexin is produced only from imported 7-ADCA, thus the prices in both columns are the same for comparative purposes.

Dichlorometane	70%	
Methylisobutylketone	85%	
Acetone	80%	

6.2.1	6-APA		193.5	Kg		0.645 Kg
6.2.2	Dane salt,ethyl potassium		282	Kg		0.94 Kg
6.2.3	Ethylchlorocarbonate		108	Kg		0.36 Kg
6.2.4	Acetone	(1050 Kg)	210	Kg	(3.2 Kg)	0.70 Kg
6.2.5	Dichloromethane	(960 Kg)	290	Kg	(3.2 Kg)	0.96 Kg
6.2.6	Methylisobutylketone	(780 Kg)	115	Kg	(2.6 Kg)	0.38 Kg
6.2.7	Triethylamine		99	Kg		0.33 Kg
6.2.8	Concentrated Hydrochloric acid					
6.2.9	Ammonia 28 Be.					

6.3 Dane Salt

Listed hereunder are the main raw materials needed for one batch of 500 Kg and the corresponding quantities for one Kg. of Dane Salt. The amounts of solvents in brackets are the quantities used, the other figures being the consumption taking into consideration an 80% recovery yield.

6.3.1	D(-)p-hydroxyphenylglycine		305 Kg		0.61 Kg	
6.3.2	Ethylacetoacetate		260 Kg		0.52 Kg	
6.3.3	Potassium Hydroxyde		102 Kg		0.204 Kg	
6.3.4	Absolute Ethanol	(2400 Kg)	480 Kg	(4.8 Kg)	0.96 Kg	

6.4 Cloxacillin Sodium Monohydrate

Hereunder are listed the main raw materials needed for one batch of 150 kg and the corresponding quantities for one kg of Cloxacillin Sodium Monohydrate. The amounts of the solvents in brackets are the quantities used,the other figures being the consumptions taking into account a 70% recovery for both solvents.

6.4.1	6-APA		85.5 Kg		0.57 Kg
6.4.2	Methylisobuthylketone	(1830 kg)	400 Kg	(12.2 kg)	2.7 Kg
6.4.3	Acetone	(975 kg)	200 Kg	(6.5 kg)	1.3 Kg
6.4.4	Sodium 2-ethylhexanoate		72 Kg		0.48 Kg
6.4.5	3-(2-chlorophenyl)-5-methyl-isoxazolyl-carboxychloride		17 Kg		0.11 Kg
6.4.6	Sodium hydroxide		108 Kg		0.72 Kg

6.5 **Cephalexin Monohydrate**

The main raw materials needed for one batch of 150 kg of Cephalexin Monohydrate and the corresponding quantitites for one kg are listed hereunder. The amounts of solvents in brackets are the quantitites used, the other figures being the consumption considering a 70% recovery for Dichloromethane and Acetone.

6.5.1	7-ADCA		111 Kg		0.74 Kg
6.5.2	Phenylglycine chloride				
6.5.3	hydrochloride		95 Kg		0.63 Kg
6.5.4	Diethylamine		39 Kg		0.26 Kg
6.5.5	Trimethylchlorosylane		52 Kg		0.345 Kg
6.5.6	Dimethylaniline		102 Kg		0.68 Kg
6.5.7	Triethylamine		61 Kg		0.41 Kg
6.5.8	Methylene chloride	(1,800 Kg)	540 Kg		3.6 Kg
6.5.9	Acetone	(1,000 kg)	300 Kg		2.0 Kg

7. Manpower requirements

7.1 The manpower requirements could be summarized as follows:

7.1.1	Plant Manager	1
7.1.2	Supervisors	4
7.1.3	Senior Production Technicians	8
7.1.4	Production Technicians	12
7.1.5	Production Aides	6
	Total	31

7.2 The additional personnel required to the already existing one at Chemfields is as follows:

	Technical Services	
7.2.1	Senior Laboratory Technician	1
7.2.2	Quality Control Inspector	1
7.2.3	Laboratory Technicians	2
	Engineering Services	
7.2.4	Utilities Operator	1
7.2.5	Mechanics/Electrician	2
	Warehouse	
7.2.6	Supervisor	1
7.2.7	Stock Clerk	1
7.2.8	Warehouse Aides	3
	Administration	
7.2.9	Clerks	2
	T o t a l	14

7.3 Qualifications and Skills

The qualifications and skills of the personnel are:

7.3.1 The Plant Manager should have a Master's Degree in Chemistry and a proven track-record, as well as experience in running a plant. If a person of that caliber is not available, it is suggested that for a minimum of one year, he should be flanked by one expatriate to gain experience in managing a chemical plant.

7.3.2 The Supervisor should have a Master's Degree in Chemistry and technical experience in running a chemical plant. This experience could be gained by working in the Chemfields plant, for instance. If an experienced Supervisor is not available, a

person with a Master's Degree in Chemistry should be trained by working for a period of six months to one year in a fine chemicals plant abroad.

7.3.3 The Senior Production Technicians should have a Bachelor's Degree in Chemistry and should have gained some practical experience in a fine chemicals production plant. In case experienced persons are not available, they should be trained for a minimum period of four months either at the Chemfields plant, or abroad.

7.3.4 The Production Technicians should have a Bachelor's degree in Chemistry; for them a more limited experience is required, since they will work together with the Senior Production Technicians and could gain experience locally.

7.3.5 For the Production Aides no previous experience is required.

7.3.6 The Senior Laboratory Technicians should have a Master's Degree in Chemistry and a specialization in analytical chemistry with experience in the use of modern equipment, such as gas chromatography, U.V., spectroscopy, HPLC, etc. If the experience required is not present, they should be trained for three to four months in the Analytical Department of a reputable Pharmaceutical Company.

7.3.7 The Quality Control Inspector should have a Master's Degree in Chemistry and be familiar with the Quality Control Procedures. If an experienced person is not available, he should be trained for a six months period in the Quality Control Department of a reputable Pharmaceutical Company.

7.3.8 The Laboratory Technicians should have a Bachelor's Degree in Chemistry and some experience in chemical synthesis. If not available, they might be trained in the Chemfields laboratory.

The additional manpower for the Engineering Department should possess the following qualifications:

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

8. Plant location

The Semi-synthetic Penicillins are sophisticated beta-lactam antibiotics. In order to avoid cross-contamination with other products, they must be produced in a plant devoted only to their manufacture, complying with the "Good Manufacturing Practice" rules. Furthermore, high technical skills are essential for their production. As a production of beta-lactam antibiotics is already running in the Chemfields factory and since the technicians employed there are already well acquainted with the technology of semi-synthetic Penicillins, it would be only natural that the plant should be located in the Chemfields factory, where 5 hectares are available for expansion.

All the technical services (quality control, maintenance, warehouse, administration, etc.) and some spare capacity for utilities being already available in the factory, a limited increase of equipment and of people would be necessary to cope with the new needs, meaning a limited investment, production and administration costs, etc.

Finally, one should also mention that there are established habits of 3 shifts working schedules, as well as of solvents transportation, storage, etc.

Thus, the majority Government equity and the shareholding of United Drugs in this enterprise are incidental and have no bearing on this recomendation.

INDUSTRIAL PROFILE No. 4

TETRACYCLINE AND OXYTETRACYCLINE HYDROCHLORIDES

PRODUCTION PLANT

Investment	:	US $ 1,180,000
Annual Output	:	35 tons
Sales Estimates	:	US $ 1,240,000
Manufacturing Costs	:	US $ 920,000
Manpower	:	21

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1. Plant description

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

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

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

2. Annual output and plant utilization

2.1 Annual output

The projected annual output of the plant is as follows:

		Tons
2.1.1	Tetracycline Hydrochloride	20
2.1.2	Oxytetracyline Hydrochloride	15
2.1.3	Total	35

2.2 Plant utilization

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

Product	Output per Batch	Duration of each batch	Number of Batches	Number of working days
Tetracycline Hydrochloride	270 kg	42 hours	74	148
Oxytetracycline Hydrochloride	270 kg	42 hours	56	112
				260

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

3. Investment costs

The estimated investments could be summarized as follows:

		US $
3.1	Equipment	550,000
3.2	Erection (Piping, mounting, electrical parts, instrumentation, insulation, painting etc.)	550,000
3.3	Engineering 7%	40,000
3.4	Assistance to the erection 7%	40,000
3.5	T o t a l	1,180,000

In these investments, the cost of technology and the training of the personnel have not been considered, which should be included in the investment for the Tetracyclinesplant.

The figures do not include buildings, since the plant will be located in the same building where the recovery of Tetracyclines takes place. Investments for the utilities are not considered, as they constitute only a very small part of the ones used for Tetracycline production included in the investments there.

4. Annual sales

The annual sales estimates are:

		Tons	US $
4.1	Tetracycline Hydrochloride	20	696,000 (1)
4.2	Oxytetracycline Hydrochloride	15	462,000 (2)
4.3	T o t a l		1,158,000

5. Manufacturing costs

The estimated total manufacturing costs are:

		US $
5.1	Tetracycline Hydrochloride	560,000
5.2	Oxytetracycline Hydrochloride	360,000
5.3	T o t a l	920,000

6. Manpower requirements

6.1 The manpower requirements could be summarized as follows:

6.1.1	Supervisors	4
6.1.2	Senior Production Technicians	4
6.1.3	Production Technicians	4
6.1.4	Production Aides	4
6.1.5	T o t a l	16

6.2 The additional personnel to be employed in the existing departments is :

Engineering Department

6.2.1	Analyst	1
6.2.2	Laboratory Technician	1

Warehouse

6.2.3	Warehouse Aides	2

Administration

6.2.4	Clerk	1
6.2.5	T o t a l	5

For other services the already existing staff could face all requirements.

(1) Present market price = US$ 348/Kg

(2) Present market price = US$ 308/Kg

7. Raw materials

7.1 Tetracycline Hydrochloride

Hereunder are listed the main raw materials needed for one batch of 270 kg and the corresponding quantities for one kg of Tetracycline Hydrochloride. The amount of solvents in brackets are the quantities used, the other figures being the consumption taking into account 80% recovery for the mixture of solvents and 70% for Acetone.

The mixture of Butanol-Ethylcellosolve is recovered from the mother liquors by distillation. Water is first removed and then the mixture is distilled and the ratio between the two components is rearranged.

7.1.1 Tetracycline		270 Kg		1.0 Kg
7.1.2 Butanol	(1150 Kg)	230 Kg		0.85 Kg
7.1.3 Ethylcelosolve mixture	(120 Kg)	24 Kg	(0.44 kg)	0.09 Kg
7.1.4 Concentrated Hydrochloric Acid		25 Kg		0.09 Kg
7.1.5 Acetone	(525 Kg)	150 Kg	(1.94 kg)	0.55 Kg

7.2 Oxytetracycline Hydrochloride

7.2.1 Oxytetracycline base		278 Kg		1.03 Kg
7.2.2 Butanol-Ethylcellosolve mixture	(1200 Kg)	240 Kg	(4.44 kg)	0.89 Kg
7.2.3 Concentrated Hydrochloric Acid		24 Kg		0.09 Kg
7.2.4 Acetone	(525 Kg)	150 Kg	(1.94 kg)	0.55 Kg

8. Plant location

The free Tetracycline and Oxytetracycline bases have a very limited market, the main commerical products being the Hydrochlorides. For this reason it is suggested to locate the plant in the same building where the recovery of Tetracyclines takes place. Thus, it will be possible to avoid transportation of the free bases and duplication of the technical services and utilities required in a production plant.

INDUSTRIAL PROFILE No. 5

ERYTHROMYCIN DERIVATIVES AND RIFAMPICIN PRODUCTION PLANT

Investment	:	US $ 1,530,000
Annual Output	:	45 tons
Sales Estimates	:	US $ 7,788,000
Manufacturing Costs:		US $ 6,859,000
Manpower	:	27

1. Plant description

1.1 Erythromycin

The installation consists essentially of two reactors, the larger having a capacity of 4000 lt and the smaller one of 1500 lt.

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

The estolate has not been considered since only one multinational company is selling this product as specialty. The thiocyanate, used in the veterinary field in small quantities has been taken into account.

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

1.2 Rifampicin

The installation consists essentially of two stainless steel jacketed reactors with stirring, one press filter (or as alternative a Sparkler type filter), one centrifuge and tanks for mother liquors. One drier (or as alternative a fluid bed drier) and equipment for grinding and sieving of the product. Solvents come from external tanks through metering pumps. Deionized water is produced in a separate unit. Centrifugal pumps are installed for circul tion. Rifampicin will be produced using as a starting material 8-formyl-rifamycin SV; Rifampicin B will be produced in the multipurpose plant, according to one of the proposedoptions.

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

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

2. Plant output and utilization

2.1 Plant output

2.1.1 Erythromycins

The projected quantities of the Erythromycin derivatives output is 25 tons annually, subdivided as follows:

	Tons
2.1.1.1 Erythromycin Stearate	11
2.1.1.2 Erythromycin Ethylsuccinate	11
2.1.1.3 Erythromycin Thiocyanate	3

2.1.2 Rifampicin

The annual output of Rifampcin is estimated at 20 tons

2.2 Plant utilization

On the following table are listed data concerning the duration of the operations for the manufacture of the products, the number of the batches required and the total time of the plant utilization:

Product	Output per batch	Duration of each batch	Number of batch	Total Working days
Erythromycin Stearate	125 Kg	1 day	88	88
Erythromycin Ethylsuccinate	165 Kg	1 day	67	67
Erythromycin Thiocyanate	165 Kg	1 day	18	18
Rifampicin	330 Kg	36 hours	61	90
T o t a l				263

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

3. Investment costs

The investment costs could be summarized as follows:

		US $
3.1	Plant	
3.1.1	Equipment (transportation included)	400,000
3.1.2	Erection (piping, mounting, electrical parts, instrumentation, insulation and painting etc.	400,000
3.1.3	Engineering 7%	60,000
3.1.4	Assistance to the erection	60,000
3.1.5	Cost of technology	300,000
3.2	Building	
3.2.1	Plant	50,000
3.2.2	Warehouse (air conditioned)	85,000
3.2.3	Laboratory equipment (additional)	105,000
3.2.4	Sub-total	1,460,000
3.3	Training of Personnel	70,000
3.4	Grand Total	1,530,000

4. Annual sales (Base 1988)

The annual sales could be summarized as follows:

		US $
4.1	Erythromycin Stearate	1,122,000
4.2	Erythromycin Ethylsuccinate	1,782,000
4.3	Erythromycin Thiocyanate	324,000
4.4	Rifampicin	4,560,000
4.5	T o t a l	7,788,000

The abovementioned figures are based on the prevailing international prices increased by 20%, deemed to cover freight, insurance, custom duties and value added tax.

5. Manufacturing costs

The total manufacturing costs could be summarized as follows:

		US $
5.1	Erythromycin Stearate	1,078,000
5.2	Erythromycin Ethylsuccinate	1,584,000
5.3	Erythromycin Thiocyanate	342,000
5.4	Rifampicin	3,980,000
5.5	T o t a l	6,859,000

In the manufacturing cost calculations, the raw materials costs were calculated based on the assumption that the Erythromycin Derivatives are produced out of imported Erythromycin Base.

6. Raw materials

6.1 Erythromycin stearate

Hereunder are listed the main raw materials needed for one batch of 125 Kg. and the corresponding quantities for one Kg. of Erythromycin stearate. The amount of solvent used is indicated in brackets, the other figure being the consumption taking into account a 60% recovery. The later is true for all Erythromycin derivatives.

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

6.2 Erythromycin Ethylsuccinate

The main raw materials needed for one batch of 165 Kg and the corresponding quantities for 1 Kg of Erythromycin Ethylsuccinate are:

6.2.1	Erythromycin base	194 Kg	1.18 Kg
6.2.2	Ethylsuccinoyl chloride	53 Kg	0.32 Kg
6.2.3	Acetone (750 Kg)	300 Kg	1.80 Kg
6.2.4	Alkali	112 Kg	0.68 Kg

6.3 Erythromycin Thiocyanate

The main raw materials needed for the production of one batch of 165 Kgs and the corresponding quantities for one Kg of Erythromycin Thiocyanate are:

6.3.1	Erythromycin base	165 Kg	1.0	Kg
6.3.2	Potassium Thiocyanate	24 Kg	0.145	Kg
6.3.3	Solvent (600 Kg)	250 Kg (3.5 Kg)	1.5	Kg

6.4 Rifampicin

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

6.4.1	8-formyl-rifampicin SV	320 Kg	0.97	Kg
6.4.2	1-methyl-4-aminopiperazine	54 Kg	0.163	Kg
6.4.3	Acetone-ethylacetate mixture (2000 Kg)	250 Kg (6.1 Kg)	1.9	Kg

The amounts of solvents used are indicated in brackets, the other figure being the consumption taking into account a 70% recovery. The mixture of Acetone-ethylacetate is recovered by distillation, restoring the requested composition by addition of the lacking component.

7. Manpower

7.1 The manpower requirements could be summarized as follows:

7.1.1	Plant Manager	1
7.1.2	Supervisors	4
7.1.3	Senior Production Technicians	4
7.1.4	Production Technicians	4
7.1.5	Production Aides	4
	T o t a l	17

7.2 The additional personnel to be employed in the existing services is as follows:

7.2.1 Technical services

Senior Laboratory Technician	1
Quality Control Inspector	1
Laboratory Technicians	2

7.2.2 Warehouse

Warehouse Aides	3
Supervisor	1
Clerk	1

7.2.3 Administration

Clerk	1
	10

The required qualifications and skills of the personnel are indicated in the industrial profile No. 3 for semi-synthetic Penicillins.

8. Plant location

The production of Erythromycin derivatives and Rifampicin has limited dimensions. For economic reasons, it is advisable to erect a new complex for the plant. The plant should be placed in the Chemfields factory in a new building, which should be separated from the one for Beta-lactam (Semi-synthetic) Penicillin production to avoid cross-contamination. The Chemfields plant has all the required facilities, an existing organization and a staff which has to be slightly increased to cope with the new needs. Some of the existing utilities have spare capacity, thus it will be possible to limit the investment.

INDUSTRIAL PROFILE No. 6

MULTIPURPOSE FERMENTATION PLANT FOR THE MANUFACTURE OF ERYTHROMYCIN, TETRACYCLINES AND RIFAMYCIN

Investment	:	US $ 33,000,000
Annual Output	:	147 tons
Sales Estimates	:	US $ 10,330,000
Manufacturing Costs	:	US $ 6,240,000
Manpower	:	220

1. Plant description

The plant is subdivided into the following sections:

1.1 Fermentation
1.2 Tetracyclines Base, Erythromycin Base and Rifamycin B Extraction
1.3 Hydrochlorides Production
1.4 Rifampicin Production
1.5 Solvent Recovery
1.6 Utilities Generation Units
1.7 Laboratories
1.8 Waste Treatment
1.9 Auxiliary Services (workshop, administration, canteen, etc.)

2. Annual manufacturing output

The annual output of the plant could be summarized as follows:

		Tons
2.1	Erythromycin Base	26
2.2	Rifamycin B	35
2.3	Tetracycline Base	20
2.4	Oxytetracycline Base	16
2.5	Chlortetracyline	50
2.6	T o t a l	147

The different sections of the plant, as well as the annual production are illustrated in the attached chart. The annual capacity was calculated on the basis of a 24 hours operation during 330 days per year.

The different antibiotics are produced by campaigns, with the plant utilization as follows:

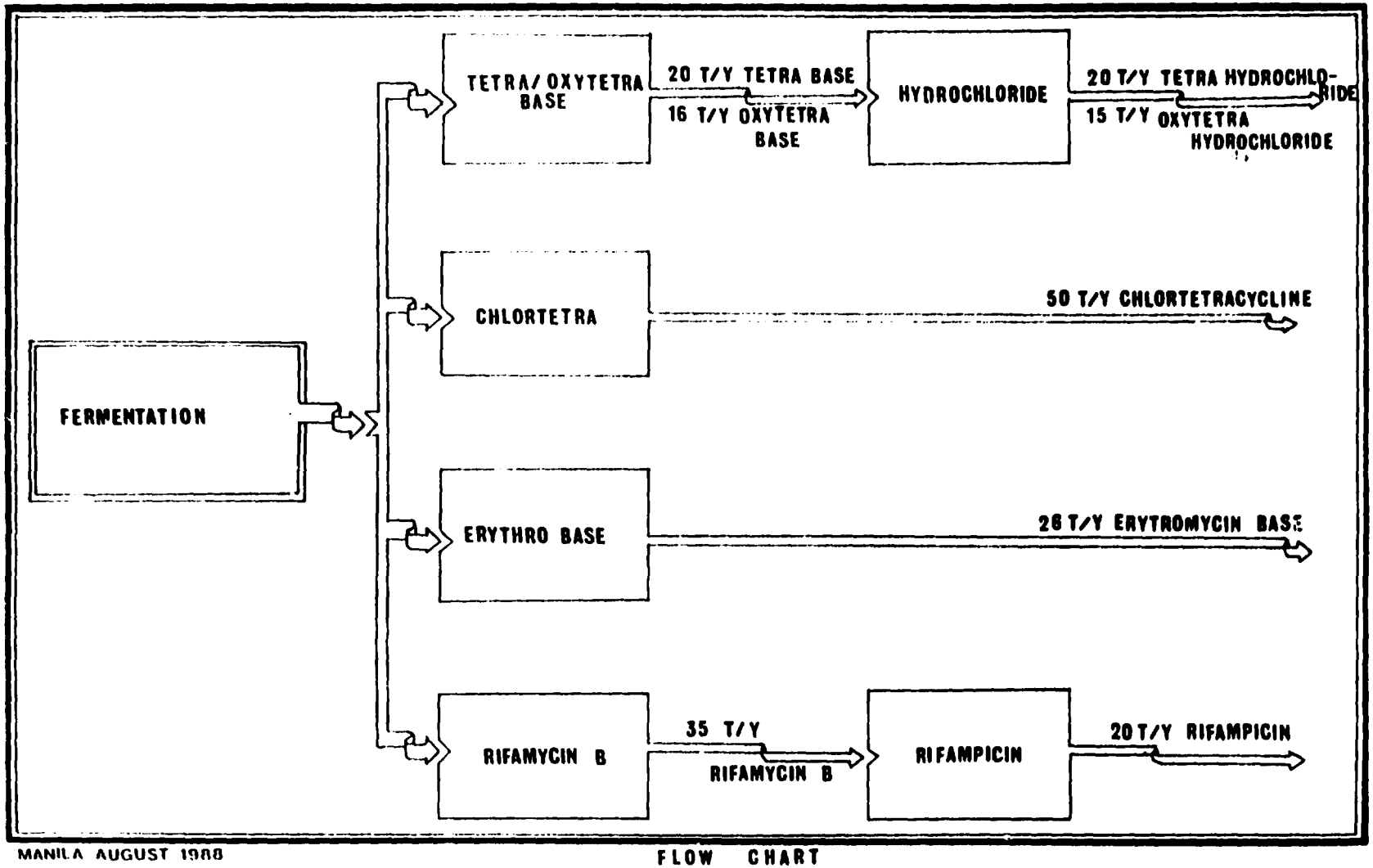
Erythromycin Base	150 days per year
Tetracycline	110 days per year
Rifamycin	70 days per year

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 eliminating it from the production program of the plant, thus reducing the investment costs.

3. Investment costs

The overall estimated investment costs of the complex are in the range between US $30 to US $33 million. The following items are included in the abovementioned estimate:

MULTI-PURPOSE PLANT



MANILA AUGUST 1988

FLOW CHART

3.1 Machinery and equipment
3.2 Bulk materials (piping, instrumentation and electric system)
3.3 Spare parts
3.4 Transportation
3.5 Erection
3.6 Civil works (including load preparation)
3.7 Engineering
3.8 Know how (Erythromycin base, Rifampicin and Tetracycline Base) including strains and technology
3.9 Personnel training
3.10 Construction and start-up assistance

4. Annual sales estimates (1988 base)

The annual Sales estimates are as follows:

	Tons	US $
4.1 Erythromycin base	26	2,860,000
4.2 Tetracycline Hydrochloride	20	750,000
4.3 Oxytetracycline Hydrochloride	15	490,000
4.4 Chlortetracycline	50	1,400,000
4.5 Rifampicin	20	4,830,000
Total sales		10,330,000

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

The abovementioned amounts are based on a projected 1995 consumption in the Philippines only, without taking into account possible exports.

5. Manufacturing costs

5.1 Total costs

The total manufacturing costs could be summarized as follows:

		US $
5.1.1	Raw materials	3,840,000
5.1.2	Manpower	900,000
5.1.3	Energy and utilities	500,000
5.1.4	Other expenses (1)	1,000,000
5.1.5	T o t a l	6,240,000

5.2 Raw materials costs

The raw materials expenses could be subdivided as follows:

5.2.1 Erythromycin base
US $40/kg x 26,000 kg/Y = US $1,040,000/year

5.2.2 Tetracycline Hydrochloride
US $18/kg x 20,000 kg/Y = US $ 360,000/year

5.2.3 Oxytetracycline Hydrochloride
US $16/kg x 15,000 kg/Y = US $ 240,000/year

5.2.4 Chlortetracycline
US $12/kg x 50,000 kg/Y = US $ 600,000/year

5.2.5 Rifampicin
US $80/kg x 20,000 kg/Y = US $1,600,000/year

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(1) All other expenses not directly connected to manufacturing.

6. Raw materials

6.1 Erythromycin Base

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

6.1.1 Soya meal

6.1.2 Corn starch

6.1.3 Glucose solution, which could be substituted by raw cane sugar or by molasses, or cane juice

6.1.4 Corn-steep liquor

6.1.5 Dextrine

6.1.6 Soy-bean oil

6.1.7 Mineral salts as Calcium Carbonate, Ammonium Sulfate Sodium Chloride, etc.

6.1.8 Sulfuric Acid, Caustic Soda, and Ammonia

6.1.9 Organic solvents such as Butyl-acetate, Amylacetate, Methylene Chloride, Ethanol and Methanol

Corn starch, Glucose , Raw sugar (or Molasses), Dextrine, Soy-bean oil (or Coconut oil) and Corn-steep liquor 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.

6.2 Tetracyclines

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

6.2.1 Corn starch

6.2.2 Dextrine

6.2.3 Maize meal

6.2.4 Corn-steep liquor

6.2.5 Saccharose (raw sugar)

6.2.6 Soy-bean oil

6.2.7 Soya meal

6.2.8 Mineral Oils as Calcium Carbonate, Ammonium Sulfate, Ammonium Chloride, etc.

6.2.9 Sulfuric Acid, Caustic Soda and Ammonia

6.2.10 Organic compounds, such as Oxalic Acid, Urea or Acquad

6.2.11 Organic solvents, such as Butanol and Ethylcellosolve (for the Hydrochlorides production) or Acetone.

Corn starch, Dextrine, Maize meal, Corn-steep liquor, saccharose, soybean 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 approximately US $ 16-18 /kg.

6.3 Rifampicin

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

6.3.1 Saccharose (raw sugar)

6.3.2 Corn-steep liquor

6.3.3 Soya meal

6.3.4 Soy-bean oil

6.3.5 Mineral salts like Calcium carbonate and Ammonium Sulfate

6.3.6 Sulfuric Acid, Caustic Soda and Ammonia

6.3.7 Organic solvents, such as Ethylacetate and Acetone

6.3.8 Lead Tetracetate

6.3.9 Manganese Dioxide

6.3.10 Pirrolidine

6.3.11 Formaldehyde

6.3.12 1 - Methyl - 4 - Amino Piperazine

Saccharose, Corn-steep liquor, Soybean oil, Coconut 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.

7. Manpower requirements

7.1 The manpower requirement for the multi-purpose plant is as follows:

	Production	Utilities, Eng. & Maintenance	Laboratories	Adminis-tration	Planning & Purchasing
Plant Manager Supervisory Personnel	10	4	3	2	2
Operators, Technicians, Clerks, and Laboratory specialists	32	15	15	7	7
Skilled Workers	36	15	7	1	1
Unskilled workers	43	20	-	-	-

Total Need: 220 persons

7.2 The personnel qualifications and skills could be summarized as follows:

Heads of Departments: (Fermentation, Installation, Utilities) — University Degrees in Chemistry, Biology or Chemical Engineering

Head of Laboratories:	PHD in Microbiology with at least 2 years experience on strains development
Laboratory technicians:	Master's Degree in Microbiology Bachelor's Degree in Biology Bachelor's Degree in Chemistry with experience in analytical chemistry and the use of modern equipment.

7.3 Laboratories (1)

The laboratories foreseen in the multi-purpose plant are:

7.3.1 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 of the following sections:

7.3.1.1 Master culture preparation and preservation
7.3.1.2 Inoculum development
7.3.1.3 Glassware cleaning and media preparation area
7.3.1.4 In-process laboratory

7.3.2 Quality Control Laboratory

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

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(1) In view of the nature of the process and the special importance of the preparation and preservation of strains, this subject has been singled out.

7.3.2.1 Chemical analysis laboratory

7.3.2.2 Microbiological laboratory

7.3.2.3 Sterility control laboratory

7.4 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 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 experts could be employed as :

7.4.1 Plant and Production Manager

7.4.2 Quality Control Manager

7.4.3 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 to Nationals.

A management and a secondment agreement with foreign companies, participating or not in this venture, could also be considered, the management team, being part of it.

8. Plant location

The plant should be installed adjacent to an existing sugar factory, for securing a cheap source of energy like bagasse, as well as carbohydrates, such as raw sugar, molasses or cane juice, minimizing the high transportation costs.

INDUSTRIAL PROFILE No. 7
MULTI-PURPOSE PILOT-PLANT FOR CHEMICAL SYNTHESIS

Investment	:	US $ 5,265,000
Annual Output	:	83 tons
Sales Estimates	:	US $ 2,040,000
Manpower	:	48

1. General consideration

The introduction and installation of a development orientated multi-purpose chemical pilot plant is viewed as the the strategy in the development of the upstream integration of the pharmaceutical industry. Although production levels tend to be lower, the plant will provide a positive contribution not only to the domestic requirements and supply of pharmachemicals but also to overhead and labour absorption in running the unit.

The most important features of the multi-purpose pilot plant are to provide the facilities to:

1.1 Introduce and develop the experience of chemical synthesis of fine chemicals and pharmachemicals,

1.2 Provide the range of equipment for adequate scaling up facilities and for research and development,

1.3 Provide some limited capacity in production of several pharmachemicals or fine chemical intermediates (e.g. in semi-synthetic antibiotics),

1.4 Provide sufficient facilities and capacity to incorpcrate development of additional upstream integration or introduction of new products,

1.5 Provide a training facility,

1.6 Develop the atmosphere for progressive advancement in scientific skills from innovation to accomplishment.

2. Plant description

A multi-purpose pilot-plant is suited for installation in developing countries when the first stage of backward integration from the pharmaceutical industry is being considered. Such plants are particularly useful in providing a secure basis for education, training and experience in chemical processing and later for the development of "in house" processes.

The installation of a multi-purpose pilot plant is coupled with the acquisition of appropriate technology which has to be determined for each unit proposed. Operation of this technology (purchase of which should include if possible prior training in the suppliers own units) gives the experience in plant operation and training of personnel. The purchase of technology also can give a lead time for development of future products.

A multi-purpose pilot-plant consists of an assembly of several reactors fabricated principally in stainless steel and glass enamel together with some smaller units in industrial glass. The sizes of the reactors will range from perhaps 50 liters through 200 liters, 500 liters and 1000 liters to a maximum in the order of 4500 liters. The reactors are fitted with the condensers and receivers mostly to furnish "general purpose" units though some may have special function such as high vacuum distillation.

Auxillary items such as pumps, centrifuges, filters, driers, etc. complete the installation.

Such plants would normally be designed to produce a maximum of 150 tons products per annum.

3. Products and Plant Capacity

The following pharmachemicals will be produced at the levels indicated:

	Pharmachemical	Tons
3.1	Trimethoprim (anti-bacterial)	1
3.2	Sulfamethoxazole (anti-bacterial)	4
3.3	Ethambutol (anti-TB)	10
3.4	Ibuprofen (anti-rheumatic,anti-inflammatory, analgesic)	10
3.5	Mefenamic Acid (analgesic and antipyretic)	5
3.6	Pyrazinamide (anti-TB)	5
3.7	Furazolidone (anti-diarrheal)	15
3.8	Glaphenine (analgesic and antipyretic)	2
3.9	Isoniazid (anti-TB)	30
3.10	Metronidazole (anti-bacterial, anti-amoebics, anti-trichomonas)	1
3.11	T o t a l	83

4. Sales

Based on an estimated annual need in 1989, the following sales values are projected:

	Pharmachemical	Estimated Annual Need 1989 (kg)	% level production proposed	Production level Sales Value US $
4.1	Trimethoprim	2,500	40 %	22,000
4.2	Sulfamethoxazole	8,000	50 %	60,000
4.3	Ethambutol	25,000	40 %	290,000
4.4	Ibuprofen	17,500	60 %	200,000
4.5	Mefenamic Acid	15,000	33 %	55,000
4.6	Pyrazinamide	10,000	50 %	215,000
4.7	Furazolidone	35,000	42 %	135,000
4.8	Glaphenine	4,000	50 %	130,000
4.9	Isoniazid	65,000	45 %	180,000
4.10	Metronidazole	2,000	50 %	15,000
	T o t a l			1,302,000 *

5. Investment Costs

5.1 The estimated costing in plant, equipment and building construction costs are based on:

5.1.1 plant and equipment prices in UK as of mid 1987 (F.O.B)

5.1.2 construction costs in the Philippines as of mid 1988.

* These figures were determined using latest and lowest prices of bulk chemicals quoted in U.K. There is some difference compared with the import prices in the Philippines in 1987. Using the reported Philippine import prices in 1987, the total sales value would be US $ 2.04 million,which is 55% higher than when using the UK prices and more comparable to the actual domestic sales turn-over value of production products.

5.2 The investment costs could be summarized as follows:

		US$ 6
5.2.1	Reaction Units, extraction	660,000
5.2.2	Centrifuges	255,000
5.2.3	Driers, filters	150,000
5.2.4	Pumps, mill, sieve	97,000
5.2.5	Tanks, mobile bins	136,000
5.2.6	Column, crubbing	56,000
5.2.7	Scales	35,000
5.2.8	Laboratory equipment	136,000
		1,525,000
5.2.9	Service utilities	200,000
5.2.10	Un-installed equipment total	1,725,000
5.2.11	Estimated installed cost	4,312,500
	Building:	
5.2.12	Production hall (1,000 m^2)	400,000
5.2.13	Hydrogeration hall (50 m^2)	17,500
5.2.14	Warehouse	120,000
5.2.15	Administration/Lab	165,000
5.2.16	Site Preparation	250,000
5.2.17	Estimated building cost	952,500
5.2.18	Total estimated cost	5,265,000
5.2.19	With contingencies	5,750,000

An alternative building with smaller production hall and hydrogenation hall may be considered. The total estimated cost of this building is:

Cost	:	US $ 5,058,000
With contingency	:	US $ 5,500,000

The price of technology, which has not been included in the figures, amounts to US $ 100,000 to $ 250,000.

6. Manpower

The manpower requirement and the corresponding qualifications can be summarized as follows:

	Total	PhD	S/BS	Other
General manager	1	1 (Chem. Eng)	-	
Senior managers	4	3 (Chem.)	-	
		1 (Eng.)		
Middle managers	5	-	3	2
Chemists	11	-	11	-
Technicians	6	-	-	6
Tradesmen	7	-	-	7
Others (administration)	7	-	-	7
Unskilled	7	-	-	7
T o t a l	48	5	14	29

The lack of experience in the field of synthesis of Filipino PhD graduates pose to be a problem in the operation of the pilot-plant. Training will therefore have to be an important feature and such should

be incorporated as part of any technology transfer package arrangement. Some months training at the suppliers establishment should be agreed.

It may also be necessary, and desirable to hire back to the Philippines some expatriate chemists, preferably those with experience learned abroad in the field of synthesis of pharma-chemicals or fine chemicals.

Insofar as the rest of the personnel are concerned, the majority requirement of the staff would be Bachelor's degree and no problems in staffing at this level are foreseen. The basic training of education at this level can certainly be assessed as good.

7. Location

The multi-purpose plant can be situated at Chemfields, Inc.(1) This arrangement will have advantages such as savings in general administration and infrastracture and possible shared facilities in some instances of chemical storage or solvent recovery facilities.

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(1) Government majority equity and the United Drug shareholding in Chemfields are purely incidental and have no bearing on the recommendation.

8. Research and Development(1)

8.1 Functions

Some the main function of the research and development department of the plant are as follows:

8.1.1 Provision of familiarisation with any transferred technologies covering not only reaction procedures but also analytical control of intermediates and products

8.1.2 Scaling up of processes

8.1.3 Supervision of, and advice on, initial production commissioning.

8.1.4 Trouble-shooting in the event of any production problems

8.1.5 Monitoring of any new or alternative supplies of critical raw materials or chemicals

8.1.6 Process improvemen'

8.1.7 Development of processes for alternative synthetic routes

8.1.8 Development of processes leading to new product

8.1.9 Defining of new products or intermediates the analytical control parameters and methods of determination.

8.2 Proposed areas of interest in R & D

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(1) This topic has been singled-out in view of the development orientation of the multi-purpose plant.

8.2.1 Process development

8.2.2 Method development for production of pharmachemicals newly, or shortly becoming, free of product patent coverage. As an example, between 1984 and 1996 some 96 drugs fall into this category.

Some of the products in consideration under this philosophy might be: Praziquantel, Fenoprofen, Dilitazem, Amikacin, Carbidopa, Nadolol, Prazepam, Cimetidine, Ranitidine, Clotrimazole and Atenolol.

MANUFACTURE OF ANTIBIOTICS IN THE PHILIPPINES

GENERAL CONSIDERATIONS

1. IDENTIFICATION OF SUBSECTORS FOR UP-STREAM INTEGRATION IN THE PHARMACEUTICAL MANUFACTURE

1.1 General Criteria

The general criteria to be evaluated for the identification and selection of subsectors for eventual up-stream integration, e.g. of products and/or product groups, with active ingredients (pharmaceutical chemicals) to be produced domestically are:

1.1.1 Present consumption of pharmaceuticals

1.1.2 Health profile of the country

1.1.3 Long and medium-term National Development Plans

1.1.4 National Drug Policy(1) including the development of the domestic pharmaceutical industry, the government health programmes, the drug procurement and their respective budget allocations, the National Formularies or other Essential Drug lists, etc.

1.1.5 Market growth potential

1.1.6 World market trends

1.1.7 Availability and possible sources of know-how, including microorganism strains, laboratory control methods and procedures, maufacturing process technologies, with eventual prices.

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(1) The up-stream integration of the pharmaceutical manufacture is in conformity with the 3rd pillar of the NDP concerning the self-reliance in pharmaceuticals.

1.1.8 Patent position(2)

1.1.9 Availability of domestic raw materials (agricultural and agro-waste products, chemicals, fine chemicals and organic solvents), as well as their quality and volume.

1.1.10 Availability of intermediates on the international market and their prevailing prices

1.1.11 Presence of down-stream manufacturing facilities and their requirements

1.1.12 Situation of the infrastructure, including transportation, supply of energy and water, and their costs

1.1.13 Presence of adequate, qualified and experienced human resources, and their potential development

1.1.14 Existing High Educational Institutions, Research and Development facilities and competence, as well as budget appropriations

1.1.15 Communication facilities and eventual language barriers(3)

Further to the analysis and evaluation of the abovementioned factors in particular, and the environment of the pharmaceutical market and industry in the Philippines in general, from an economical, ideological, social and legal point of view, the prevailing opinion of the Experts, many members of the Academe and several representatives of the public and private sectors, is that the main thrust of the country's efforts in the field of pharmaceuticals, should be directed towards the development of the antibiotics.

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(2) Some "super-strains" of microorganisms are also registered

(3) The Philippines are in a very favorable position due to the level of understanding and usage of the English language.

2. THE ANTIBIOTICS

2.1 Definition and Mechanism of Action

An antibiotic is defined as "a substance produced by small microorganisms, which has the capacity of inhibiting the growth and even of destroying other microorganisms by the action of very small amounts of the substance" (Waksman, 1951). This is the classical definition of antibiotics. The word has taken a broader meaning and now includes substances having the same functions but produced by higher forms of life such as marine organisms (seeweeds, algae, sponges), plants, insects and higher animals. Antibiotics may be bacteriostatic or bactericidal depending on the concentration used and the pathogen. They affect microbial growth through any of the following modes of action:

2.1.1 inhibition of bacterial cell wall formation
2.1.2 disruption of bacterial cell membrane
2.1.3 inhibition of protein synthesis
2.1.4 inhibiton of nucleic acid metabolism
2.1.5 interference of intermediary metabolism.

The antimicrobial activity of the antibiotics is selective - each is characterized by a specific spectrum of activity against different microorganisms; some have a broad spectrum activity against various gram-positive and gram-negative bacteria, others - a narrow one. Table 1 illustrates the sensitivity of bacteria to major antibiotics.

Aside from their clinical applications, they are also used in animal nutrition and food preservation and as plant-protecting agents.

2.2 Production of Antibiotics

Antibiotics are usually produced by fermentation using organisms which secrete these substances. They may also be produced by chemical synthesis, but this method is used to a much lesser extent than fermenta-

TABLE 1. SENSITIVITY OF BACTERIA TO MAJOR ANTIBIOTICS

ANTIBIOTICS \ BACTERIA		Gram-Positive				Gram-Negative									Others			
		Coccus				C.	Bacillus											
		Staphylococcus																
		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					
Tetracycline	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	Cephaloridine	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			
Macrolide	Josamycin	X	X	X	X													
	Midecamycin	X	X	X	X													
	Erythromycin	X	X	X	X	X											X	X
Aminoglycoside	Kanamycin	X	X			X	X	X					X	X				
	Fradiomycin						X											
	Gentamicin		X				X	X		X	X		X	X				
	Bekanamycin	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.

tion, with chloramphenicol and pyrrolnitrin as the only antibiotics produced in commercial quantities (Perlman, 1979). In fermentation, the microorganisms grow and multiply in an appropriate substrate which contains carbon and nitrogen sources, usually in the form of starch or sugar and inorganic nitrogen salts. The desired product is separated and purified from the culture medium. These steps depend on the chemical structure of the antibiotic. The isolated compound may be transformed chemically into what are known as semi-synthetic antibiotics, or biochemically to produce analog structures or hybrid antibiotics. The development and commercialization of an antibiotic may require several years depending on the existing regultions of the country concerned and could cost as much as US$ 100 million .

2.3 Brief Historical Overview

In 1928, Alexander Fleming discovered that the mold Penicillium notatum destroyed laboratory cultures of Staphylococus aureus. The substance responsible for this activity was later identified by Florey as the antibiotic Penicillin. Now, more than 5,000 antibiotics of microbial origin have been isolated, mostly from the genus Streptomyces. However, not all antibiotics are of clinical use and only about 100 are produced commercially (Floss, 1987). Although the discovery of antibiotics has revolutionized human therapy and has enabled the cure of many diseases, some of these compounds have undesirable side effects and may cause allergic reactions. Furthermore, continuous and widespread use of these substances have caused some pathogenic organismsto acquire resistance to the drug. One should also mention that due to some similarities in the mode of action, there are possibilities for cross-resistance to several antibiotics. Thus, there is need to discover or develop more effective antibiotics particularly for the treatment of diseases such as viral and fungal infections, as well as for use in cancer chemotherapy.

The need for these antibiotics has brought about continuous work on the discovery of new compounds, or the transformation of the compounds into new ones which are also active. The isolation of microorganisms in

the hope of discovering new compounds is becoming less popular because this method usually results in the rediscovery of already known ones. A very good classical example involving transformation of compounds that are of commercial importance is the addition of sodium phenylacetate to the penicillin fermentation to produce Penicillin G, or the addition of sodium phenoxyacetate to produce Penicillin V. More recent biochemical methods used to transform antibiotics are mutasynthesis and hybrid biosynthesis to produce analog structures. These methods involve mutation and the use of inhibitors so that analogs may be used as precursors to produce antibiotics. Another recent development in this field is the one making use of recombinant DNA techniques to produce a microorganism having two biosynthetic pathways which normally operate in different organisms. This method enables the production of a compound different from that produced by the parent organisms.

2.4 Systematization of Antibiotics

The basic principles regarding the systematization of antibiotics were taken up in a Round Table Discussion during the VIth International Congress of Chemotherapy held in 1970 (Berdy, 1974). Practical and theoretical aspects were thought to be important considerations in the classification of antibiotics. However, these considerations had raised different opinions from the various groups involved. The physicians would like the classification to be based on the effectiveness of antibiotics; the pharmacologists, clinical specialists, and some biochemists, according to the mechanism of action; other biochemists would like the classification to be based on biosynthetic pathways; the microbiologists, according to the source of origin of the antibiotics; and the chemists, according to chemical structure. Unfortunately, there is no such system that could satisfy the needs all of these groups. The best system that caters to the needs of some groups, as well as satisfies other requirements, is one that is based according to chemical structure, the structure determining all the properties of an antibiotic chemical, physical, microbial, pharmacological and clinical.

2.4.1 The main antibiotic families based on chemical structure are (Berdy, 1974):

2.4.1.1 Carbohydrate antibiotics
2.4.1.2 Macrocylic lactone (lactam) antibiotics
2.4.1.3 Quinone and similar antibiotics
2.4.1.4 Amino-acid, peptide antibiotics
2.4.1.5 Nitrogen-containing heterocyclic antibiotics
2.4.1.6 Oxygen-containing heterocyclic antibiotics
2.4.1.7 Alicyclic antibiotics
2.4.1.8 Aromatic antibiotics
2.4.1.9 Aliphatic antibiotics
2.4.1.10 Miscellaneous antibiotics (with known structures)

2.4.2 The Philippine Index of Medical Specialties (April, 1988) has a different system used in the Pharmacological Classification Index. The system is not based on the chemical structure of antibiotics and does not include all antibiotics, as shown in the following:

2.4.2.1 Aminoglycosides - gentamicin,kanamycin, neomycin
2.4.2.2 Cephalosporins - cefaclor, cephradine, cephalexin
2.4.2.3 Chloramphenicols - chloramphenicol, thiamphenicol
2.4.2.4 Macrolides - erythromycin
2.4.2.5 Penicilins - penicillins, semi-synthetic penicillins such as ampicillin, amoxycillin, cloxacillin, carbenicillin.
2.4.2.6 Quinolones - nalidixic acid, rosoxacin
2.4.2.7 Tetracyclines - tetracycline, chlortetracycline, oxytetracycline, minocycline
2.4.2.8 Antifungals - griseofulvin, nystatin
2.4.2.9 Antibacterial combinations
2.4.2.10 Others - lincomycin, rifampicin

In this latter classification, antibiotics such as streptomycins are also classified under Other Chemotherapeutics.

Whatever system of classification is adopted, antibiotics still remain as biologically active chemical substances with a wide variety of structures that are produced by living organisms or by chemical means.

3. FERMENTATION

3.1 Definition

Fermentation is defined as the biochemical activity of a microorganism in its growth, physiological development and reproduction, possibly even senescense and death (Greenshields and Rothman, 1986). The word is derived from the Latin verb fermentare which means "to boil", as in brewing. In the strict sense, fermentation refers to microbial biochemical activity in the absence of air, which means that the process takes place anaerobically. However, the current usage has given the term a wider meaning and now refers to the general cultivation of microorganisms in liquid media.

Fermentation is presently used for the following purposes (Greenshields and Rothman, 1986):

3.1.1 Production of cell biomass: single cell protein, baker's yeast;

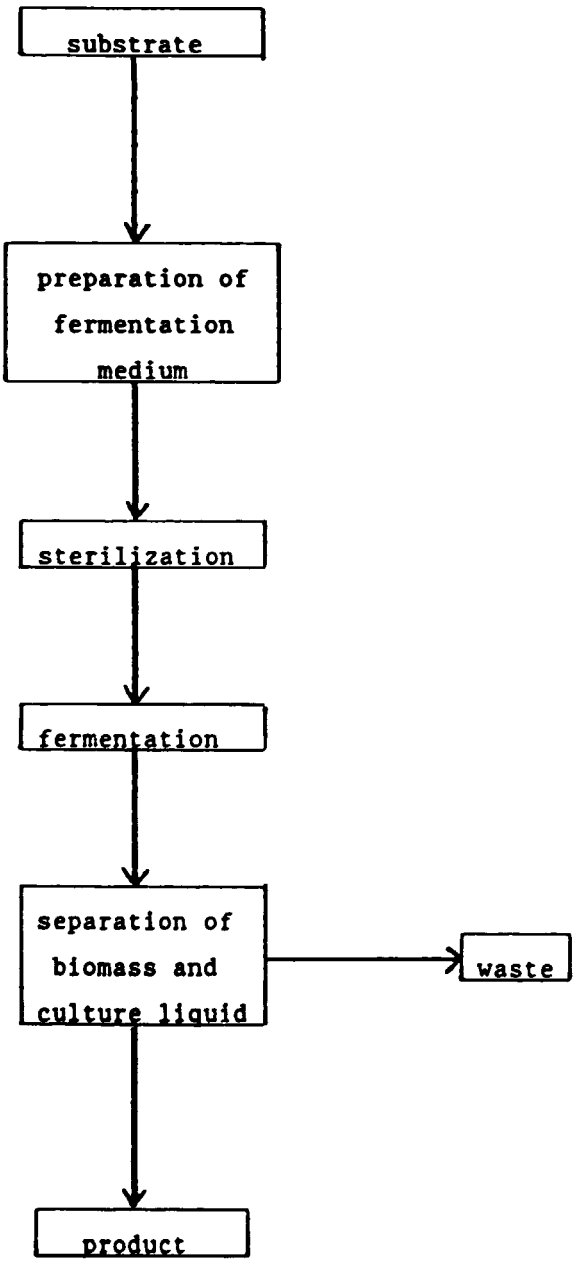
3.1.2 Production of cell components: enzymes, hormones, nucleic acids;

3.1.3 Production of metabolites (chemical products of metabolic activity): ethanol, lactic acid, antibiotics;

3.1.4 Catalysis of specific single-substrate conversions: glucose to fructose, penicillin to 6-amino penicillanic acid (6-APA);

3.1.5 Catalysis of multiple-substrate conversions: biological waste treatment.

A simplified diagram of product formation by fermentation is as follows:



The heart of the operation is the fermenter, but the products have to be separated and purified from the culture medium, after which they are incorporated into the marketable product form.

Down-stream process operations are as important as the production phase itself and cover the following:

* separation
* concentration
* purification
* modification
* drying

3.2 The Fermenters

The fermenter is the container within which the biochemical activity of the microorganisms takes place, a container where organisms grow. Today, a fermenter may be used to cultivate all kinds of cells: plant, animal, human, insects, protozoa, algae, and viruses.

Fermenter design and control are rapidly progressing due to the advances in microelectronics and biological sensors. It is now possible in certain cases to control the fermentation process quite precisely.

A simplified design of a typical fermenter is given on figure 1.

3.3 The Overall Biotechnological Process

A better appreciation of the role of fermentation can be gained from the schematic overview presented in Figure 2 (Smith, 1984). The schematic diagram illustrates the extent of technological infrastructure needed to support a fermentation-based industry.

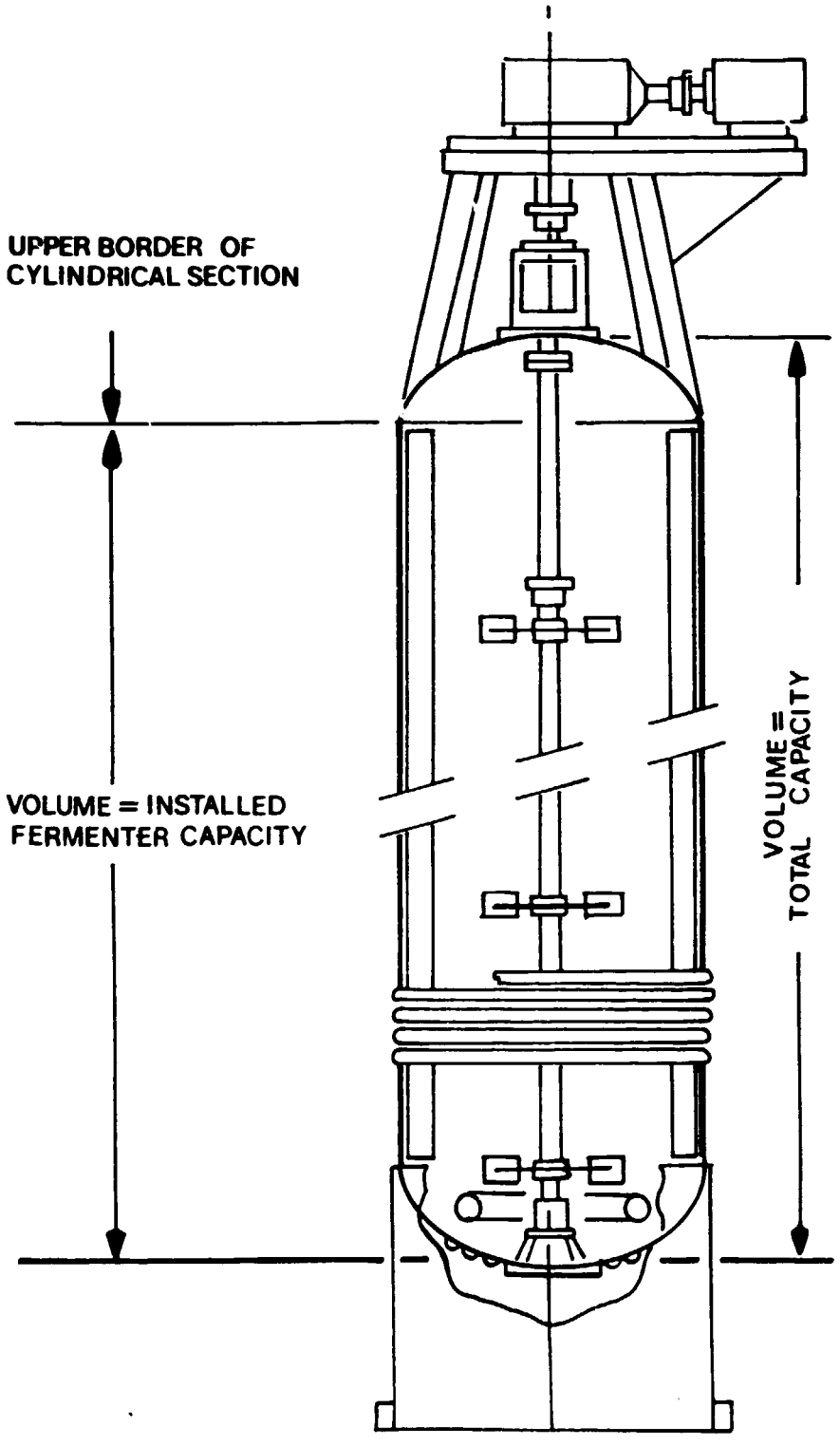
In the Philippines, the kinds of fermentation industries are as follows:

3.3.1. Beverage ethanol production - 19 alcohol distilleries with about 0.5 liters ethanol/day

3.3.2. Beer production - 2 companies

3.3.3. Production of monosodium glutamate

FIGURE 1
TYPICAL FERMENTER



MANILA- AUGUST 1988

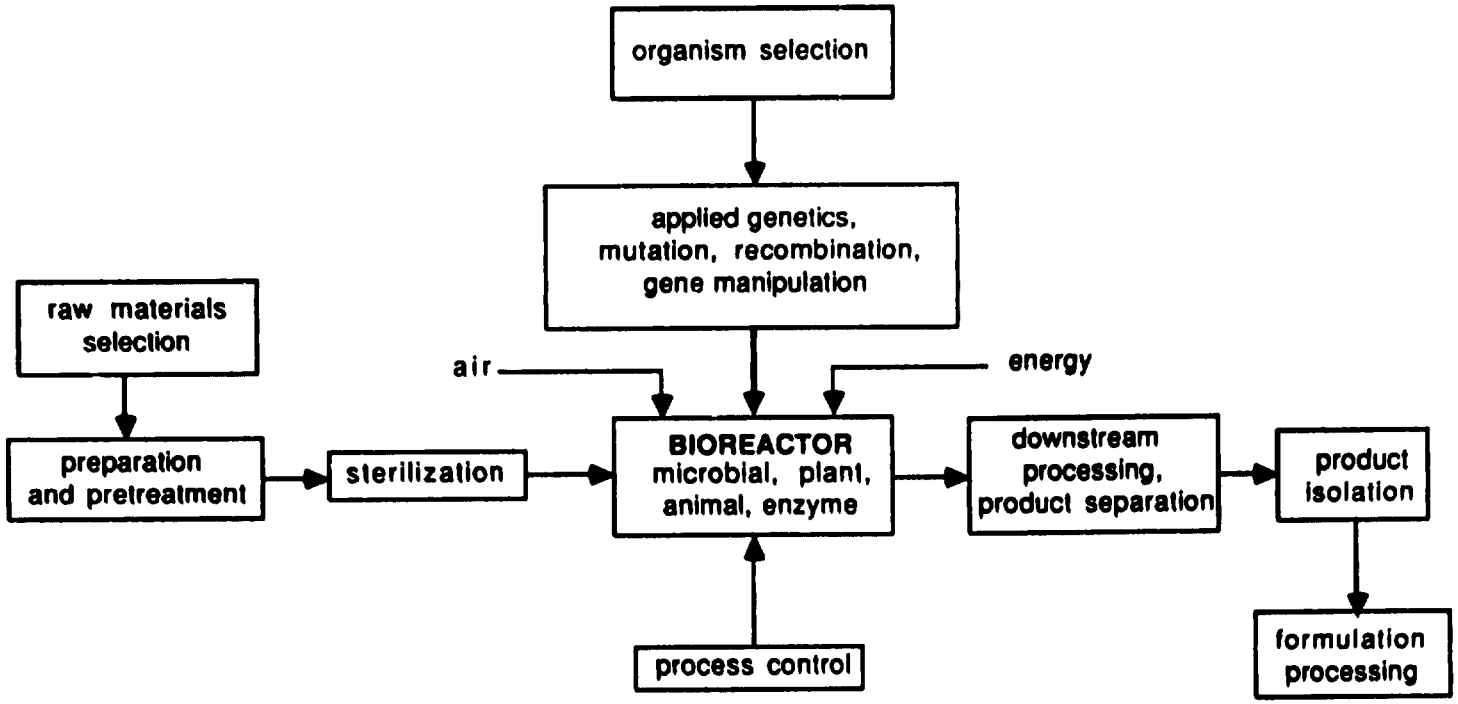


Figure 2. Flow sheet of biotechnological process.

3.3.4. Vinegar production

3.3.5. Large-scale biogas production - Maya Farm Farms

The coverage is limited and there is no activity in the fine chemicals and antibiotics.

4. SEMI-SYNTHESIS OF ANTIBIOTICS

The isolated compounds by fermentation, separated from the culture medium and purified, could be further transformed chemically into what is known today as semi-synthetic antibiotics.

For instance, the chemical transformation of the compound 6-Amino-Penicillanic Acid (6-APA) into Ampicillin and Amoxycillin, two semi-synthetic antibiotics produced by Chemfields in the Philippines, could be summarized as follows:

4.1 Ampicillin

4.1.1 Principle of the Method

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

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

4.1.2 Description of the Method

The 6-APA is dissolved in Anhydrous Methylene Chloride and Diethylamine and Trimethylchlorosylane are added. After the reaction, Dimethylaniline is added and after cooling to -20 C solid D(-) Phenylglycine Chloride Hydrochloride is added portionwise. After the reaction has taken place, water is added to hydrolyze the sylilester.

The Dichloromethane phase is separated and the aqueous solution, after treatment with active carbon, is basified with triethylamine; the precipitated Ampicillin is centrifuged, washed and dried.

On figure 3 is presented a schematic diagram illustrating the method.

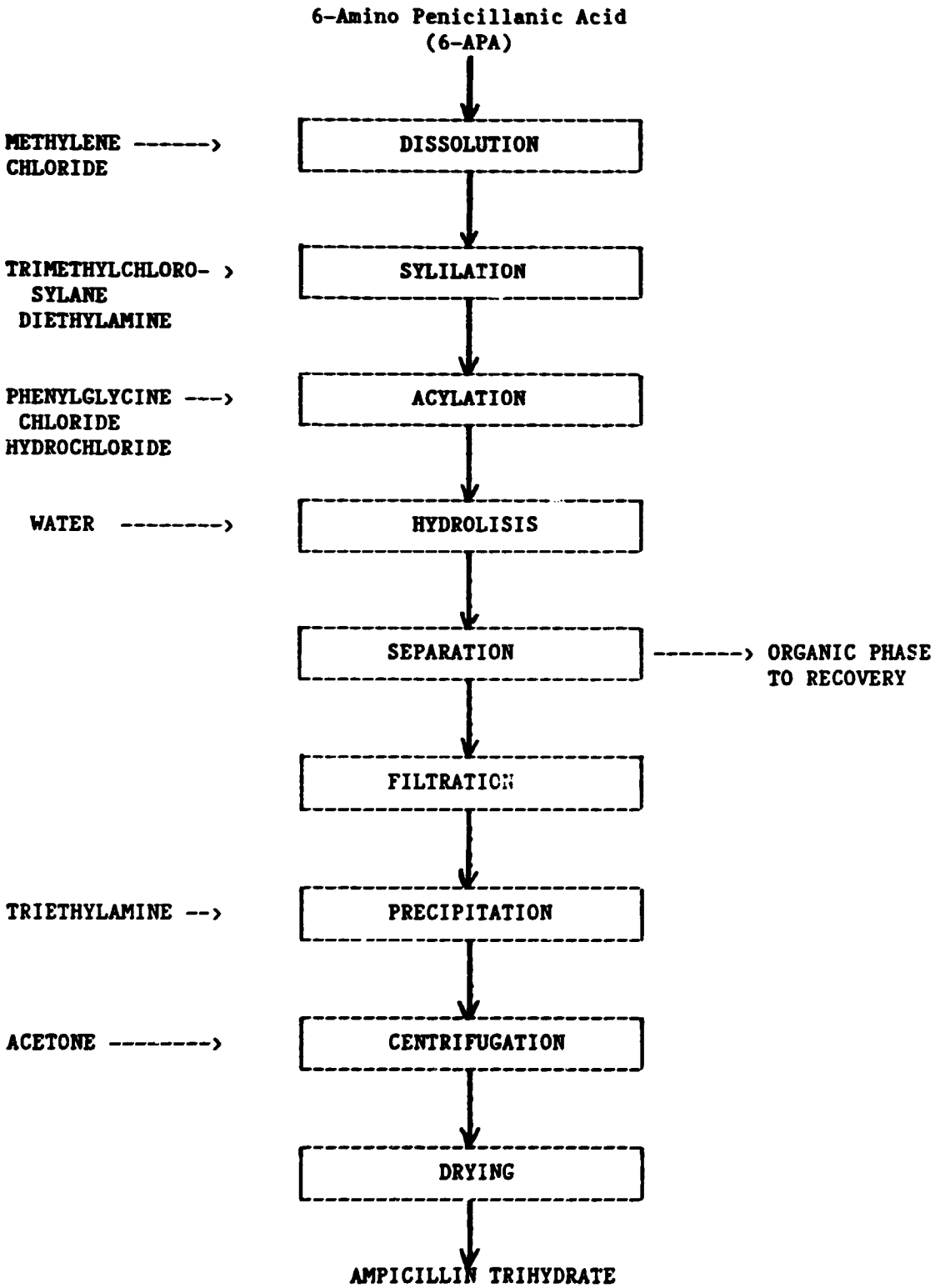


Figure 3. Flow sheet of Ampicillin Trihydrate semi-synthesis

4.2 Amoxycillin

4.2.1 Principle of the method

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

1.)Preparation of the mixed anhydride

2.)Condensation with 6-APA

4.2.2 Description of the Method

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

2) Preparation of Amoxycillin : 6-APA is suspended in Acetone water in a stainless steel reactor and dissolved bysalification with Triethylamine at -10 to 25 ^{o}C . The solution of the mixed anhydride in Acetone is then added keeping the temperature under 0^{o}C. After the reaction has taken place, the Dane Salt is hydrolysed by addition of Hydrochloric Acid.
The resulting solution is extracted with Dichloromethane - Methylisobutylketone which extracts organic solvents and other products. After filtration, the Amoxycillin is precipitated from the aqueous phase by alkalinization, isolated by centrifugation, washed and dried. Amoxycillin trihydrate is obtained.

On figure 4 is presented a schematic diagram illustrating the method.

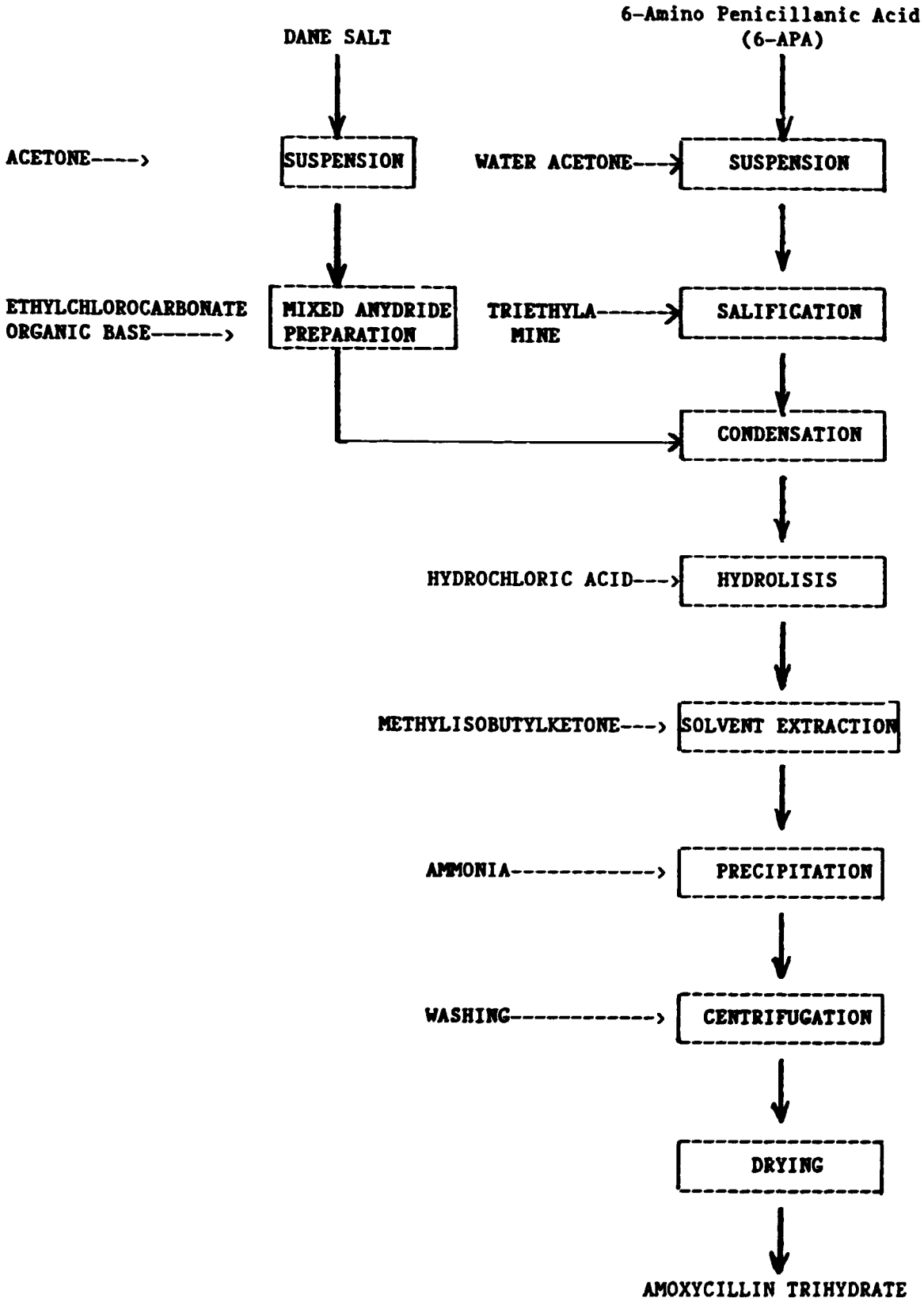


Figure 4. Flow sheet of Amoxycillin Trihydrate semi-synthesis

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5. THE CONSUMPTION OF ANTIBIOTICS

5.1 The World Market

The total 1985 world sales of antibiotics have reached US$ 14.64 billions and could be subdivided as follows:

	US $ (millions)
United States	1,980
Western Europe	5,300
Japan	2,500
Latin America	1,060
Rest of the World	3,800
Total	14,640

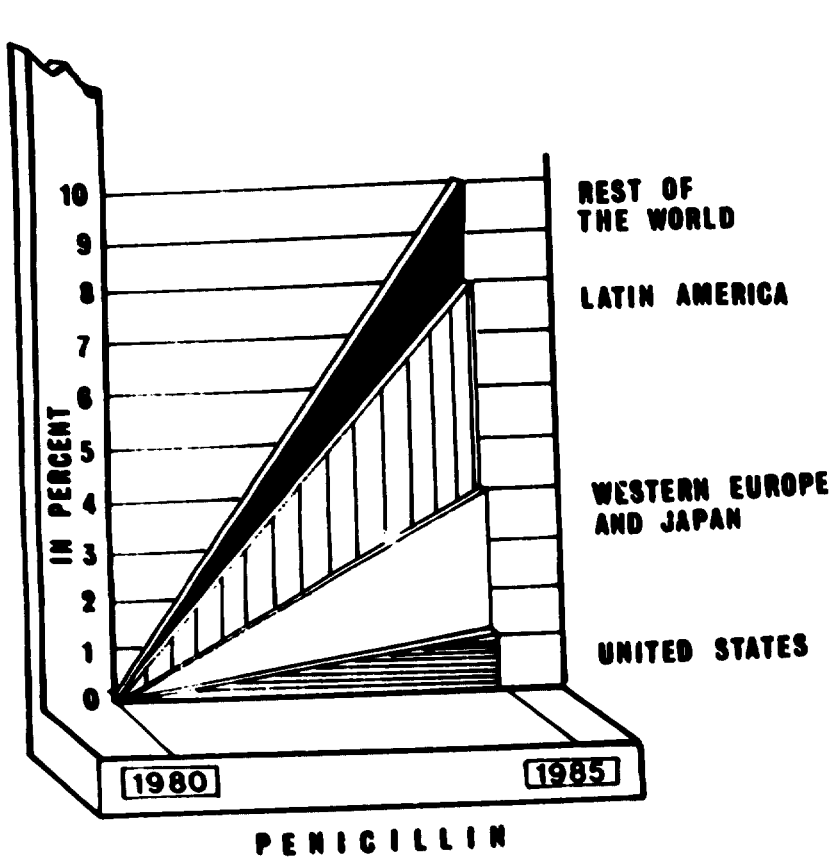
For a period of five years, from 1980 to 1985, the world consumption grew from a total of US$ 11 billions with a compounded annual growth rate of 5.79%. The fastest growing area was the "Rest of the World" by 9% per annum, followed by Japan with 8%, Latin America - by 6% and Western Europe and the USA - by 4% each.

When analyzing the five major antibiotic groups namely, Penicillins, Cephalosporins, Tetracyclines, Erythromycins and Aminoglycosides, two different consumption profiles could be noticed - the one of the "Rest of the World" and "Latin America" characterized by a marked annual growth of the Penicillins by 12% and 8% respectively, and the one of "Western Europe", the United States and Japan with a Cephalosporins annual market growth of 10%, 7% and 11% respectively.

These two profiles are graphically presented on Figure 5. Tables 2 to 6 on the following pages give details of the abovementioned figures.

FIGURE 5

CONSUMPTION PROFILES OF PENICILLINS AND CEPHALOSPORINS FROM 1980 TO 1985



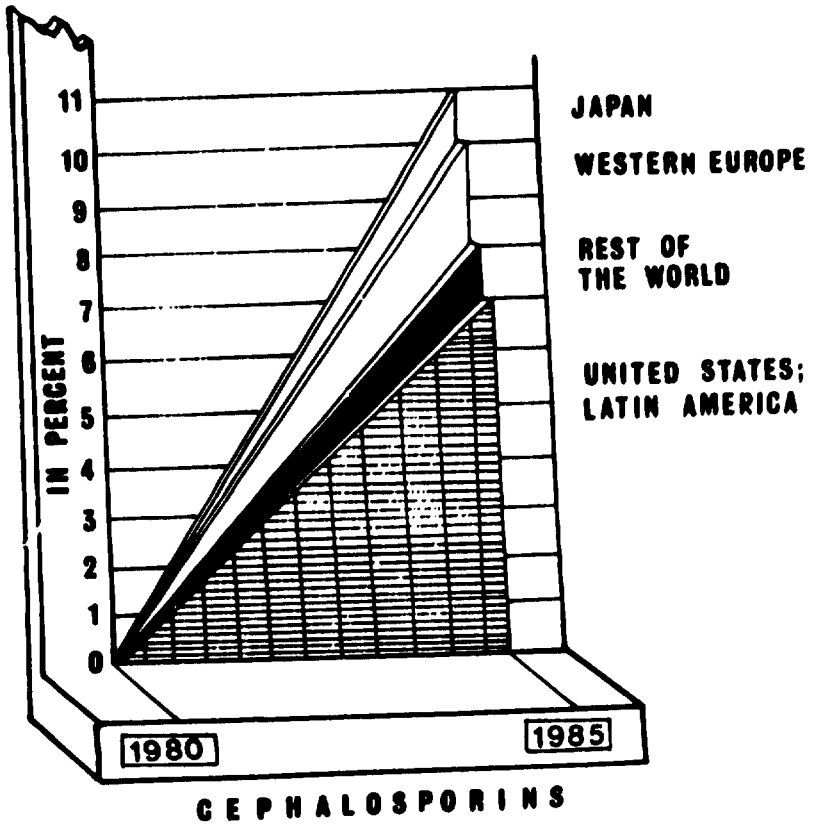


TABLE 2

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 3

GROWTH OF WESTERN EUROPE ANTIBIOTIC SALES BY MAJOR CATEGORY

Sales in $ Million 1985 Dollars

	1980	1985	Percent 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 4

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

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 6

GROWTH 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

5.2 World Market Growth Forecast

The forecasted 10 years antibiotic market growth of the "Rest of the World", from 1985 to 1995 is illustrated on table 7.

The salient points are:

5.2.1 A high initial annual growth rate of the Penicillins of 14% from 1985 to 1990, declining to 10% from 1990 to 1995.

5.2.2 An initial annual growth rate of Cephalosporins of 8% from 1985 to 1990, increasing to 10% from 1990 to 1995.

By the end of 1995, we are talking of a total antibiotics market in the "Rest of the World" of over US$ 9 billions, out of which the Penicillins, with US$ 3.85 billions, will represent 42%.

TABLE 7

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	870	1,350	8	10
T o t a l	3,800	5,980	9,185	10	9

Private Sources

5.2.3 A brief review of the world production trends of 6-Amino-P penicillanic Acid (6-APA) is given on Table 8, keeping in mind the importance of this intermediate in the manufacture of the semi-synthetic Penicillins - Ampicillin, Amoxycilin and Cloxacyllin in the existing down-stream facilities of Chemfields.

TABLE 8

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

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

Private Sources

5.3. The Consumption of Antibiotics in the Philippines

With a consumption of P 1,872,554,000 in 1987, the systemic antibiotics are the most important group representing about 20% of the total drug consumption in the Philippines. Table 9 gives the details.

While drugstores and hospital sales figures in value were reasonably accurate, those concerning volumes, initially unavailable and obtained quite late, proved to be incomplete and inconsistent.

5.3.1. The Imports

The main discrepancies pertaining to imported volumes of pharmaceuticals in bulk, semi-finished and finished forms, were as follows:

5.3.1.1 Data concerning different groups of the pharmacological classification index were consolidated, such as anthelmintics and antihistamines together with antibiotics, for example.

5.3.1.2 Weights, as kilograms or grams, were confused and mixed producing sometimes, astronomical figures, or in other cases, negligible volumes. By the same token, "Non-Medicaments", i.e.bulk pharmaceuticals were comfounded with "Medicaments", i.e. finished pharmaceutical forms.

Table 9

Consumption of Antibiotics, 1987

(in P)

	Drugstores	Hospitals	Total
1. Tetracyclines and combinations	102,495,000	3,742,000	106,237,000
2. Chloramphenicols & combinations	109,195,000	18,578,000	127,773,000
3. Broad Spectrum Penicillins	604,913,000	108,775,000	713,688,000
4. Cephalosporins & combinations	123,165,000	85,992,000	209,157,000
5. Trimethroprim and combinations	90,492,000	7,993,000	98,485,000
6. Macrolides and similar types	142,787,000	9,693,000	152,480,000
7. Quinolones	49,502,000	9,908,000	59,410,000
8. Medium & Narrow Spectrum Penicillins	169,938,000	26,262,000	196,200,000
a) Medium & Narrow Spectrum Penicillins Plain	162,527,000	25,873,000	188,400,000
b) Penicillin and Streptomycin combinations	7,411,000	389,000	9,800,000
9. Aminoglycosides	34,193,000	36,926,000	71,119,000
10. Carbenicillin and similar types	3,212,000	2,575,000	5,787,000
11. Rifampicin/Rifamycin	124,072,000	4,812,000	128,884,000
12. Other antibiotics	2,544,000	845,000	3,389,000
T O T A L	1,556,508,000	316,046,000	1,872,554,000

Source: IMS, 1987

5.3.1.3 Antibiotics belonging to different groups, at the second classification level, such as Terramycin, Streptomycin and Neomycin, were included under Aminoglycosides.

5.3.1.4 At different times, a wide variety of information concerning the same subject was provided by the same source, apparently depending from the person in charge for releasing the information on that day.

5.3.1.5 Some batches of feed-grade Chlortetracycline and Oxytetracycline having a 5 - 10% content of the active principle were considered as 100% pure substance.

The list (see attachment A), might illustrate some of the above statements, including completely different figures of the same group of antibiotics on different pages.

Various data sources have been tapped, such as the Department of Health, the DOST, NEDA, the BOI, the Central Bank, IMS, the Business Statistics Monitor, private sources, the NCSO[1], etc.

The latest amended list of imported antibiotics, not published by the Foreign Trade, is attached (see Attachment B).

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(1) The final amended data were submitted by the latter on Thursday, October 13th 1988.

Table 10 shows the different volumes of imported antibiotics originating from IMS, the BSM and the NCSO.

Table 10

Imports of Selected Antibiotics (1987)

Metric Tons

No.	NAME	IMS	BSM	N C S O			
1	PENICILLINS	17.77	64.86	-	-	-	-
2	SEMI-SYNTHETIC PENICILLINS	40.88	10.83	-	-	-	-
3	SUB-TOTAL	58.65	75.69	102.30	107.67(1)	64.60	104.99(2)
4	TETRACYCLINES	14.21	63.00	109.69	114.10	70.10	113.85
5	ERYTHROMYCINS	7.95	12.30	15.89	17.35	13.31	15.62
6	CEPHALOSPORINS	3.60	3.95	-	-	4.97	-
7	RIFAMPICIN	6.72	6.60	-	-	7.95	-
8	OTHERS	-	-	44.68	35.20	-	-

(1) Including 29.925 T of 6-APA

(2) Including 29.565 T of 6-APA

5.3.2 DOH procurement

The Department of Health does not import drugs, but purchases them locally, either directly from importers, manufacturers, or distributors, or more often, through tenders. These purchases should, normally be covered by the figures pertaining to imports or local manufacture of drugs, but discrepancies in this field seem also to exist.

In this particular case of antibiotics, the following figures were provided by the DOH for 1987 and 1988:

	1987	1988
Erythromycins	1,100 kg	3,900 kg
Rifampicin	13,350 kg(1)	10,800 kg
Amoxicillin Trihydrate	11,500 kg	23,370 kg

There are also direct purchases of antibiotics from the regions, on a similar basis as the central purchases of the DOH, with precise data on the respective volumes lacking. The following information could only give a general idea:

5.3.2.1 Penicillin G	400	kg
5.3.2.2 Penicillin V	1,300	kg
5.3.2.3 Ampicillin	3,600	kg
5.3.2.4 Amoxycillin	1,600	kg
5.3.2.5 Tetracycline	830	kg
5.3.2.6 Oxytetracycline	150	kg
5.3.2.7 Erythromycins	280	kg
5.3.2.8 Rifampicin	35	kg

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(1) In accordance to the figures for Rifampicin provided by IMS and the Business Statistics Monitor, the total import of Rifampicin for 1987 amounted to 6.60 - 6.72 tons only.

5.3.3. Local Manufacture of Antibiotics

The only domestic manufacturer of antibiotics is Chemfields, producing semi-synthetic Penicillins from imported 6-APA (6-Amino Penicillanic Acid). The annual outputs could be summarized,in net metric tons, as follows:

	1985	1986	1987
5.3.3.1 Ampicillin Trihydrate	39.90 T	30.75 T	51.60 T
5.3.3.2 Amoxycillin	16.30 T	15.25 T	22.50 T
5.3.3.3 Cloxacillin	-	0.50 T	-
5.3.3.4 Anhydrous Ampicillin	1.15 T	1.56 T	1.35 T
T o t a l	57.35 T	48.06 T	75.44 T

One should mention that Chemfields (a Government majority equity enterprise) does not supply, neither the DOH, nor the other DOH suppliers with antibiotics produced in the Philippines.

5.3.4 Projections

Further to previous comments concerning the status of available data in the majority of the developing countries, and as a result of discussions with the private sector and among the experts, as well as after analyzing and evaluating the various sources of information, the opinion of the experts is that the following estimates, without having necessarily a scientific base, represent reasonably acceptable levels, probably on the conservative side(1).

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(1) Sophisticated models for evaluation of the future consumption ha·· been used in projecting market trends in constant values.

5.3.4.1 Penicillins

The projections for 1995, the third year of manufacturing, have been based on a 6-7% compounded annual consumption growth, except for the feed-grade of Penicillin G of 3.5%. Although 6 tons of Cephalexin have been foreseen for 1995, this group of products has not been considered in evaluating the Penicillin G requirements, since its production from Pen G would involve the establishment of a plant for 7-ADCA production and such a plant, characterized by complexity and high investment costs, would not be viable for a Cephalexin annual production capacity of 6 Tons.

5.3.4.1.1 Penicillin G

The Penicillin G potassium (Pen GK) estimated consumption in 1995 could be summarized as follows:

	B.U/year	MT/year
- Pen G K Semi-synthetic Penicillins : (through 6-APA)	352,000	220.7
- Pen G K for Injectable Penicillins G :	37,000	23.2
- Pen G K for Feed-grade Penicillins G :	11,000	6.9
T o t a l	400,000	250.8

5.3.4.1.2 Penicillin V

The Penicillin V consumption in 1995 is estimated at about 69,000 BU/year, corresponding approximately to 45 Tons.

5.3.4.2 Erythromycin Base

The Erythromycin base consumption in 1995 for the manufacture of Erythromycin Stearate, Ethylsuccinate and Thiocyanate, based on an annual growth rate of 6% up to 1991 and of 4% up to 1995, is estimated at about 25 Tons (11 Tons Stearate, 11 Tons Ethylsuccinate and 3 Tons Thiocyanate).

5.3.4.3 Rifampicin

The 1988 projected consumption figures for Rifampicin in kgs by the DOH are as follows:

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
T o t a l	10,923	9,991	8,480	7,900	7,607

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

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

5.3.4.4 Tetracyclines

With a 3% anticipated annual growth, the Tetracyclines market in 1995 is estimated at 20 Tons of Tetracycline Hydrochloride,15 Tons of Oxytetracycline Hydrochloride and 50 Tons of feed-grade Tetracyclines (expressed in 100% antibiotic).

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

	Tons/year
5.3.4.4.1 Tetracycline Base	20
5.3.4.4.2 Oxytetracycline	16
5.3.4.4.3 Chlortetracycline	50

As indicated previously, (Table 10), there is a very large discrepancy in the Tetracyclines import figures for 1987, moving from 63 Tons to 113.85 Tons. This difference, or a part of it, is interpreted as due to the Tetracyclines for vetrinary use, included in the figures as total purchased quantities, whereas Oxytetracyclines and Chlortetracyclines are commonly sold as products with a 5 - 10% antibiotic content. In the latest figures provided by the NCSO on October 13th 1988, Chlortetracycline, for instance, represents more than half of the total Tetracyclines imports in 1987.

5.3.4.5 Summary

The summary of the 1995 estimated consumptions is as follows:

	Tons/year
5.3.4.5.1 Penicillin G	250
5.3.4.5.2 Penicillin V	45
5.3.4.5.3 Erythromycins	25
5.3.4.5.4 Rifampicin	20
5.3.4.5.5 Tetracyclines	86
5.3.4.5.6 T o t a l	426

ATTACHMENT A

QUANTITY AND FCB VALUE OF IMPORTATION OF SELECTED ANTIBIOTICS, 1987

	Qty(gms)	Value (FOB$)	Qty (kgs)	Value (FOB$)
Fa - AMINOGLYCOSIDES				
Amikacin	-	-	93.90	511,844.00
Gentamicin	-	-	100.00	2,569.00
Neomycin	-	-	2,378.19	68,792.00
Netilmicin	-	-	1,735.90	160,570.00
Dibekacin	-	-	84.00	368,606.00
Streptomycin	501,000.00	26,500.00	16,510.00	754,403.00
Fb - CEPHALOSPORINS				
Cephalexin	-	-	3,572.25	883,693.00
Cepharadine	-	-	350.00	208,743.00
Cephalothin	-	-	-	-
Cefuroxime	14,925.00	49,518.00	46.70	1,046.00
Cefadroxyl	-	-	581.30	350,076.00
Cefachlor	-	-	422.80	279,900.00
Total			4,973.05	
Fc - CHLORAMPHENICOL	1,699,224.00	142,874.00	19,179.00	844,659.00
Fd - MACROLIDES				
Erythromycin	-	-	2,265.60	258,954.00
Erythromycin Stearate	-	-	6,496.00	848,427.00
Erythromycin Ethyl-succinate	-	-	3,398.00	592,967.00
Erythromycin Estolate	-	-	652.00	66,800.00
Spiramycin	-	-	495.00	54,734.00
Total			13,306.60	
Fe - PENICILLINS				
Ampicillin Trihydrate	-	-	1,498.00	120,156.00
Ampicillin Anhydrous	-	-		
Amoxycillin Trihydrate	-	-	1,080.60	10,866.00
Ampicillin Sodium Inj.	-	-	298.16	134,702.00
Cloxacillin	-	-	-	-
Epicillin	-	-	756.20	223,146.00
Becampicillin	-	-	100.00	20,937.00
Nafcillin Sodium	-	-	2,903.00	895,727.00
Oxacillin	-	-	-	-
Penicillin G Potassium	-	-	9,678.40	475,583.00
Penicillin G Sodium	-	-	4,650.00	389,750.00
Penicillin G. Procaine	-	-	10,950.00	381,545.00
Penicillin G. Benzathin	-	-	201.00	16,816.00

Attachment A...cont.

Penicillin V. Potassium	-	-	31,441.00	1,295,050.00
Penicillin V. Acid	-	-	1,042.00	46,773.00
Total			64,598.36	

Fg - TETRACYCLINES

Tetracycline Base	-	-	70.00	3,870.00
Tetracycline Hydrochloride	-	-	3,984.00	135,408.00
Oxytetracycline Hydrochloride	-	-	6,346.00	194,919.00
Chlortetracycline	-	-	57,965.00	535,503.00
Total			68,365.00	

Fj - OTHERS

Rifampicin	-	-	7,950.00	1,934,737.00
Griseofulvin	-	-	235.00	30,664.00
Lineomycin	-	-	2,100.00	418,353.00
Total			10,285.00	

Source: NCSO, Sept. 27, 1988

Attachment A ...cont.

QUANTITY AND FOB VALUE OF IMPORTATION OF ALL DRUGS CLASSIFIED AS ANTIBIOTICS, 1987

5413909 - Other Antibiotics n.l.s. (Non-medicaments)

Name of Drug	Qty (kgs)	Value (FOB $)
Aluminum Sucrose Sulfate	200.00	3,533.00
Amikasin	93.99	511,844.00
Ampholerecin	21.12	5,706.00
Amproleum	800.00	25,680.00
Apresoline	65.00	42,604.00
Atarax Hydrochloride	37.00	27,750.00
Bacitracin	12.00	3,890.00
Benzalkonium Chloride	0.15	182.00
Bonine (Meclizine)	25.00	8,215.00
Calcium Di-Terramycin	48.56	5,976.00
Captopril	12.00	60,140.00
Cefachlor	422.80	279,900.00
Cefadroxyl Monohydrate	581.30	350,076.00
Cefuroxine	46.77	1,046.00
Cefoperazone	20.00	68,930.00
Cephalexin	3,572.25	883,693.00
Cephradine Oral	350.00	208,743.00
Ceporex	36.23	902.00
Chloropropamide	443.00	21,160.00
Ciprofloxacin	8.00	1,177.00
Citrate Monohydrate	61.32	6,781.00
Clindamycin HCl	1,208.00	619,055.00
Clobetasol Propionate	0.10	6,505.00
Corbadox	167.60	14,916.00
CTC HCl Oral Powder	66.00	4,360.00
Deonil/Glinbenchlamide	10.00	41,476.00
Dequalinium Chloride	2.00	3,034.00
Ephedrine Sulphate	225.00	12,860.00
Ergonovine Maleate	50.00	589.00
Ethocel 45	50.00	962.00
Framycetin Sulphate	4,00	918.00
Fungizone	4.50	795.00
Gentamycin	100.00	2,569.00
Gramicidine	3.00	1,655.00
Griseofulvin	235.00	30,664.00
Halquinol	720.00	13,154.00
Hydrocartisone Acetate	94.00	7,451.00
Hydroxypropyl	10.00	353.00
Hygromycin	200.00	6,520.00
Kita Tartate	350.00	16,631.00
Lincomycin	2,100.00	418,353.00

Name of Drug	Qty (kgs)	Value (FOB $)
Monocycline HCl	75.00	118,591.00
Morantel Citrate	207.00	22,762.00
Mupiracin	5.00	27,500.00
Mycostatin	342.85	112,547.00
Nadolol	28.00	92,148.00
Netilmicin	84.00	368,606.00
Nystatin BP	35.04	7,574.00
Ofloxacin	1,180.00	1,112,548.00
Oxantel Pamoate	228.06	52,207.00
Parbendozole	150.00	4,833.00
Paromomycin Sulphate	440.00	87,054.00
Piroxicam	75.83	402,818.00
Polymyxin	255.47	295,238.00
Prazosin HCl	1.00	16,004.00
Proxyphylline	25.00	685.00
Pseudo Ephedrine HCl	50.00	3,163.00
Pyrantel Pamoate	644.62	72,955.00
Rasoxacin	5.00	26,014.00
Rifampicin	7,950.00	1,934,737.00
Rifaten Powder	10.00	302.00
Rimactane	300.00	216,299.00
Rosoxacin	20.00	104,015.00
Salbutamol Sulphate	5.00	14,748.00
Salinomycin 350	924.80	22,273.00
Serpasil	0.40	1,311.00
Sodium Citrate	50.00	8,545.00
Spectinomycin Sulphate	5.00	1,550.00
Spiramycin	495.00	54,734.00
Sucralfate Granules	550.00	9,735.00
Tetrahydrozoline	10.22	14,767.00
Tetramethyl Thiuram Monosulphate	2,000.00	7,566.00
Thiostrepton	48.00	2,185.00
Thyroxine Sodium Triturate	2.50	3,160.00
Tiamulin Tech.	4,325.00	728,821.00
Tinidazole	399.90	123,439.00
Tioconazole	1,00	2,417.00
TM HCl	1.00	382.00
Tobramycin	24.99	140,440.00
Trianulin	50.00	15,091.00
Triamcinolone	17.50	48,555.00
Trimethoprim	140.00	6,876.00
Troleandomycin	20.20	6,108.00
Tylosin Base	50.00	3,590.00
Vancocin	4.00	260.00
Total	33,692.07	10,015,901.00

Attachment A ...cont.

5413905 - Erythromycin (Non-Medicaments

Name of Drug	Qty (kgs)	Value (FOB $)
Erythromycin Base	2,265.00	258,954.00
Erythromycin Estolate	652.00	66,800.00
Erythromycin Ethyl Succinate	3,398.00	592,967.00
Erythromycin Stereate	6,496.00	848,427.00
Erythromycin Thiocyanate	4,254.00	247,838.00
Total	17,065.600	2,014,986.00

5417109 - Erythromycin (Medicaments)

Name of Drug	Qty (gms)	Value (FOB $)
Ery-max Capsules	169,055.00	85,730.00
Erythromycin Lactobionate	1,850.00	7,775.00
Erythromycin Tablets	104,522.00	23,169.00
Sammycin Suspension	7,500.00	944.00
Total	282,927.00	117,618.00

5413100 - Penicillins and their derivatives (Non-Medicaments

Name of Drug	Qty (gms)(1)	Value (FOB $)
Aminopenicillianic Acid	29,925.00	2,001,496.00
Amoxillin	1,800.00	213,363.00
Ampicillin Sodium	298.16	134,702.00
Ampicillin Trihydrate	1,498.00	120,156.00
Bacampicillin	100.00	20,937.00

(1) They meant certainly kgs.

Name of Drug	Qty (gms)[1]	Value (FOB $)
Cloxacillin Sodium	5,263.02	1,074,867.00
Cyclacillin Anhydrous	240.00	40,836.00
Epicillin	756.20	223,146.00
Nafcillin Sodium	2,903.00	895,727.00
Ospen 500 granular powder	113.00	9,414.00
Penicillin G Procaine	10,950.00	381,545.00
Penicillin Potassium	1,750.00	71,082.00
Penicillin Procaine	411.00	22,367.00
Penicillin Sodium Buffered	450.00	28,915.00
Penicillin G Benzathine	201.00	16,816.00
Penicillin G Potassium	9,678.40	475,583.00
Penicillin G Sodium	4,650.00	389,750.00
Penicillin Mic	90.00	7,885.00
Penicillin V Acid	1,042.00	46,773.00
Penicillin V Potassium	31,441.00	1,295,050.00
Penicillin V Sodium	428.00	28,830.00
Sodium Epicillin	8.00	6,540.00
Amoxycillin Trihydrate	1,080.60	10,866.00
Total	105,178.38	7,528,862.00

5417119 - Other Antibiotics n.e.s. (Medicaments)

Name of Drug	Qty (gms)	Value (FOB $)
Amikin	10,460.00	109,383.00
Amphroprim	5,000.00	1,523.00
Bleomycin	1,000.00	2,000.00
Cefamandole Nafate	27,330.00	36,120.00
Ceferroxime	14,925.00	49,518.00
Ceporex	10,000.00	43,273.00
Ceradolan	2,000.00	5,408.00
Chlorobicine	12,050.00	5,750.00
Chloramsulfa	22,351.00	10,453.00
Ciprobay	35,750.00	113,746.00
Claforan	35,850.00	76,324.00
Fortum	1,035.00	7,390.00
Fucicort	6,140.00	716.00
Fucidin Ointment	9,510.00	1,047.00
Keflin Neutral	27,500.00	19,601.00
Lakdocyn	12,250.00	1,379.00
Lederiff Rifampicin	90,000.00	29,765.00
Laxinor	287,500.00	121,284.00

(1) They meant certainly kgs.

Name of Drug	Qty (gms)	Value (FOB $)
Lysozome	900.00	7,331.00
Mycifradin Sulfate	10,000.00	4,608.00
Myocostatin Effervescent	121,433.00	22,701.00
Neomix	48,040.00	14,075.00
Neozym	7,200.00	6,879.00
Panmycin	125,000.00	10,465.00
Rifater	300,000.00	177,471.00
Scanicol Injection	16,000.00	1,108.00
Sodium Cefazolin	9,000.00	15,576.00
Trimerin	76,870.00	13,208.00
Trobicin	10,000.00	8,457.00
Tylak	12,250.00	2,206.00
Plivacal	109,000.00	12,670.00
Vagimycin	28,400.00	15,133.00
Velosef	30,000.00	9,210.00
Total	1,514,744.00	955,778.00

5413309 - Other Tetracyclines (Non-Medicaments)

Name of Drug	Qty (kgs)	Value (FOB $)
Chlortetracycline HCl	57,965.00	535,503.00
Doxycycline HCl	438.44	408,011.00
Oxytetracycline	21,688.00	369,491.00
Oxytetracycline Amphoteric	490.00	97,152.00
Oxytetracycline Chlorhydrate	300.00	7,923.00
Oxytetracycline Dihydrate	280.00	16,848.00
Oxytetracycline HCl	6,346.00	194,919.00
Oxytetracycline Quarternary salt	9,939.00	185,814.00
Tetracycline blend	70.00	3,870.00
Tetracycline Chlorhydrate	12,600.00	346,667.00
Tetracycline HCl	3,984.00	135,408.00
Total	114,100.44	2,301,606.00

5417104 - Penicillin (Medicaments)

Name of Drug	Qty (gms)	Value (FOB $)
Amoxil	105,475.00	85,370.00
Ampicillin	298,424.00	342,491.00
Ampiclox	32,718.00	61,140.00
Augmentin	181,250.00	105,155.00
Bacacil FC Tablets	580,000.00	201,718.00
Baypen	14,550.00	41,787.00
Cloxampicin	25,000.00	22,548.00
Cypercil Parenteral	51,792.00	62,659.00
Kedacillin Injection	104,000.00	74,120.00
Moxillin	20,600.00	21,709.00
Orbenin	54,900.00	78,028.00
Pneglobe	560,000.00	106,161.00
Penicillin Procaine	2,000.00	2,765.00
Pentrexyl Par	120,739.00	150,328.00
Prostaphlin Par	18,450.00	29,947.00
Sumoxil	48,100.00	49,617.00
Unasyn IV/IM Injection	79,000.00	80,655.00
Dublocid	35,000.00	20,823.00
Empicillin	50,000.00	37,950.00
Magnipen	19,125.00	8,603.00
Moxillin	55,513.00	53,760.00
Pediamox	7,500.00	9,720.00
Servicillin	10,500.00	3,074.00
Ticarpen	6,000.00	7,575.00
Total	2,498,636.00	1,693,528.00

Source: NCSO, Sept. 27th 1988

ATTACHMENT B[1]

ANTIBIOTICS (NON-MEDICAMENTS)
QUANTITY AND FOB VALUE OF IMPORTED ANTIBIOTICS, 1987

	Qty (Kgs.)	Value (US $)
A. 5413100 - Penicillins	104,988	7,620,049
B. 5413200 - Streptomycins	16,510	754,403
C. 54133 - Tetracyclines	115,564	2,614,406
C.1. 5413301 - Aureomycin	0	0
C.2. 5413302 - Terramycin	1,719	160,952
C.3. 5413309 - Other Tetracyclines & their derivatives	113,845	2,453,454
D. 54139 - Other Antibiotics	122,657	13,897,499
D.1. 5413901 - Bacitracin	7	3,512
D.2. 5413902 - Chloramphenicol	19,179	880,659
D.3. 5413903 - Tyrothricin	0	0
D.4. 5413904 - Neomycin	2,373	68,792
D.5. 5413905 - Erythromycin	15,619	2,013,860
D.6. 5413906 - Antibiotics for veterinary use	52,168	1,316,319
D.7. 5413909 - Other Antibiotics	33,311	9,614,357
Total	359,719	24,886,357

(1) Source NSCO, October 13th 1988

Attachment B... cont.

A. 5413100 - Penicillin and their derivatives (non-medicaments)

	Qty (Kgs.)	Value (US $)
Amino-Penicillanic Acid	29,565	1,961,927
Amoxicillin	2,160	252,872
Ampicillin Sodium	303	134,702
Ampicillin Trihydrate	1,498	120,156
Becampicillin	125	26,162
Bicillin/Penicillin G Benzathine	278	23,807
Cloxacillin Sodium	5,266	1,074,667
Epicillin	748	216,778
Nafcillin Sodium	2,903	895,727
Ospen 500	113	9,414
Penicillin G Procaine	11,750	405,636
Penicillin Potassium	1,650	68,403
Penicillin Sodium	450	28,915
Penicillin Procaine	453	24,527
Penicillin G Potassium	8,746	442,978
Penicillin V Potassium	31,737	1,298,695
Sodium Epicillin	16	12,908
Penicillin G Sodium	4,869	419,781
Penicillin V Acid	989	46,773
Penicillin Produral	48	5,725
Cyclocillin Anhydrous	240	40,836
Amoxycillin Trihydrate	1,081	108,660
Total	104,988	7,620,049

B. 5413200 - Streptomycin	16,510	754,503

Attachment B... cont

		Qty (Kgs.)	Value (US $)
C.	54133 - Tetracyclines		
C.1.	5413301 - Aureomycin	0	0
C.2.	5413302 - Terramycin	1,719	160,952
C.3.	5413309 - Other Tetracyclines (Non-Medicaments)		
	Chlortetracycline HCl	58,018	539,863
	Doxycycline HCl	652	433,222
	Oxytetracycline Quarternary Salt	8,758	185,804
	Oxytetracycline Amphoteric	587	97,152
	Oxytetracycline Chlorhydrate	100	2,623
	Oxytetracycline Dihydrate	50	1,912
	Oxytetracycline HCl	6,011	200,779
	Tetracycline Blend	70	3,870
	Tetracycline Chlorhydrate	13,200	379,858
	Tetracycline HCl	4,478	193,982
	Oxytetracycline	21,921	414,389
	TOTAL	113,845	2,453,454

Attachment B... cont

	Qty (Kg.)	Value (US$)
D. 54139 - Other Antibiotics		
D.1. 5413901 - Bacitracin	7	3,512
D.2. 5413902 - Chloramphenicol	19,179	880,659
D.3. 5413903 - Tyrotricin	0	0
D.4. 5413904 - Neomycin	2,373	68,792
D.5. 5413905 - Erythromycin (Non-Medicaments)		
Erythromycin Base	2,212	262,546
Erythromycin Estolate	852	100,200
Erythromycin Ethyl Succinate	3,266	565,901
Erythromycin Estearate	6,261	837,375
Erythromycin Thiocyanate	3,028	247,838
TOTAL	15,619	2,013,860
D.6. 5413906 - Antibiotics for Veterinary Use	52,168	1,316,319

Attachment B... cont

D.7. 5413909 - Other Antibiotics, nes (Non-Medicaments)

NAME OF DRUG	Qty (Kgs.)	Value (US$)
Aluminum Sucrose Sulfate	200	3,533
Amikasin base	93	511,844
Amphotericin Crystals	20	5,706
Bacitracin	12	3,890
Benzalkonium Chloride BP Solution	2	182
Calcium Di-Terramycin	61	5,796
Captopril	12	60,140
Cefactor	441	279,900
Cefadroxil Monohydrate	578	350,076
Cefaroxine	47	1,046
Cefoperazone Sodium Crystalline	52	68,930
Cephalexin	3,559	883,693
Cephradine	320	208,743
Ceporex	36	902
Ciprofloxacin Sensitivity Discs	8	1,177
Clindamycin HCl	1,228	619,055
Corbadox	168	14,916
Daonil/Glinbenclamide Micronized	10	41,476
Framycetin Sulfate Micronized	4	918
Fungizone 50mg	4	795
Gentamycin Sulfate Injection	100	2,570
Gramicidin	2	1,655
Griseofulvin	305	40,234
Halquinol	620	13,154
Hydroxypropyl Cellulose	10	353
Hygromycin B Concentrate	200	6,520
Lincomycin HCl	2,102	418,353
Minocycline HCl Powder	75	118,591
Mupiracin	6	27,500
Mycostatin	338	112,547
Netilmicin Sulfate	379	368,606
Nystatin BP	35	7,574
Ofloxacin	1,170	1,112,548
Paromomycin Sulfate	440	87,054
Peroxicam	70	402,818
Polymixin B Sulfate	346	295,238
Prazosin HCl	2	16,004
Pyrantel Pamoate	666	75,025
Rasoxacin	25	130,029
Rifampicin	7,973	1,934,737
Rifater Powder	10	302
Rimactane/A.S.	465	216,299
Salinomycin	1,193	22,273
Spectinomycin Sulfate Tetrahydrate	8	1,550
Spiramycin Base	451	54,734

Attachment B... cont

NAME OF DRUG	Qty (Kgs.)	Value (US$)
Sucralfate Granules	550	9,735
Tetrahydrozoline	12	14,767
Tetramethyl Thiuram Monosulphide	3,814	11,108
Thiostrepton Pulverized	31	2,185
Thyroxine Sodium Triturate	3	3,160
Tiamulin	4,348	728,821
Tinidazole	409	123,439
Tiocanazole	7	19,791
Tobramycin	18	140,440
Trainulin Base	50	15,091
Trimothoprim	140	6,876
Troleandomycin 100mesh non-sterile	20	6,108
Tylosin Base Vet Grade	50	3,590
Vancocin	3	260
TOTAL	33,311	9,614,357

Attachment B... cont

ANTIBIOTICS (MEDICAMENTS)

	Qty (gms.)	Value (US$)
A. 5417101 - Bacitracin	0	0
B. 5417102 - Aureomycin	0	0
C. 5417103 - Chloramphenicol	1,715,224	143,982
D. 5417104 - Penicillin	3,618,995	1,673,283
E. 5417105 - Streptomycin or Dihydro-streptomycin	501,000	26,500
F. 5417106 - Terramycin	0	0
G. 5417107 - Tyrothricin	0	0
H. 5417108 - Neomycin	0	0
I. 5417109 - Erythromycin	276,027	119,002
J. 5417111 - Antibiotics for Veterinary Use	2,134,624	530,421
K. 5417119 - Other Antibiotics	1,042,946	810,621

Attachment B... cont

D. 5417104 - Penicillins	Qty (gms.)	Value (US$)
Amoxil	145,975	85,370
Ampicillin	457,929	376,860
Ampiclox	56,764	50,257
Augmentin	180,940	105,155
Bacacil	361,750	206,884
Baypen	9,525	41,787
Cloxampicin	69,950	22,276
Cypercil Parenteral	46,872	62,659
Kedacillin Injection	96,150	74,120
Moxillin	570,670	75,182
Orbenin	18,000	35,825
Penbritin	70,248	67,648
Penglobe	560,000	106,161
Penicillin	200,000	2,765
Pentrexyl Par	127,691	150,320
Phrostaphilin	62,750	29,947
Sumoxil	264,405	49,617
Unasyn IV/IM Injection	79,001	80,655
Magnipen	19,125	8,603
Servicillin	105,000	3,074
Pediamox	75,250	9,720
Dublocid	35,000	20,823
Ticarpen	6,000	7,575
TOTAL	3,618,995	1,673,283

Attachment B... cont

	Qty (gms.)	Value (US$)
I. 5417109 - Erythromycin		
Erythromycin Lactobionate	2,450	10,103
E-mycin	2,522	7,822
E-mycin Tablets	102,000	15,347
Ery-Max Capsules	169,055	85,730
TOTAL	276,027	119,002

J. 5417119 - Other Antibiotics, n.e.s.

	Qty (gms.)	Value (US$)
Amikin	10,460	109,383
Amproprim	5,000	1,523
Cefamandole Nafate	74,897	36,120
Cefuroxime	109,925	49,968
Ceforex	10,000	43,273
Ceradolan	2,000	5,408
Chlorbicine	12,050	575
Chloramsulfa/Ciprobay	22,056	124,199
Claforan	35,850	76,324
Fortum	1,035	7,390
Fucicort	4,995	716

Attachment B... cont

	Qty (gms.)	Value (US$)
Fucidin Ointment	10,655	1,047
Keflin Neutral	27,000	19,601
Lakdocyn	9,424	1,379
Lederrif Rifampicin	90,000	29,765
Lexinor	28,750	121,284
Lysozome	30	7,331
Mycifradin Sulfate	1,000	4,608
Mycostatin Effervescent	275,433	22,701
Neozym	7,200	6,879
Penmycin	124,410	10,465
Rifater	30,000	177,477
Sodium Cefazolin	9,000	15,576
Trimerin	76,870	13,208
Trobicin	10,000	8,457
Tylak	15,076	2,206
Plivacol	930	12,670
Vagimycin	28,400	15,133
Velosef	3,000	9,210
Sammycin Suspension	7,500	944
TOTAL	1,042,946	810,621

6. HEALTH PROFILE

As in the majority of the developing countries, health statistics are incomplete and do not necessarily reflect the exact morbidity and mortality situation. More often than not, the declared notifiable diseases are much lower than should be normally expected, either because they are not properly diagnosed and declared or not registered. A typical example would be, for instance, the 1985 deaths due to Acute Rheumatic Heart Disease and those due to Venous Thrombosis and Embolism of 25 and 54 cases, respectively, in the entire country with a then population of 54.67 millions.

The following tables 11 and 12 are illustrating the evolution of the leading causes of illness and death from 1982 to 1987.

Table 11

LEADING CAUSES OF DEATH 1982-1987

(Number of Death Reported)

D I S E A S E S	1982	1983	1984	1985	1986	1987
1. Pneumonia	45,373	45,686	45,971	52,888	50,621	50,923
2. Disease of the heart	36,819	28,208	31,347	36,242	39,163	28,829
3. Tuberculosis, All Forms	28,309	28,208	27,999	31,650	30,604	23,500
4. Diseases of the Vascular System	21,511	20,593	27,107	27,184	29,402	20,842
5. Malignant Neoplasm	16,832	15,703	17,700	18,143	18,395	10,984
6. Diarrhea	12,735	14,964	11,553	11,516	10,839	7,991
7. Measles	7,136	6,098	7,987	8,043	6,249	-
8. Nutritional Deficiencies *	6,068	7,463	6,825	7,114	6,145	1,706
9. Accident	5,863	9,712	10,445	10,070	10,348	9,716
10. Nephritis, Nephrotic Syndrome and Neophroses	4,470	4,262	4,916	5,470	5,273	-

Source: 1982-1986- Philippine Health Statistics (PHS) 1987
DOH Annual Report

* Includes Avitaminosis in the nomenclature used by PHS.

Table 12
LEADING CAUSES OF ILLNESS 1982-1987
(Number of Cases)

DISEASES	1982	1983	1984	1985	1986	1987
1. Bronchitis	280,431	352,447	606,880	586,427	602,851	725,818
2. Diarrheal diseases	221,191	275,068	551,560	522,762	552,613	722,972
3. Influenza	226,237	256,534	453,926	447,550	397,715	578,514
4. Pneumonias	106,563	123,420	193,594	205,387	190,208	215,368
5. Tuberculosis, all forms	104,715	106,300	154,021	153,406	153,129	200,534
6. Malaria	40,496	55,019	107,485	121,975	124,153	135,231
7. Accidents **	-	-	84,637	96,684	105,886	133,421
8. Diseases of the Heart	-	-	70,596	70,238	78,516	80,744
9. Measles	35,989	43,684	75,290	62,959	59,375	76,232
10. Malignant Neoplasms	26,867	25,838	75,290	62,959	59,375	76,232

Source : 1982-1986 - Philippine Health Statistics 1987 - DOH Annual Report

** Declared Notifiable Disease in 1984

Unfortunately, it is extremely difficult to draw a parallel of this evolution with the annual growth rates of the antibiotic market in the country, or to translate for instance, the number of cases of bronchitis, pneumonia and diarrhea into volume or value of antibiotics used, in these cases mainly penicillins, tetracyclines and neomycin. Obviously, not only all cases of these diseases are not reported, but many other illnesses treated with the same antibiotics, rightly or wrongly, escape detection. The situation is quite different in the case of Tuberculosis, due to the Government Health Programme in this field and the 1988 procurement of 11 tons of Rifampicin for that purpose.

While it is well known that the Philippine population is very young with 52.8% below the age of 20, 40% below 14 and 19.9 below the age of 7 (1985), and that with the aging of the population there will be a different

disease pattern with a probable shift towards cardiovascular diseases, malignant neoplasms, metabolic diseases, etc., it is also difficult to foresee how this will translate into kilograms or tons of antibiotics and in which ones.

An example of the abovementioned could be seen on Figure 5a, concerning the sales of therapeutic class from January to September 1968, as follows:

Analgesics/Anti pyretics	1,482,627
Antibiotics	3,097,671
Cardiovascular Prep.	448,912
Cough/Colds Prep.	2,258,638
Non-steroid Top. Derma Prep.	595,255
Dietetics	1,020,338
Hematinics	478,563
Hormones	988,946
TB Therapy	941,448
Vitamins/Minerals	2,103,314
All Others	4,892,894

In other words, twenty years ago, the antibiotics represented the largest part of the market, as it is today.

Many other factors, such as the protein-energy malnutrition prevalent in about 20% of the children between 0-6 years and its future evolution, the prescription patterns and auto-medication habits, the number of prescribers and health facilities, the development of the Government Health Programmes, etc., could affect the consumption and market size of the antibiotics.

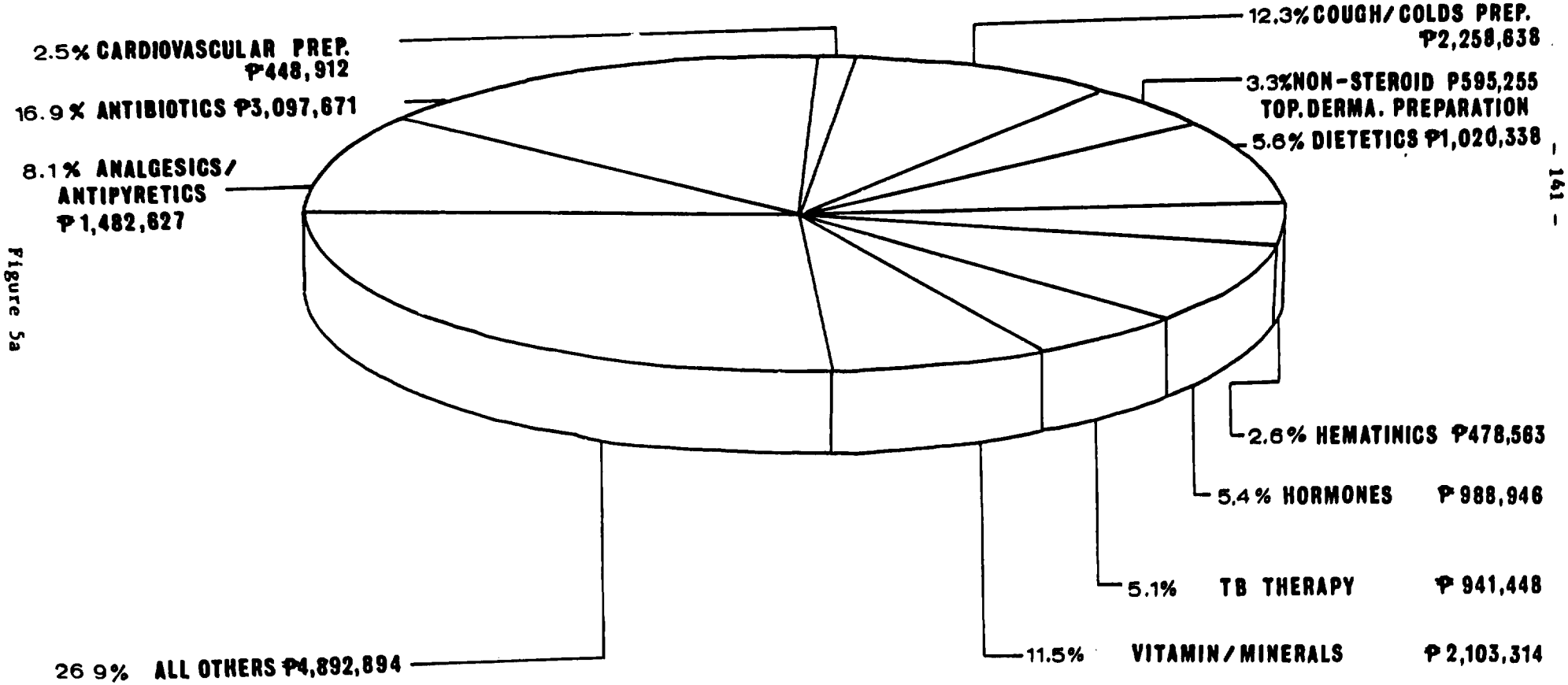
7. PATENTS AND KNOW-HOW

7.1 Patents

While some "Superstrains" of microorganisms, their maintenance, storage and reproduction are still under patent protection, as will be probably all new developed ones, the well known strains, as well as the manufacturing

SALES BY THERAPEUTIC CLASS

JANUARY - SEPTEMBER
1968



SOURCE: BUSINESS MONTH - DEC., 1968

Figure 5a

processes technologies (the fermentation media and their specifications, the fermentation conditions, the extraction, the crystallization, the purification, etc.) and the laboratory control specifications are not protected by patents.

This pertains to Penicillin G and V, 6-Amino Penicillanic Acid (6-APA), Ampicilin, Amoxycillin, Cloxacillin, Erythromycin Base and derivatives, Rifampicin, Tetracycline Base and derivatives, Oxytetracyclines and Chlortetracycline, antibiotics considered in the study and figuring in the projects.

7.2 Know-how

Penicillin, being a strategic antibiotic as a source for the manufacture of 6-APA and several semi-synthetic Penicillins the following notes pertaining to the know-how of its production might be pertinent.

The mold presently used for Penicillin production is Penicillium chrysogenum. There is no single magic recipe used for the production of the antibiotic usually a closely guarded industrial secret. However, potato dextrose agar may be used to culture the organism and corn-steep liquor medium (Perlman, 1979) at pH near neutral and with the following components, may be used to produce Penicillin:

Carbohydrate source	:	blackstrap molasses, raw sugar starch or glucose
Organic acids	:	acetic acid *
		lactic acid *
Special precursors	:	phenylethylamine and other precursors *
Main nitrogen sources	:	corn-steep liquor
Other nitrogen sources	:	ammonia*

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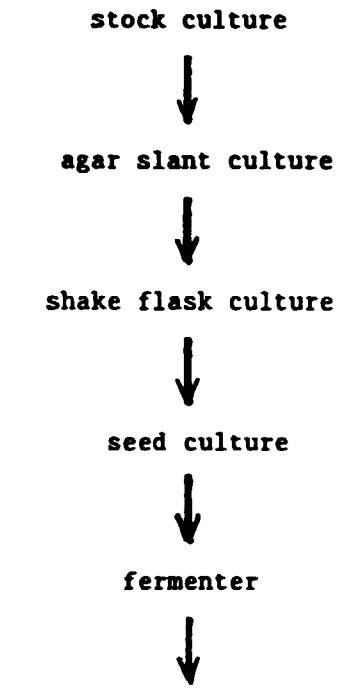
* Concentration depends on the corn-steep liquor used

The following diagram shows the production of Penicillin by fermentation:



Stock cultures of P. chrysogenum can be maintained for several weeks or months on agar slants and can be stored for years in soil, in liquid nitrogen, or in lyophilized form.

The recovery of Penicillin from fermentation liquors is done by solvents extraction. The process involves filtration to separate the mycelia from the broth, followed by extraction, with amyl or butyl acetate. After further extraction with an aqueous solvent, Penicillin is crystalized from the mixture.

Since the discovery of Penicillin by Fleming in 1928, tremendous work had been done to increase the yield. The strain that was originally discovered to produce Penicillin, gave very low yields, producing only

about 120 mg/li Penicillin even after several attempts to improve the strain. Furthermore, it did not perform well in submerged cultures. Thus, other strains of this organism and the related mold P. chrysogenum were investigated until P. chrysogenum NRRL 1951 was found to be a better producer in submerged culture. In 1945, a strain of this organism, designated as Wisconsin Q176, was found to produce 720 mg/li Penicilin. This strain was adopted by most Penicillin manufacturers.(P. chrysogenum NRRL 1951 and Wisconsin Q176 are both available in BIOTECH).

There is continuous work on strain improvement for a cost-effective production of Penicillin. The overwhelming amount of work done, as shown in figure 6, may make one wonder, if the mold is still P. chrysogenum, especially because variability is one of the characteristics of molds producing Penicillin. Although it is now possible to produce up to 30 g/li [1/] of Penicillin G (Hacking, 1986) through strain improvement[(1)], it is a general observation that the higher the yield, the more unstable is the organism, i.e., morphological and physiological changes occur at a faster rate than ordinary. With the advances in molecular biology, much more improvement could be done to increase the yield and further change the organism.

1/ Present Penicillin fermentation yields reach levels of 60,000-80,000 U/ml.

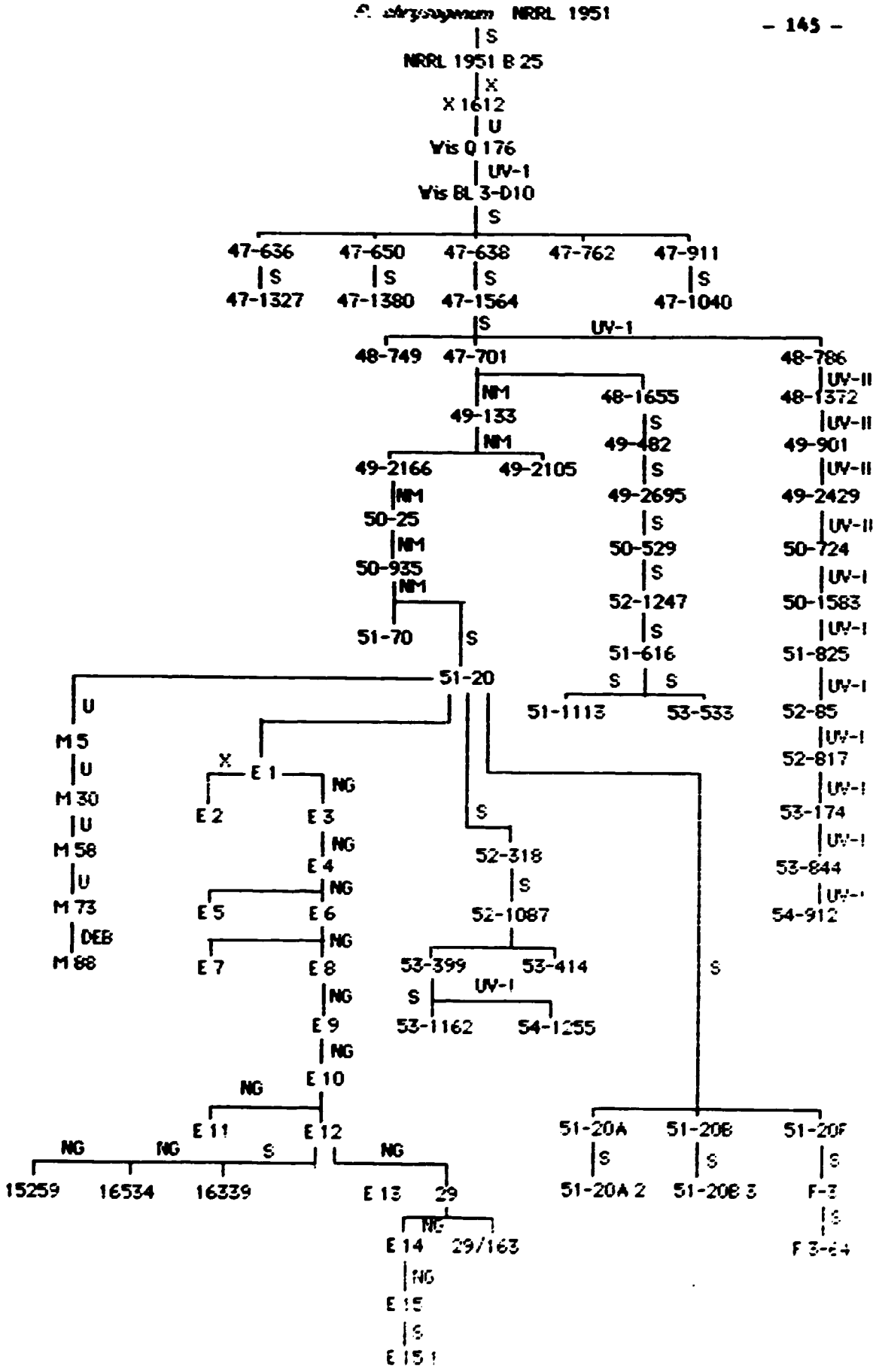


Figure 6. Strain improvement of *F chrysogenum*. Key. S - spontaneous, X - X-ray irradiation, U - uv irradiation, wavelength unspecified, UV-I - 275 nm, UV-II - 253 nm, NM - nitrogen mustard, NG - nitrosoguanidine, DEB - diepoxybutene (Elander and Chang, 1979)

Penicillin is produced in commercial quantities in Austria, England, Finland, France, Holland, Hungary, Bulgaria, Japan, Sweden, United States and West Germany. Some pharmaceutical companies involved are :

Austria -	Biochemie GmbH
England -	Glaxo Laboratories
Finland -	Fermion Oy
France -	Rhone-Poulenc
Holland -	Gist-Brocades n.v.
Hungary -	Biogal
Japan -	Banyu Pharmaceutical Co.
	Meiji Seika Kaisha Ltd.
	Toyo Jozo Co. Ltd.
Sweden -	Aktiebolaget Astra
	Aktiebolaget Fermenta
United States -	Bristol-Meyers Co.
	Eli Lilly Co.
	Pfizer, Inc.
	E.R. Squibbb & Sons
	Wyeth Laboratories
West Germany -	Hoechst AG, etc.

Strains and technologies are available and could be purchased either directly from the manufacturers, or through brokers. They could be also a part of a joint-venture, or a technological assistance agreement with third parties.

The prices could vary from several hundreds of thousands of US Dollars, to several millions, depending on the extent of the purchased know-how, the strains, the desired manufacturing yields and the respective guarantees provided.

8. AVAILABILITY OF DOMESTIC RAW MATERIALS

8.1 Raw Materials for Fermentation of Antibiotics

The raw materials utilized for the fermentation of Antibiotics could be summarized as follows:

8.1.1 carbohydrates and proteins sources, represented mainly by agricultural products.

8.1.2 chemicals and fine chemicals

8.1.3 Organic solvents

In the first group of products, several agricultural and/or agro-waste materials are available in the country and could be utilized.

In the second category, only a very small number of chemicals, such as sulfuric acid produced by Chemphil Manufacturing Corporation,are locally available. All fine chemicals should be imported.

The organic solvents most commonly used for the production of antibiotics are presently imported in the Philippines, except for Ethanol.

The assessment of the raw materials for drug manufacture is based on the assumption that biotechnological processes shall be used, with a distinct advantage that they can utilize agricultural raw materials, therefore renewable.

Hacking (1986) has listed the different raw materials for biological processes, which are being currently used (see table 13).
Six out of these items are available in the Philippines - corn starch, glucose, sucrose (raw), sucrose (refined), molasses and ethanol.

Table 13

Raw Materials for Biotechnological Process

Substrate	Carbon Content g-mol C per mol substrate	Carbon Content relative to glucose (%)
Corn starch	0.44	100
Glucose	0.4	100
Sucrose-raw	0.42	105
Sucrose-refined	0.42	105
Molasses *	0.2	50
Acetic Acid	0.4	100
Methanol	0.375	94
Ethanol	0.52	130
Methane	0.75	188
Corn oil (crude)	0.8	200
Palm oil	0.8	200
n-alkanes	0.87	218

* 48% by weight fermentable sugar.

Source: (Hacking, 1986)

Missing from the list of Hacking are some mineral nutrients which may be sources of nitrogen and phosphorous, as well as high protein substrates like soybean meal and cotton seed meal that are added to the fermentation medium. Also missing from the list is cassava starch which is readily available in the Philippines.

8.2 Domestically Available Agriculture Raw Materials

The domestically available agricultural raw materials, which could be utilized for the fermentation of antibiotics, could, thus, be summarized as follows:

8.2.1 Sugar cane based raw materials

- 8.2.1.1 raw sugar
- 8.2.1.2 molasses
- 8.2.1.3 cane juice
- 8.2.1.4 bagasse (see energy sources)

The following 1987 material balance on a national level data, may be useful (Sugar Regulatory Administration, 1987):

1 MT sugar cane produces:

- 287 kgs bagasse
- 98 kgs raw sugar
- 35 kgs molasses
- 710 liters cane juice

Taking the average yield of approximately 51 metric tons of sugar cane per hectare, the following may be derived:

- 14.6 MT bagasse
- 5.0 MT raw sugar
- 1.8 MT molasses
- 36.2 MT cane juice

Table 14 shows the sugar industry production data from 1980-1987.

Table 14

Sugar Industry Production Data from 1980-1987

Crop Year	Area Harvested (ha)	Cane milled (MT)	Raw Sugar Production (MT)
1979-1980	442,202	22,489,847	2,265,910
1980-1981	382,439	23,033,970	2,317,866
1981-1982	495,674	25,037,127	2,442,862
1982-1983	463,577	24,062,736	2,463,789
1983-1984	487,378	25,969,151	2,335,622
1984-1985	406,750	18,719,339	1,719,033
1985-1986	307,547	16,124,014	1,518,944
1986-1987	269,058	13.751,501	1,337,095

Source: Sugar Regulatory Administration, 1988

8.2.1.1 Raw sugar

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. 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, 1988).

8.2.1.2 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%. Actual prices of black-strap molasses are 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.

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

However, it should 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 the 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 (Priority Export commodities Series, 1987)

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

The following average figures of the molasses final analysis could provide a general idea about volume and quality:

1987 production	475,118 MT
Brix	88.37
Apparent purity	37.21
Gravity purity	40.71
Ash	8.42
Reducing sugar	21.25

8.2.1.3 Cane juice

Cane juice could be a cheaper carbohydrate source compared to raw sugar and its quality should be more reliable than the one of molasses, in order to ensure acceptable fermentation yields. Available quantities are certainly adequate to satisfy the requirements of an industrial fermentation plant. One should notice, however that the cane juice is perishable, starting rapidly a fermentation process, especially when collected under unhygenic conditions. Present market price could be estimated at 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 transportation costs could greatly influence the actual price.

8.2.2 CORN-BASED RAW MATERIALS

The Corn-based raw materials are as follows:

8.2.2.1 Starch

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

A typical specification is as follows:

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 greatly affect the actual price (transportation costs within M. Manila area could reach 2 Pesos per bag).

8.2.2.2 Dextrine

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

8.2.2.3 Modified Starches

Available at Universal Robina. Production Capacity and prices are equivalent to those of dextrine.

8.2.2.4 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 Robina, glucose is obtained from cassava starch by acid hydrolisis, a rather obsolete method in western countries.

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

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

This quality is rather poor for utilization in high technology fermentation plants and therefore local glucose solutions should be previously checked in laboratories and/or pilot-plants.

About 250 Tons per month of glucose solution are produced at Universal Robina. This capacity is insufficient to supply a large fermentation plant, but it could be increased.

8.2.2.5 Corn-steep liquor

This product appears to be hardly marketed at present in the Philippines and is mainly utilized as animal feed. Some factories, as in the case of Universal Robina, do not concentrate the corn-steep liquor to 40-50% of total solids, as usual, leaving it in a concentration of 6-7% of solids.
The reason for this is the high cost of energy required for concentration, making the operation uneconomic.

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

There are no data concerning the corn-steep liquor quality, which could greatly affect the fermentation yields. Therefore, only laboratory and pilot-plant tests could demonstrate the possibility of utilization of this important raw material.

Diluted corn-steep liquor prices are at present in the range of 1 to 2 Pesos per kg. Concentrated corn-steep liquor 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.

8.2.3 Vegetable oils

The available vegetable oils are as follows:

8.2.3.1 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 Robina factory (Metro Manila) is of 120 MT per day at present.

8.2.3.2 Pork Lard oil

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

8.2.3.3 Coconut oil

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

9. HUMAN RESOURCES

In the country, there is a pool of trained microbiologists, chemists and engineers from which the human resources requirements for the pharmaceutical industry development projects can be met. Some of

these skilled persons are active in University research and/or teaching.

The following figures (figure 7 and 8) give, for instance, an indication of the Chemists and Engineers passing the board examinations, as well as the Mechanical Engineering board examination trend from 1983 to 1987.

In most cases additional training will be required, either in the Philippines or abroad, in Universities or especially in industrial plants. In the case of local training, when no suitably qualified Filipino trainers are available, foreign trainers of the national staff, or trainers of trainers should be employed.

Table 15 gives an overall summary of the highly qualified and qualified manpower requirements for the projects.

FIGURE 7

CHEMISTS AND ENGINEERS
PASSING THE BOARD EXAMS

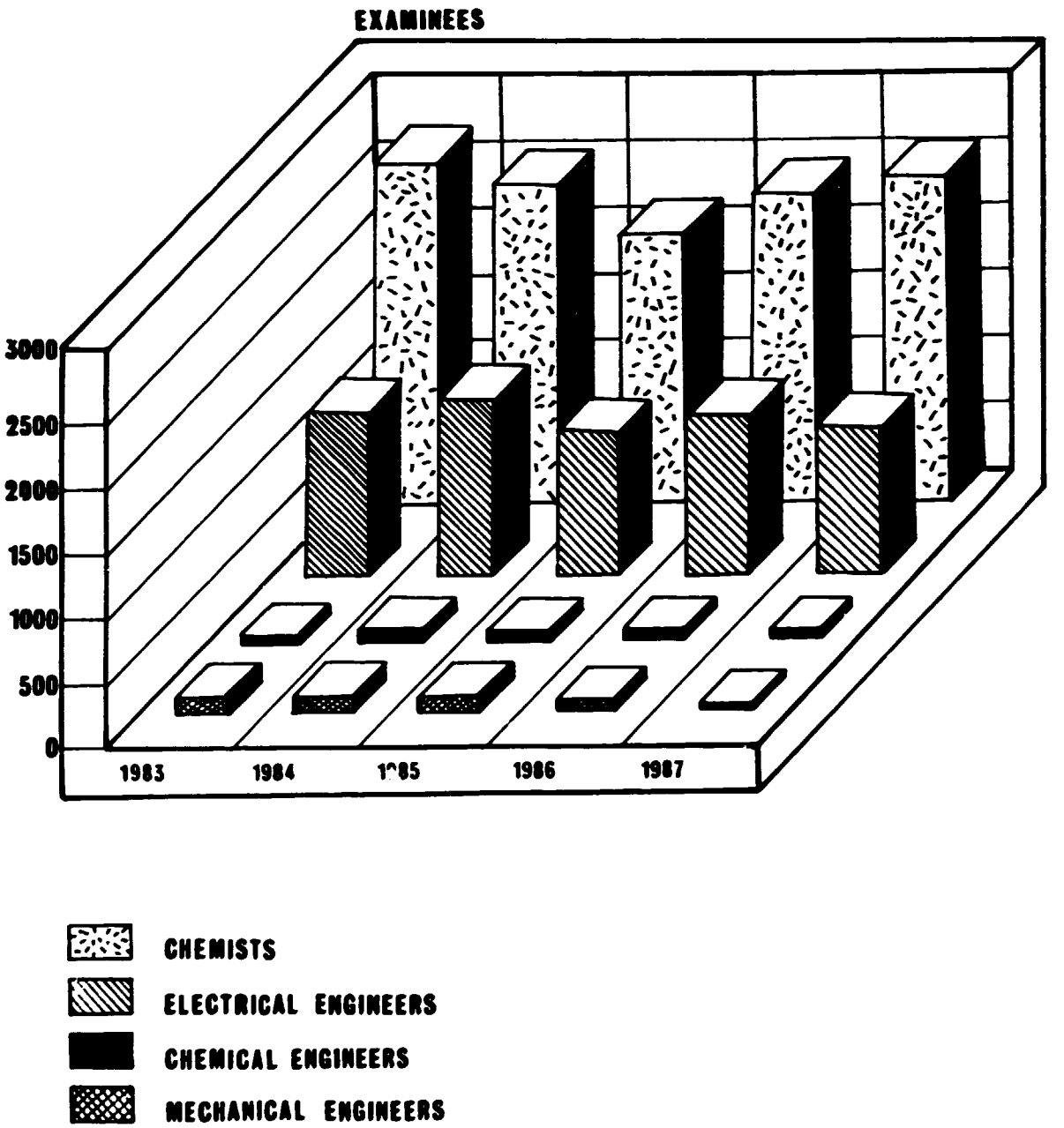


FIGURE 8

MECHANICAL ENGINEERING

BOARD EXAM TREND

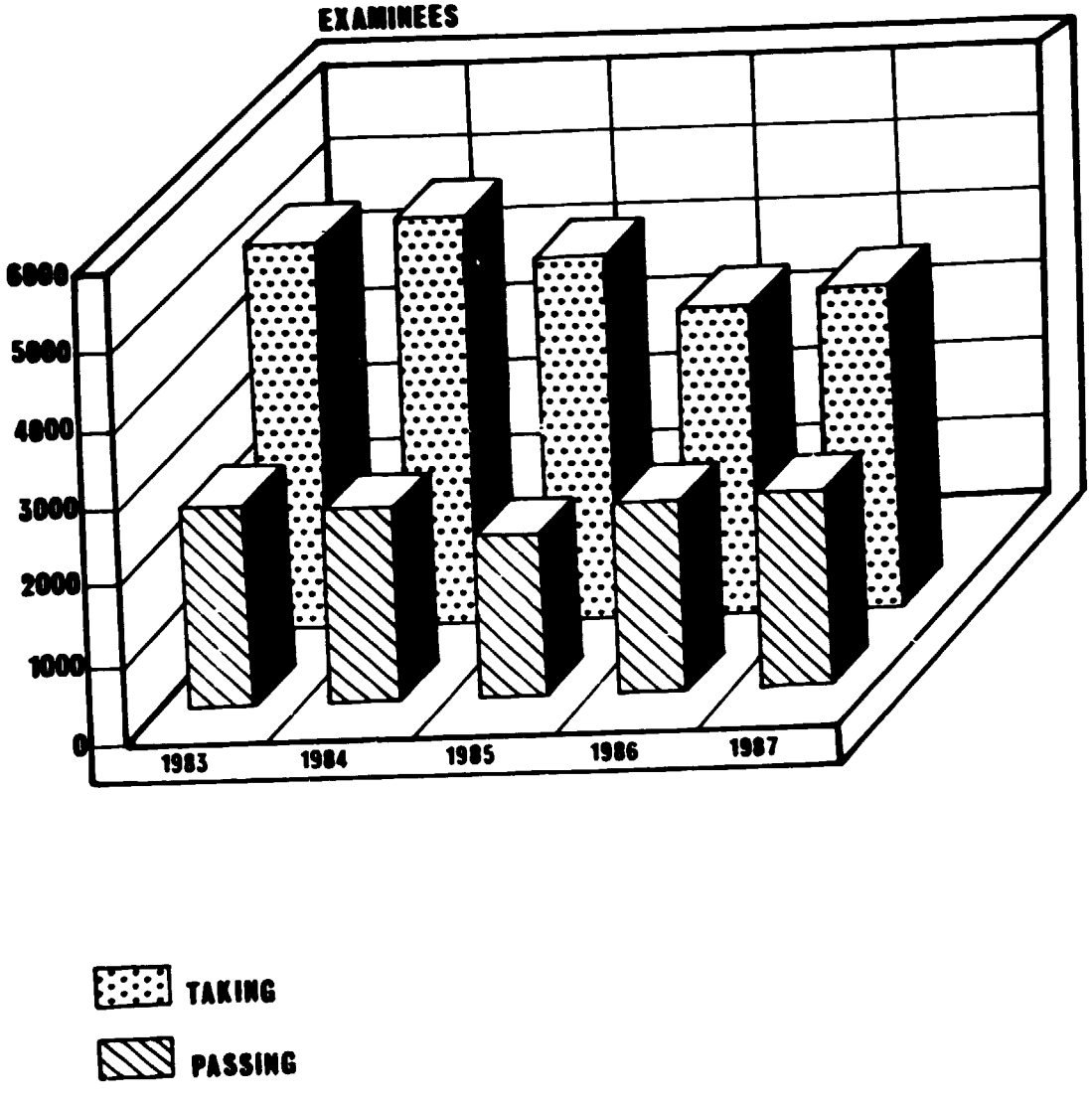


Table 15

MANPOWER REQUIREMENTS FOR THE DRUG PRODUCTION PROGRAM

Position	Qualifications	M.L.	P.P.	P.F.	M.F.	S.P.	R.E.	T.H.	Total
Team Leader	PhD Microbiology	1	-	-	-	-	-	-	1
Senior Microbiologist	MS Microbiology	2	2	2	2	-	-	-	8
Microbiologist	BS Microbiology	2	3	-	-	-	-	-	5
Team Leader	MS Chem or Bio	-	1	-	-	-	-	-	1
Chemical Engineer	MS Chem. Eng.	-	1	-	-	-	-	-	1
Department Head	BS Chem/Bio/Chem. Eng.	-	-	8	8	-	-	-	16
Head of Laboratory	PhD Microbiology	-	-	1	1	-	-	-	2
Biologists	BS Biology	-	-	2	2	-	-	-	4
Chemists	BS Chemistry	-	-	2	2	-	-	-	4
Plant Manager	MS Chemistry	-	-	-	-	1	1	-	2
Supervisor	MS Chemistry	-	-	-	-	4	4	4	16
Senior Production Technician	BS Chemistry	-	-	-	-	8	4	4	20
Production Technician	BS Chemistry	-	-	-	-	12	4	4	3
Senior Laboratory Technician	MS Chemistry	-	-	-	-	1	1	1	2
Quality Control Inspector	MS Chemistry	-	-	-	-	1	1	-	5
Laboratory Technicians	BS Chemistry	-	-	-	-	2	2	1	7
Foreign Experts	-	-	-	3	3	-	1	-	-
Total		5	7	18	18	29	18	14	109

Legend
M.L. = Microbiology Laboratory
P.P. = Pilot-Plant
P.F. = Penicillin Fermentation
T.H. = Tetracycline HCl
M.F. = Multipurpose Fermentation
S.P. = Semi-synthetic Penicillins
R.F. = Rifampicin, Erythromycin

The estimated total training costs for all projects is indicated on Table 16.

Table 16

ESTIMATED TRAINING COSTS

MANPOWER REQUIREMENT FOR THE DRUG PRODUCTION PROGRAM

Qualification	No. of months for Special Training			Financial Requirements *	
	No.	Local	Abroad	Minimum	Maximum
Ph.D. Microbiology	3	-	36	P3,189,600	P4,374,600
M.S. Microbiology	8	-	34	3,239,200	4,311,700
M.S. Chemistry	14	-	96	8,780,400	1,065,400
M.S. Chemistry	2	-	12**	1,109,000	1,377,000
M.S. Chemistry	3	9	-	216,000	618,000
M.S. Chemical Eng.	1	-	-	0	134,000
M.S. Chemistry or Bio.	1	-	6	554,500	688,500
B.S. Chem, Bio., or Chem. Eng.	11	-	-	0	0
B.S. Chemistry, Bio., Chem. Eng.	5	-	20	1,920,000	1,920,000
B.S. Biology	4	-	16	1,536,000	1,536,000
B.S. Chemistry	16	-	64	6,144,000	6,144,000
B.S. Chemistry	4	12	-	288,000	288,000
B.S. Chemistry	28	-	-	0	0
B.S. Microbiology	2	-	-	0	0
Sub-total	102	21	284	26,977,200	32,048,200
Experts					
Foreign Experts	7***	-	-	31,863,000	31,863,000
Local Trainors	2	-	-	360,000	360,000
Total	112	21	284	P58,840,200	P63,911,200

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* The maximum financial requirement assumes hiring at B.S. level and includes fellowship beyond the B.S. level and special training only.

** Alternatively, the training may be done locally.

*** The total number of man/months is estimated at 156 (72 for the Penicillin manufacture, 72 for the multipurpose fermentation plant and 12 for the Erythromycin and Rifampicin fermentation)

The total manpower required for the entire antibiotics program is estimated at about 571 persons, as follows:

9.1	Penicillin fermentation (including 6-APA)	190
9.2	Fermentation Pilot-plant	20
9.3	Multipurpose-fermentation plant	220
9.4	Erythromycins and Rifampicin Unit	27
9.5	Semi-synthetic Penicillins Unit (expansion of Chemfields)	45
9.6	Tetracycline HCL, Oxytetracycline HCL and Chlortetracycline Unit	21
9.7	Multi-purpose Pilot-plant for Chemical Synthesis	48

An upgrading of Universities and Colleges is urgently needed, particularly in the field of sciences and engineering. The general deficiency of the system, even among the better Universities remains in the training of the students in the practical aspects of these disciplines.

A system of accreditation, in which Universities and Colleges of a given region associate and group around leading Universities, would be one way to accelerate the up-grading.

10. INFRASTRUCTURE

10.1 Energy

Fermentation is characterized by high energy requirements, an important part of the latter being due to the refrigeration necessity, particularly in climates like the one in the Philippines. The average air and water temperatures in the country, will make the utilization of once through well or river water for refrigeration, very problematic. The available water temperature during the hot season, is reaching up to 30°C and in localities like Los Banos, - 40°C. Furthermore, the utilization of once through well water would require very large continuous flow rates, unavailable in many localities. On the other

hand, the utilization of river water would require important treatment units, due to the sometimes high amount of suspended solids, greatly increasing the fouling factors 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% lower than in 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 in 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 irreversible effects and eventually the death of the micro-organisms. To avoid this risk, the first condition is to guarantee the absolute continuity of the electrical power supply.

Due to the high costs of fuel oil, the utilization of local energy sources like Bagasse would be very important to ameliorate the economics of the plant operations.

10.1.1 Bagasse

Bagasse is a lignocellulosic residue derived from Sugar Cane and burned as fuel, especially in large sugar mills with refinery operations. In 1982, it was estimated by a UNIDO team, that after accounting for the possible uses of bagasse, around 544,000 dry tons are

annually available as surplus, covering very largely the total energy requirements of a fermentation plant of about 100,000 tons, as in the case of the Penicillin fermentation, or about 80-85,000 tons as in the case of the multipurpose-fermentation plant.

Some of the average characteristics of Bagasse produced by various sugar plants in 1987 are as follows:

Metric tons	3,949,806
Moisture %	47.31
Fiber %	43.83
Cane %	28.72

The surplus bagasse being hardly marketed, its cost is practically negligible, if not affected by the transportation costs. For this reason, it would be 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 carbohydrate fermentation substrates, such as raw sugar, cane juice and/or molasses.

10.2 Water

Refrigeration requirements of process equipments should be covered by closed-loop systems of chilled water at about 10°C, produced by mechanically refrigerated units and of 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 seems 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.

11. INVESTMENT PRIORITIES PLANS AND GOVERNMENT INCENTIVE PROGRAMMES

"The 1988 Investment Priorities Plan (IPP) identifies 277 areas of economic activity that are to be entitled to investment incentives[1] under the Omnibus Investment Code of 1987.

In essence, it serves as the vehicle to direct investments into those areas where the country's need is greatest - those where there is maximum potential to create much needed jobs, make use of locally available resources, accelerate the process of industrialization and develop competitiveness in the international marketplace".

11.1 Investment Priorities

The priority areas identified in the pharmaceutical field are:

11.1.1. Antibiotics (P)

a) Penicillins

b) Streptomycins

c) Tetracyclines

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(1) See - 1988 Investment Priorities Plan (Board of Investments)
Foreign Investment Policies in the Philippines (Board of Investments, January, 1988)
The Omnibus Investments Code of 1987 (July 1987, Board of Investments)
Comparative Investment Incentives (The SGV Group), 1988
Doing Business in the Philippines (The SGV Group),1988
Rules and Regulations to Implement Executive Order No.226 otherwise known as the Omnibus Investments Code of 1987 (Board of Investments, April 1988)

11.1.2. Acetylsalicylic acid (P)

11.1.3. Parenteral therapy systems and components thereof (P)

11.1.4. Herbal medicines (NP)

11.1.5. Other pharmaceuticals (P/NP)

11.2 Incentives

The investment incentive schemes elaborated in the "Omnibus Investments Code of 1987", are summarized as follows:

11.2.1. Income Tax Holiday

11.2.2. Additional Deduction for Labour Expense

11.2.3. Tax and Duty Exemption on Imported Capital Equipment

11.2.4. Tax Credit on Domestic Capital Equipment

11.2.5. Exemption from Contractor's Tax

11.2.6. Simplifications of Customs Procedures

11.2.7. Tax Credit for Taxes and Duties on Raw Materials

11.2.8. Exemption from Taxes and Duties on Imported Spare Parts

11.2.9. Exemption from Wharfage Dues and Any Export Tax, Duty Impost and Fee

11.3 Comparative Investment Incentives

According to several foreign investors, especially from Japan and Taiwan, the investment incentives offered in the Philippines do not make the country particularly attractive to foreign businessmen, but merely put the country on equal footing with some of its Asian neighbors.

These observations are supported by the findings of a recent survey conducted by the "SGV Group" on the investment incentives offered by nine Asian countries. The survey compared the nine countries using as yardstick 39 incentives commonly offered to investors. These range from the provision of basic rights and guarantees to tax and tariff exemptions, and assistance to investors.

Out of the 39 incentives, the Philippines offers only 20, the second lowest in the region after Hongkong with 19.

The Country's ASEAN neighbours are more generous with incentives: Indonesia provides 22, Thailand 26, Singapore 27 and Malaysia 31. Of the other "tiger economies", Taiwan offers 29 incentives and South Korea 27.

The incentives not offered by the Philippines, but offered by other Asian countries are:

11.3.1. Guarantee against losses due to nationalization
11.3.2. Guarantee against losses due to damage caused by war
11.3.3. Guarantee against losses due to incovertibility of currency
11.3.4. Preference in the granting of government loans
11.3.5. Protection against import competition
11.3.6. Protection against Government competition
11.3.7. Real estate ownership by alien investors
11.3.8. Exemptions from capital gains taxes
11.3.9. Exemptions from taxes on royalties
11.3.10. Exemptions from withholding tax on interest on foreign loans (tax credits)
11.3.11. Accelerated depreciation allowance
11.3.12. Carry forward of capital allowance during the relief period
11.3.13. Carry forward of loss
11.3.14. Export allowances or deductions
11.3.15. Deduction of organization expenses
11.3.16. Deduction of pre-operating expenses
11.3.17. Deduction of reinvested profits
11.3.18. Investment tax credits
11.3.19. Technical assistance to investors

12.THE UP-STREAM INTEGRATION OF THE PHARMACEUTICAL INDUSTRY IN THE PHILIPPINES.

12.1 Chemfields

Chemfields was registered with the Board of Investments as a preferred-pioneer enterprise engaged in the manufacture of semi-synthetic Penicillins from imported intermediates and started manufacturing in 1981.

After 8 years of continuous operations, Chemfields, with an initial capacity of 25 m tons, has reached a production volume of over 75 m tons of semi-synthetic Penicillins and is still the only up-stream integrated entity in the pharmaceutical industry of the Philippines.

In 1982, Chemfields was granted protection with the issuance of Executive Order No. 776, taking the form of import regulations. Importations of semi-synthetic antibiotics already being produced in the country would be allowed only if it could be demonstrated that their recent landed costs were at least 20% lower than the prices of the domestic manufactured products.

What did Chemfields achieve and was it worth to grant privileges and protective measures?

12.2 Assessment of Chemfields' Economic Contributions

Among the major economic contributions that the Chemfields'semi-synthetic antibiotics project promised to deliver were: (1) price moderation of the prices of finished dosage forms through lower raw material prices and their slower growth, (2) foreign exchange savings by means of effective import substitution, and (3) technological upgrading of the pharmaceutical industry.

12.2.1 Price moderation

With an annual compound growth rate of 16.2%. Peso depreciation in the period 1982-1988, at the very least the prices of Ampicillin and Amoxycillin, as well as the prices of finished dosage specialties manufactured from them, would have increased at the same rate had they been imported. Over the same period, however, the actual prices of locally-produced Ampicillin and Amoxycillin increased at annual compound growth rates of only 7.8% and 3.8%, respectively. In fact, during the inflationary period of 1984-1986, Chemfields did not increase its prices, although any price increase in this period would have been easily justified. In 1987, Chemfields even decreased the prices of all its products.

Table 17

RATE OF PRICE INCREASE : AMPICILLIN AND AMOXYCILLIN vs FOREX

1982-1988

A. Rate of Price Increase: Ampicillin Prices VS. Forex

1982-1988

Year	Peso/US$ Rate	% change	Ampicillin peso per kg.	% change
1982	8.37		1,402	
1983	12.16	12.2%	1,526	8.8%
1984	14.00	14.0%	1,985	30.1%
1985	20.60	47.1%	2,290	15.4%
1986	20.42	-0.9%	2,290	0.0%
1987	20.46	-0.2%	2,275	-0.7%
1988	21.05	2.9%	2,200	-3.3%
Annual Compound Growth Rate		16.6%		7.8%

B. Rate of Price Increase: Amoxycillin Prices VS. Forex
1982-1988

Year	Peso/US$ Rate	% change	Amoxycillin peso per kg.	% change
1982	8.37		2,210	
1983	12.16	12.2%	2,231	1.0%
1984	14.00	14.0%	2,633	18.0%
1985	20.60	47.1%	2,970	12.8%
1986	20.42	-0.9%	2,970	0.0%
1987	20.46	-0.2%	2,925	-1.5%
1988	21.05	2.9%	2,700	-7.7%
Annual Compound Growth Rate	16.6%			3.8%

This had a definite moderating effect on the price increase of finished dosage specialties manufactured from locally-produced Ampicillin and Amoxycillin. Price data of finished dosage specialties showed that while the prices of finished dosage specialties using imported materials rose at almost the same rate as the average rate of Peso depreciation, those of finished dosage specialties manufactured from locally-produced Ampicillin and Amoxycillin increased at much slower rates, as shown in the following table:

Table 18

AVERAGE PRICES OF SELECTED MEDICINES, 1982 & 1988

	Average price/capsule		Annual compound growth rate
	1982	1988	
Ampicillin 250 mg. capsule	1.34	2.78	12.9%
Amoxycillin 250 mg. capsule	1.83	4.11	13.7%
Cloxacillin capsule	1.70	4.21	16.3%
Chloromycetin capsule	0.69	2.53	24.1%
Penicillin capsule	1.31	3.50	17.8%
Tetracycline capsule	0.30	0.75	16.5%
Oxytetracycline capsule	0.68	2.37	23.2%
Doxycycline	3.65	10.08	18.5%

12.2.2 Foreign exchange savings

The estimated net foreign exchange savings to the country of the local production and sale of Ampicillin and Amoxycillin from 1983, when import regulation started to the first semester of 1988, was about US$ 40.0 million. This estimate was based on the 1980-1982 average import prices of Ampicillin and Amoxycillin and the equivalent US dollar prices of the locally-manufactured products.

Table 19

ESTIMATED FOREIGN EXCHANGE SAVINGS

	Import Price $C&F/KG	Local Price $C&F/KG	Local Qty.Sales KGW	Import Price x Qty.Sales $ 000	Local Price x Qty.Sales $ 000	Forex Savings $ 000
A. Ampicillin						
1983	188.19	97.70	26,480	4,983	2,587	2,396
1984	188.19	110.40	32,792	6,171	3,620	2,551
1985	188.19	86.55	37,524	7,062	3,248	3,814
1986	188.19	87.30	30,220	5,687	2,638	3,049
1987	188.19	86.57	47,268	8,895	4,092	4,803
1stSem 88	188.19	82.80	13,053	2,456	1,081	1,376
Total				35,255	17,266	17,989
B. Amoxycillin						
1983	391.39	142.83	8,600	3,366	1,288	2,138
1984	391.39	146.44	11,462	4,486	1,679	2,806
1985	391.39	112.24	15,939	6,238	1,789	4,449
1986	391.39	113.23	15,069	5,898	1,706	4,192
1987	391.39	111.30	20,349	7,964	2,265	5,700
1stSem 88	391.39	101.62	6,559	2,567	667	1,901
Total				30,520	9,334	21,186
Total Foreign Exchange Savings(1)						39,175

(1) The foregoing estimate of foreign exchange savings is actually understated, since only a portion of Chemfield's price represents reported inputs.

12.2.3 Total Taxes Paid

The domestic production is at a disadvantage as compared to imports due to the relatively high taxes imposed. This situation is apparent from a review of the total taxes paid by Chemfields to the Government from the year 1981 to the firstsemester of 1988, which indicates a total of P 165 millions, or about 23 % to 26% of sales inspite of incentives.

Competing products from other established export producers are enjoying subsidy on exports. Aside from a duty and tax free imports of raw materials, some foreign producers from countries such as India, for instance, are being given a 6 % bonus based on FOB prices, in addition to tax free profit made from the operation. Others receive very special credit terms, as a part of the country's export promotion policies.

This is further compounded by the situation wherein duties and taxes on the raw materials used to manufacture the local product are at the same level as importation of competing bulk raw materials.

12.2.4 Industrial development

For the first time in the country, national scientists and technicians were given the opportunity to learn and perform chemical synthesis in an actual industrial setting.

The few years of experience have already yielded some fruits:

a. The local plant is now considered as a very efficient plant in its class

b. Similar plants were built in Thailand and Indonesia by means of technology transfer provided by Chemfields.
   Today, Filipino scientists occupy key operating positions in these plants.

More important perhaps is the confidence provided by this experience to scientists to evaluate the feasibility to move one step farther to fermentation, towards a full up-stream integration in this subsector of the pharmaceutical industry.

The general perception is, however, that in order to achieve this, there should be a strong political will with firm commitments and sustained Government efforts, with stable and consistent rules of the game and with reduced flexibility in the implementation of incentives.

Table 20

RECAPITULATION OF THE PROPOSED PLANTS

Product	Investment (millions US $)	Manuf. Capacity (M. Tons)	Sales (000 US $)	Prod. Costs	Manpower (No.)
1. Penicillins and 6-APA	26-30.00	295	11,630	6,600	190
2. Fermentation pilot-plant	1.5-2.00	-	-	-	20
3. Erythromycin Base, Rifamycin and Tetracycline Base	3300	147	10,330	6,240	220
4. Semi-synthetic Penicillins (Ampicillin, Amoxycillin, Cloxacillin, Cephalexin)	5.90	74	7,620	6,461	45
5. Erythromycin Derivatives and Rifampicin	1.53	45	7,788	6,859	27
6. Tetracycline Hydrochloride Oxytetracycline Hydrochloride	1.20	35	1,240	920	21
7. Multi-purpose pilot-plant for Chemical Synthesis	5.2	83	1,302	-	48

ANNEX I

LIST OF PARTICIPANTS

Panel Members

Dr. Christian Noe	(Austria)
Dr. Janos Fari	(Hungary)
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Dr. M. Philippe	(Belgium)
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Dr. A. Tcheknavorian-Asenbauer - Chaiperson of the meeting

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ANNEX II

SUMMARY OF TECHNICAL DISCUSSIONS OF A SEPARATE SESSION OF THE AD-HOC PANEL ON THE MULTIPURPOSE FERMENTATION PILOT-PLANT FOR ANTIBIOTICS

The total list of equipment proposed for the plant was reviewed in detail and considered suitable and sufficient for the scaling up of technologies before full industrial production.

It was confirmed that the following fermenters should be supplied in addition to the existing ones at Biotech :

6(vessels only)	fermenters of 2 liters(glass)
6	fermenters of 10 liters(glass)
2	fermenters of 100 liters
1	fermenter of 1000 liters

The existing fermenters of 30, 130 and 200 liters should be utilised exclusively for the work on Rhizobium. The other fermenters could also be utilised in the process development for the production of the enzyme used in the biological transformation of Penicillin into 6-APA.

Concerning the equipment, it was suggested by the experts to delete from the list the Podbielniak extractor and in its place to purchase a decanter from Westfalia, for the plant to conduct direct broth extraction trials. This was recommended, since this method is being utilised more frequently in most modern operations.

Regarding the pilot-plant premises the following recommendations were made :

- The pilot-plant for antibiotics should be separated and independent from the other operations of the plant.
- The microbiology laboratory should be close to the pilot-plant.

- All possible efforts should be made to remove the operations on Rhizobium from the existing building, where the pilot-plant has been recommended to be installed.
- Although Biotech has at present a waste treatment system, which is sufficient for the beginning of the operation, provision should be made for the treatment of possible contaminated batches.

The following personnel are absolutely necessary for the running of the antibiotics pilot-plant:

A) For the microbiology laboratory :

1 team leader
2 senior microbiologists
2 microbiologists
3 workers

B) For the pilot-plant :

1 team leader
2 senior microbiologists
3 chemists
5 workers
1 chemical engineer

The above personnel should work full time for the pilot-plant and should be available from the first year of the execution of the project.

It was considered of utmost importance to make the plant available for training activities. Accordingly, provisions of the necessary space for this purpose should be made during the planning stages.

Although the entire training programme for the plant staff should be elaborated in detail, it was considered necessary as a first step to send 2 microbiologists and 1 chemist for training abroad.