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PHILIPPINES PHARMACEUTICAL INDUSTRY DEVELOPMENT STUDY

DP/PHI/87/019

PHILIPPINES

Technical report: Multi-purpose pilot-plant for chemical synthesis*

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

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Vienna

* This document has not been edited.

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TABLE OF CONTENTS

PART 1. INTRODUCTION

1. Objective.

1.1 As a part of the overall analysis programme to propose a plan of action for the Development of the Pharmaceutical Industry in the Philippines, this report will deal with some aspects of the possible back integration of the existing state of the Industry. It should only be considered part of the Pharmaceutical Industry insofar as it deals with the production of Fine Chemicals which are bulk active ingredients (otherwise described here as Pharmachemicals) for use in the true Pharmaceutical Industry already established.

1.2 Objects of the investigation were to try to :-

- identify, together with other experts, any raw materials of commercial interest indigenous to the Philippines which could be utilised in Chemical synthesis.
- examine the possibility of establishing dedicated, multi-product or multi-purpose plant installations of appropriate size for the production of Pharmachemicals.
- recommend what type, if any, of production should be considered for development.
- recommend lines of products, or mixes of products which could form the basis eventually for a profitable and viable industry which would be of interest to investors, either National or Foreign.
- suggestions as to means by which profitability could be acheived especially in the early years of production or development.

In the event of a positive feeling that production of Pharmachemicals should be studied further some outline specifications for an appropriate production unit, or indeed units (if it is pertinent to consider such) will be indicated.

2. Approach.

2.1 The first priority should be to analyse the importation of drug products in both bulk and dosage forms and also to analyse the consumptions of finished products supplied both through hospital pharmacies and drug stores. There may also be some supplies through specific health programmes, such as malaria and leprosy.

2.2 Some consideration will be given to determine market growth in the various classes of therapeutics and in certain specific products.

2.3 It is considered of high priority to try to select products of especial importance in treating the most prevalent and serious maladies and diseases needing treatment in the Philippines.

2.4 It is unlikely that it will be appropriate to consider high volume, low price products (such as acetylsalycylic acid or paracetamol) either produced in multi-purpose plants (where capacity is limited) or in dedicated plants which must necessarily be large and of high capital expenditure. However, such considerations will not be ignored.

2.5 It is not considered likely at first sight that the approach of multi-product plants will be relevant to the Philippines for the volumes of the various related products which could be produced are likely to be too large for solely domestic consumption. Also generally one product is found to be predominantly preferred and the others of too low volume to warrant production. Such plants benefit greatly by being able to serve an export market when a better spread of production levels can be acheived.

2.6 The use of domestically available chemicals and materials, insofar as possible, has to be considered. As little chemical industry would appear to exist in the Philippines especial attention must be given to the utilisation of plant, animal, marine or waste product resources. These will also be under the consideration of various other experts.
Also, as far as plant sources are concerned, this section will be limited only to any plant products extractable in pure and defined form or capable of simple chemical transformation to Pharmachemicals.

2.7 Some raw materials of great potential interest are outside the scope of this section of the report, not being active ingredients. Many of these fall under the umbrella of excipients such as glycerine, sorbitol, dextrose USP, sodium chloride. Other important products such as alcohols, acetone etc. can be obtained from agricultural products such as coconut, cassava, molasses etc.

3. Types of production units.

3.1 Extraction plants. These use natural plant (or sometimes animal) products as feed material. Production using such plants usually involves solvent extraction of suitably prepared material. Materials may be prepared simply by cutting or comminution and then extracted, but frequently some chemical pre-treatment is also performed.
Such production can be performed in either dedicated or multi-purpose extractors operated under batchwise or continuous conditions. Assessment has to be based on volume and variety of the input materials.
The isolation of the pure ingredients can usually be performed in relatively simple equipment although this refining of crude isolates or extracts is usually a specialised and complex operation.

3.2 Dedicated chemical plants. These can be considered as chemical production units designed specifically to process only one product. They are usually high capacity units and may be either batch type or continuous. Such plants have little flexibility and are used for long term production of the same products. Cross contamination is no problem.

3.3 Multi-product chemical plants. May be considered as plant and equipment which is designed essentially to produce a range of related products. The definition of 'related products' may be wide and could be based on the following, as examples :-

- starting production from a common starting material, e.g. phenol for acetyl salicylic acid and paracetamol.
- from similar, but different, starting materials to produce a chemically similar group of products, e.g. sulphonamides.
- confining production to the consideration of similarity of side chain variations, e.g. Clotrimazole, Econazole, Isoconazole and Miconazole from Imidazole.
- similar methods of preparation of the benzylimidazoles Mebendazole, Lobendazole, Albendazole and Oxibendazol could form another suitable group of products.

The scale of such plants, to be economical, should be medium to large and would be expected to process in excess of 500 tons. products per annum.

There is not usually much flexibility for change of product outside of the design group.

3.4 Multi-purpose or multi-purpose pilot plants. The advantage of these plants is their flexibility. They can not only produce a wide range of products, but also it is possible to change product mixes readily as market needs dictate.

These plants also provide the opportunity for small scale production and process improvement work to provide more precise economic evaluation and feasibility of establishment of larger multi-product or even dedicated plants in the future as demands dictate.

Such plants consist 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 reactors will range from perhaps 50 liter through 200 liter, 500 liter and 1000 liter to a maximum in the order of 4500 liter. The reactors are fitted with condensers and receivers mostly to furnish 'general purpose' units though some may have special function, such as high vacuum distillation. Ancilliary 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.

Such plants are particularly attractive for installation in developing countries when the first stage of backward integration from the pharmaceutical industry is being considered.

Such plants are particularly useful also in providing a secure basis for education, training and experience in chemical processing and later for development of 'in house' processes.

Initially, however, the installation of such units 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. Choice of technologies is very important and should be such to give experience in as wide a range of unit operations and processes as possible.

Although it is not too realistic to expect such units to be operated economically as such, particularly in the early years, some contribution should be realised. Some limited domestic supply of pharmachemicals for the pharmaceutical industry will be realised and although cost prices may be higher than the world market there should be inherent benefits such as saving of foreign currency, some reduction in borrowing costs as a result of lower inventories, some security of domestic supply etc.
The real benefits will be derived in later years, perhaps after five or even ten years.

It must be realised that there is a price to be paid for the progress sought in such back integrations.

4. Research and Development.

4.1 Research and Development facilities must be incorporated in the design of any multi-purpose pilot plant. This involves not only the provision of laboratory facilities with equipment up to 20 liter capacity, but also use of the plant units from 50 liter upwards.

4.2 Although ultimate Research and Development facilities should be an integral part of the production pilot plant it would be wise to set up laboratory facilities (or better utilise existing facilities in either Universities or Technical Units) at the very earliest stage so that work could be commenced on developing processes which could be considered for pilot production products of a second generation, i.e. after the successful commissioning and operation of the purchased technologies. Thus some three years work could well be completed by the time any production unit could be designed, built and commissioned. Whether such an operation should be continued after the provision of the Production facility would be judged on results. Such work would, of course, need immediate funding.

4.3 The Research and Development function should satisfy several criteria :-

- process development for the full scale production.
- trouble shooting.
- process improvement.
- scaling up.
- investigation of any further backward integration.
- development and scaling up of processes leading to new products ('In house' development).
- monitoring alternative sources intermediates and chemicals.

New products in this context means additional products to those originally scheduled and are likely to be products which would currently be ending their patent life. Generally these can be expected to be higher price products and likely to be more profitable (though a drop in price must always be expected after a patent expires and several other manufacturers enter the market).

5. Quality control and production control.

5.1 Apart from good documentary control of production a facility is necessary for the control of purchased intermediates and chemicals, for the monitoring of manufactured intermediates and for the analysis of the final pharmachemicals according to the appropriate pharmacopoeias or customers specifications.

5.2 Although it is normal for an analytical laboratory to report on the quality of production intermediates, it is equally usual for the production department to also have laboratory facilities for the reaction control and preliminary product control.

6. Infra-structures in the Philippines for the Establishment of any manufacturing operation have to be examined and analysed.

6.1 The aspects of supply and reliability of electricity, water, effluent disposal, waste solid disposal and other services will be investigated. It may well be that at the next stage of design considerations installations to deal with any problems must be considered in depth.

6.2 Although not likely to be defined in this report some views on location will be considered if appropriate.

6.3 Fire fighting and Hospital services will be considered.

6.4 Existing support services such as vessel fabricators, piping contractors, designers, boiler manufacturers, generator manufacturers, pump manufacturers and particularly maintenance service need to be considered.

6.5 A view of the availability of existing support services such as research, investigation or analytical.

6.6 Of paramount importance is the question of Human Resources.

7. Patent situation.

7.1 The patent situation in the Philippines will be considered for pharmachemicals and processes. However, this cannot be considered in depth until technologies are specifically under consideration. The situation is not likely to have any bearing on any initial technologies under review.

PART 2. INVESTIGATIONS.

1. General situation.

In order to even consider the possibility of back integration to chemical synthesis of pharmachemicals it was necessary to determine first-hand the state of the Pharmaceutical Industry existing in the Philippines. To this end a cross section of Filippino owned and Multinational Pharmaceutical Companies were visited. These comprised :-

Hizon Laboratories,Inc.
Interphil Laboratories,Inc.
Pfizer,Inc.
Warner Lambert Philippines,Inc.
United Laboratories,Inc.
Pascual Laboratories,Inc.
Hoechst Philippines,Inc.
Abbott Laboratories Philippines.

In addition table discussions were held with Senior Executives of Cyanamid Philippines, Inc. and Schering Corporation (Phil.) Inc.

In all cases the reception was extremely good, discussions very open, viewing premises very extensive and questions readily answered.
In general there is an over-capacity and both Multinational and Filippino Companies expressed openly their wish to assist with the provision to the Government of the Philippines of cheaper drugs by using up the excess capacity and producing drugs at a price essentially of component costs and labour, excluding any normal overheads or margins. There is also an added bonus of increasing the income of the Filippino workers. The cost could be further reduced by processing ingredients bulk purchased by the Government.

This is an immediate benefit to the Health care of the Philippine people and it has to be recommended that any such offers should be taken up.

The conclusion from all visits was that an excellent industry of Pharmaceutical formulation and packaging is well established in the Philippines and it equals any other in the Developed and Western Countries.

It is something to be proud of and it should be noted a considerable proportion is in the hands, and under the management, of Filipino professionals. Nonetheless, the beneficial effect of the Multinationals must also not be ignored. The overall effect is well balanced.

The level of Research and Development existing in the Philippines is not high for all the Multinationals rely on Centralised R & D at the parent Companies, but the results are available to the Philippine Companies. The largest Filipino Company, United Laboratories, Inc. is the exception in having its own very extensive and excellent Research and Development facilities. The facilities of the smaller Filipino Companies are accordingly limited but the aspect of R & D not ignored.

Conclusion: The Pharmaceutical Formulation and Packaging Industry of the Philippines is of World Class and from this point of view the Country is well advanced to consider back integration into the synthesis of Pharmachemicals.

The question of consumption has next to be considered.

2. Analysis of consumptions and trends.

Criteria for the choice of products for possible chemical synthesis, level of production needs and the type of production unit(s) are:-

- needs of the Philippines Health system and prevalent diseases.
- needs and consumptions of the local formulation industry.
- levels of consumptions, current and future, for the determination of most appropriate productions.

- the suitability and compatibility of technologies for operating a multipurpose chemical pilot plant for any chosen mix of products.
- availability of technologies and patent situation.
- 'technology transfer' value of technology.
- economy of production.

It is considered, in a first step of backward integration, best to give preference to Pharmachemicals already being imported in bulk active form and less emphasis on those still imported as bulk formulations and finished dosage forms.

It is suggested that, certainly in the first stage of backward integration, the inclusion of any bulk active ingredient patented and/or supplied by Multinationals from their own production should be excluded. Not to do so could be counter-productive for the general Health service. The Multinationals contribute greatly to the Health treatment by their local presence and ability to introduce most modern medicines to the Philippine market as they become available.

2.1 Drug needs of the Philippines and Prevalent Diseases.

Recent studies have been made and lists prepared indicating the most important and priority drugs considered relevant for the Philippines.
The proposed contents of the Department of Health, Philippines Formulary for Hospitals and Primary Health Care 1988 and the corresponding Formulary for Rural Health Units are most important, but it is interesting to compare with the Philippines Medical Association 'Formulary for Medical Practice in the Philippines 1988' (draft).

For the purposes of this report the Formularies are not reproduced in full, but emphasis given only to products which might be considered for chemical synthesis.
Anti-biotics and Vaccines, subjects of study by other experts, are recorded in an Appendix.

Ref.	Group	DOH Hospitals and Primary Health Care	DOH Rural Practice	Philippine Medical Association
1	Analgesic	Acetylsalicylic acid Paracetamol	Acetylsalicylic acid Paracetamol	Acetylsacylic acid Paracetamol
2	Anaesthytics	Diazepam Lidocaine HCL Propypoxycaine HCL	– Lidocaine HCL Propoxycaine HCL	Diazepam Lidocaine HCL –
3	Antacids and other anti-ulcer	Cimetidine	–	–
4	Anti-Allergics	Chlorpheniramine maleate Hydrocortisone Prednisolone	Chlorpheniramine maleate –	Chlorpheniramine maleate –
5	Anti-anaemic	Hydroxycobalamin	–	–
6	Anti-coagulants	–	–	–
7	Anti-convulsants	Carbamazepine Clonazepam Diazepam Ethosuximide	– – – –	Carbamazepine – Diazepam Ethosuximide
8	Anti-diabetes	Acetohexamide Glibenolamide	– –	– –
9	Anti-dotes	Diphenhydramine HCL Atropine sulphate Naloxone Protamine sulphate Pyridoxine HCL	– Atropine sulphate – – –	Diphenhydramine HCL Atropine sulphate Naloxone Protamine sulphate Pyridoxime HCL
10	Anti-emetics	Promethazine HCL –	 Dicyclomine HCL	Promethazine HCL –
11	Anti-Gout	Indomethacin	–	–
12	Anti-hypertension	Furosemide Hydrochlorthiazide Spironolactone Alprenolol Clonidine HCL Proponalol HCL Hydralazine	– Hydrochlorthiazide – – – – –	Furosemide Hydrochlorthiazide – – – – Hydralazine

Ref.	Group	DOH Hospitals and Primary Health Care	DOH Rural Practice	Philippine Medical Association
13	Anti-infective	Furazolidone	–	Furazolidone
		Metronidazole	–	Metronidazole
	(sulphonamides)	Cotrimoxazole (Sulphamethoxazole/ trimethoprim)	–	Cotrimoxazole
		Sulfisoxazole	–	–
		Sulfaxone sodium	–	–
		Triple sulfa	–	–
	(Anti-leprosy)	Clofazimine	–	–
	(Anti-leprosy)	Dapsone	–	Dapsone
	(Anti-tuberculosis)	Ethambutol	–	–
	(Anti-tuberculosis)	Isoniazid	Isoniazid	Isoniazid
	(Anti-tuberculosis)	Pyrazinamide	Pyrazinamide	Pyrazinamide
	(Urinary Antiseptic)	Nalidixic Acid	–	Nalidixic Acid
	(Anti-helminthics)	Mebendazole	Mebendazole	Mebendazole
	(Anti-helmenthics)	Piperazine citrate	Piperazine citrate	Piperazine citrate
		Praziquantel	–	Praziquantel
	(Ameabicides)	Diloxamide furoate	–	–
		Metronidazole	Metronidazole	Metronidazole
	(Anti-malaria)	Amodiaquine	Amodiaquine	Amodiaquine
		Chloroquine	Chloroquine	Chloroquine
		Primaquine	Primaquine	Primaquine
		Quinine	Quinine sulphate	Quinine
		Sulfadoxine/ Pyrimethamine	Sulfadoxine, etc.	Sulfadoxine, etc.
	(Anti-Schistosomals)	Praziquantel	–	Praziquantel
14	Anti-migrane	Acetylsalicylic acid	–	–
		Paracetamol	–	–
		Propanolol HCL	–	Propanolol
15	Anti-neoplastic and mimuno-suppressive drugs	Megestrol acetate	–	–
		Vincristine sulphate	–	Vincristine
		–	–	Vinblastine
16	Anti-Parkinsons Drugs	Diphenhydramine HCL	–	–
		L-Dopa + Benserazide	–	L-Dopa
		L-Dopa + Carbidopa	–	–
17	Anti-pyretic	Acetylsalicilic acid	–	–
		Paracetamol	–	–
18	Anti-rheumatic (Non-steroidal anti-inflamatory drugs – NSAID)	Acetylsalicylic acid	Acetylsalicylic acid	–
		Indomethacin	–	–

Ref.	Group	DOH Hospitals and Primary Health Care	DOH Rural Practice	Philippine Medical Association
19	Anti-spasmodic (Smooth Muscle Relaxants)	Atropine sulphate	Atropine sulphate	Atropine sulphate
		Belladonna tincture	–	–
		Dicyclomine HCL	Dicyclomine HCL	Dicyclomine HCL
		Hyoscine N.Butyl bromide		–
20	Anti-thrombic agents (Anti-platelet adhesiveness)	Acetylsalicylic acid	–	Acetylsalicylic acid
		Dipyridamole	–	Dipyridamole
21	Anti-tussive	Dextromethorpan	Dextromethorpan	–
22	Biologicals	–	–	–
23	Bronchodilators	Ephedrine salts	–	–
		Salbutanol sulphate	Salbutanol sulphate	Salbutanol sulphate
		Terbutanol sulphate	Terbutanol sulphate	Terbutanol sulphate
		Tulabutanol	–	–
		Theophylline anhyd	Theophyline anhyd	Theophyline anhyd
				Beclomethasone
24	Cardiovascular agents	Isoproterenol	–	–
		Alprenolol	–	–
		Lidocaine HCL	–	Lidocaine HCL
		Propanolol HCL	–	Propanolol HCL
		Quinidine sulphate	–	Quinidine sulphate
		Metaprolol	–	Metaprolol
25	Carthastics and laxatives	Glycerine	–	Glycerine
		Standardized senna extract	–	–
26	Cholinergic agents	–	–	–
27	Corticosteroids	Beclomethasone Diprop.	–	–
		Dexamethasone	–	Dexamethasone
		Hydrocortisone sod. succinate	–	Hydrocortisone sod.succinate
		Prednisolone	–	Prednisolone
		Prednisone	–	Prednisone
28	Dermatological agents	Blotrimazole	–	Blotrimazole
		Betamethasone	–	Betamethasone
		Dexamethasone	–	–
		Hydrocortisone	–	–
		Prednisolone	–	–
		Triamcinolone acetonide	–	–

Ref.	Group	DOH Hospitals and Primary Health Care	DOH Rural Practice	Philippine Medical Association
29	Diagnostic agents	–	–	–
30	Disinfectant and Antiseptics	–	–	–
31	Diuretics	Furosemide	Furosemide	Furosemide
		Hydrochlorthiazide	–	Hydrochlorthiazide
		Spironolactone	–	Spironolactone
32	Eye, Ear, Nose and Throat preparations	Sulfacetamide	–	Sulfacetamide sodium
		Dexamethasone	–	Dexamethasone
		Prednisolone acetate	–	Prednisolone acetate
		Pilocarpine nitrate	–	Pilocarpine nitrate
		Lidocaine HCL	–	Lidocaine HCL
		Ephedrine salts	–	Ephedrine salts
		Atropine sulphate	–	–
		–	–	Triamcinolone
33	Gonodal hormones	Sodium estrone sulphate	–	–
		Testosterone propionate	–	–
34	Hemostatics	–	–	–
35	Mucolytics	–	–	–
36	Oxytocics	–	–	–
37	Peripheral vasodilators	Isoxsuprine HCL	–	–
38	Pressor agents	Metaraminol Bitastrate	–	–
39	Psycho-therapeutic agents	Imipramine	–	Imipramine
		Bromazepam	–	–
		Chlordiazepacide	–	–
		Diazepam	–	Diazepam
		Flurazepam	–	–
		Lorazepam	–	–
		Midazolepam	–	–
		Chlorpromazine	–	Chlorpromazine
		Estazolam	–	–
40	Skeletal Muscle Relaxants	Diazepam	–	Diazepam

Ref.	Group	DOH Hospitals and Primary Health Care	DOH Rural Practice	Philippine Medical Association
41	Solutions Correcting water electrolyte and acid based imbalance Caloric agents	–	–	–
42	Thyroid Hormones and Anti-thyroid agents	Basbimaxole	–	–
		Methimazole	–	Methimazole
		Propanolol HCL	–	Propylthiourocil
43	Tocolytic agents (Urinary relaxant	Isoxsuprine	–	–
		Terbutaline Sulphate	–	–
44	Vitamins and Minerals	Vit.A (Retinol)	Retinol	Vitamin A (Retinolj)
		Vit.B Complex	–	–
		Nicotinamide	–	–
		Pyridoxine HCL	–	Pyridoxine Vit.B6
		Thiamine HCL	–	Thiamine HCL
		Vit.C (Ascorbic acid)	–	Ascorbic acid
		Vit.D (L.hydroxy Vit.D2)	–	Vit.D
		Menadione (K3)	–	–
		Phytonadione (K1)	–	–
		–	–	Vit.E (d1 tocopherol)
		–	–	Vit.B2 (Riboflavine)
		–	–	Ca. pantothenate (B5)
45	Miscellaneous	Methyl salicylate	–	–
		Paracetamol powder	–	–
		Theophylline	–	–

APPENDIX.

PRIORITY PRODUCTS AS SELECTED IN DOH FORMULARIES - OTHER THAN THOSE ANALYSED FOR CHEMICAL SYNTHESIS.

Ref.	Group.	Product.
13.	Anti-infective	Amikacin sulphate Gentamycin sulphate Chloramphenicol Erythromycin Amoxycillin Cloxacillin sodium Nafcillin Penicillin G (K or Na) Penicillin V (K phenoxymethyl) Ticarcillin Rifampicin
22.	Biologicals	B.C.G. Vaccine Diphtheria Antitoxin Serum Diphtheria-Tetanus Toxoid & Pertussis Vaccine (DPT) Diphtheria-Tetanus Toxoid (TD) (Children over 7 and Adults) Hepatitis-B Vaccine (Recombinant DNA) Hyperimmune Tetanus Globulin (Standard Human) Live Attenuated Trivalent - Poliomyelitis Vaccine (TOPV) Live Measles Vaccine (Further attenuated) Tetanus Toxoid

ANALYSIS OF LISTINGS FROM DOH, PHILIPPINES FORMULARIES AND PHILIPPINES MEDICAL ASSOCIATION FORMULARY.

1. Products common to all lists.

Acetylsalicylic acid
Paracetamol
Lidocaine hydrochloride
Chlorpheniramine maleate
Atropine sulphate
Hydrochlorthiazide
Isoniazid
Mebendazole
Piperazine citrate
Metronidazole
Chloroquine
Primaquine
Quinine
Sulfadoxine/Pyrimethamine
Dicyclomine hydrochloride
Salbutamol sulphate
Terbutaline sulphate
Theophylline anhydrous
Furosemide
Retinol (Vitamin A)

2. Products considered of highest priority.

Pyridoxine hydrochloride
Chlorpheniramine maleate
Metronidazole
Cotrimoxazole (Sulfamethoxazole/trimethoprim)
Clofazimine
Dapsone
Pyrazinamide
Quinine
Sulfadoxine/Pyrimethamine
Dicyclomine hydrochloride
Isoniazid
Mebendazole
Diloxanide furoate

PRODUCTS USED IN HEALTH PROGRAMMES.

Programme	Product	Form
1. ANTI-LEPROSY	Clofazimine	100 mg. capsule
	Dapsone	100 mg. tablet
	Rifampicin Oral	150 mg. "
		450 mg. "
		500 mg. "
		600 mg. "
	Sulfoxone sodium	300 mg. "
2. ANTI-TB	Ethambutol HCl	200 mg. tablet
	Isoniazid Oral	100 mg. "
		400 mg. "
	Pyrazinamide	500 mg. "
	Rifampicin Oral	150 mg. "
		300 mg. "
		450 mg. "
		600 mg. capsule
		100 mg/5ml syrup- 50 & 60 ml
	Streptomycin sulphate	1 gm vial
3. ANTI-MALARIAL	Amodiaquine Oral	200 mg. tab. DiHCl
		150/5 ml sus. HCl
	Chloroquine	250 mg. tab. Phos. (150 mg. base)
	HCl	150 mg/3 ml. Inj.
	Primaquine	26.3 mg. tab. (15 mg. base)
	Quinine Oral	325 mg. tab. sulp.
		100 mg/ml. Inj. (5 ml. DHCl.)
	Sulfadoxine/ Pyrimethamine Oral	500/ 25 mg. tab.

DRUGS USED IN OTHER MAJOR DISEASES.

1. FILARIASIS.	Diethylcarbamazine
2. SCHISTOSOMIASIS.	Praziquantel
3. MALIGNANT NEOPLASMS.	Cyclophosphamide Adriamycin Vincristine Methotrexate Fluorouracil Mitomycin-C Prednisone

POSSIBLE DELISTING OF DRUGS.

The National Drug Committee of the Ministry of Health of the Philippines has recently issued recommendations for possible de-listing of certain drugs. While no comment will be made on the wiseness of some recommendations when considering the Health picture in the Philippines, such possible de-listings have to be taken into account in terms of backward integration.

RECOMMENDATIONS FOR POSSIBLE DELISTING. ISSUED 18 MARCH 1988

(To Bureau of Food and Drugs, BFAD Philippines)

1. Oral proteolytic enzymes
2. Oxyphenbutazone & phenylbutazone
3. All sulfas (with exception of silver sulfadiazine and mafenide) and penicillin topical skin preparations, because they are highly sensitizing.
4. Chloramphenicol in fixed dose combinations.
5. Analgesics in combination with vitamins (B_1, B_6, B_{12}).
6. Antihistamines/barbiturates combination.
7. Ergot in combination.
8. Sulfaguanidine.
9. Estrogen-progesterone.
10. Hormonal pregnancy test.
11. Lead oxide and lead salts in cosmetics.
12. Nikethamide in cough preparations.
13. Stanazolol in combination (e.g. Cetabon with Fe.)
14. Metamizole sodium (also known as dipyrone, noramidopyrine, sulpyrine)
15. Atropine in combination, except atropine with diphenoxylate (atropine in combination with analgesics, antipyretics or anti-infectives shall be banned/withdrawn).

Additional recommendations:-

1. Cyproheptadine should be allowed as antihistaminic in single formulation. Its fixed dose combination with vitamins for weight gain should be withdrawn.
2. Ethylestrenol, an anabolic agent, should have product restrictions among children. All drops and syrup preparations should be withdrawn from the market.
3. Nandrolone phenylpropionate and nandrolone decanoate should have labelling restrictions. It should not be indicated as an anabolic agent in children, but may be used in selected patients with neoplasms and some types of aplastic anemia.

Remarks: This analysis simply gives an overall picture suggesting which Pharmachemicals might be of most interest when considering chemical synthesis and indicating which have to be treated with reservations.
It is not sufficient to concentrate only on the priority drugs for in some cases the synthesis may not be suitable nor the scale of production. Conversely pharmachemicals will not be excluded because they do not fall into a priority category.

2.2 Preliminary listing of Pharmachemicals for synthesis.

At an early stage a list of possible pharmachemicals for chemical synthesis (i.e. excluding any involving a stage fermentation) had to be drawn up as a basis for investigating the consumptions of individual products.
No detailed analyses of individual consumptions could be given either on request or in any foreseeable, reasonable time other than for DOH Central purchases. This list is reproduced later, but such a list only covers a small portion of the market. In 1985 Government Hospitals only represented 2.80% of total sales. Also the spread of drugs is not representative of the overall spread of medicines.

The preliminary list was drawn up by considering first drugs deemed to be of prime interest and need. Thus drugs generally fall in the categories of :-

1. Anti-TB
2. Anti-malarial
3. Anthelminthic

4. Anti-inflammatory
5. Anti-hypertensive
6. Anti-leprosy
7. Cardiovascular

In fact this listing was later found to correspond very closely with the Medical priorities listed by the Philippine Department of Health, namely :-

1. Tuberculosis
2. Malaria
3. Schistosomiasis (Bilharziasis)
4. Leprosy
5. Diarrhoea
6. ARI (Acute respiratory infections)

The primary list drawn up consisted of the following Pharmachemicals.

Pharmachemical.	Use.
1. Mebendazole	Anthelminthic
2. Praziquantel	Anthelminthic
3. Propanolol hydrochloride	Anti-hypertensive
4. Hydralazine hydrochloride	Anti-hypertensive
5. Trimethoprim	Anti-bacterial, urinary
6. Sulfamethoxazole	Anti-bacterial, urinary
7. Nalidixic acid	Urinary antiseptic
8. Ibuprofen	Anti-inflammatory
9. Dapsone	Anti-leprosy
10. Clofazimine	Anti-leprosy
11. Salbutamol sulphate	Anti-asthmatic
12. Terbutaline sulphate	Anti-asthmatic
13. Isoniazid (INH)	Anti-tuberculosis
14. Ethambutol	Anti-tuberculosis
15. Pyrazinamide	Anti-tuberculosis
16. Chloroquine phosphate	Anti-malarial
17. Sulfadoxine	Anti-malarial
18. Pyrimethamine	Anti-malarial
19. Quinine salts	Anti-malarial
20. Dicyclomine hydrochloride	Anti-spasmodic (anti-emetic & anti-diarrhoeal in combination)
21. Chlorpheniramine maleate	Anti-allergic
22. Diloxanide furoate	Anti-amoebic
23. Metronidazole	Anti-amoebic

At this stage no consideration can be given as to the possibility of economic production of any of the above products. When consumptions have been determined many of the above possibilities are likely to be eliminated - but other possibilities may also be realised.

DEPARTMENT OF HEALTH (CENTRAL OFFICE) PURCHASES FOR 1987.

Pharmachemical.	Volume kgs	Speciality sales value ₱
Acetylsalicylic acid	1,322	201,291
Paracetamol	3,080	1,661,282
Aluminium hydroxide Magnesium hydroxide	108,364 216,691	2,163,150
Ferrous sulphate	6,072	5,366,127
Diphenhydramine HCL	N/R	1,780,850
Amoxycillin	N/R	3,103,890
Mebendazole	821	4,584,690
Piperazine citrate	194	4,746,690
Metronidazole	413	372,600
Diloxanide furoate	N/R	929,745
Isopropyl alcohol	1,000 (1t)	214,367
Benzalkonium salts	N/R	192,594
Benzyl benzoate	N/R	17,309
Dicyclomine HCL	121	886,226
Dextromethorphan HBr	1,161	7,847,774
Theophylline	1,661	2,233,778
Menadione	N/R	268,673
Hydrocortisone	N/R	126,963
Nitrofurazone	N/R	1,239,963
Benzal/sulfur	N/R	9,213
Furosemide	17	86,961
Methylergotamine maleate	N/R	356,004
Prednisone	N/R	105,300
Ascorbic acid	206	271,440
Retinol (Vit.A)	4	6,454,447

N/R = not recorded.

These figures supplied by the Philippines Department of Health.

Little can be read into the figures as they represent a very small portion of the market and distribution is not very representative.

2.3 Importations of bulk active ingredients and dosage (bulk or finished) forms.

A study was made of some volumes (kgs.) and values of drugs imported into the Philippines over several years. These were taken from Customs and Excise statistics and records were generally abstracted to cover the specific interest of this report section dealing with Pharmachemicals and having chemical synthesis potential.

The following figures are tabulated in the subsequent pages : -

1. Importations: Selected Group Headings from Custom & Excise Statistics (1981 - 1986) - Bulk chemicals.
2. Importations: Selected Group Headings from Custom & Excise Statistics (1981 - 1986) - Dosage forms (bulk and finished).
3. Importations: Further selected Group Headings (1985-1987). Abstracts from Customs & Excise and Central Bank statistics.

Conclusion. The figures are of little value for the identification of specific products but do give the picture of the extent to which bulk active chemicals are imported for formulation compared with directly imported formulated or packaged items. The very large group of 'Other medicinal and pharmaceutical products' makes analysis very difficult, but it can be concluded that already a very high proportion (in excess of 90%) of bulk actives are compounded and formulated in the Philippine pharmaceutical houses.

With regards to trend over the years 1981 - 1987 the picture is clouded due to the cash and currency crisis of 1983, but a positive upward trend can be observed over the period of 1985 to 1987 even allowing for weakening of currency. Sales values will be studied later.

IMPORTATIONS: SELECTED GROUP HEADINGS FROM CUSTOMS AND EXCISE STATISTICS

(EXCLUDING ANTIBIOTICS, ANIMAL PRODUCTS, VACCINES) : DOSAGE FORMS (BULK AND FINISHED)

YEAR	1981		1982		1983		1984		1985		1986	
	VOL. KGS	FOB US$ + 10^6	VOL. KGS	FOB US$ + 10^6	VOL. KGS	FOB US$ + 10^6	VOL. KGS	FOB US$ + 10^6	VOL. KGS	FOB US$ + 10^6	VOL. KGS	FOB US$ + 10^6
COMMODITY												
Vitamins (inc. vet.)	39.56	1.794	29.35	1.726	46.58	1.551	23.20	1.319	18.98	0.874	23.66	1.177
Adrenal Corticoids	29.02	0.103	18.69	0.091	12.38	0.069	18.05	0.067	3.58	0.016	8.96	0.072
Other Hormones	1129.8	0.338	794.8	0.489	795.7	0.325	113.4	0.150	253.4	0.136	11.49	0.394
Quinine	2.5	0.001	169.8	0.015	85.0	0.009	–	–	8.96	0.002	5.0	0.002
Other Alkaloids	228.8	0.026	345.4	0.043	52.3	0.003	–	–	150.0	0.002	–	–
Sulfonamides	125.3	0.069	555.2	0.05	1482.0	0.080	2406.7	0.090	–	–	128.9	0.023
Anaesthetics	16,436.0	0.407	8,597.0	0.179	11,875.0	0.358	14,848.0	0.444	18,328.0	0.239	17,932.0	0.210
Analgesics & Antipyretics	21,057.0	0.157	11,917.0	0.123	399.0	0.006	875.0	0.007	–	–	–	–
DOSAGE TOTAL	39,048.0	2.835	22,427.2	2.716	14,748.0	2.401	18,284.4	2.077	18,762.92	1.269	18,110.0	1.878
BULK & DOSAGE TOTAL		38.479		46.985		45.993		36.620		33.896		47.377
ALL DRUGS INC. ANTIBIOTICS, ETC. TOTAL	–	71.967		81.892		75.913		58.194		52.402		–

IMPORTATIONS: SELECTED GROUP HEADINGS FROM CUSTOMS AND EXCISE STATISTICS

(EXCLUDING ANTIBIOTICS, ANIMAL PRODUCTS, VACCINES AND OTHER VETERINARY PRODUCTS) BULK CHEMICALS

YEAR	1981		1982		1983		1984		1985		1986	
	VOL. KGS	FOB US$ + 10^6	VOL. KGS	FOB US$ + 10^6	VOL. KGS	FOB US$ + 10^6	VOL. KGS	FOB US$ + 10^6	VOL. KGS	FOB US$ + 10^6	VOL. KGS	FOB US$ + 10^6
COMMODITY												
Provitamins & Vitamins	578,694	7.429	711,882	8.652	1,284,888	9.545	991,383	8.461	944,408	5.802	874,383	8.329
Caffeine	58,997	0.541	107,185	0.995	77,832	0.698	131,530	0.996	122,479	0.949	113,266	0.980
Quinine	478	0.038	758	0.063	472	0.032	460	0.032	250	0.020	70	0.005
Other alkaloids	17,277	0.905	26,578	0.963	29,198	1.138	15,241	0.740	19,718	0.999	17,471	1.222
Hormones	12,808	1.654	842	1.577	11,000	2.136	1,899	1.720	1,755	1.201	7,673	2.540
Glycosides	27,967	0.120	14,375	0.087	11,530	0.048	4,011	0.084	81,259	0.035	170,114	0.053
SUB-TOTAL BULKS	696,221	10.687	861,620	12.337	1,364,920	13.597	1,144,424	12.033	1,169,869	9.006	1,182,977	13.129
Other medicinal & pharmaceutical products	2,685,246	24.957	2,934,167	31.932	3,607,817	29.995	1,855,148	22.510	2,013,418	23.631	2,382,629	32.370
BULK TOTAL	3,381,467	35.644	3,795,787	44.269	4,972,737	43.592	2,999,572	34.543	3,183,287	32.637	3,565,606	45.499

IMPORTATIONS: FURTHER SELECTED GROUP HEADINGS 1985, 1986 & 1987.*

	1985		1986		1987	
	Vol.	Value.	Vol.	Value.	Vol.	Value.
BULK ACTIVE.	kgs.	FOB ** US $	kgs.	FOB US $	kgs.	FOB US $
Provitamins	944,408	5.08	874,323	8.33	1,007,267	14.10
Caffeine	122,479	0.95	113,286	0.98	80,410	1.02
Quinine	250	0.02	70	0.01	450	0.03
Alkaloids	19,719	0.90	17,671	1.22	21,662	2.11
Hormones	1,755	1.20	7,673	2.54	49,467	3.52
Sulfonamides	80,614	1.31	120,846	1.80	127,605	1.83
Total:		10.18		14.88		22.61
DOSAGE.						
Vitamins	18,980	0.87	23,656	1.18	32,254	1.59
Caffeine	-	-	-	-	-	-
Quinine	9	0.002	5	0.002	12	0.009
Alkaloids	150	0.002	-	-	108	2.03
Hormones	253	0.14	12	0.04	107	0.04
Sulfonamides	-	-	129	0.02	235	0.02
Total:		1.014		1.242		3.689

* This table was compiled from Customs Statistics 1985 & 1986 together with Central Bank Statistics 1987.

** All FOB values x 10^6

In all cases the predominance of bulk active chemical importation can be clearly observed.

2.4 Consumptions of Pharmaceutical products.

To gain an idea about the consumptions of finished products the IMS records were consulted. For sales a period of three years, 1985 to 1987 are compared. The actual sales are compared by Major Therapeutic class for both Drug Stores and Total Hospitals (Private and Government) in the first table. This also shows the percentage uptake of sales for each class out of the total sales.

VALUE OF SALES BY MAJOR THERAPEUTIC CLASS.

Major Therapeutic class	Sales ₱ ÷ 10^6			% total sales		
	1985	1986	1987	1985	1986	1987
Systemic anti-infectives	1611	1788	2278	25.2	24.0	24.4
Respiratory system	1065	1271	1448	18.1	17.2	15.5
Alimentary tract & metabolism.	1025	1201	1531	17.1	16.2	16.4
Central Nervous System	489	553	706	7.4	7.5	7.6
Cardiovascular System	356	480	643	5.7	6.5	6.9
Dermatologicals	286	355	458	4.9	4.8	4.9
Blood & blood forming org	374	452	605	3.8	6.1	6.4
Genito-urinary & sex Hormones	191	229	270	3.1	3.1	2.9
Musculo-skeletal System	169	211	327	2.8	2.9	3.5
Systemic Hormones	113	134	168	1.7	1.8	1.3
Sensory organs	104	99	125	1.7	1.3	1.8
Parasitology	80	87	107	1.3	1.2	1.2
Cytostatics	13	15	18	0.2	0.2	0.2
Others	466	536	640	7.1	7.2	6.9
TOTAL SALES	6,342	7,401	9,325			

This table shows the increase in value of sales over the period. There is little change in the distribution of sales amongst these Major Therapeutic Classes
The percentage changes can be seen for each Class and for Total sales in the following table which is derived from the above table.

ANALYSIS OF ANNUAL PERCENTAGE CHANGE IN CONSUMPTION FOR YEARS 1985/1986 AND 1986/1987.

Major Therapeutic class	% change Total sales 1985/1986	% change Total sales 1986/1987
Systemic anti-infectives	10.4	28.1
Respiratory system	19.3	13.9
Alimentary tract & metabolism	17.2	27.4
Central Nervous System	13.1	27.7
Cardiovascular System	34.8	34.0
Dermatological	27.6	29.0
Blood & blood forming organs	20.9	33.8
Genito-urinary & sex hormones	19.9	17.9
Musculo-skeletal System	24.9	55.0
Systemic Hormones	18.6	26.4
Sensory organs	(4.8)	23.0
Parasitology	8.8	23.0
Cytostatics	15.4	20.0
TOTAL	16.7	26.0

It can be further seen from the following table that there has been little change over a ten year period in the mix of medicaments being sold. This table shows drugs classified by second level Therapeutic class

Therapeutic class	% sales 1975	% sales 1984	% sales 1985
Antibiotics	20.1	19.3	21.2
Cough & cold preparations	12.7	11.6	11.4
Vitamins	9.3	7.6	7.4
Analgesics	7.3	5.6	5.8
Tuberculostatics	4.3	4.1	4.1
Anti-asthmatics	N/A	2.6	3.0
Antacids & antipeptic ulce:	N/A	2.5	2.6
Anti-anaemics	N/A	1.9	1.7
Topical corticosteroids	N/A	1.7	1.7
Others	N/A	43.1	41.1

Another consideration has to be taken into account, which is whether populace are in fact getting the drugs which they require (in adequate quantity also) for the maladies which need treatment.

Such a study is reproduced here in the form of a table comparing requirements and consumptions.

ESTIMATED DRUG REQUIREMENT AND ACTUAL CONSUMPTION BY MAJOR THERAPEUTIC CLASS 1985 & 1987.

Major Therapeutic class	REQUIREMENT 1985 P	%	1987 P	%	CONSUMPTION 1985 P	%	1987 P	%	DIFFERENCE * 1985 P	1987 P
Systemic anti-infective	1.845	4.59	2.278	4.39	1.611	25.39	2.278	24.44	(235)	(0)
Respiratory System	1.948	4.85	2.236	4.31	1.065	16.78	1.448	15.52	(883)	(788)
Alimentary Tr. & Metab.	646	1.61	678	1.31	1.025	16.16	1.531	16.42	379	853
Central Nervous System	2.627	6.54	5.233	10.09	489	7.71	706	7.57	(2.138)	(4.527)
Cardiovascular	12.892	32.07	13.557	26.13	356	5.62	443	6.89	(12,536)	(12.914)
Dermatologicals	445	1.11	103	0.20	286	4.51	458	4.92	(159)	355
Blood & blood forming	14.350	35.70	17.557	33.84	374	5.90	605	6.49	(13,975)	(16.952)
Genito-urinary & Sex H.	33	0.08	77	0.15	191	3.01	270	2.89	158	193
Musculo-skeletal System	312	0.78	388	0.75	169	2.66	327	3.50	(144)	(61)
Systemic Hormones	2.048	5.10	2.837	5.47	113	1.78	168	1.81	(1.935)	(2.668)
Sensory Organs	9	0.02	11	0.02	104	1.64	125	1.34	96	114
Parasitology	2.396	5.96	5.557	10.71	80	1.27	107	1.15	(2.316)	(5.449)
Cytostatics	-	-	-	-	13	0.22	18	0.19	14	18
Others	639	1.59	1.367	2.63	466	7.34	660	6.86	(174)	(727)
TOTAL	40.193		51.879		6.344		9.324		(34.495)	(44.086)
									645	1.533
								Net.	(33.850)	(43.553)

* (-) Shortfall on requirement
- Excess over requirement

All values in millions of Pesos.

VALUE ORDER OF DRUG REQUIREMENTS AND CONSUMPTIONS, 1985 & 1987.

	1985	1987	1985	1987
Blood & blood forming organs	1	1	7	6
Cardiovascular system	2	2	5	5
Central Nervous system	3	4	4	4
Parasitology	4	3	12	12
Systemic Hormones	5	5	10	11
Respiratory system	6	7	2	3
Systemic anti-infectives	7	6	1	1
Alimentary Tr. & Metab.	8	8	3	2
Dermatologicals	9	10	6	7
Musculo-skeletal	10	9	9	8
Genito-urinary & Sex Hormones	11	11	8	9
Sensory organs	12	12	10	10
Cytostatics	13	13	13	13

There is very little change in the requirement order or in the consumption order, but both orders are significantly different. Ignoring the drug group of blood and blood forming organs (which is part of the subject of another expert's report) the difference could partly be put down to prescribing habits of the physicians.

A very great difference can be observed between requirement and consumption with particularly marked increased need of drugs for the Central Nervous system and Parasitology but no response in consumption. It is felt this large discrepancy must largely be due to the lack of purchasing power for drugs which are sorely needed to raise the general health status of the poor people in the Philippines. There is no actual lack of availability of the range of necessary drugs in the highly developed pharmaceutical Industry of the Philippines.

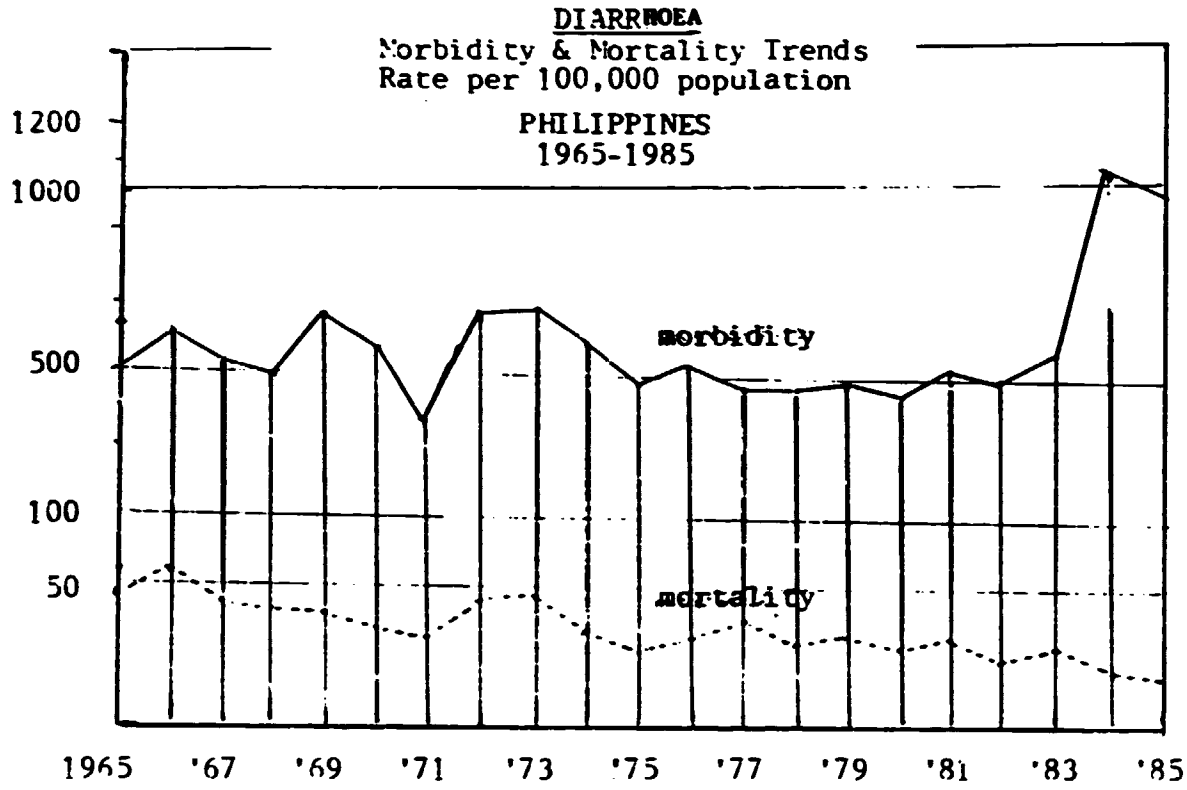
There has been a slight increase in respect of consumption satisfying need from 15.8% in 1985 to 18.0% in 1987, but this is slow progress if it continues only at the same rate. One significant point to note is that the current Philippine market is very small for the population but becomes quite significant if the demand requirement can be met. This is an important factor when considering if back integration is a wise policy.

It is pertinent to consider the trends of some selected Notifiable diseases for which statistics are available. Again because it is a subject of another experts report those diseases controllable by vaccines will not be included.

2.5 Past trends and future forecasts for some Notifiable diseases.

The following statistics were provided by the Department of Health, Philippines and are being reproduced in graphical form for the extended period 1965 to 1985 and the later years of 1980 to 1985 in tabular form indicating total numbers involved.

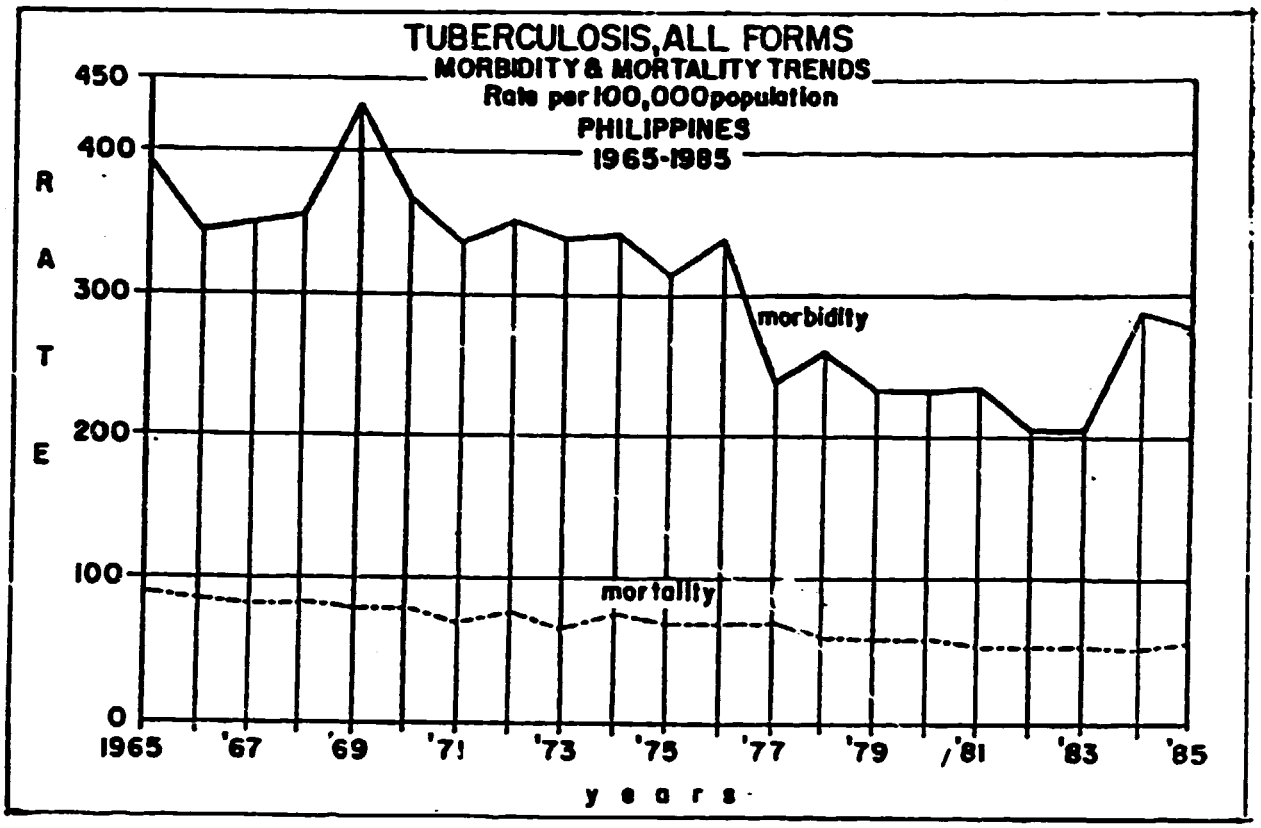
Figures for the following diseases will be presented :- Diarrhoea; Tuberculosis; Leprosy; Schistosomiasis (Bilharziasis); Filariasis; Malignant neoplasms and Malaria.



Year	CASES		DEATHS	
	Number	Rate	Number	Rate
1980	199,574	413.0	13,492	27.9
1981	239,117	482.7	16,196	32.7
1982	221,17	435.6	12,735	25.1
1983	275,068	529.2	15,090	29.0
1984	551,560	1036.9	11,553	21.7
1985	522,762	956.2	11,516	21.1

Rather dramatic increase in recent years, perhaps due to increased prevalence of closer living, unsanitory communities. Can be self propagating under unhygenic conditions. Death rates have reduced in recent years possibly due to drug treatment, but perhaps are greatly contributed to by a lack of available (cost basis) preparations (e.g. glucose, sodium bicarbonate, potassium bicarbonate & citric acid) to combat dehydration.

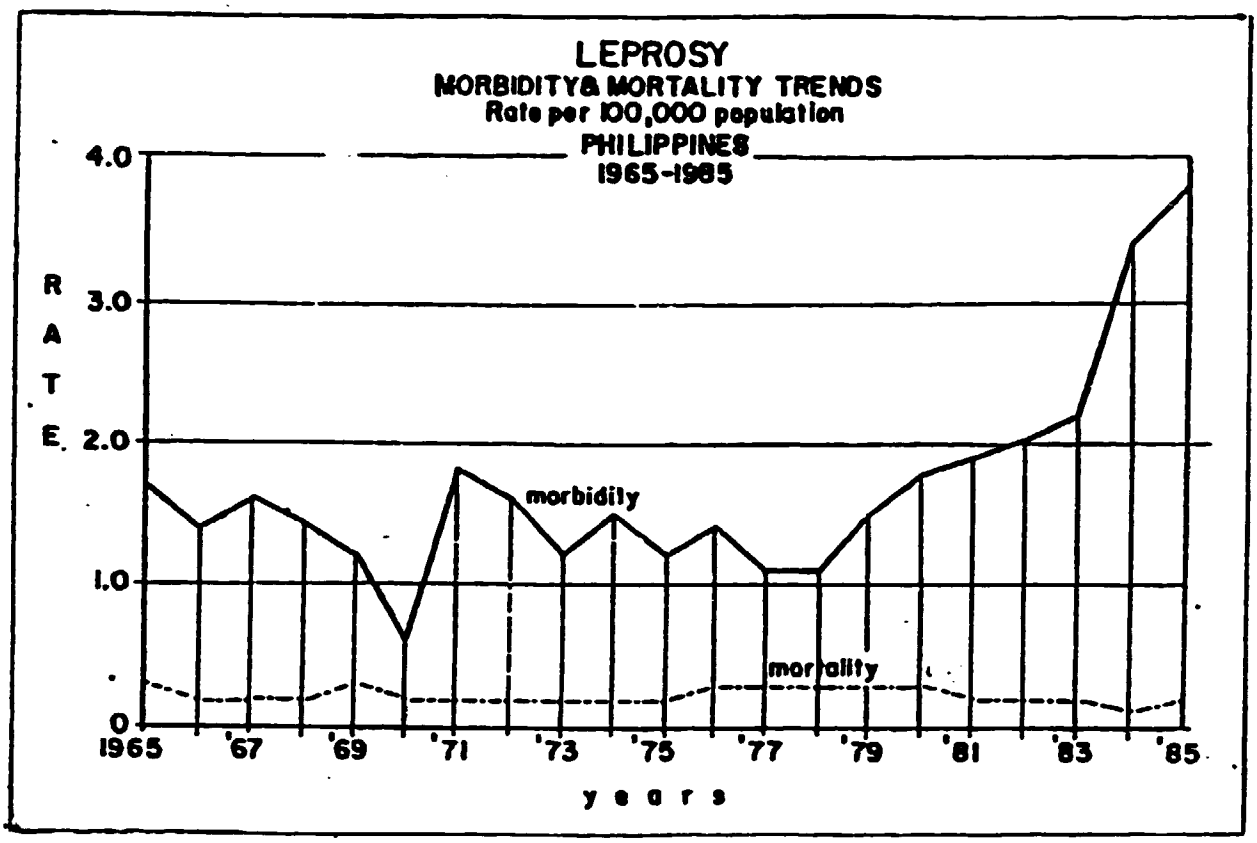
Removal of the cause must be the priority treatment but the requirment of drug treatment is likely to be significant for some years.



Year	CASES		DEATHS	
	Number	Rate	Number	Rate
1980	112,307	232.4	28,798	59.6
1981	116,821	235.8	27,317	55.1
1982	104,715	206.2	28,309	55.7
1983	106,300	204.5	28,580	55.0
1984	151,867	285.5	27,320	51.4
1985	151,028	276.3	31,650	57.9

An Anti-tuberculosis programme is in operation already. It is estimated that the number of cases for treatment will gradually decrease over the coming years from 140,000 in 1988 to about 100,000 by 1992.

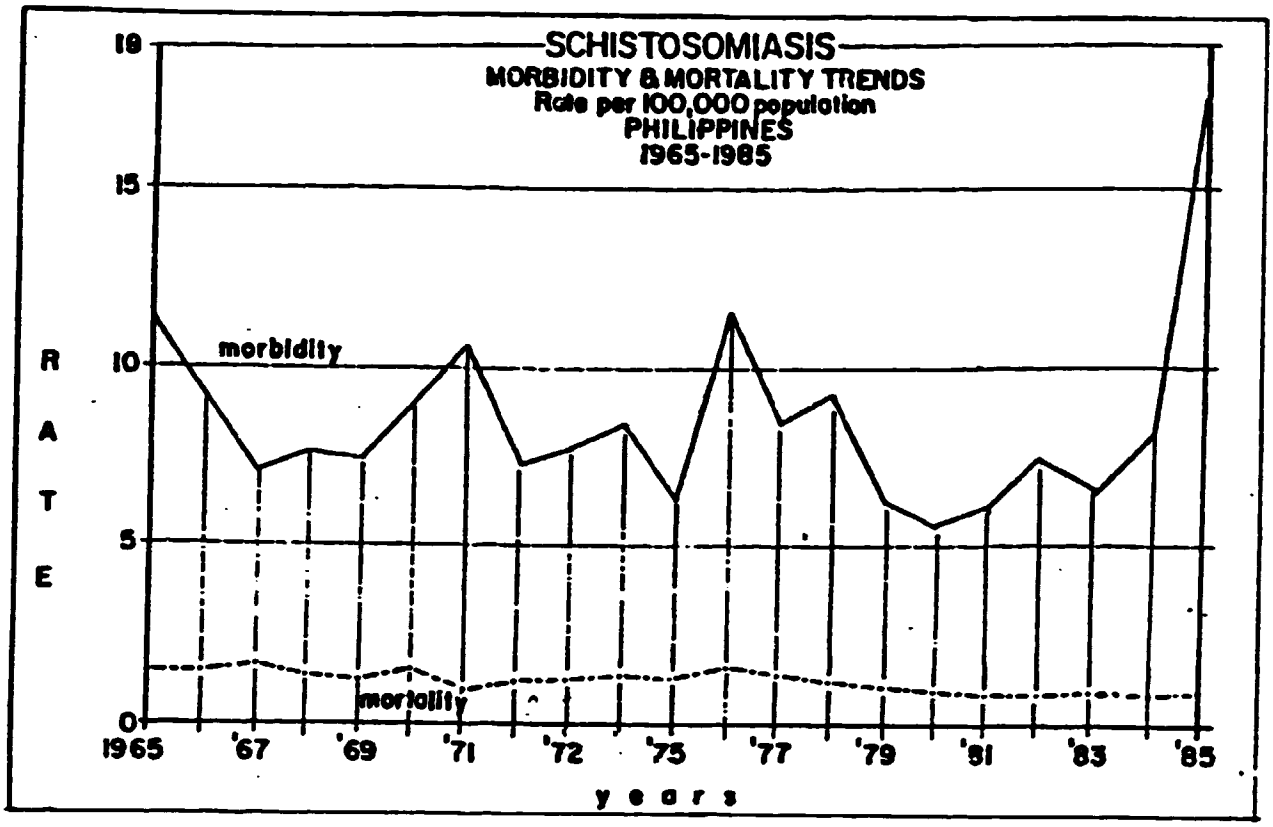
The drugs used in treatment are given on page 20 of this report.



Year	CASES		DEATHS	
	Number	Rate	Number	Rate
1980	886	1.8	137	0.3
1981	958	1.9	123	0.2
1982	997	2.0	107	0.2
1983	1,158	2.2	89	0.2
1984	1,798	3.4	68	0.1
1985	2,090	3.8	124	0.2

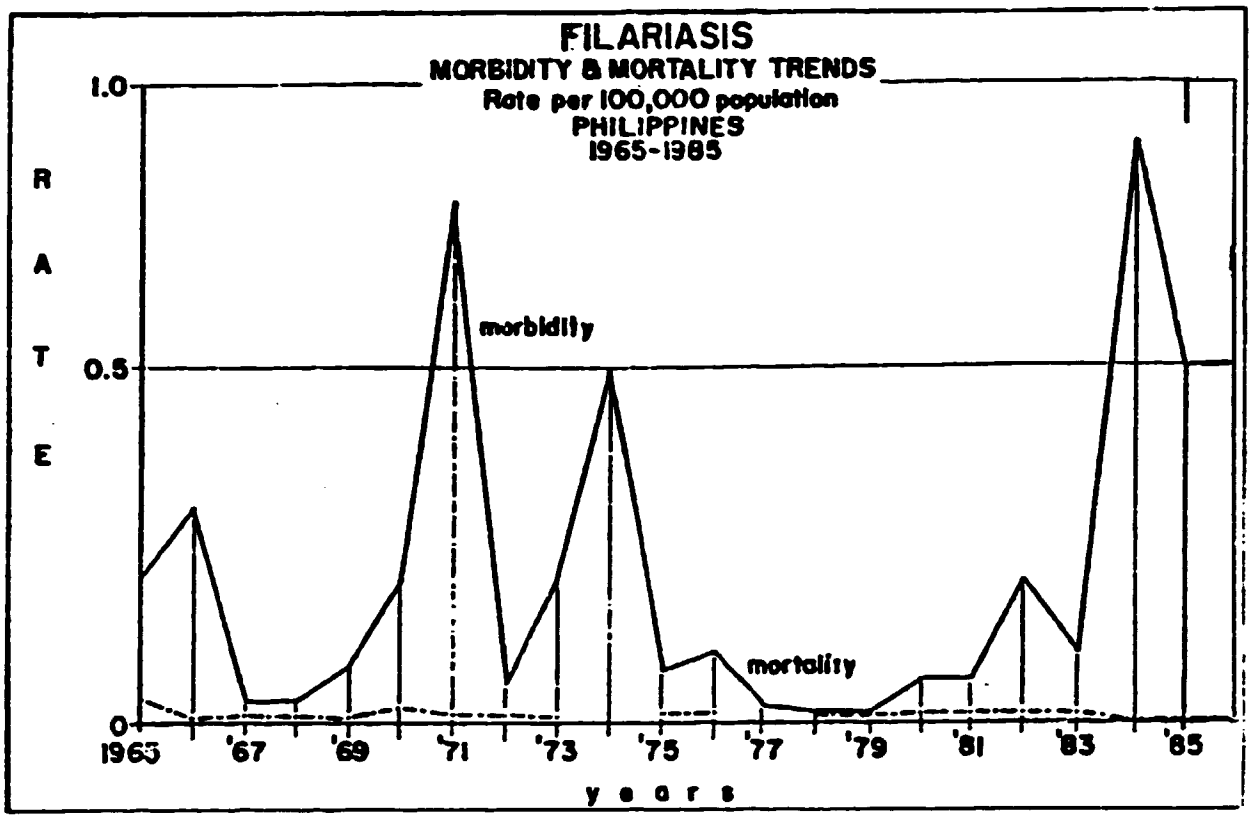
An Anti-leprosy programme is established and although the recent rate of increase of incidence looks high the number of incidences is not so high. Of the two types it is forecast that for Paucibacillary (PB) the programme will be noticeably effective by 1989 and in the case of Multibacillary (MB) by 1990.

The drugs currently used in treatment are given on page 20 of this report.



Year	CASES		DEATHS	
	Number	Rate	Number	Rate
1980	2,686	5.6	426	0.9
1981	3,009	6.1	398	0.8
1982	3,801	7.5	426	0.8
1983	3,454	6.6	452	0.9
1984	4,388	8.2	416	0.8
1985	9,764	17.9	416	0.8

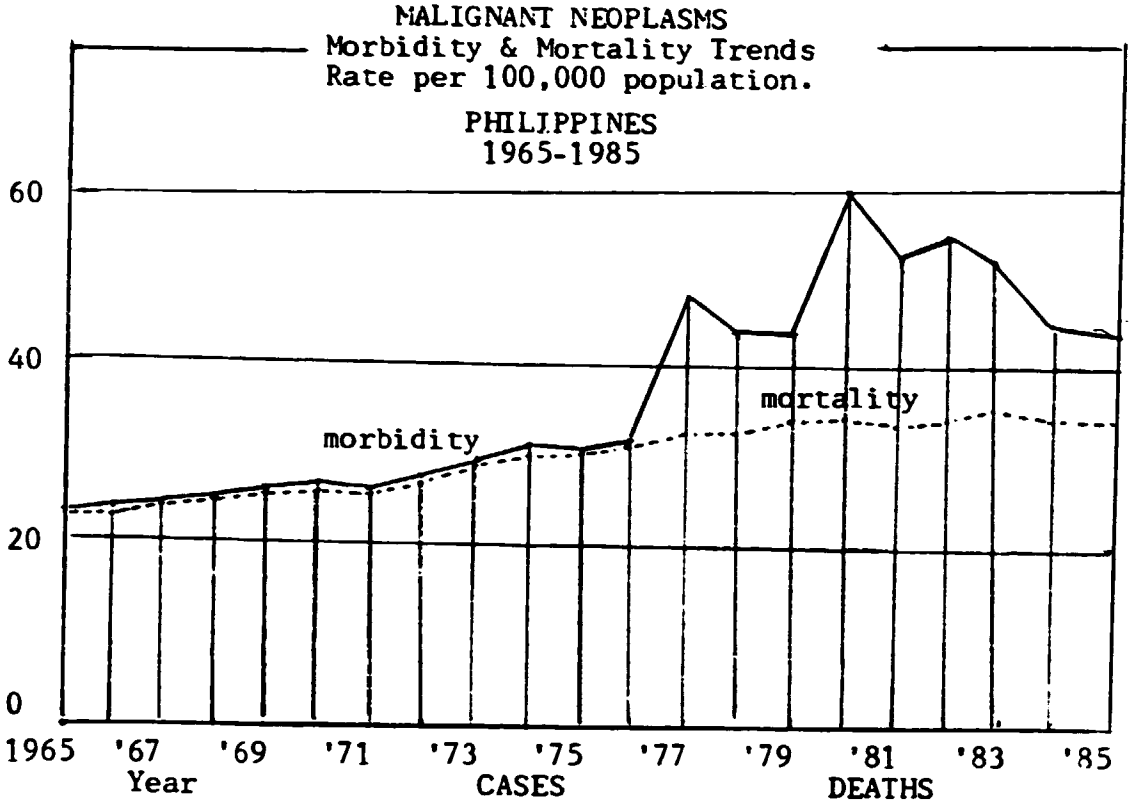
Otherwise known as Bilharziasis and transmitted by water snails, the parisitic worms spending the immature stages of their life cycle as parasites in the water snails. Transmitted to human being who bathe in, or drink, the water in which the snails reside. Enter body through feet or intestine. To complete cycle eggs of parasites leave the human body in faeces which can enter streams, stagnant water etc. where snails reside.
The incidence is rising steeply and becoming rather a serious problem.
Drugs for treatment are principally Mebendazole and Praziquantel, both of which are under consideration for synthesis.



Year	CASES		DEATHS	
	Number	Rate	Number	Rate
1980	30	0.06	4	0.01
1981	28	0.06	4	0.01
1982	77	0.20	4	0.01
1983	74	0.10	5	0.01
1984	493	0.90	2	0.004
1985	259	0.50	2	0.004

Not such a serious problem at this level. This is another parisitic worm disease, the larvae being transferred from one human being to another by mosquitoes. The mature worms, which can be up to 2 inch long live in the lymphatic system. Drug treatment is with Diethylcarbamazine, but the elephantiasis produced often has to be treated surgically.

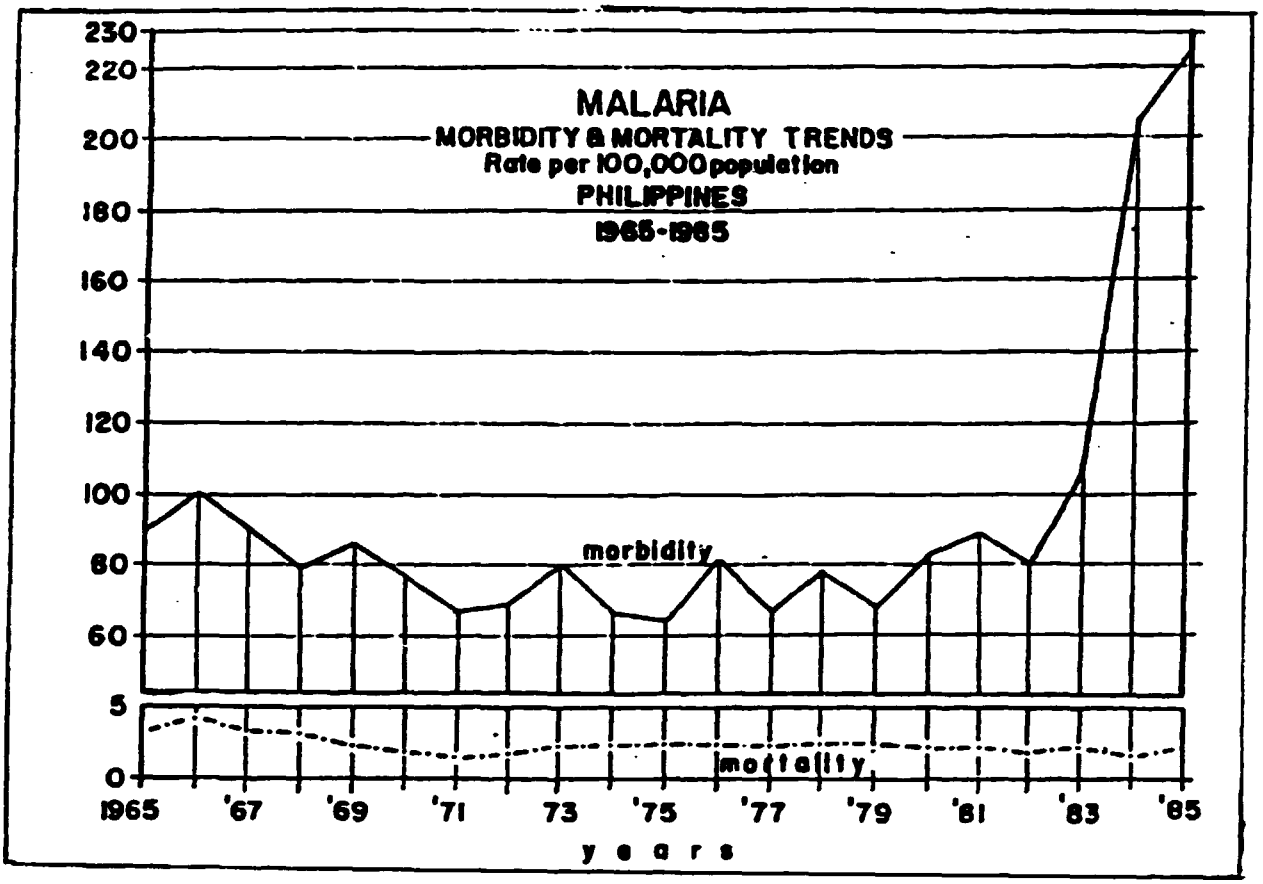
The increase in incidence since 1983 is probably as a result in cut back in insecticidal control of mosquitoes and control of streams and swamps and a similar effect can be seen later in the cases of Malaria.



Year	CASES		DEATHS	
	Number	Rate	Number	Rate
1980	28,905	59.8	16,019	33.1
1981	24,777	50.0	16,059	32.4
1982	26,876	52.9	16,832	33.1
1983	25,838	49.7	17,997	34.6
1984	24,191	45.5	17,700	33.3
1985	24,270	44.4	18,143	33.2

Drugs used in treatment are given on page 21 of this report. The analysis refers to a range of cancers covering seven areas ;- lung; breast; colon; stomach; liver; uterus/cervix and lymphoma.

There has been little change in the mortality rate over the years, i.e. it is increasing approximately at the same rate as population increase. More analysis is necessary to really consider whether there is a true decrease in incidents needing treatment.



Year	CASES		DEATHS	
	Number	Rate	Number	Rate
1980	39,678	82.1	1,091	2.2
1981	44,118	89.1	1,071	2.2
1982	40,496	79.7	985	1.9
1983	55,019	105.9	1,086	2.1
1984	107,485	202.1	923	1.7
1985	121,975	223.1	1,166	2.1

An Anti-malarial programme is currently in operation and steps are being taken to try to firstly control and subsequently reduce the problem which is quite serious. Two treatments with respect to drugs are operated, Presumptive (treating with Chloroquine and Primaquine) and Radical (treating with Chloroquine, Sulfadoxine/ Pyrimethamine and Quinine). The ratio of Presumptive to Radical treatments expected are in a ratio of 10:1. The forecast up to 1992 is that the incidence of both treatments will increase regularly at a rate of about 2.4% (i.e. just slightly less than the current rate of population increase of 2.9%).

MALARIA CONTROL PROGRAM - Situation at end of 1987.

As at the end of 1987 there were estimated to be some 10,585,598 people at risk of contracting malaria throughout the regions. Although this risk population apparently decreased from 16,297,226 at the end of 1982, the present level is a considerable proportion of the Filipino population (18.9%) and is a serious problem. This is, of course, realised and hence the existance of the Malaria Control Program.

Re-organisation of the Program took place in early 1987 and the following achievements were realised :-

- a 10% surveillance of risk population was acheived in 1987.
- House spraying achieved 61.3% of the target (270,279 out of 441,819). Although inadequate this probably controlled a potential epedemic.
- Biological control (limited to use of Poecilia reticulata and Cambusia affinis) was only applied in 30 of the endemic provinces. This attack is aimed at reducing the density of aquatic stages of malaria vector and should eventually reduce the adult density below the level of effective transmission and thereby increase the effectiveness of other attack measures. A total of 2,452 streams were seeded with P. reticulata.
- Environmental control was also used as another supportive measure. Aimed at changing the environment of the breeding places, thus making them unsuitable for development of the mosquito larvae, some 2,496 streams were seeded and 4,394 cleared.
- There is a program of joint drug supply with the WHO. A comparison of treatments and forecast annual requirements 1987-1988 are abstracted in the following page.

COMPARISON OF TREATMENTS 1987 AND 1988 (6 MONTHS) AND NEEDS; SUPPLY PATTERN DOH AND WHO: QUANTITY OF DRUGS USED.

Drug.(Year)	Ratio: Allocation / Need x100%	% supply DOH	% supply WHO	Calculated total used kgs.
Amodiaquine				
1987 (12 mnth)	74.4	50.0	50.0	228.6
1988 (6 mnth)	67.1	77.3	22.7	145.8
Chloroquine				
1987 (12 mnth)	125.8	100.0	0.0	734.9
1988 (6 mnth)	84.7	100.0	0.0	293.8
Primaquine				
1987 (12 mnth)	50.1	73.5	26.5	412.0
1988 (6 mnth)	41.8	82.7	17.3	125.6
Sulfadoxine/ Pyrimethamine				
1987 (12 mnth)	374.1	70.4	29.6	186.8/9.35
1988 (6 mnth)	874.0	93.6	6.4	178.5/8.93
Quinine tablets				
1987 (12 mnth)	18.4	93.1	6.9	58.7
1988 (6 mnth)	240.5	100.0	0.0	354.7
Quinine ampoules				
1987 (12 mnth)	N/A	100.0	0.0	4.5
1988 (6 mnth)	N/A	100.0	0.0	7.7

COMPARISON OF FORECAST ANNUAL REQUIREMENTS 1987 AND 1988.

Drug.	1987 Units	1988 Units	1987 kgs	1988 kgs
Amodiaquine	2,106,970	1,741,830	526.7	435.0
Chloroquine	2,336,023	2,584,800	581.5	646.2
Primaquine	5,480,200	3,997,300	822.5	599.6
Sulfa/Pyrim.	99,800	84,300	49.4/2.5	42.2/2.1
Quinine tablets	1,263,000	1,179,300	315.8	294.8
Quinine ampoule	Nil	Nil	Nil	Nil

It is difficult to readily assess how much of the overall requirement is satisfied because of the difference in the consumption mix compared with forecast requirement.
It would appear that in 1988 the supplies from the WHO have probably been very slow in becoming available for use.

It is noticed that in spite of the higher use of sulfadoxine - pyrimethamine in 1987 the forecast level for 1988 was not increased. In fact already in the first six months of 1988 the usage of this combination was even higher.

Research 1987.

- testing was performed on the effectiveness of alternative insecticides compared with DDT. Those investigated were Othrine, Fican, Solfac and Sumitron.
- Extensive monitoring of areas with P. falciparum resistance to chloroquine, amodiaquine, mefloquine, Quinine and Sulfadoxine were carried out with the following results :-

In-Vitro Sensitivity Test of P. falciparum to :-	Subjects	Results
Mefloquine	4	100% sensitive
Ouinine	15	100% sensitive
Amodiaquine	26	8 sensitive 18 resistant
Chloroquine	20	9 sensitive 11 resistant
Sulfadoxine/Pyrimethamine	15	6 sensitive 6 failure 1 resistant

- Battery operated portable incubators, test kits and plates for In-vitro studies were produced in collaboration with WHO for World-wide distribution. 31 incubators were supplied to a total of 16 Countries (a worthy contribution to World Health care !)
- A drug combination of Quinine, Quinidine and Cinchonine (in ratio 1:1:1) was tested and found to be an effective drug against cases of P. falciparum resistant to chloroquine.

  Comment: Although this combination is interesting it is not a natural combination in respect of proportions and would prove expensive to compound. What is wanted is a combination that can be readily obtained perhaps as a total extract directly from Cinchona bark. This tree is indigenous and grown in the Philippines. Opportunity was not found to discuss this aspect during the mission to the Philippines, and (as reported later) little positive information could be gained regarding the species and the

analysis of barks therefrom. Efforts were made to visit the plantations in Mindanao but permission to travel was not granted in time from the authorities. The type of extract which could be obtained from Cinchona bark depends on the species of the tree and the conditions under which it has been grown. The levels of all alkaloids present varies considerably as does the relationship to one another. A good Ledgeriana could give a crude extract (isolated in such a way as to strip off cinchonidine) perhaps containing a ratio of quinine:cinchonine:quinidine of 10:1:0.05. whereas Officinalis might produce something like a ratio of 5:1:0.2.

Some problems of the Malaria Control Program are observed:-

- Technical: increasing resistance of P. falciparum ; resurgance of malaria in non-malarious areas due to frequent population movement from malaria areas.
- Operational: inadequate cover of endemic areas; poor and inadeouate vector control measures; some Health workers not fully functional.
- Administration: slow delivery of insecticides and drugs by DOH to Provincial Health Offices; inadequate resources.

2.6 Quantities of Pharmachemicals Imported and Consumed.

It was difficult to obtain figures relating to quantities of Pharmachemicals imported as such and for the consumption of total Pharmachemicals in purchased pharmaceuticals. A source was located for the importation of pharmaceutical products and including pharmachemicals. This was the Business Statistics Monitor publication of a Company of the same name. This publication records the importations into the Philippines routed through the Manila port in one set of records and the the Manila International Airport in a second set. Copies were procured for the period January 1987 until end May 1988. These were analysed in respect of the considered most important bulk pharmachemicals and results are tabulated overleaf. It was not possible, or indeed necessary for the purpose of this report, to extend the analysis over a longer period of time.

It is considered that this survey should cover in excess of 90% of all legal importations.

An analysis was also carried out to determine the quantities of pharmachemicals consumed during a year in pharmaceutical preparations. To acheive this a selected list of the most interesting pharmachemicals was drawn up. With the aid of PIMS (a quick reference to ethical preparations available in the Philippines) the corresponding pharmaceutical preparations containing these pharmachemicals were located in the IMS records for both Drug Stores and Total Hospitals (Private and Government) and the pharmachemical contents of the annual sales were calculated. These were recorded together with the sales values. This analysis was performed for only one year, that of 1987. The results of the analysis are recorded in three following tables entitled :-

- Analysis of IMS reports for 1987 - Sales of drugs through drug stores and hospitals (total private and Government). Quantity of Pharmaceuticals.
- Values of specialities and specific pharmachemical component.
- Some further examples of single product dosage forms indicating contribution to cost of pharmachemical.
- Some examples of combination dosage products indicating contribution to cost of pharmachemicals.

ANALYSIS OF IMPORTATIONS THROUGH MANILA SEA AND INTERNATIONAL AIRPORTS:

SOURCE: BUSINESS STATISTICS MONITOR

	12 months Jan - Dec 1987			5 months Jan - May 1988		
	Volume	Value		Volume	Value	
	Kgs	CF $	LC ₱	Kgs	CF $	LC ₱
Paracetamol	348,184	1,541,818	37,003,632	67,399	326,324	8,740,695
Trimethoprim	1,869			3,318		
Sulfamethoxazole	6,857	202,263	4,651,713	3,212	90,750	2,158,691
Salbutamol	6	2,155	52,811	13	5,522	131,062
Phenylpropanolamine HCL	9,770	296,829	7,570,112	4,590	105,562	3,341,301
Ibuprofen	15,850	426,334	12,236,903	5,000	141,950	3,263,704
Dicyclomine HCL	375	25,411	603,330	400	38,910	900,604
Clotrimazole	32.5	59,148	1,392,892	11	18,550	431,378
Quinine HCL	450	36,983	845,055	25	1,902	44,915
Ethambutol	22,200	974,021	23,989,861	4,140	211,937	5,039,120
Metronidazole	1,000	72,000	1,656,000	700	51,336	1,262,171
Benzoyl - metronidazole	512	68,703	1,580,169	725	22,765	546,178
Nicotinamide	17,840	114,667	2,865,960	6,010	41,528	996,672
Sulfamethazine (Sulfadimidine)	34,500	352,551	8,461,224	16,240	156,392	3,611,406
Furazolidone	32,375	233,100	5,749,406	22,300	151,865	3,896,229
Mefenamic acid	14,845	337,169	9,089,662	8,000	181,040	4,258,245
Pyridoxine HCL	10,665	396,663	9,128,850	2,700	117,323	2,741,842
Ascorbic Acid (Vit. C.)	154,545	1,545,450	38,626,250	39,375	420,982	10,389,255
Chlorpropamide				470	22,404	530,801
Chloroquine HCL	1,060	29,526	892,216	860	27,489	1,479,374
Nalidixic Acid	390	37,248	859,519	620	59,253	1,370,149
Chlorpheniramine maleate				500	23,766	570,384
Terbutaline Sulfate	83	209,871	5,125,889	29	78,551	1,814,131
Glaphenine	3,345	349,735	8,049,790			
Albendazole	2,020	95,265	2,145,206			
Loperamine	10	55,452	1,291,792			
Acetyl Salicylic Acid	91,760	277,325	6,312,176	42,000	133,140	3,195,360
Nicotinic acid				150	50,354	1,208,400
Piroxicam	91	854,680	22,196,866	9,100	264,000	6,103,417
Parbendazole	540	25,589	574,954	540	25,705	628,262
Diazepam	223			10		
Isoniazid	60,120	610,814	15,209,268	15,055	168,509	3,936,197
Pyrazinamide	7,600	574,288	13,204,164	1,975	108,183	2,507,513
Mebendazole	100	4,500	105,699	275	7,836	186,479
Rifampicin	6,594	1,448,372	33,247,389	2,357	598,523	13,879,300
Pyrimethamine	325	22,328	526,952	150	9,257	208,197

NO IMPORTATIONS FOUND

Diloxanide
Dapsone
Propanolol HCL
Sulfadoxine
Hydralazine
Praziquantel

ANALYSIS OF IMS REPORTS FOR 1987 - SALES OF DRUGS THROUGH DRUG STORES AND HOSPITALS (TOTAL PRIVATE AND GOVERNMENT).

QUANTITY OF PHARMACHEMICALS.

Pharmachemical	Drug stores	Hospitals (total)	Total consumption
	kgs.	kgs.	kgs.
Trimethoprim	2037.5	159.6	2,197.1
Sulfamethoxazole	6,971.3	404.6	7,375.9
Ethambutol	12,910.7	601.4	13,512.1
Mebendazole	118.3	3.7	122.0
Pyrimethamine	18.1	0.3	18.4
Sulfadoxine	295.0	5.0	300.0
Mefenamic acid	7,372.4	574.2	7,946.6
Pyridoxine	1,103.0	40.9	1,143.9
Ibuprofen	466.0	24.0	490.0
Pyrazinamide	6,817.0	180.5	6,997.5
Furazolidone	107.7	14.6	122.3
Terbutaline sulphate	27.0	2.0	29.0
Metronidazole	1,606.5	223.9	1,830.4
Sulfadimidine	158.7	1.7	160.4
Nicotinamide	-	16.0	16.0
Salbutamol sulphate	37.6	2.2	39.8
Dapsone	50.0	-	50.0
Chloroquin phosphate	900.7	8.3	909.0
Dicyclomine HCl	260.4	6.7	267.1
Propanolol HCl	100.1	6.2	106.3
Clofazimine	6.0	-	6.0
Acetylsalicylic acid	6,569.0	102.5	6,671.5
Phenylpropanolamine HCl	1,050.2	53.7	1,103.9
Chlorpheniramine maleate	167.6	5.2	172.8
Rifampicin	3,242.9	229.9	3,472.8
Isoniazid (INH)	30,271.9	882.6	31,154.5
Paracetamol	107,867.1	2,642.8	110,509.9
Ascorbic acid	19,303.9	1,208.6	20,512.5
Streptomycin	1,070.2	166.3	1,236.5
Clotrimazole	16.4	1.0	17.4
Diphenylhydantoin	475.7	51.2	526.9
Indomethacin	31.8	1.3	33.1
Reserpine	1.2	0.0	1.2
Quinine sulphate	-	0.0	0.0

The sales values of the specialities containing the Pharmachemicals listed above are given on the next pages.

VALUES OF SPECIALITIES AND SPECIFIC PHARMACHEMICAL COMPONENT.

Pharmachemical	Content kgs.	Speciality sales ₱ ÷ 10^3	Pharmachemical component cost $ ($ ÷ 10^3)		% Pharm/sale
Trimethoprim	722	32,670	28,876	(578)	1.77
Ethambutol	13,512	99,604	592,840	(11,857)	11.90
Mebendazole	122	4,222	5,490	(110)	2.60
Pyrimethamine	18	5,775	1,251	(25)	0.43
Sulfadoxine	300	4,716	3,000	(60)	1.27
Mefenamic acid	7,947	64,819	201,900	(4,038)	6.22
Pyridoxine (Vit B6)	1,144	52,854	42,324	(847)	1.60
Ibuprofen	490	4,181	14,700	(294)	7.03
Pyrazinamide	6,998	52,854	349,875	(6,998)	13.20
Furazolidone	122	7,649	880	(176)	0.23
Terbutaline sulphate	29	52,071	73,328	(1,467)	2.80
Metronidazole	1,830	44,892	36,600	(732)	1.60
Sulfadimidine	160	602	1,604	(32)	5.30
Nicotinamide	16	352	1,028	(21)	5.80
Salbutamol sulphate	40	58,925	14,328	(287)	0.49
Dapsone	50	359			
Chloroquin phosphate	917	7,131	25,684	(514)	7.20
Dicyclomine HCl	267	69,064	18,163	(363)	0.52
Propanolol HCl	106	10,950	23,386	(47)	0.43
Clofazimine	6	297			
Acetylsalicylic acid	6,672	261,825	20,015	(400)	0.15
Phenylpropanolamine	1,104	180,201	525,624	(10,512)	5.64
Chlorpheniramine maleate	173	179,062	8,294	(166)	0.10
Isoniazid	31,155	234,243	311,546	(6,231)	2.70
Paracetamol	110,510	186,100	525,624	(10,512)	5.64
Ascorbic acid	20,512	37,122	205,121	(4,102)	11.10
Clotrimazole	17	17,748	31,668	(633)	3.60
Diphenylhydantoin	527	20,925	7,902	(158)	0.76
Indomethacin	33	3,423	1,056	(21)	0.61
Reserpine	1	3,654	300	(6)	0.16
Quinine sulphate	0	2	-	-	-

This table is based on IMS figures for 1987.

Pharmachemical component cost is based on latest available C & F unit US $ prices.

Note: Care must be taken in interpretation of the last column (%) as it is affected by many factors such as :-

(1) the above do not always represent single product dosage forms - see example of acetylsalicylic acid given below for single product and examples of multi-product dosage forms in next table.
(2) Dosage level. With low dosage of active ingredient cost of excipients becomes more significant.
(3) Unit cost of active ingredient.
(4) Formulation of speciality, i.e. tablet, suspension, capsule, suppository etc.

EXAMPLE SINGLE PRODUCT

Acetylsalicylic acid	1,648	499	4,944	(99)	19.84

SOME FURTHER EXAMPLES OF SINGLE PRODUCT DOSAGE FORMS

INDICATING CONTRIBUTION TO COST OF PHARMACHEMICAL.

Pharmachemical T = tablets C = capsules Sus = suspension	Form *		Unit sale cost pack ₱	Pharma-chemical cost ₱	% Pharm/ sale.
Mefenamic acid	T	500mgx100	299.44	25.00	8.35
	T	250mgx100	167.53	12.50	7.46
	T	500mgx 50	85.85	12.50	14.56
	T	500mgx100	379.00	25.00	6.60
	C	250mgx100	223.00	12.5	5.61
	C	250mgx100	196.00	12.5	6.38
	C	500mgx100	350.00	25.00	7.14
	Sus	600mg	18.80	0.30	1.60
Ethambutol	T	400mgx100	251.45	35.20	14.00
	T	400mgx100	280.00	35.20	12.60
	T	200mgx100	127.00	17.60	13.86
	T	400mgx100	215.00	35.20	16.37
Furazolidone **	T	100mgx100	197.10	1.44	0.73
	T	100mgx100	199.95	1.44	0.72
	T	100mgx100	137.50	1.44	1.05
	T	100mgx500	676.50	7.20	1.07
	T	100mgx100	165.59	1.44	0.87
Ibuprofen	T	200mgx100	205.00	12.00	5.85
	T	400mgx100	283.00	24.00	8.48
	T	400mgx100	271.25	24.00	8.84
Metronidazole	T	500mgx100	505.00	20.00	3.96
	T	500mgx 50	259.15	10.00	3.86
	T	500mgx200	679.15	40.00	5.89
	T	250mgx500	408.00	50.00	12.25
	Sus	750mg/30ml	20.90	0.30	1.44
	Sus	1500mg/60ml	39.50	0.60	1.52
Dicyclomine HCl	T	10mgx100	40.80	1.36	3.33
	Syp	120mg/60ml	23.30	1.63	6.99
	Syp	240mg/120ml	32.85	3.26	9.92
	Syp	120mg/60ml	15.60	1.63	10.44

* This table was prepared comparing products from different Pharmaceutical Houses. Although it shows the expected effect that higher dose content and/or larger pack size result in a higher contribution to cost of the pharmachemical, the effect of higher unit cost of this ingredient is not so obvious.

The most important observation is that the pharmachemical rarely reaches as high as 20% of the sales price.

** These figures need reviewing. Most product used in Veterinary field may have some effect.

SOME EXAMPLES OF COMBINATION DOSAGE PRODUCTS INDICATING CONTRIBUTION TO COST OF PHARMACHEMICALS.

Pharmachemical combinations	Content kgs.	Speciality sales ₱÷10³	Pharmachemical component cost $ (₱÷10³)	% Pharm/sale
Trimethoprim	1,475	94,341	59,008 (1,180)	1.25
Sulfamethoxazole	7,376		199,149 (3,983)	4.22
				5.47
Rifampicin	1,348	47,177	296,648 (5,933)	12.57
Isoniazid	871		8,706 (174)	0.37
				12.94
Rifampicin	463	22,988	101,860 (2,037)	8.86
Isoniazid	314		3,135 (63)	0.27
Pyrazinamide	983		73,688 (1,474)	6.41
				15.54
Rifampicin	30?	10,582	67,540 (1,351)	12.77
Isoniazid	397		3,970 (79)	0.75
Ethambutol	409		16,360 (327)	3.09
Pyridoxine	26		962 (19)	0.18
				16.79

This table again shows that the cost contribution of the constituent pharmachemicals is less than 20%.

COMPARISON OF RECORDED BULK PHARMACHEMICAL IMPORTATIONS AND CONSUMPTIONS IN PHARMACEUTICAL MEDICINE SALES IN 1987.

This comparison is derived from the preceeding tables.

Pharmachemical	bulk importations kgs.	Sales kgs. active ingredient
Paracetamol	348,184	110,510
Ascorbic acid	154,545	205,125
Acetylsalicylic acid	91,760	6,672
Isoniazid	60,120	31,154
Sulfamethazine	34,500	160
Furazolidone	32,375	122
Ethambutol	22,200	13,512
Nicotinamide	17,840	16
Ibuprofen	15,850	490
Mefenamic acid	14,845	7,947
Pyridoxine HCL	10,665	1,144
Phenylpropanolamine HCL	9,770	1,104
Pyrazinamide	7,600	6,998
Sulfamethoxazole	6,857	7,376
Rifampicin	6,594	3,473
Glaphenine	3,345	n.r.
Albendazole	2,020	n.r.
Trimethoprim	1,869	2,197
Chloroquine salts	1,060	743 *
Metronidazole	1,000	1,830
Parbendazole	540	n.r.
Benzoylmetronidazole	512	n.r.
Quinine	450	59 *
Nalidixic acid	390	n.r.
Dicyclomine HCL	375	267
Pyrimethamine	325	18
Diazepam	223	n.r.
Mebendazole	100	122
Piroxicam	91	n.r.
Terbutaline sulphate	83	29
Clotrimazole	33	17
Loperamine	10	n.r.
Salbutamol sulphate	6	40
Dapsone	n.r.	50
Propanolol HCL	n.r.	106
Sulfadoxine	n.r.	300

* includes DOH supplies for Malaria Control Program.

Note: Some discrepances between Importations and Sales may possibly be explained by stock holdings at either the beginning or end of the year. Apparently it is not uncommon to hold up to six months stock. Other differences are too large for this explanation.

2.7 Population trends.

The trend in the rate of increase of population should be a factor considered in looking at consumption of pharmaceuticals in the future. The relationship should be a straightforward one of rather similar rate of consumption to rate of population increase, but this is only so if the existing market is fully satisfied and no special medical problems exist. This is not the case in developing Countries and certainly not in the case of the Philippines where only about 20% of requirement is satisfied and several particular problem diseases exist.

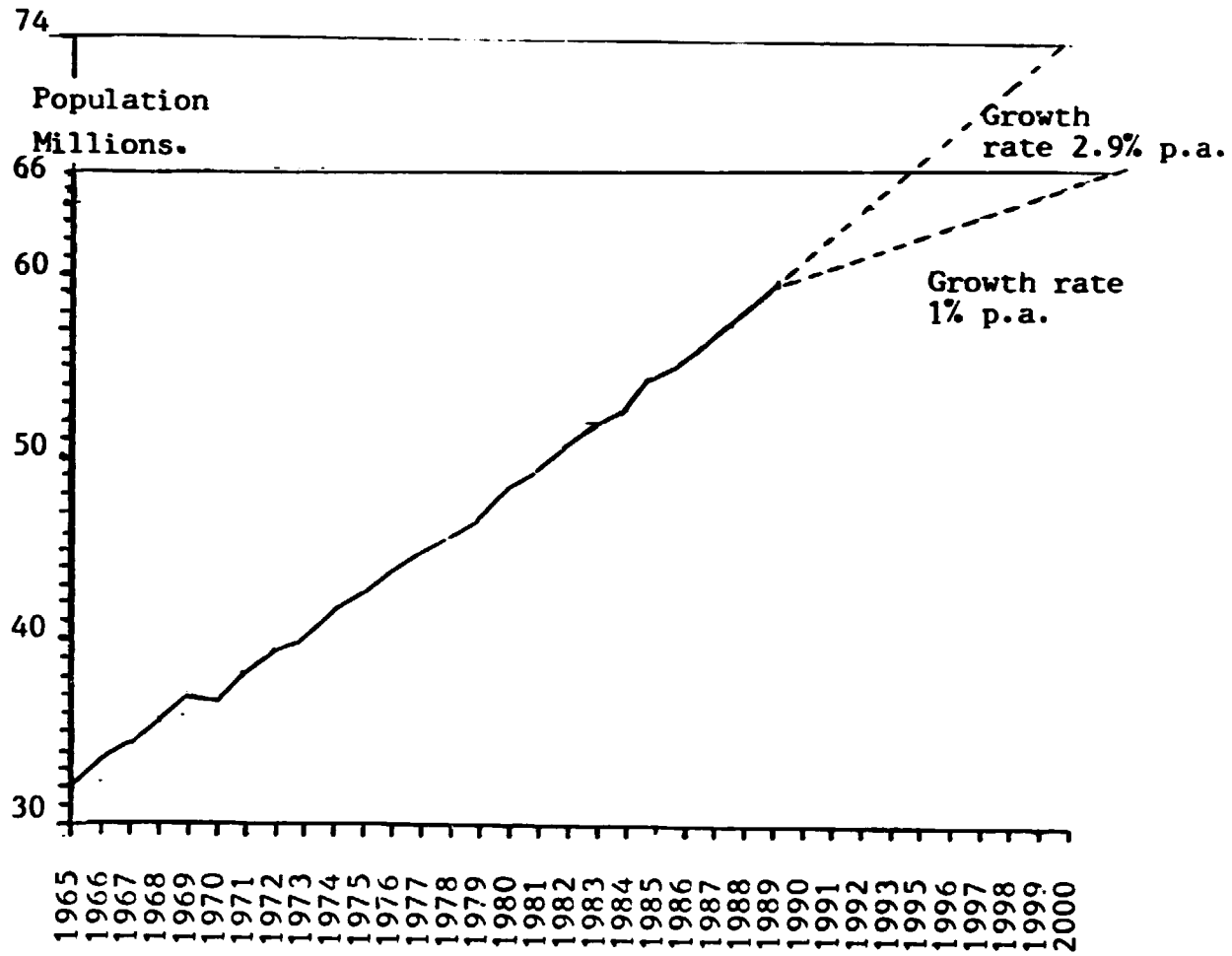
The current birth rate and rate of increase of population is too high, being reported at 2.9% per annum. It is suggested that a more appropriate rate should be nearer 1%. A graph showing the likely gross population figures at these rates of 2.9% against 1% over the period 1987 to 2000 and the historical picture since 1965 is given overleaf. This shows at the high birth rate as at present a population of about 74 million would be reached by the year 2000, but could be restricted to about 66 million at the lower rate.

The question of whether control of population is a desired feature of the development of the Philippines must be a decision of the people and Government of the Philippines. The subject cannot, however, be ignored here for it can have an effect on the consumption of pharmaceuticals and possibly pharmachemicals.

In a previous report (Pharmaceutical Industry in Asean Countries - Philippines, 1975, Kintanar) predictions were made as to the possible pattern of consumption and use of steroid oral contraceptives. In that report it was forecast that by 1980 some 17.65% of women of child bearing age (15 years to 44 years old) would be taking oral contraceptives and by 1985 this would have risen to 22.9%. Although detailed figures were not procured during the mission it would not appear that this forecast has been realised.

Calculations have been made to determine the level of sales market that could develop if this form of contraception was considered more generally as an acceptable method, and used to a sufficient degree to have a marked effect on population growth.

POPULATION GROWTH RATE.



ANNUAL GROWTH RATES OF POPULATION, 1970 - 1987.

Year	Rate %
1970/71	3.0
1971/72	2.9
1972/73	0.7
1973/74	5.5
1974/75	2.5
1975/76	2.8
1976/77	3.0
1977/78	1.1
1978/79	2.4
1979/80	3.7
1980/81	2.5
1981/82	2.5
1982/83	2.4
1983/84	2.3
1984/85	2.8
1985/86	2.8
1986/87	2.9

INDICATION OF TREATMENT NEEDED TO CONTROL BIRTH RATE AND INCREASE IN POPULATION.

Year	Controlled Population (million)	% child bearing	No. child bearing (million)	No. needing contraception (million)
1986	54.4	22.6	12.303	-
1987	56.0	22.6	12.660	-
1988	57.6	22.1	12,749	8,134
1989	59.3	23.1	13,450	8,835
1990	59.9	23.4	13,786	9,171
1991	60.5	23.9	14,172	9,557
1992	61.1	24.3	14,597	9,982
1993	61.7	24.4	14,758	10,143
1994	62.3	24.7	15,112	10,497
1995	62.9	25.4	15,671	11,056
1996	63.5	25.7	16,063	11,448
1997	64.2	26.1	16,465	11,850
1998	64.8	26.5	16,860	12,245
1999	65.5	26.8	17,248	12,633
2000	66.1	27.3	17,730	13,115
2001	66.8	27.8	18,227	13,612
2002	67.5	28.3	18,756	14,141
2003	68.1	28.6	18,943	14,328

Responsible parenthood is essential to control the high rate of population increase. It is difficult to see this being acheived by entirely natural control. Some help by physical and chemical means seems relevant.

With respect to chemical means, specifically using steroid hormones there are available essentially four modes of treatment ; -

- Progestogen-only contraceptive tablets.
  These daily tablets contain only progestogen as either ethynodiol diacetate, Levonorgestrel, Norethisterone or Norgestrel.
  They are not available on the Philippine market.

- Combined estrogen/progestogen contraceptives.
  There are 11 brands available in the Philippine market. These contraceptives contain combinations of ethinyl estradiol (estrogen) and either Norethisterone acetate, Norethisterone, Desogestrel, Norgestrel, Levonorgestrel, Norethindrone or Lynestrenol (Progestogens).
  The dose level of the estrogen falls in the range of 30 - 50 mcg., while the level of progestogen is more variable from 150 - 5,000 mcg. per tablet.
  Packs contain either 21 or 22 tablets containing active ingredients for one-month supply. In some packs there are also 7 tablets containing no active ingredient.

- Phased estrogen/progestogen.
  There is only one brand on the Philippine market containing three different combinations of ethinyl estradiol and Levonorgestrel (6 x 30 mcg. EE + 50 mcg.LN; 5 x 40 mcg. EE + 75 mcg. LN; 10 x 30 mcg. EE + 125 mcg. LN).

- Depot contraceptive injections.
  Only one brand is available currently on the Philippine market. Supplied in 1 ml. vials containing 200 mg. of Norethisterone. After an initial injections a further 3 injections are given at 8 week intervals and any further at 12 week intervals.

Potential market for oral contraceptives in the Philippines.

For calculation purposes it has been assumed that the use of oral contraceptives for birth control might be applied in 50% of the cases which have been determined as necessary for control of population. For 1989 this would mean supply of contraceptive pills to a total of 4,417,500 women. This is 32.8% of the child bearing population and for a concerted effort at population control is not an unreasonable figure. The other 50% would be expected also to take precautions against contraception.

An estimate of consumptions and sales market is given in the following table which assumes a balanced and free choice of products. However, more minor consumptions of Phased and Depot contraceptives have been excluded.

% market	No. pills million	EE kgs	NG kgs	LG kgs	NA kgs	LN kgs	Market value ₱ million
25	278.3	13.92	139.2	-	-	-	216.0
12.5	139.2	4.18	-	20.9	-	-	128.1
12.5	139.2	6.96	-	34.8	-	-	119.7
12.5	139.2	6.96	-	-	55.7	-	305.8
12.5	139.2	6.96	-	-	139.2	-	225.6
12.5	145.8	7.28	-	-	-	145.6	113.6
12.5	145.8	7.28	-	-	-	36.4	106.7
100.0	1,126.7	53.54	139.2	55.7	194.9	182.0	1,215.5

EE = Ethinyl estradiol
NG = Norgestrel
LG = Levonorgestrel
NA = Norethisterone acetate
LN = Lynestrenol

This sales value is quite considerable amounting to about 10% of the total annual sales at current level.

The cost could be reduced by using entirely the cheapest pack of oral contraceptive on the market which sells at ₱ 16.10. The annual cost at this level would be ₱ 893,000,000.

The growth rate, in terms of pill volume would increase at an average of 2.6% until year 2005 and 1% annually thereafter.

It is appreciated that in practice the desired level would not be achieved in a single year as indicated, but could be reached over 3 to 4 years.

2.8 Some general effects on trends and forecasting.

In the case of developing Countries and perhaps particularly so for the Philippines it is not a simple matter to forecast trends in an accurately quantitative manner. Several factors contribute, some leading to increasing demands and some eventually to decreases. Some examples may be quoted:-

- market penetration can have a dramatic effect on consumption as currently only 20% of the population requirements are considered to be met.

- market penetration would only largely be achieved by a larger number of the population having increased incomes and purchasing powers.
- supply of sufficient drugs to deal particularly with endemic diseases such as tuberculosis, malaria, schistomiasis and filiariasis. These would really need to be supplied by the Government free of charge to reach the large numbers of most needy impoverished people. Nonetheless they have to be paid for even if from Government funds so they equally will boost the sales market. A high demand can be anticipated for some years, with subsequent reduction (in spite of increased population) in the longer term as these diseases are controlled or essentially eliminated.
- use of contraceptive drugs to aid control of population growth, as seen in the previous section, can make a considerable increase in the market size but is dependant on acceptability. Nonetheless it has to be pointed out that one years treatment can be procured for as little as ₱ 193 at current prices. Economically this can be more than compensated for by savings in food and clothing.
  An initial considerable increase in sales, probably gradually over 2-3 years could be anticipated and the level then increasing over the next fifteen years at an average rate of 2.6% and thereafter at 1% per annum.

  Conversely other most needed measures would, when implemented, reduce the demand for drugs. Namely :-

- general improvement in supply of potable water throughout the Philippines.
- provision of improved and adequate sanitary conditions and sewage disposal and treatment.
- hygiene education in schools, homes, offices and eating places.

  These measures, and the supply of free medicines, will be expensive and all cannot be achieved immediately. However, the provision of considerable funding is necessary to get to grips with the Health problems existing.

It is suggested that the budget for the Philippines Department of Health for 1989 granted at ₱ 7.4 billion (3.2% of total budget) is rather meagre.
The WHO guideline for expenditure on Health at 5% of GNP has been set for acheivement by the year 2000. The figure at this level for 1987 in the Philippines would have amounted to some ₱ 34.4 billion.

2.9 REVIEW OF ANALYSIS OF CONSUMPTIONS AND TRENDS WITH CONCLUSIONS.

This review is made to analyse whether it is realistic to suggest any back integration of the Philippine pharmaceutical industry into the chemical industry of producing pharmachemicals by synthesis.

Several criteria should be met to consider taking this step.

1. A good pharmaceutical industry, with high level of GMP, should exist in the Country.
   The Philippines are excellently served in this area.

2. Existance of a suitable sales volume.

   For either dedicated or multi-product plants it is considered that a sales level of about US $ 600 million should exist. Furthermore the level of production for the individual products or group of products in the case of a multi-product plant should normally be in excess of 500 metric tons.
   Neither condition exists in the Philippines and there are no other special considerations to consider production.
   This eliminates consideration of the low priced products such as acetylsalicylic acid and paracetamol. Ascorbic acid must also be included here, although as the starting material is glucose a more detailed study of this product may be worthwhile.

   Consideration of a multi-purpose pilot plant for chemical synthesis is considered valid if the existing sales values of pharmaceuticals in the Country lie within the range of US $ 300 million to US $ 600 million. The sales value in the Philippines is currently at a level of about US $ 500 so this criteria is met.

3. Existance of a reasonably expansive market.

A multi-purpose pilot plant is a first training and investigative unit and although it will produce some limited supplies of pharmachemicals for use in the domestic pharmaceutical industry it cannot normally be considered as a particularly directly economic venture. However, it does give the experience of production and the in-road to future and larger production. Therefore the future larger markets, domestic primarily but not excluding possibilities of export, must be apparent.

Considering the vast under-supply of drugs to the population of the Philippines this condition is met on domestic prospects alone.

4. Existance of suitable product grouping.

Apart from the overall sales market and potential it is also important to be able to identify a suitable group of pharmachemicals which can form the basis to justify the installation and use of a multi-purpose pilot plant. The individual production levels for these products should be at a reasonable level so that larger scale production can be seen to be viable and also to provide contribution to the expenses of running the unit.

In the Philippines there is, perhaps from one view point, a too good variety of drugs and component pharmachemicals. There are, in fact, in excess of 900 such pharmachemicals listed in PIMS. As a result the levels of consumptions of some pharmachemicals of interest may be rather low. Although often very useful active ingredients and interesting from a synthesis point of view, with high technology content, several have had to be eliminated from initial consideration. The picture which has developed is that there is a rather limited , though important, package of products which can be recommended. This takes consideration of both individual consumption levels and total package consumption level. The more normal level for a pilot plant capacity (unless designed for rather specific products such as steroids) would be in the range of 120 to 150 metric tons per annum.

For the Philippines the current level which seems realistic is rather less than 100 metric tons and so it might be considered debatable and a borderline case whether a unit should be recommended. It is considered that this is tempered by the large gap between requirement and supply, particularly considering the time by which such a unit would be operable, and not a sufficient reason to discount a positive proposal.

It is not a disadvantage only having a relatively small package of products for consideration in establishment of a multi-purpose pilot plant, for any technology to start such an operation needs to be obtained by some form of technology transfer and this has to be paid for.

It is concluded that the installation of a multi-purpose chemical pilot plant of appropriate size to be determined can be recommended in the Philippines. It is at the same time indicated that a more in-depth study should be performed.

5. Existance of an interesting proposition to investors.

It is unlikely that a proposition could be put forward to interest investors without considerable assistance being given both initially and over the several first few years of operation. Such a time scale could be considered as up to 10 years. This could take the form of assistance in procurement of equipment and technology together with help in funding of buildings. Assistance would also be needed in the general running costs of such a development project. Many types of incentives or assistances could be envisuaged from both outside agencies and the Philippine Government. The Government contribution could take several forms, as might be appropriate to the Philippines, such as low rental land, industrial de-rating, equipment grants, tariff levels on imports, Company tax nolidays for up to 10 years, training grants etc. It is of paramount importance to establisn a unit that some package of incentives be provided.

As stated earlier in the report 'there is a price to pay for progress'.

6. Provision of a Research and Development facility.

Although a Research and development facility will need to be an integral part of any multi-purpose plant, it is seriously suggested that this aspect be considered of prime and early importance. By performing such R & D work, albeit limited to laboratory work, during the planning and the construction time for a factory would be very worthwhile. It is likely that by the time all the initial products have been commissioned some further 'in-house' products, which are likely to be more profitable, could be ready for scaling up and production. Facilities and personnel could easily be found to perform this work and although funding would be necessary no capital investment need be involved.

An early start of a Research and Development Program, performed in a Universtiy or Research Centre, must be strongly recommended.

7. General.

To complete the review of the facts presented in this section, it must be brought to attention that the fact of any back integration into production of pharmachemicals by chemical synthesis is not going result in any dramatic reduction in cost of pharmaceutical products. Indeed, as far as the cost of the active ingredient is concerned, there may be an initial increase in cost. It has been seen that, at the very most, the pharmachemical contribution to the cost of the final product will not exceed 20%. This means also that even if the locally produced pharmachemical is a little more expensive than imported material the cost of the final product will not be greatly influenced.

However, there are other fringe benefits which might result, to some degree, in cost reduction of the final product. Thus the formulators might be able to hold much smaller inventories of pharmachemicals or even finished pharmaceuticals thus saving money interest charges. There would be the important benefit of preserving foreign exchange and also provision, even if not very dramatic, of additional employment and income for the Filipino workers.

The provision of new technology, training and introduction of a new industry must also not be discounted.

CONCLUSIONS.

In principle, and subject to aspects which will be considered in the subsequent sections, the following conclusions can be summarised ;-

- No consideration should be given at this time to the installation of dedicated or multi-product chemical plants in the Philippines.
- The environment in the Philippines is such that the installation of a small multi-purpose chemical pilot plant can be recommended for consideration.
- An initial package of pharmachemicals which can be put forward for further consideration is proposed.
- The pharmachemicals proposed, and which will be discussed in more detail in a later section, comprise ;-

  Trimethoprim; Sulfamethoxazol; Ibuprofen; Metronidazole; Mefenamic acid; Pyrazinamide; Furazolidone; Isoniazid; Ethambutol and Glaphenine.

3. Raw Materials.

These were looked at from the point of view of availability of any locally produced products and potential sources from plant materials or other natural resources.

3.1 Locally produced products.

The only locally produced chemicals in the organic field comprise refined sugar, glycerine, alcohol and starch.

The use of sugar for production of Dextrose USP, which is imported in large quantities, will no doubt be considered in the report on Excipients. It has to be noted, however, that previously one of the Multi-national pharmaceutical Companies was prepared to supply the technology but could not realise any interest in the production by the sugar industry on account of investment needed in analytical equipment.

Another possible use of D-glucose could be for the production of Ascorbic acid for which there is a large market and world wide demand as well as in the Philippines. An investigation in more detail might be worthwhile for the product.

Glycerine is used in pure form and dehydrated in two medicinal preparations. One, Glylax, is a suppository used as a laxative or purgative for constipation. The second, Auralgan Otic, is an Otitis media used for ear treatment. Although usage is probably low such purified and dehydrated glycerine could probably be prepared in the pilot plant.

There are also some derivatives of glycerine. Phanquinone or Phanquone, a derivative of 2,5-diaminoanisole (which is a bacteriocide)and Oxiquinol or Oxin, a derivative of 2-aminophenol(an antiseptic or disinfectant) do not appear to exist on the Philippine market.

Glyceryl trinitrate is used in the Philippines, but in small quantity and because of its explosive nature when prepared it would not be proposed to manufacture this product.

Finally Glyceryl guaiacolate (Guaiacol glyceryl ether or Guaiphenesin) is used in a very large number of cough and cold preparations being an anti-tussive. This compound is

a simple derivative of guaiacol and could be readily made in a multi-purpose pilot plant if quantity requirements are sufficient to warrant doing so. These need to be determined.

Ethanol is produced in the Philippines from molasses of sugar. There are currently 10 major producers with a total daily capacity of 446,000 liters. Two further distilleries expect to start operation in 1988 and 1989 generating a further 90,000 liters per day. In addition there is a further 198,500 liters per day potential capacity in inactive distilleries.

Ethanol is already used in the pharmaceutical industry, in the beverage industry and paint/varnish industry.

The distilleries also produce carbon dioxide which is used in the soft drinks industry, but there is also some potential use for pharmachemical production.

Ethanol is also used widely in Fine chemical synthesis work, both in pure (potable) and de-natured forms. Grades of 99% and 95% are most common.

There are several inorganic materials also produced in the Philippines. These are sodium chloride, sodium hydroxide, sodium carbonate, sodium hypochlorite and ferric chloride. Hydrochloric acid is also produced, but whether good quality and BP or USP grades are available was not established.

A range of commercial gases are also available in the Philippines, most of which are manufactured by CIGI (Consolidated Industrial Gases, Inc.) which is Southeast Asia's largest and most modern industrial gas manufacturer. Bulk storage and good backup services are consequently available. The gases of interest for chemical synthesis which are available comprise nitrogen, carbon dioxide, hydrogen, acetylene, sulfur dioxide and ethylene oxide.

Chlorine gas is also available in the Philippines but the quality is believed not to be very good. No details were obtained.

The following table indicates some facts on locally available materials.

LOCALLY MANUFACTURED AND COMMERCIALLY AVAILABLE CHEMICALS.

Industrial Chemical Industries Inc.

Sodium hydroxide (solid & solution)	100% basis	Price ₱16/kg.
Sodium hypochlorite (67% available chlorine)		Price ₱3.6/kg.
Hydrochloric acid	32%	Price ₱ 3/kg.
Ferric chloride (solution)	40%	Price ₱ 5/kg.

CIGI (Consolidated Industrial Gases, Inc.)

Nitrogen, liquid.	Vacuum insulated evaporators of 1,000, 3,000 & 6,000 gals. available for rental at ₱ 7,000 - 15,000/month.	Price ₱38/m^3
Hydrogen, gas.	Containers 750m^3 and bullet trailers of 1,500m^3. 1,800psi.	Price ₱40/m^3
Acetylene, gas.	Cylinders 3.5m^3	
	Industrial grade (200psi.)	Price ₱110/m^3
	Instrument, spectro.(200psi.)	Price ₱330/m^3
Argon, gas.	Ultra high purity 99.999%	Price all grades ₱200/m^3
	High purity 99.99%	
	Industrial welding 99.9% 1,800psi.	

No prices for other gases but following grades available:-

Carbon dioxide.	Industrial over 99.9%	
	Medical 99.9%	
	High Purity	
	Food grade 99.9%	
Ethylene oxide	99.7%. Pressurised cylinders with nitrogen to 100psi.	

Pilipinas Kao Inc.

Refined glycerine	Price ₱27.25 per kg.

United Coconut Chemicals.

Glycerine	Price ₱12.10 per kg.

Asian Alcohol Corp.

Ethyl alcohol	No grade stated.	Price ₱7.45 per lt.

Interland Chemicals Inc.

Activated charcoal	(suitable water treatment only)	Price ₱17.10 per kg.

3.2 Products from Medicinal and Other Plant materials.

Consideration is given here only to Medicinal plants which produce substances with pharmacological activity and are used directly (or after only simple chemical transformation) in pharmaceutical preparations. Examples of such would be hyoscine, hyosyamine, quinine, morphine. 'Other Plant materials' refer to plants or materials derived from them which yield substances (not having direct useful pharmacological activity) which can be chemically converted to useful pharmachemicals. Examples of these are Dioscorea or Costus Sp. producing Diosgenin or Solanum Sp. from which Solasodine can be isolated. These are basic starting materials for establishment of a steroid industry. Another example would be sisal (Agave sisaliana) the juice from which, after separation of fibre, can be used for the isolation of Hecogenin which is a starting material for production of some corticosteroids.

All other aspects of Medicinal Plants, together with plant materials yielding Essential Oils, will be dealt with in the report of the Expert in this field.

In the Philippines there appears to be no significant evidence of the current abundance or cultivation of any plant materials, nor records of any interesting contents of ingredients in the specific areas under study whereby it is possible to suggest or recommend the installation of an extraction unit.
This apparent lack of useful plant materials, in spite of an excellent climate and verdant growth in the Philippines, is supported by the fact that in the field of Medicinal plants there seems to be no history of the collection, exploitation or export of any such plants. This is, perhaps, not so much a lack of potential sources as a lack of appropriate research into them.

Some comments will be made on a small selection of plants which it had been thought might have been of interest. In fact it could still be worthwhile to do some further research into these as facts were very sparse and something might have been missed.

Dioscorea. Contains diosgenin which could provide an entry into the field of steroid production.
No real records of work or results could be obtained. Some analysis work had been performed but based on very old literature (1956). The species of Dioscorea was not recalled.

This would possibly be Dioscorea Esculenta which is recorded as being present in the Philippines. It would be expected to have a low diosgenin content, not greater than 1%.
The preferred species are Dioscorea deltoidea (natural environment where contents of 5% are recorded) and Dioscorea Floribunda (cultivated, where content may be about 3%).
Cultivation of Florabunda is much easier than Deltoidea and yields of both tubers and ultimate diosgenin per hectare are superior. The purity of the isolated diosgenin from the Florabunda is less good than the very pure product from Deltoidea, but the impurities can be removed during the chemical processing.

Solanum. Many species are known with very variable contents of solasodine. The only species which seem to be present in the Philippines are Solanum Verbascifolium and Nigrum. No analysis work on these plants was located.
Solanum species yield solasodine, a steroidal alkaloid, which on degradation yields the same product as derived from diosgenin. This is pregnadienolone.

Datura species. Many Datura species tend to contain a predominance of hyoscyamine (from which Atropine can be made). The minor constituent is hyoscine or scopolamine which is now a more valuable and desired product. Datura Metel species is recorded to contain a predominance of hyoscine and little hyoscyamine. It is a more interesting species. Datura metel is reported as growing in the Philippines and, if a good content was recorded, might be worth consideration as a source of scopolamine and the chemically derived product of N-butyl scopolamine hydrobromide. Content can reach 0.5%. No analysis of Philippine material was available.

The best source, and most economic, for hyoscine is now Duboisia myoporoides which is grown in Australia. The content can reach at least 2%.

Cinchona Sp. Although there are known to be Cinchona plantations covering, it is believed, some 1,067 hectares near Cagayan de Oro in Mindanao information tends to suggest these plantations may not have been well tended or given good husbandry for some years.

It was unfortunate that permission could not be obtained in time to visit the plantations, and as a consequence no first hand information could be obtained in assessing the current state of these plantations. From previous knowledge it is thought there may be a problem of access into the deeper parts of the plantation which would hamper any harvesting.

No information could be positively located to indicate the species or distribution of trees. One source did suggest Cinchona Officinalis was the main species but could not be confirmed.

Some current analysis work is planned and believed to be in progress but no results were to hand and no indication could be given as to the sampling methods.

It was a pity that more information could not be obtained in the time for it could just be possible that the Philippines have here an asset which could be exploited, not only for the domestic need for quinine but also as an export potential. It is, perhaps though, something that should have been implemented some time ago.

There is a demand domestically, and world wide, for quinine and its salts and also for quinidine. This latter could increase significantly over the years. Quinidine is prepared chemically from quinine although minor amounts do occur in the extract of Cinchona bark. The export market is needed to justify the level of investment needed.

To run a profitable business it is essential to have some excellently run plantations and a planned planting program to generate a reasonably constant or planned supply of harvestable Cinchona Bark. If such a program had to be started now there would be about 8 to 10 years of agricultural investment before any fresh raw material would be available for processing. Certainly, if planting were started early

the trees might reach 50% maturity by the time any extraction unit could be fully operational. The current, assumed old, trees could perhaps, supply sufficient bark to operate the extraction plant until the new crops became available.

Another problem might be the source of seeds for re-planting. Cinchona Officinalis is thought to be the predominant species. This is not the best species for high content or quality of quinine. The preferred species is a Cinchona Ledgeriana hybrid. Quinine contents as high as 12% can be realised with this.

To process Cinchona most economically it is very desirable to locate the extraction plant in the vicinity of the plantation. Apart from the investment in the agricultural program, the cost of the extraction plant, refinery and ancilliary buildings have to be considered. A very rough estimate for this, including buildings and warehousing, can be made. For a unit processing some 1,200 tons Cinchona bark to produce 75 tons quinine per annum the installed cost could be about US $ 8 million. For a unit to produce 150 tons quinine per annum the cost would rise to the region of US $12 million.

Because of the facts related the only recommendation which can be made is that this specific subject be a subject of a further fact finding mission, followed by a feasibility study if appropriate.

Artemesia Annua. Some studies on this product in terms of cultivation in the Philippines could be worthwhile. The isolate, Artemesinin, does seem to have a good potential as an anti-malarial of the future.

3.3 Resources of Animal and Marine Sources.

Products from animal sources are the subject of another expert's report.

No discussions were held regarding the possibility of materials originating from Marine sources. The subject of Shark Fish liver oil is included in the Animal report and might be a source for squalene or Retinol.

3.4 General and conclusions.

For the development of pharmachemical production there is some misconception that it is a pre-requisite to have a very developed petrochemical industry established in the Country. This is a falacy. It is more important, perhaps, to have production of solvents. Even with a developed petrochemical and organics industries it is not likely that many of the requirements of intermediates for pharmachemical production would be produced in any one Country. Quantities are usually relatively small and there is availability in the world markets. The situation in the Philippines should be no deterrent in considering initiation of a pharmachemical or fine chemical industry.

Importations of certain chemicals such as gases which need special containers and are hazardous merchandise to transport could be considered a disadvantage. Fortunately the Philippines are well served in this area and no supply problem exists.

4. Infra-structures.

This section is divided into several areas dealing with availability and quality of services, supplies, disposal and human resources.

4.1 Electricity. This is only dealt with in fairly general terms but an overall conclusion can be reached. The electrical supply follows the American system of 60 cycles and voltage availability at 110v, 220v and 380 v. This poses no problem except for specifying on an electrical equipment orders. The supply situation does vary a little from area to area. Some areas are already affected by insufficient capacity and the situation is expected to worsen during the next year to 18 months.
A new 300 mega watt gas turbine generator is to be installed in the Manila area and should ease the situation by late 1989.

As is common the tariff system for electricity charges is not simple. A price of ₱ 1.395 per KWH plus a general charge of ₱5,800 was given at one site. Another indicated an overall figure of ₱2 per KWH.

The electrical loading of a multi-purpose pilot plant will not be particularly heavy, but the continuity of supply is very important and occassionally essential (for heterogeneous reactions and particularly hydrogenations).

It would therefore be essential to include in the specification of any pilot plant a stand-by generator of adequate capacity and with automatic cut-in.

There are no local regulations against this and indeed the inclusion of a generator in even office and residential building of 4 or more stories is mandatory.

The supply of all flame proof or explosion proof equipment would have to be imported.

4.2 Water supplies. Again this can only be dealt with in general terms as there are significant differences from area to area. In the Manila area sometimes piped mains water is available. The quality is good but treatment for hardness by de-ionisers is necessary.

It is necessary in areas outside, and in some cases even within, the Manila area to sink boreholes. Generally again the quality of water is reasonably good but needing filtration and de-ionising treatment. Water temperatures are rather variable from 24°C-25°C at best. Other areas reported 28°C-35°C whilst in the volcanic area of Los Banos the water temperature can rise to 42°C. This area should be avoided for chemical production.

The volume of water likely to be used in a multi-purpose plant is not usually very large (possibly up to 200,000 gals per day) and volume supply would be no problem.

Mains water cost was quoted at ₱ 0.83/m^3.

4.3 Boiler fuel. Most operators fired their boilers with bunker fuel though small users employed diesel. One pharmaceutical Company had a Filipino designed boiler fuelled with wood!

Bunker fuel is the cheapest fuel. No price was obtained.

4.4 Effluent disposal. The only establishment visited having a problem which would be similar to the effluent from a chemical multi-purpose plant was Chemfields who manufacture semi-synthetic antibiotics. The treatment comprised principally of stripping by distillation of organic solvents, charcoal treatment, settlement and filtration. It is then handed to contractors for final discharge to the lagoon.

For any chemical plant, consideration would have to be given to the inclusion of an effluent treatment plant in the design.

4.5 Solid waste disposal. This does not involve substantial quantities of material in the case of a chemical plant. The mode of treatment is generally by incineration or burying. The necessity to include an incinerator in a production unit design is unlikely.

4.6 Fire-fighting services. It is certain that any unit would have to incorporate its own fire-fighting facilities. In the first instance this could involve the provision of a large buffer pond of water (some Companies make use of this for the secondary purpose of supplying the staff with the recreational facility of a swimming pool!).
Additionally to the supply of normal foam and powder fire

fighting cylinders, some larger fire-fighting tenders would need to be provided. Training in the use of the equipment by factory personnel would be of highest priority.

This 'in-house' facility is a result of the congested traffic situation and the distance any Municipal service might be located from the factory.

4.7 Safety equipment. A selection of products such as gas masks, respirators, canisters, cartridges, safety caps, spectacles, goggles, face shields, helmets, gloves, self contained breathing apparatus and safety shoes are available for supply through CIGI (Consolidated Industrial Gases Inc.).

4.8 Hospital services. Availability of facility will vary with the location of site. First aid and possibly doctor service will be provided at the factory.

4.9 Service equipment manufacture. This is probably limited to boiler manufacture and supply. There are no manufacturers, perhaps surprisingly, of generators or refrigeration equipment. Pumps also have to be mainly imported.

4.10 Vessel fabrication and piping. Facilities are available for the fabrication of stainless steel reaction vessels and receivers for operation under moderate pressure and vacuum. Jacketted versions available. Condensers can also be fabricated although tube bundles are usually imported. Design work, piping and installation facilities are also available. This manufacture is performed by the Asean subsidiary of a well known International Company registered as APV Philippines, Inc.
It is not to be expected that supplies from this Company will necessarily be cheaper than other imported equipment, but they would be available in local currency. The most important aspect is having such a Company readily available.

4.11 Maintenance and spare parts. The Philippines are not well served in this area. It will be necessary to budget for a substantial inventory of spare parts. This problem will also make it very essential to impose a planned maintenance schedule in any plant at the very beginning.

Selection of control equipment for either plant or laboratory should, wherever possible, be tempered very much by the available service back-up.

4.12 Building construction. Facilities are available in the Philippines, although it is likely that detailed assistance and guidance will be necessary for the special requirements of a chemical plant. This is of particular relevance in relationship to floor finishings, drainage and special electrical installations.

The cost of building erection was discussed with various contacts. Only a general picture is available at this stage but is sufficient for any budget calculations. The figures intimated by one construction Company, D.M.Consunji, Inc. are given as an example.

Construction Costs

As per D.M.Consunji, Inc.
June, 1988

	Construction cost/ m^2
1. Warehouse	₱ 3,500 - 4,000
2. Offices:	
4 storey, no elevator	₱ 5,000 - 6,000
4 storey, with elevator	₱ 8,000 - 9,000
3. Animal house	₱ 1,500
4. Production facilities:	
Without cooling system	₱ 4,000 - 5,000
With cooling system (air con!)	₱ 5,000 - 6,000
Excludes outside facilities, e.g. parking, roads, drainage.	
Also not accounting for any special flooring, higher than normal eave height etc. Only ordinary illumination - no special electrics.	
5. Laboratory (within building)	₱ 8,000 - 9,000
6. Civil works (excluding fencing and external illumination):	
Site development	₱ 200 - 300
With intensive drainage system	₱ 400
With complex roadway system	₱ 500

Generally construction costs include basic plumbing, telephone and electrics.

Costs expected to rise by 10-15% or inflation rate per year.

4.13 Human Resources and Training. The whole subject of Human Resources is a most important factor in the development of any industry, new or old.

Training, methods, facilities and staff have all to be examined together with identification of resources available to assist with this need.
It is proposed that this whole subject will reviewed and reported upon by a National expert. Only the facts of the situation and the requirements will be reported upon here.

The subject of Human resources was discussed extensively, covering many aspects, with a wide range of Filipino professionals. These ranged from academics from several Universities, senior personnel in Government establishments, senior managers in Industry (covering pharmaceuticals, chemical and engineering) and with members of the Chemical Society of the Philippines.

The corner stone to support the introduction of a pharma-chemical industry to the Philippines must be the academically trained scientist. Disciplines of organic chemistry and chemical engineering are particularly relevant.
For senior Research management and possibly Factory management personnel with the higher degree of Ph.D. are of special importance. A survey of the situation of availability of such manpower in the Philippines compared with other disciplines is presented below.

MAN POWER RESOURCES IN NATURAL SCIENCES AND ENGINEERING.
Philippines, 1988.
Scientific personnel with Ph.D. and M.Sc. degrees.

	Ph.D.	M.Sc.
1. Biology	153	130
2. Chemistry	66	60
3. Mathematics & Statistics	50	120
4. Earth Science	14	12
5. Physics	35	15
6. Engineering Sciences	78	90

Data collected by Dr.Ester Albano-Garcia,
PCASTD. May, 1988.

DISTRIBUTION OF CHEMISTRY PERSONNEL.

	Ph.D.	M.Sc.
1. U.P. Diliman.	13	1
2. U.P. Los Banos.	11	10
3. Ateneo de Manila Univ.	6	6
4. De La Salle Univ.	2	5
5. Univ. Santa Tomas	1	-
6. Other institutions	2	15

In addition 5 Ph.D. graduates were known to be located in Industry at United Laboratories, Inc., San Miguel Corporation and Pascual Laboratories, Inc. The location of the remainder was not recorded.

In the Philippines a program leading to the degree of Doctor of Philosophy in Chemistry was initiated in 1982. The course is offered by the Consortium of U.P., Ateneo University and De La Salle University. It is supported by the National Science and Technology Authority, the International Development Program of Australia and the Japan Society for the Promotion of Science. It includes a 6 - 12 month research stay abroad in either Australia, Japan, Great Britain or West Germany. Students have to return to the Philippines before they can graduate and this increases the likelihood that the student will remain to work in the Philippines.

The program started with an intake of 5 students in 1982. Of these 3 have graduated and one should complete soon. One student left the course.
A second intake of 5 was taken in 1984 and 3 should graduate between July and September 1988. The other two are completing their study abroad, one in Japan and the other in West Germany. Intakes currently are every two years.

A Ph.D. program in Chemistry is also expected to be offered by the University of Los Banos within the next 5 years

Research experience. Research experience relevant for the chemical work which would be involved in the synthesis of pharmachemicals is extremely limited. Of all programmes surveyed only five can be recalled which bear any resemblance,

and only marginal in some cases, to the type of synthetic work likely to be encountered in the sythesis of pharmachemicals.

These were: -

- Synthesis of thionucleosides.	Natural Sciences Research Institute (₱ 103,025)
- Preparation of Quaterniary Ammonium salts from Coconut Oil.	Natural Sciences Research Institute (₱ 52,603)
- Preparation of sorbitol and Mannitol from sucrose by catalytic hydrogenation.	Natural Sciences Research Institute (₱ 33,229)
- Synthesis of heteroaromatic aldehydes using dibromoacetonitrile as Synthon: A synthesis of s-Triazine trialdehyde.	Natural Sciences Research Institute (₱ 65,000)
- Synthesis of Lauryl Glyceryl Ethers	Institute of Chemistry, U.P. Los Banos.

The fundings in brackets are quoted to indicate the very meagre funds allocated to the projects.

The majority of Ph.D. graduates are engaged in education and have little real opportunity for much research work due to the serious lack of funding. There is also some limitation on equipment. Talents are not fully utilised.

Facilities. The general impression was that the Universities as such are not particularly well furnished with equipment, although the situation in the privately funded Universities was markedly different from the Government sponsored. This picture was also reflected in the salary levels of staff. This situation is another factor controlling research.

Similarly in the areas of laboratory and pilot plant seen at the DOST there are obvious further needs in terms of equipment.

Conversely, there are Research organisations, such as PIPAC and BIOTECH, with the most excellent facilities; dreams of any researcher throughout the world. The same can also be said of the Bureau of Food & Drug of the Philippines.

PIPAC - The Philippines Institute of Pure and Applied Chemistry is an independant scientific institute organized to conduct chemical research, analysis and training. It was founded in 1973 by professors of the Department of Chemistry of the Ateneo de Manila University and is located at the Ateneo campus. It was financed by a grant from the

Japanese Government, while other instruments were also acquired through a grant from the Alexander von Humboldt foundation of West Germany.
The Institute operates as a private, non-stock, not-for-profit corporation governed by a board of trustees elected from the business sector, academics and Government.

The facilities of this institute, both in equipment and environment are excellent but it . felt that it is not utilised to its full capacity. One area is lacking, for although provisions have been included in the building for the inclusion of pilot chemical plant there is currently no such equipment installed. It would be a great asset to have such a pilot plant which would be useful not only for scale up and investigative work, but also as an important facility in the field of training in chemical plant operation for chemists and technicians.

Senior staff at the institute number nine, including 7 Ph.D., 1 M.S. and 1 B.S. (Pharmacy & chemistry) while the total staff is about 20.

It is suggested that this institute could be the ideal starting point as a facility for commencing advanced Research and Development work in advance of setting up a pharmachemical industry in the Country. There need be no lead time to starting work. The institute is also a valuable long term asset as support to any production facility ultimately operating.

BIOTECH - National Institutes of Biotechnology and Applied Microbiology is a unit of the University of the Philippines at Los Banos, Laguna. It operates with funds from a regular budget of the National Government and from external grants. Again excellent facilities and instrumentation; but once again it is felt under-utilised no doubt to lack of funding for staff.

This unit, although excellent, is not initially so important or interesting as a back up facility for the development of a pharmachemical industry as envisuaged at present.

However, at a later stage, it might be a great asset for it does possess a most excellent pilot plant containing a variety of fermenters from 2 to 1,000 liters, one of 30 liters being fully computer controlled. Back integration into pharmachemicals is only initially being considered in terms of pure synthetic chemistry, but for later considerations the inclusion of microbiological transformations cannot be excluded and then this equipment facility could be very valuable. Such processes could be involved in the field of steroid chemistry if being developed from basic materials.

B.S. Level. The second level of staff to be considered are the Batchelor of Science graduates. In the Philippines such graduates also have to be licenced to practice chemistry and regular renewal is required. Licence is issued by the Professional Regulation Commission.

From discussions, particularly in the Industrial field where such workers have to prove themselves, it is clear that the general standard of the Philippine B.S. graduate is good. Confirmation of this must lie in the fact that many students are accepted into the higher degree courses at Overseas Universities in America, Great Britain, Japan, West Germany and elsewhere.

There is a current drop of the in-take of students studying for the B.S. in Chemistry. Though not immediately serious this should be watched carefully if, as it is sincerely hoped, the chemical industry expands quickly in the coming years. This drop may be due to a current lack of suitable situations available after graduation.

The B.S. level of graduate in chemistry could expect to be employed in any of several positions in a multi-purpose chemical pilot plant, viz:-

- as quality control or production control chemists.
- as chemical assistants in Research and Development.
- as production chemists, supervisors or operators.

Plant operators. For actual plant operation it has been indicated above that graduate chemists would be utilised on the production floor. The lowest level of operator would still have to have a reasonable academic training for the

Technician level. This would correspond to a minimum of 3 years appropriate college training.

Unskilled labour should only be used for carrying and cleaning.

Engineering. A works engineer is an important position in any plant and particularly in a multi-purpose plant where a very wide range of items are involved. A mechanical engineer is probably most appropriate for this position and his most important job in a factory in the Philippines should be preventative maintenance.
There is no doubt that this position could be easily filled for many well trained and experienced engineers must be available in the Philippines.

The works engineer would be responsible for the various disciplines including such trades as pipe fitting, welding, maintenance (mechanical, instrument and electrical).
It is understood that this level of worker would have to be very carefully selected and given extensive training.

Office administration. The extent of office administration could vary greatly with the organisation of the Company. Some financial expertise, secretarial and typing would be expected, but as it would not be essential to have any special knowledge of the chemical industry these positions would not pose any problems.

Management. Most management positions, both senior and middle can be expected to be filled by technically qualified people because of the nature of the work which will be performed in the plant.
The General Manager might best be a chemical engineer. This is not a discipline very advanced in the Philippines and might only relate to an expatriate. The alternative would be a chemist with a bent towards engineering as well as management.

Although sales and marketing are normally of prime importance in the management of a Company there is no great need of emphasis in this aspect initially. It would come later as a result of any development of the pilot plant.

Staffing. Only a general picture can be presented at this stage, but it is necessary to assess the recruitment possibilities.

A total staff of 45/50 can be anticipated.

The general breakdown could be:-

	Total	Ph.D.	B.S./M.S.	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 (office)	7	-	-	7
Unskilled	7	-	-	7

4.14 Review of Infra-structures and conclusions.

One area of infra-structure has not been covered and this is communications. This can cover road, rail, sea and air access and telecommunications.

For a multi-purpose pilot plant the transportation aspects are not of any great significance. Any factory should be served by good roads for delivery of plant and chemicals and this must be incorporated into the design. (This is not the case of the one semi-synthetic antibiotic plant, Chemfields, in the Philippines and the completely unsatisfactory road surface for the last few kilometers to the factory must prove a great problem at times).

Telecommunications in certain areas around Manila are not good, often affected by heavy rain. Radio communication has to be used in some areas. Again this is not a serious problem, only a nuisance perhaps, in running a multi-purpose pilot plant. It would be a much greater problem when substantial sales were involved and overseas contact important. Telefax facilities in the Philippines are poor, telex reasonable.

All the aspects of infra-structure may now be summarised and conclusions proffered.

Conclusions on Infra-structures are:-

- there are no insurmountable problems with the supply of services, but design characteristics will need to be included dependant in some cases on location. Universally a generator for electricity will be needed on site; in most locations wells will need to be sunk for water; the question of effluent treatment will need to be analysed.
- in-house water storage and fire fighting facilities will need to be included in design.
- there is very limited manufacture of equipment for services in the Philippines other than boilers. Generators, refrigeration plants and pumps have all to be imported. This implies high levels of spare parts must be stocked on site.
- there is the possibility of the fabrication of stainless steel plant in the Philippines including reaction vessels, receivers and condensers up to any standard likely to be required. Design, installation and piping facilities are also available. This can incorporate supply of pumps and instrumentation. This is available from APV Philippines Inc.
- maintenance is a foreseen problem. Not only must high spare stock levels be held but it is essential from the first operation of any plant to start a planned maintenance program.
- care should be taken when possible in the selection of laboratory instrumentation that the supplier can offer a maintenance service.
- expertise is available with respect to building construction and erection, but possibly little experience of some of the special features needed in a the multi-purpose pilot plant. These can be dealt with provided the specifications are laid down.
- human resources, experience and training pose the main problems. It would be hoped, perhaps by some Governmental incentives, to encourage some expatriate Filipino Ph.D's to return to take up employment. Hopefully some could be selected who, while abroad, have gained some years

experience in the field of synthesis of pharmachemicals and on return would be able to assist in shaping the future of the Philippines. Numbers required are not large.

- recruitment of some of the new Filipino Ph.D. graduates should be possible.
- the recruitment of B.S./M.S. chemists and other levels of workers poses no real problems.
- the training of workers, particularly those technically qualified who will work in production or R & D scaling up and tradesmen, is a problem that has to be faced.
- in the event of deciding to proceed with the design, construction and operation of a multi-purpose chemical pilot plant, it is suggested that a Research or Research and Development program be immediately initiated using the facilities at PIPAC. Staffing could be partly by consultant professors and partly by salaried staff who would later transfer to the factory.
- additionally if funding could be found to instal some pilot chemical plant in PIPAC this could also be used as a training centre.
- when tendering for supply of technology it should be a condition that training for several chemists and technicians for some months be included in the offer.

Overall there are no problems of such severity as to suggest that the proposition of consideration to build a multi-purpose chemical pilot plant in the Philippines should not stand.

5. PATENTS,

The Patent Law and situation will be dealt with and reported by the Local legal expert. It appears that several proposals for changes in Patent Law are being put before the Government.

There is said to be a 17 year cover of Patents for both product and processes. The Philippines are not a Member of the Convention and so a Priority situation in a Home Country will not be upheld.

Patents will not be any serious problem for production in the Philippines. but an awareness of the situation for any product under consideration for production or research is necessary and valuable.

Any technology transferred or purchased will not necessarily, and indeed probably rarely, be the very latest in the state of the art. Being aware of patents can indicate the ongoing current interest in the product and also give some indication of what development progress could perhaps be realised by in-house development.

Another advantage of the knowledge of the Patent situation on drugs is as a lead into longer term research with a view to developing syntheses of pharmachemicals whose patent life is near to ending. Successful research can lead to the timely introduction of these products to product range and production with profitable results.

PART 3.

CONSIDERATIONS RELATING TO THE INSTALLATION OF A MULTI-PURPOSE CHEMICAL PILOT PLANT IN THE PHILIPPINES.

Consideration will be given in this section to some of the implications of proposing the possibility of setting up a multi-purpose chemical pilot plant in the Philippines.

This will consist of :-

- analysis of the utilisation of the pharmachemicals which have been suggested for first consideration as a package to be manufactured.
- schematic indication of the chemical transformations likely to be involved in the production of the pharmachemicals proposed.
- indications of what the multi-purpose chemical pilot plant should provide as a facility and what can be done in it.
- provisional indication of production levels and sales values.
- outline description and sizing of equipment.
- provisional costing of installed equipment, buildings and site.
- location suggestions for pilot plant and relationship to any other proposed or existing facilities.
- Research and Development. Suggestion of approach and program.
- Conclusions.

1. SURVEY OF PHARMACHEMICAL USE.

Considering the list of Pharmachemicals proposed as possible candidates for initial production in the Philippines there follows a survey indicating the medical use of he product, the ethical products produced in which they are to be found, principal sales and quantity of Pharmachemical contained in these.

1.1 TRIMETHOPRIM AND SULFAMETHOXAZOLE.

This combination is often referred to as COTRIMOXAZOLE. Sulfamethoxazole always occurs in combination with trimethoprim in a constant ration of 5:1.

Therapeutic use: Anti-bacterial combination.

Indications: Respiratory tract infections. Genito-urinary infections.

Brands available: Of 29 brands listed in PIMS, 19 were located in IMS reports for 1987 for Drug stores and 14 for Hospitals.

Brands:

Bacidal	Mucorama TS
Bactrim (+ Forte)	Rezoprim
Broncho Bactrim	Septrim (+ Forte)
Cotrimol	Sulfotrim (+ Forte)
Drilozole	T/S Pascual
Expectorant Comp.	Trimerin
Groprim	Trisulcom
Lagatrim	Trizole
Lexitrole	Uro-bactrim *

Largest sales:

Bactrim (+ Forte)	₱ 39,196,000	Roche
Broncho-Bactrim	₱ 13,883,000	Roche
Septrim (+ Forte)	₱ 12,450,000	Wellcome
Uro-Bactrim	₱ 9,248,000	Roche

Quantities in largest sales:

Pharmachemicals		
Bactrim (+ Forte)	Trimethoprim	709.7 kg.
	SM	3,548.5 kg.
Broncho-Bactrim	Trimethoprim	99.8 kg.
	SM	498.8 kg.
Septrim (+ Forte)	Trimethoprim	209.2 kg.
	SM	1,046.0 kg.
Uro-Bactrim	Trimethoprim	147.2 kg.
	SM	736.0 kg.

Comments:

SM = Sulfamethoxazole.
* also contains Phenazopyridine.

Market dominated by Roche.

Certain amount material imported as a granulate mixture.

1.2 TRIMETHOPRIM.

Trimethoprim is also used in one product as sole constituent and in 5 other products in combination with pharmachemicals other than sulfamethoxazole.

Therapeutic use: Anti-bacterial.

Indications: Respiratory tract infections. Genito-urinary infections.

Brands available: All 6 brands listed in PIMS were located in IMS reports. All 6 were available through Drug stores and 4 through Hospitals.

Brands:	Brands.	Combination.	
	Biroxin	Sulfadiazine	
	Kelfiprim	Sulfamethopyrazine	
	Lidaprim	Sulfametrole	
	Monotrim	-	
	Supristol	Sulfamoxole	
	Triglobe	Sulfadiazine	
Largest sales:	Triglobe	₱ 18,896,000	Astra.
	Lidaprim	₱ 9,810,000	Nattermann.
	Kelfiprim	₱ 3,060,000	Farmitalia Carlo Erba.

Quantities in largest sales: Pharmachemicals			
	Triglobe	Trimethoprim	404.4 kg.
	Lidaprim	Trimethoprim	219.6 kg.
	Kelfiprim	Trimethoprim	80.6 kg.

Comments: Smaller market in terms of trimethoprim. Wider distribution between Companies.

1.3 ETHAMBUTOL HYDROCHLORIDE.

Ethambutol hydrochloride (as usually described) is, in fact, the dihydrochloride.

It is present in 8 products listed in PIMS as the sole component. 7 of these are available at Drug stores and 5 in Hospitals. Additionally a generic, USA Ethambutol is to be found in both Drug stores and Hospitals.

Apart from one product, Rambutol, where ethambutol hydrochloride is used in combination with Rifampicin, INH and Vit. B6 (available in both Drug stores and Hospitals) all other combination products additionally contain only INH and Vit. B6. There are 20 such products listed in PIMS. 18 are to be found in Drug stores and 12 in Hospitals.

1.3 ETHAMBUTOL (CONT.)

Therapeutic use: Anti-tuberculosis agent.

Indications: Initial treatment and re-treatment of active tuberculosis. All types of tuberculosis, prophylaxis and treatment of pulmonary and extra-pulmonary tuberculosis.

Brands available: The availability of brands has be reviewed in the forward.

Brands: Single component.

Abbutol
Danbutol
Ethambin
Interbutol
Myambutol
Odetol
Triambutol
USA Ethambutol

Multi-component with INH and Vit. B6.

Abbutol-INH-B6
Combutol
Danbutol Plus
Dredoxin
Ebid
Ebutol (+ Forte)
EMB
Etamison (+ Forte)
Etham 500
Ethambin-INH
Ethamizid
Ethi 200/Ethi 400
Forbutol
Isonic Forte
Myambutol + B6 + INH
Pediambutol w/INH + B6
Ronah - 500
Triambutol

Multi-component with Rifampicin, INH & Vit. B6

Rambutol

Largest sales:

EMB	₱ 27,816,000	Lederle
Myambutol+B6+INH	₱ 9,797,000	Lederle
Ethambin-INH	₱ 8,818,000	United American
Ethamizid	₱ 7,547,000	Biomedia
Isoetam	₱ 6,767,000	Nattermann
Ronah-500	₱ 6,709,000	A.H.Robins
Abbutol-INH-B6	₱ 5,986,000	Abbott

Quantities in largest sales:

Pharmachemical.

EMB	3,740.0 kg.
Myambutol+B6+INH	1,185.3 kg.
Ethambin-INH	1,230.7 kg.
Ethamizid	1,156.0 kg.
Isoetam	920.9 kg.
Ronah-500	1,125.0 kg.
Abbutol-INH-B6	760.C kg.

Comments: Apart from predominance of Lederle the sales are distributed over a range of suppliers at similar level.

1.4 IBUPROFEN.

Therapeutic use: Anti-rheumatic, Anti-inflammatory Analgesic.

Indications: Osteoarthritis and Rheumatoid arthritis. Arthritic conditions, painful musculo-skeletal disorders. Pain and inflammation after dental treatment. Dysmenorrhea. Post surgical pain. Adjunct to chemotherapy in respiratory infections.

Brands available: Only 2 brands listed in PIMS and both are available in both Drug stores and Hospitals.

Brands: Brufen
Motrin

Largest sales:	Brufen	₱ 3,510,000	Boots
	Motrin	₱ 673,000	Upjohn

Quantities in largest sales: Pharmachemical.	Brufen	402.0 kg.
	Motrin	84.0 kg.

Comments. Ibuprofen is compounded as a single component product.
This product needs to be looked at again as errors were found in the record of the pharmacists abstractions from IMS.
It is an important product worldwide and the import figures would appear to be more reliable than these consumptions.

1.5 MEFENAMIC ACID.

Therapeutic use: Analgesic and Antipyretic. Mefenamic acid is a Non-steroidal anti-inflammatory drug (NSAID) with relatively weak action.

Indications: Relief of mild to moderately severe somatic and neuritic pains. Headache, migraine, rheumatic, post partum, post operative and dental pains. In pain and fever following various inflammatory conditions. Dysmenorrhea. Menorrhagia accompanied by spasm or hypo-gastric pain.

1.5 MEFENAMIC ACID (CONT.)

Brands available: Of the 6 brands listed in PIMS all are reported available by IMS in Drug stores and 6 in Hospitals. Two additional products; Rucidol, is recorded as available in the Drug stores and USA Mefenamic acid fully.

Brands:
Danostel
Dolfenal
Ponstan
Pontalon
Rucadol
Spegic
USA Mefenamic acid
Vi-Mefenamic acid

Largest sales:	Ponstan	₱ 59,371,000	Parke Davis.
	Dolfenal	₱ 4,201,000	Therapharma.
Quantities of largest sales:	Ponstan	6,240.0 kg.	
Pharmachemical.	Dolfenal	950.0 kg.	

Comments: Ponstan is an original product of Parke Davis research and this dominates the market. It is not clear whether there is a special feature of their formulation which makes this brand so much more expensive relative to the Mefenamic acid content.
The two products above consume 97.2% of the Mefenamic acid used and 98% of sales value.

1.6 PYRAZINAMIDE.

Mostly used as single component, but there are two combination products with Rifampicin and INH.

Therapeutic use: Anti-tuberculosis agent.

Indications: Treatment of various forms of pulmonary and extra-pulmonary tuberculosis.
Particularly recommended for initial intensive chemotherapy (usually in first two months) in combination with other anti-tuberculosis drugs.

1.6 PYRAZINAMIDE (CONT.)

Brands available: Of the listed 9 brands in PIMS, 8 are available according to the IMS. These 8 are to be found in the Drug stores, while 5 can be found in Hospitals. Two other brands can be found in the Drug stores, Infra-2 and Zirostat.

Brands:

Single component.

Braccopiral
Pyzamed
PZA (Lederle)
PZA (Ciba)
PZA (Pascual)
Trifamicyl
Infra-2
Zirastat

Combination. (with Rifampicin and INH)

Pyrina
Rifater

Largest sales:

Rifater	₱ 22,420,000	Merrell Dow
PZA (Ciba)	₱ 13,569,000	Ciba
PZA (Lederle)	₱ 5,744,000	Lederle
Pyzamed	₱ 3,400,000	Medichem

Quantities of largest sales. Pharmachemical.

Rifater	934.5 kg.
PZA (Ciba)	3,010.0 kg.
PZA (Lederle)	1,225.0 kg.
Pyzamed	845.0 kg.

Comments: In fact Ciba and Lederle are the main customers for pyrazinamide. In terms of material content Braccopirol of Bracco enters the top list consuming 625 kg. per annum (in 1987).

1.7 FURAZOLIDONE.

Therapeutic use: Antidiarrhoeals.

Indications: Specific and symtomatic treatment of bacterial or protozoal diarrhoea, dysentry and enteritis caused by suseptible organisms.

1.7 FURAZOLIDONE. (CONT.)

Brands available: Of the 8 brands listed in Pims, only 6 could be located in the IMS. In the Drug stores 5 were available and in the Hospitals only 4. Two brands contain only furazolidone (Diazept tablets and Furoxone tablets and liquid), while the others are compounded with kaolin and pectin.

Brands.

Single compound.

Diazept (tablets)
Furoxone

Combination (with kaolin and pectin)

Diafuran
Diapectolin
Diazept (suspension)
F-Zolidone
Pseudo-Ambin

Largest sales:	Diazept (all forms)	₱ 3,869,000	Rorer
	Furoxone	₱ 3,578,000	Norwich Eaton.

Quantities of largest sales:	Diazept	56.6 kg.
Pharmachemical.	Furoxone	63.2 kg.

Comments: This product will need to be checked again Importations are of a reasonably high level for which reason it has been included as of interest for synthesis. Most material used outside of the direct pharmaceutical industry. (Veterinary)

1.8 GLAPHENINE.

Therapeutic use: Analgesics and Anti-pyretics.
Muscle relaxant (in combination)

Indications: Moderate to severe pains like traumatic, neurological, post operative, rheumatic and others as in dentistry and gynecology-obstetrics.

Brands available: No analysis was abstracted from PIMS for this product.

1.8 GLAPHENINE (CONT.)

Brands: Brands listed in PIMS.

Single component.

Glafen
Glanin
Glifanan
Revalan
Unilab Glafenine

Combination.

Gliferelax (with thiocolchicoside)

Skelan Forte (with phenyl butazone & carisoprodol)

Largest sales: Not determined.

Quantities of largest sales: Not determined.

Comments: This should be reviewed further. There are records of 3,345 kgs imported.

1.9 ISONIAZID.

Used in very many products. Apart from Unilab Isoniazid and Globizid 400 which are single component products it is always found in combination products.

Therapeutic use: Antituberculosis agents.

Indications: Tuberculosis.

Brands available: Of 62 brands listed in PIMS only 42 were located in IMS. 40 of these could be obtained from Drug stores and 25 from Hospitals. In addition 3 brands were available but not listed in PIMS. Two of these, Zidrid and Dipicin, were available at Hospitals. Both, together with Pertix could be found at Drug stores.

Brands: Single component.

Globidiz 400
Unilab Isoniazid

Combination (with B6 & Niacinamide)

Isovical

Combination (with Vit.B1 and B6)

Primafort
Trisofort

1.9 ISONIAZID (CONT.)

Brands:

Combination (with Rifampicin & Pyrazinamide)

Pyrina
Rifater

Combination (with Rifampicin, Ethambutol, and pyrazinamide)

Rambutol

Combination (with Rifampicin)

Iso-Ramp
Ramicin Iso
Rifatrexin-INH
Rifmah
Rimactazid 150/225/300

Combination (with Vit.B6)

Comprilex
Eurocoxin/Forte
Globizid w/B6
Isodexid/Forte
Isonic
Isovip
Nicetal/Forte
Odinah
Pulrevin
Pyrifort
Pyrobin-H
Rotazid
Trisovit

Combination (with Ethambutol and Vit.B6)

Abbutol-INH-B6
Combutol
Danbutol
Dredoxin
Ebid
Ebutol/Forte
EMB
Etamison Forte
Etham 500
Ethambin-INH
Ethamizid
Ethi 200/Ethi 400
Forbutol
Pediambutol+INH+B6
Ronah 500
Triambutol-INH-B6

Combination unknown.

Dipicin
Pertix
Zidrid

Largest sales:

Rimactazid	₱ 33,348,000	Ciba
EMB	₱ 27,816,000	Lederle
Rifater	₱ 22,420,000	Merrell Dow
Trisovit	₱ 13,068,000	Westmont
Trisofort	₱ 13,031,000	Westmont
Rifinah	₱ 11,064,000	Merrell Dow
Ethambin-INH	₱ 9,261,000	United American
Nicetal	₱ 8,954,000	Wander
Comprilex	₱ 8,459,000	Pediatrica
Pyrobin-H	₱ 6,109,000	A.H.Robins
Etham 500	₱ 4,420,000	United American

1.9 ISONIAZID (CONT.)

Quantities of largest sales: Pharmachemical.

Trisofort	5,850.0 kg.
Trisovit	2,960.0 kg.
Nicetal	2,375.0 kg.
Comprilex	2,037.0 kg.
EMB	1,870.0 kg.
Rimactazid	981.0 kg.
Ethambin-INH	757.0 kg.
Pyrobin	432.0 kg.
Etham	299.0 kg.
Rifater	291.0 kg.
Rifinah	260.0 kg.

Comments: As a result of the different combinations of active ingredients the picture of sales values and quantities of isoniazid present are quite different. For this reason order of brands has been altered in the quantity table to indicate rather the order of importance from the pharmachemical point of view with respect to the market for sale of this ingredient.
Westmont are by far the biggest consumer, followed by Wander, Pediatrica and Lederle.

1.10 METRONIDAZOLE.

Therapeutic use: Antibacterial. Antiamoebics. Vaginal Conditions.

Indications: Treatment of serious infections caused by susceptible anaerobic bacteria. Indicated in patients needing surgery who have, or are believed to have, anaerobic sepsis (such as septicemia, peritonitis, subphrenic or pelvic abscesses.) Vaginitis and urethritis due to Trichomonas vaginalis and/or Giardia lamblia (non-specific vaginitis.)

Brands available: PIMS lists 9 brands but only 7 recorded in IMS records. 4 additional brands were recorded, Flagystatin, Metronidazole USA, Metronidazole Bull and Podoyl all available in Drug stores only. 7 remaining PIMS brands available in Drug stores, but only 4 in Hospitals.

1.10 METRONIDAZOLE (CONT.)

Brands available: Usually used as sole constituent. One product (Entamizole) is a combination with Diloxanide. It is not known if the products Flagystatin and Podogyl are single or combination preparations.

Brands:

Single component.

Amibazol
Anerobia
Flagyl
Metrolag
Metroxyn
Metryl 500/IV
Metronidazole USA
Metronidazole Bull

Combination. (with Diloxanide)

Entamizole

Others.

Flagystatin
Podogyl

Largest sales:	Flagyl	₱ 29,950,000	Rhone Poulenc
	Flagystatin	₱ 5,616,000	Rhone Poulenc ?
	Anerobia	₱ 3,408,000	Searle

Quantities of largest sales: Pharmachemical.	Flagyl	1,111.0 kg.
	Flagystatin	198.0 kg.
	Anerobia	208.1 kg.

Comments: These three products, dominated by Rhone Poulenc, represent 91.7% of the bulk market and remainder comprising 145 kg.

Summary: The group of products cover four therapeutic classes, all of high priority. These are :-

Anti-bacterial	(3)
Anti-tuberculosis	(3)
Anti-inflammatory/analgesic	(3)
Anti-diarrhoeal	(1)

2. Schematic indication of the back integration synthesis of the ten selected pharmachemicals are given in the following pages.

As is most prudent when entering into such back integration the number of chemical stages are limited. It is usually possible later to back integrate further, but not always prudent to do so.
It is considered it is not good to indulge in any synthesis of more than 5 stages in a multi-purpose plant.

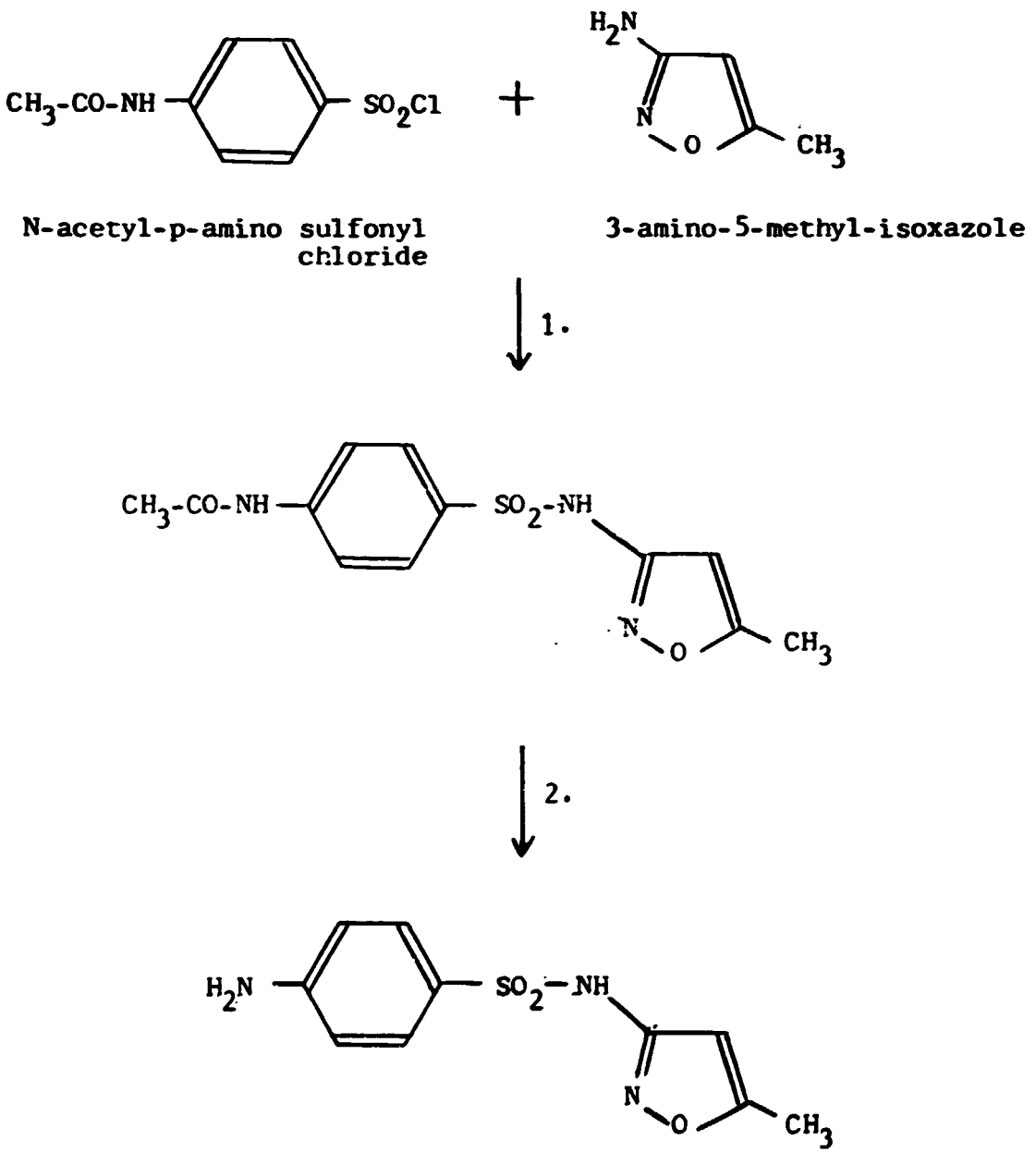
These products do exhibit a reasonable spread of different reactions. This is important for it must always be remembered that the multi-purpose pilot plant is not only a small production unit but also a training instrument.

The range of reactions covered are summarised below.

Sulphonamide formation.
Hydrolysis (De-acetylation).
Knoevenagel condensation.
Michael addition and ring closure.
Condensation (aliphatic amine & halide).
Friedel Crafts.
Oxidation.
Condensation (aromatic amine & halide).
Ammonolysis.
Cyclisation.
Schiff's base formation.
Replacement.
Catalytic reduction.
Condensation (hydrazone formation).
Nitration.
N-alkylation.

The routes for the ten pharmachemicals are given in the following flow sheets.

2.1 SULFAMETHOXAZOLE.

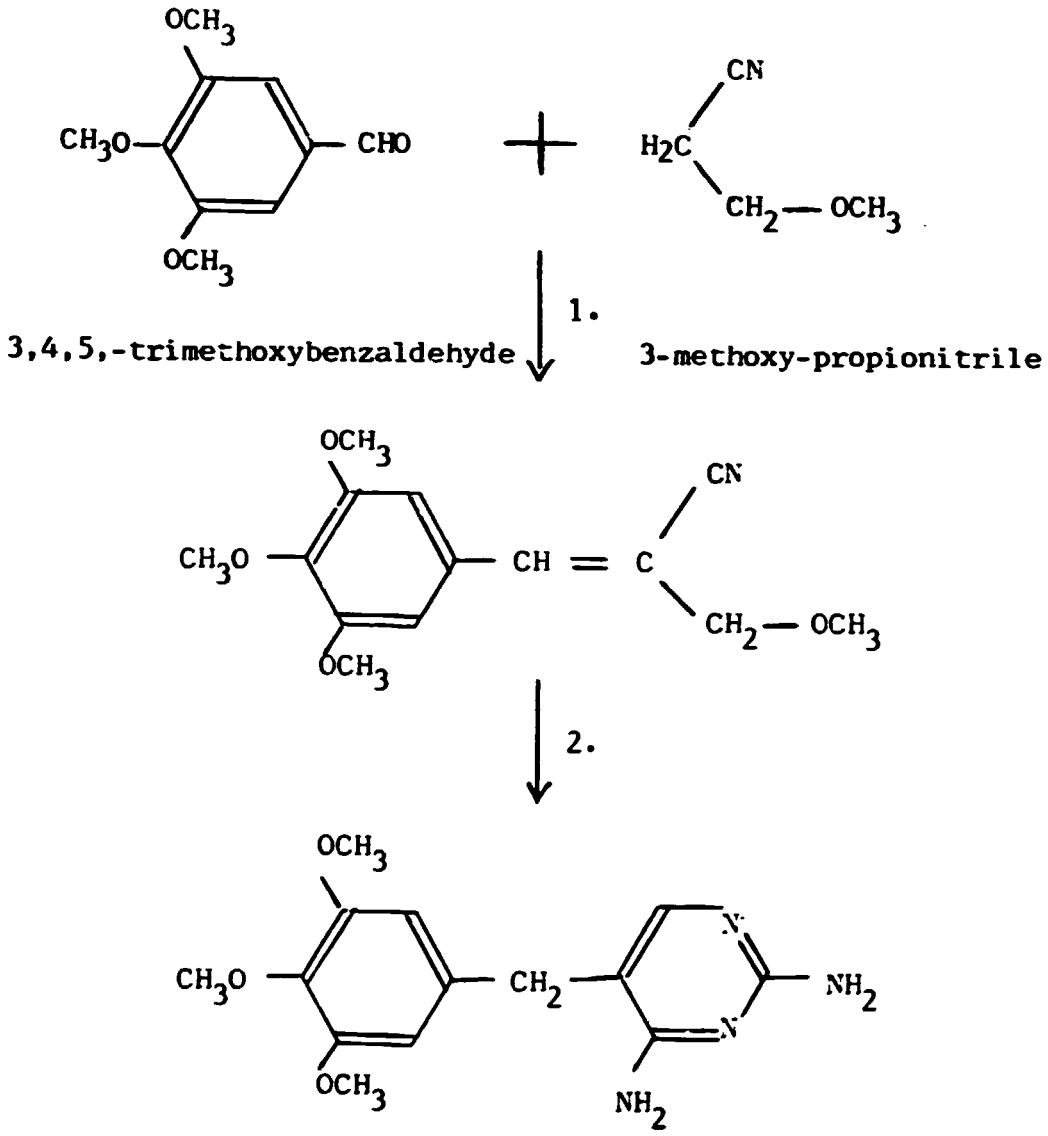


N-acetyl-p-amino sulfonyl chloride

3-amino-5-methyl-isoxazole

1. Sulfonamide formation.
2. Hydrolysis. Sodium hydroxide.

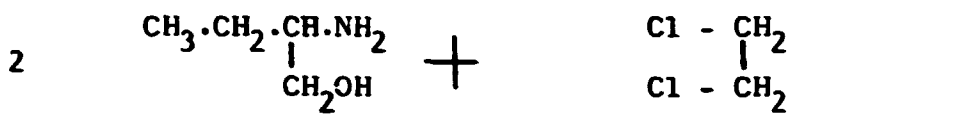
2.2 TRIMETHOPRIM.



1. Knoevenagel condensation — Sodium/methanol
2. Michael addition & ring closure — Guanidine HCl/sodium methoxide

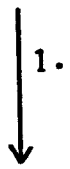
Note: Many other methods available.

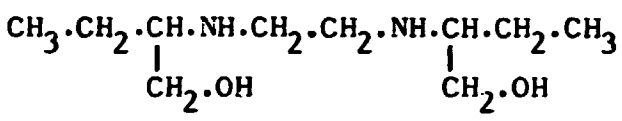
2.3 ETHAMBUTOL.



D - 2 - aminophenol

1,2 - dichloroethane

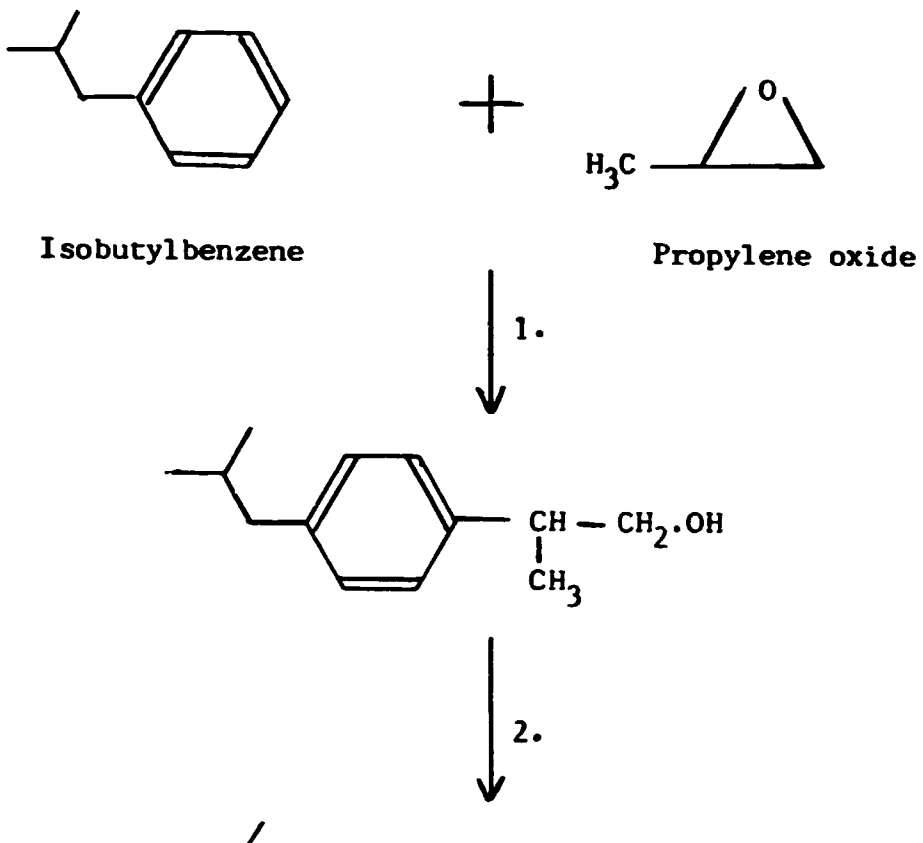




1. Condensation

Sodium hydroxide

2.4 IBUPROFEN.



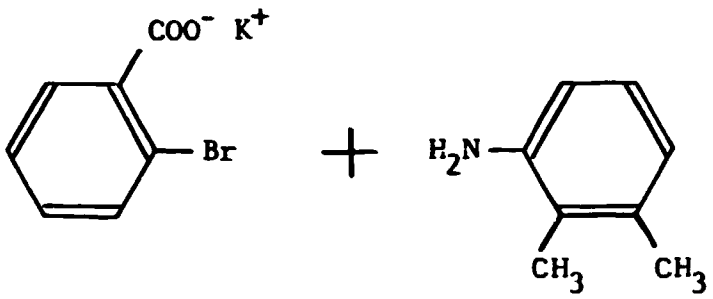
Isobutylbenzene

Propylene oxide

1. Friedel Craft. Aluminium chloride.
2. Oxidation. Chromic oxide.

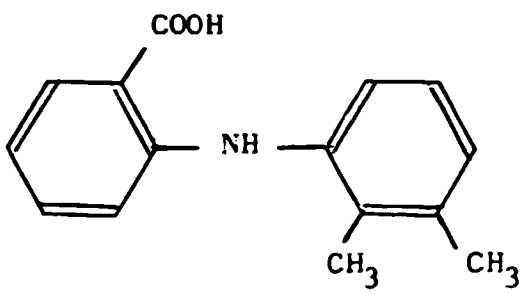
Note: Several other methods available.

2.5 MEFENAMIC ACID.



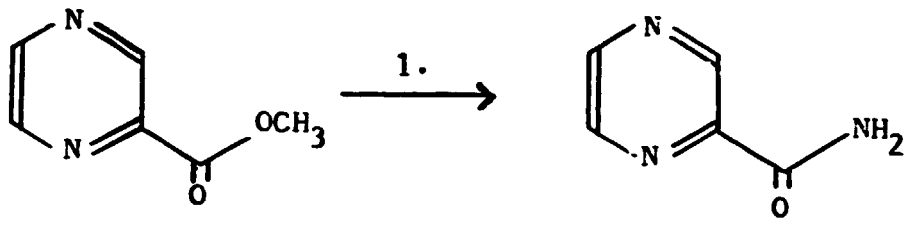
2 - bromo - benzoic acid (potassium salt.)

2,3 - dimethylaniline



1. Condensation. Cupric acetate.

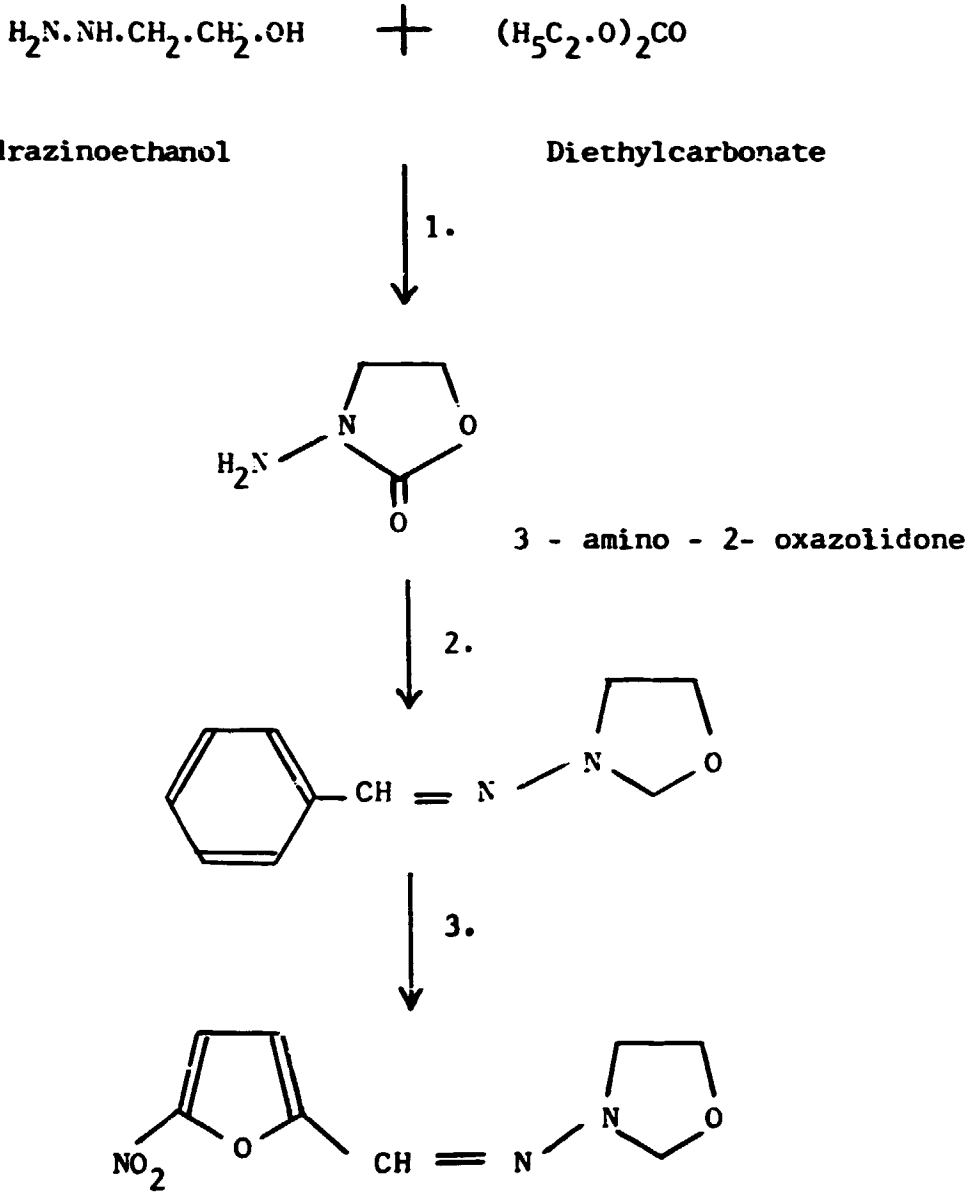
2.6 PYRAZINAMIDE.



Pyrazine - 3 - carboxylic acid, methyl ester

1. Amination. Ammonia. Methanol.

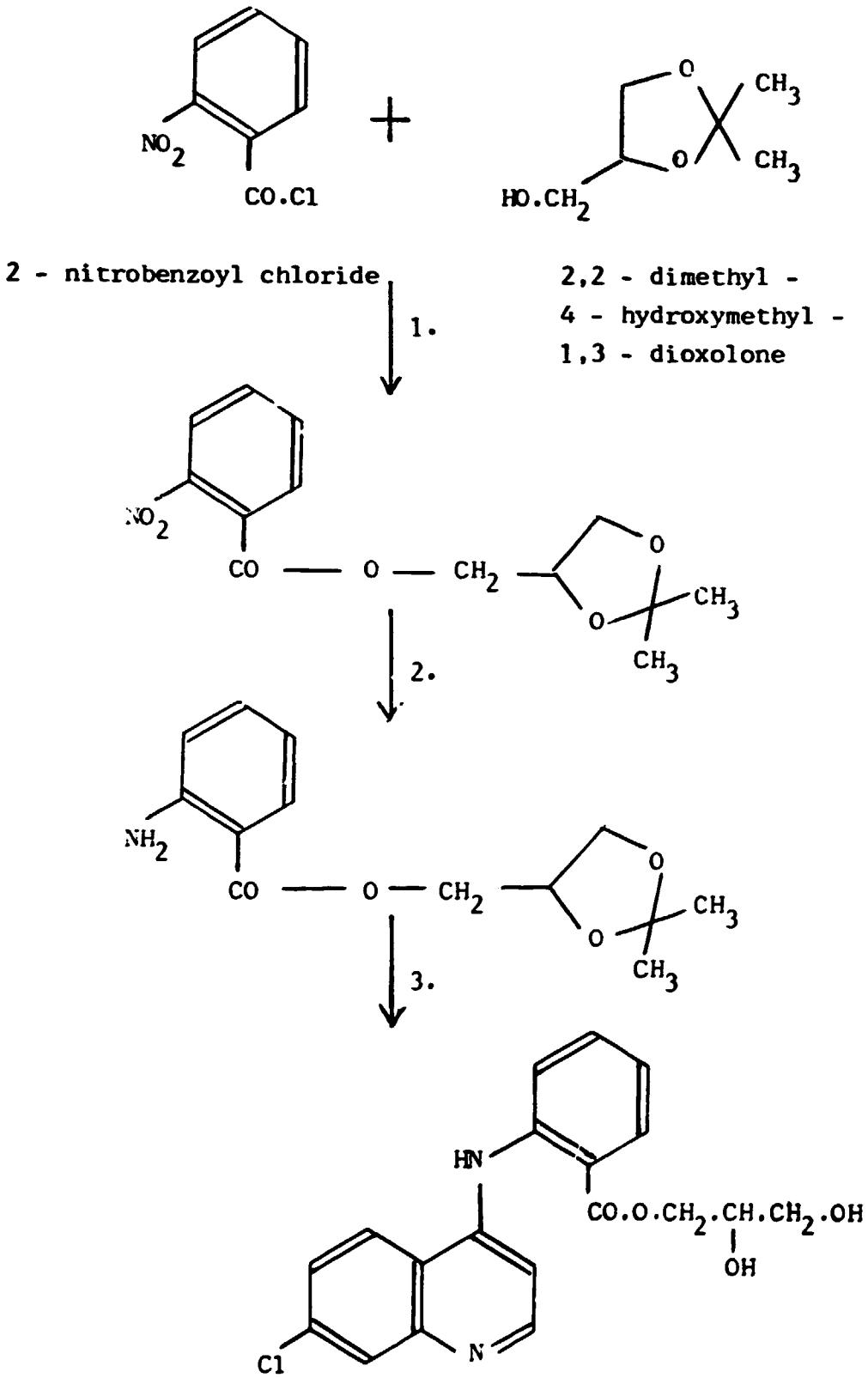
2.7 FURAZOLIDONE.



1. Cyclisation.
2. Schiffs base formation.
3. Replacement.

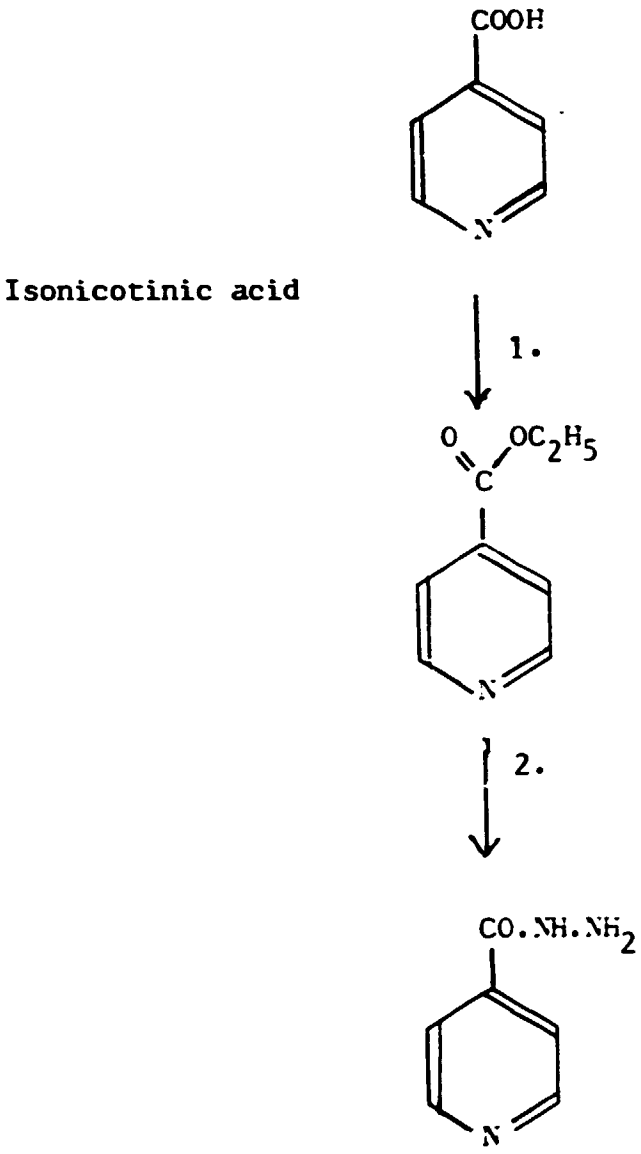
5 - nitro - furfural
or 5 - nitro - 2 - furfuraldehyde diacetate

2.8 GLAPHENINE.



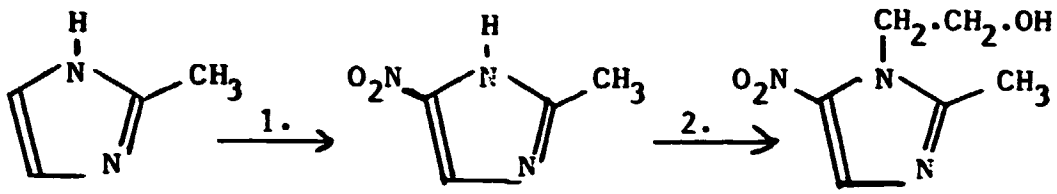
1. Esterification.
2. Catalytic reduction — Pd/carbon, hydrogen.
3. Condensation. — 4,7 - dichloroquinoline HCl

2.9 ISONIAZID.



1. Esterification. Ethanol. Sulphuric acid.
2. Condensation. Hydrazine hydrate.

2.10 METRONIDAZOLE.



2-methyl-
imidazole.

1. Nitration. Nitric acid
2. N - alkylation Ethylene oxide or

3. A SELECTION OF TYPICAL REACTIONS WHICH COULD BE PERFORMED IN A MULTI-PURPOSE PILOT PLANT. BY FUNCTIONAL GROUP.

1. Aromatic:	Friedel Crafts acylation. Friedel Crafts alkylation. Reimer Tiemann. Nitration. Substitution, nucleophilic. Diazotisation.
2. Carbonyl:	Oxime formation. Hydrazine formation. Schiff base formation. Enamine formation. Knoevanagel condensation. Strecker synthesis. Benzoin condensation. Ethinylation. Grgnard reactions. Reduction. Bucherer-Bergs reaction.
3. Hydroxyl:	Esterification. Ether formation. O - alkylation. Clofibric acid formation. Schotten Baumann. Oxidation. Oppenauer.
4. Amine:	N - alkylation. N - acylation. N - tosylation. N - detosylation. N - deformylation. Quaternization. Hofmann degradation. Sulfonamide formation.
5. Carboxylic acid:	Ester formation. Amide formation. Acid chloride formation. Hydrazide formation. Lactone formation.
5. Unsaturation: (Double bond)	Halogenation. Halohydrin formation. Epoxylation. Oxidation.

This list is indicative only. It does not imply that other reactions are necessarily excluded.

A further selection is given in the next table analysed by reaction type.

3. SELECTION OF TYPICAL REACTIONS WHICH COULD BE PERFORMED IN A MULTI-PURPOSE PILOT PLANT. BY REACTION TYPE.

1. Hydrolysis or Saponification:	Esters. Amides. Nitriles. Glycosides.
2. Oxidation:	Chromic acid. Sodium dichromate. Potassium permanganate. Peracid. Nitric acid. Oppenauer. N - Bromosuccinimide, acetamide etc
3. Reduction:	Clemmensen. Sodium - alcohol. Sodium borohydride. Aluminium isopropoxide (Meerwein Ponndorf)
4. Halohydrin formation:	Epoxide opening.(Halogen acid) N - Bromosuccinimide, etc.
5. Condensation:	Michael. Acyloin. Aldol. Claisen.
6. Rearrangements:	Beckmann. Baker - Venkataranan. Benzidine. Benzilic acid. Curtius.
7. Miscellaneous:	Ring closures. Aromatisation. Aromatic hydroxylation.
8. Others which can be catered for but need slight special conditions.	Metal - ammonia reductions. Reduction (active hydrides) Hydrogenation (low pressure) Hydrogenolysis (low pressure) Halogenations.

3.1 OBJECT OF INSTALLATION OF A MULTI-PURPOSE CHEMICAL PILOT PLANT.

The introduction and installation of a multi-purpose chemical pilot plant is the first strategy in the development of the back integration of the Pharmaceutical industry.

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

- introduce and develop the experience of chemical synthesis of fine chemicals and pharmachemicals.

- provide the range of equipments for adequate scaling up facilities and for Research and Development.
- provide some limited capacity for production of several pharmachemicals or fine chemical intermediates, (e.g for semi-synthetic antibiotics etc.)
- provide sufficient facilities and capacity to incorporate development of additional back integration or introduction of new products.
- provide a training facility.
- develop the atmosphere for progressive advancement in scientific skills from innovation to accomplishment.

3.2 EQUIPMENT CONSIDERATIONS FOR A MULTI-PURPOSE CHEMICAL PILOT PLANT.

The primary need is to have a flexible plant installation. This must deal with a wide range of unit operations and processes.
It must have an appropriate range of reactor sizes. Considerations to be taken into account are :-

- to have a range of sizes of reactors. Small reactors are needed for experimental work and trouble shooting and scale-up from laboratory. Medium size units may be used for further scale-up and possibly small scale speciality production. The largest units are used for moderate scale production work.
  The size of the largest vessels in a pilot production plant is not large. In some of the larger units the capacity may be as large as 3,500 - 4,500 lts, but for the plant to be proposed for the Philippines the largest vessels will be in the range of 1,000 - 1,350 lts.
- provision of adequate capacity for development of some further back-integration. This might be in the form of space provision, rather than necessarily installed plant.
- to have a variety of materials of construction. The extent of these are likely to be industrial glass, glass enamel, PTFE lined and bonded, stainless steel (limited to 316) and rubber lined.

Plastics such as PVC, polyethylene, polypropylene and PTFE may be used in some instances.
For a multi-purpose plant mild steel is rarely considered,

- flexible use of such ancilliary facilities such as gas scrubbing or gas feeding and monitoring systems.
- provision of good ventilation system.
- provision of all ancilliary eouipment necessary, such as centrifuges, filters, pumps, comminution, drying, sieving, scales, mobile bins etc.
- provision of adequate instrumentation, particularly for temperature and pressure/vacuum for recording or control.
- provision and correct sizing of all service requirements. These can vary with the location, but in the Philippines are likely to cover electrical supply (with stand-by generator), water supply (through well drillings), steam (by oil fired boiler), chilled water and refrigeration (glycol) supplies, compressed air, vacuum (though local provision for units is preferred to centralised system) and possibly bulk gas supply (e.g. bulk liquid nitrogen installation.)
- treatment of liquids and gases with respect to water purification, water cooling (cooling tower), effluent treatment both for water and gases (scrubbing).
- good plant design and layout, making use of gravity when possible.
- easy plant operation and readily identifiable service facilities.
- full plant protection against hazardous conditions.
- the provision of a plant as 'fool-proof' as possible (the most difficult problem !).

Finally there is a need for :-

- determinig the complement, size and distribution of plant items needed to satisfy the planned capacity and level of facilities.
  Such capacity will be determined partly by considered reasonable level and range of pharmachemicals to be produced and development facility.

4. VOLUME AND POTENTIAL SALES VALUE.

Pharmachemical	Estimated annual need 1989	Production level	Sales value US $
TRIMETHOPRIM	2,500 kg.	1,000 kg.	22,000
SULFAMETHOXAZOLE	8,000 kg.	4,000 kg.	60,000
ETHAMBUTOL	25,000 kg.	10,000 kg.	290,000
IBUPROFEN	17,500 kg.	10,000 kg.	200,000
MEFENAMIC ACID	15,000 kg.	5,000 kg.	55,000
PYRAZINAMIDE	10,000 kg.	5,000 kg.	215,000
FURAZOLIDONE	35,000 kg.	15,000 kg.	135,000
GLAPHENINE	4,000 kg.	2,000 kg.	130,000
ISONIAZID	65,000 kg.	30,000 kg.	180,000
METRONIDAZOLE	2,000 kg.	1,000 kg.	15,000
			1,302,000

These figures were determined using latest prices quoted in U.K. for bulk pharmachemicals. They are only a guide being independant of volume and not C & F inclusive. There is some difference compared with the import prices into the Philippines in 1987.

Pharmachemical.	Imported price Philippines 1987	U.K. price 1988
TRIMETHOPRIM	-	22.0
SULFAMETHOXAZOLE	29.0	15.0
ETHAMBUTOL	43.9	29.0
IBUPROFEN	26.9	20.0
MEFENAMIC ACID	22.7	11.0
PYRAZINAMIDE	75.6	43.0
FURAZOLIDONE	7.2	9.0
GLAPHENINE	104.6	65.0
ISONIAZID	10.6	6.0
METRONIDAZOLE	72.0	15.0

If these prices are reliable it means, insofar as domestic sales are concerned, there is rather more of a margin available than might be apparent from the so-called 'World prices' as recently quoted from a U.K. source.
Using the reported import prices into the Philippines in 1987 the total sales value would be US $ 2,044,000.
This is 55% higher than when using the U.K. prices.

4. The levels of production, or rather the percentage of total annual need, might be considered somewhat high. It is considered, however, since all are important pharmachemicals for the Philippines that it is not unreasonable to select such levels. It is better in the early days to limit the number of products and have somewhat higher production levels. Economically this should be an advantage. At the same time, as can be seen on page 111, a wide range of technological reactions will be experienced.

5. PRELIMINARY EQUIPMENT CHOICE FOR COSTING PURPOSES.

This preliminary list has not involved any detailed design considerations and the main reaction units have been costed on the basis of being general purpose units comprising jacketted, agitated reactors with FLP motor units and fitted with appropriate condensers and receivers. Stainless steel units would be fitted with Stainless steel condensers and receivers; glass enamel or Corbund units with glass or carbon condensers and glass enamel receivers.
Glass enamel reactors should not be fitted with stainless steel condensers (as can often be observed) for this limits the versatility of the unit and the condensers can be open to corrosion. It is acceptable to fit glass condensers to stainless steel reactors, but except in the case of reflux only and for cost reasons, not to be recommended.
All reaction units in a multi-purpose plant are operated on a batch basis. The multi-purpose plant does not lend itself to continuous processes.

This plant list has not been strictly compiled with relation to the production volumes, for as will be stated later, a more detailed study will have to be performed. The project time of the mission was too short for the subject of chemical synthesis to achieve this depth accurately.

The accuracy will be sufficient for policy making decisions.

In the suggested plant list equipment has been included for provision of low pressure hydrogenation facilities. In fact catalytic hydrogenation is a stage in the synthesis of one of the products (Glaphenine). Irrespective of this such a facility would have been proposed. This type of unit is not

exactly a general purpose plant, but can certainly be considered as a unit of a multi-purpose plant. It does require special housing conditions, but the size and standards are not onerous. Such a facility is not always a common feature of multi-purpose plants but this expert considers it can be a great asset for this very reason. There are several products of potential interest whose sythesis can be achieved using this process. It could give a better opportunity in the future of entering the export market because of less competition. It is also relevant to suggest such reactions as the supply of hydrogen is readily available in the Philippines.

The proposed preliminary equipment lists are given in general outline in the following pages. These lists are later used for determination of the approximate equipment costs which would be involved.

5.1 PRELIMINARY LIST OF EQUIPMENT PROPOSED FOR MULTI-PURPOSE PILOT PLANT FOR THE PHILIPPINES.

	Number	Capacity	Description.
REACTION UNITS:[a.]	2	1,000 lt.[b.]	Glass enamel.[c.]
	4	1,000 lt.	Stainless steel.[d.]
	3	600 lt.	Stainless steel.
	1	600 lt.	Corbund.[e.]
	1	200 lt.	Stainless steel.[f.]
	2	400 lt.	Stainless steel.[g.]
	3	400 lt.	Glass enamel.[g.h.]
	2	200 lt.	Stainless steel.
	2	200 lt	Glass enamel.
	2	100 lt.	Glass (industrial).
EXTRACTOR:[i.]	1	2,250 lt.	Stainless steel.
CENTRIFUGES:	2	1 m Ø	Stainless steel.
	1	1 m Ø	Rubber.
DRIERS:	1		Vacuum, Stainless steel.
	3		Air drier.
FILTERS:	5	Various.	Pressure/vacuum.
PUMPS:	-[j]	5 - 100 m^3/h	Various.
TANKS, STORAGE:	-[j]		Various.
DIVERSE:			
CHROMATOGRAPHY COLUMNS.	1 set.		-
WEIGH SCALES.	-		-
MOBILE BINS.	-		-
MILL & SIEVE.	1		-

Legend:

a. Generally jacketted, agitated, FLP motor units fitted with condensers and receivers for vacuum operation and moderate pressure.

Legend. (Cont.)

a. One stainless steel unit (1,000 lt.) possibly oil heated and fitted cooling coil.

b. Nominal rating given to be taken as minimum. For example nearest of some glass enamel suppliers might be 1,350 lts.

c. Glass enamel has been specified at this stage but consideration could be given to new PTFE coated reactors which have advantages and are not necessarily more expensive.

d. Normally 316 grade.

e. This is example of PTFE coated reactor. Specified here to extend versatility.

f. High vacuum unit fitted with appropriate pumps.

g. One likely to be fitted with fractioning column.

h. One to be used as low pressure hydrogenator.

i. Complete with agitator and pump.

j Number and variety need to be selected in detailed specification.

This is a general list composed from experience, but not related in detail to proposals and cannot be used as a specification. The main use is for preliminary costing purposes and an indication of facilities anticipated.

Laboratory facilities are not detailed at this stage but a blanket figure will be included in the following summary costing.

Other items of equipment that have to be included comprise those for service facility. Again a more detailed examination will be necessary for the ratings, but should not differ too significantly from those indicated.

5.2 PRELIMINARY SERVICE EQUIPMENT.

1. STEAM BOILER	2,500 kg/hr. 10 bar	One unit.
2. CHILLED WATER	30 T. +8°C.	One unit.
3. GLYCOL REFRIGERATION	50 T. -15°C,	One unit
4. DEMINERALISER	3.5 m^3/hour.	Two units.

5.2 PRELIMINARY SERVICE EQUIPMENT (CONT.)

5.	WATER COOLING TOWER.	100 m^3/hour	One unit.
6.	COMPRESSOR.		One unit.
7.	HOT OIL UNIT.	70,000 Kcals/hour	One unit.
8.	ICE MAKING.	70 Kg/day	One unit.
9.	GENERATOR.	200 KVA.	One unit.
10.	WELL PUMPS.		Two units.

6. PRELIMINARY SITE AND BUILDING FACILITIES.

There are two choices to consider, one to design simply for the equipment initially scheduled to be installed or, secondly, to allow for some extention within initial buildings for some expansion in plant. It is suggested that this should always be considered from the start and accordingly the two alternative costs are indicated.

SITE SIZE:	A fully fenced and secure level site of 10,000 m^2.
PRDUCTION HALL:	(1) 500 m^2. or (2) 1,000 m^2. Height 10 m.
HYDROGENATION HALL:	(1) 30 m^2. or (2) 50 m^2. Height 6 m.
WAREHOUSING, DRYING, MILLING AND PACKAGING:	600 m^2. Height 5 m.
ADMINISTRATION AND LABORATORIES:	500 m^2. (Laboratory 100 m^2.)
OTHER ASPECTS:	SINKABLE WELLS FOR WATER. TEMPERATURE PREFERRED AS LOW AS POSSIBLE. SOLVENT BUND AREA. POND FOR WATER STORAGE. INTERNAL ROAD SYSTEM. GOOD METALLED ROAD ACCESS.

The provisional costings for plant, equipment and building construction costs are based on :-

(1) U.K. mid 1987, FOB U.K. port prices for plant & equipment.

(2) Philippines construction costs mid. 1988.

In the case of the Production Halls an allowance has been incorporated for the special flameproof and explosion proof electrical standards and for special ventilation needs.

6.1 PROVISIONAL COST FOR INSTALLED PLANT, BUILDINGS AND SITE WORK.

REACTION UNITS, EXTRACTOR.	US $ 660,000	
CENTRIFUGES.	US $ 255,000	
DRIERS, FILTERS.	US $ 150,000	
PUMPS, MILL, SIEVE.	US $ 97,000	
TANKS, MOBILE BINS.	US $ 136,000	
COLUMNS, SCRUBBING.	US $ 56,000	
SCALES.	US $ 35,000	
LABORATORY EQUIPMENT.	US $ 136,000	
	US $ 1,525,000	
SERVICE UTILITIES	US $ 200,000	
UN-INSTALLED EQUIPMENT TOTAL	US $ 1,725,000	
ESTIMATED INSTALLED COST		US $ 4,312,500
BUILDINGS:		
PRODUCTION HALL (1,000 m^2)	US $ 400,000	
HYDROGENATION HALL (50 m^2)	US $ 17,500	
WAREHOUSE ETC.	US $ 120,000	
ADMINISTRATION/LAB.	US $ 165,000	
SITE PREPARATION ETC.	US $ 250,000	
ESTIMATED BUILDING COSTS		US $ 952,500
TOTAL ESTIMATED COSTS.		US $ 5,265,000
WITH CONTINGENCY, SAY:-		US $ 5,750,000
ALTERNATIVE BUILDING SMALLER PRODUCTION HALL & HYDROGENATION HALL.		
TOTAL ESTIMATED COSTS.		US $ 5,058,000
WITH CONTINGENCY, SAY:-		US $ 5,500,000

It must be noted that these estimates should not be used for any planning purposes, but only for basic decision taking. In view of the time necessary for any deeper study, receiving tender offers etc. an inflation element of about 15% should be added to the estimated totals bringing the top figure to US $ 6,612,500.

The price of technology has not been included in this figure and could, perhaps, amount to US $ 100,000 to $ 250,000.

As the figures suggest it can be very prudent to consider building in an expansion plan during the initial construction stage.

7. LOCATION.

In view of the nature of a chemical synthesis plant, when considering a new unit, a location should be sought outside of a metropolis.
Urban land, if available, would be much more expensive. It is very likely planning permission would not be permitted. There would be little chance of planning for future expansion.

In contrast seeking areas a little outside of towns almost inevitably will result in cheaper land prices. More important, plans for future expansion can invariably be dealt with at the very earliest stages of planning. This can be achieved by either acquirement of more land than initially required or an option for future procurement agreed.

Without more than cursory investigation into this subject there is one very obvious location which could, and should be investigated. This is the area already occupied by Chemfields, Inc. which is situated at Laguna. (Address: Bgy. Don Jose Sta. Rosa Laguna).

Indeed it is not unreasonable to suggest that it could be a great advantage if any Multi-purpose pilot plant which might be installed had an association with the Chemfields organisation. This could have advantages such as savings in general administration infra-structure and possible shared facilities in some instances of chemical storage or solvent recovery facilities.

Apart from this rather broader thought it is an area worth further investigation at a later planning stage.

Advantages that can be seen are :-

- general infra-structure in the area is good, with the exception of the immediate road access in respect of the road surface.
- even in spite of the above problem there is already an established history of supplies to the site including solvents, fuels, chemicals and gases.
- there is good water availability and facilities established for the disposal of liouid effluent.
- there is experience in the area of the semi synthetic anti-biotics plant which is not dissimilar to the proposed multi-purpose plant.
- it is a pleasant environment in which to work and the existance of Chemfields establishes the possibility of attracting labour to the area.
- there is a history of 24 hour working.

7.1 RELATIONSHIP WITH OTHER ASPECTS OF DEVELOPMENT.

The subject of production, and research into the production, of anti-biotics by semi synthesis and by fermentation is being investigated currently by two other Experts.

A lack of facilities was observed in the Chemfields factory for development and scale up work.

Although it is not appropriate to mix facilities for production by chemical synthesis, semi synthetic anti-biotics and fermentation it might be worthwhile considering housing the research and pilot scale work within the same general site - indeed within the same factory unit with appropriate segregation. Substantial savings could be made in terms of common service facilities and laboratory equipments.

With a good calibre of chemists and microbiologists the larger research establishment would almost inevitably lead to the cross pollination of ideas as a result of intercourse between disciplines and thus stimulate development.

8. LABORATORY FACILITIES; RESEARCH AND DEVELOPMENT.

There are usually three functions involved in using laboratory facilities :-

- Analytical Control.
- Production & Process Control
- Research & Development.

All have ouite different functions, but there is naturally some areas where they overlap. Laboratory facilities are better segregated although some equipments may be jointly used.

Analytical Control Laboratory. This section should have its own Departmental Head especially as it is a decision making unit. The Chief Analyst has supreme power in the decision of the release of products for sale or pharmaceutical processing. The department is responsible for :-

- quality control of all raw materials employed.
- quality evaluation of alternative sources of raw materials and chemicals (prior to complementary work possibly necessary in R & D monitoring also).
- quality evaluation or confirmation of isolated production intermediates. In this instance the Analytical Department should perform an advisory capacity rather than decision making.
- quality control of final products. Here the Department has absolute control over the decision to release products for sale.
- investigation of analytical methods suitable for intermediates control, especially for developing products. This work is likely to be performed in conjunction with the R & D section.
- monitoring of effluent water and materials. Also for monitoring atmospheric conditions in the factory.

Process and Production Control. This work would normally be performed by the Production chemists and operators. It would not be a separate Department. The work would cover such aspects as :-

- pH control
- TLC monitoring of reactions and crude intermediate and final products.

- preliminary analysis of salient features of intermediates.
- Karl Fischer water determination.
- specific gravities.
- moisture determinations.
- melting points.
- sieve analysis.
- titrations.

8.1 RESEARCH AND DEVELOPMENT.

Some of the main functions of the Research and Development Department will cover:-

- Laboratory proving of, and familiarisation with, Tranferred Technologies. This will cover not only reaction proceedures but also analytical control of intermediates and products.
- scaling up of processes.
- supervision of, and advice on, initial production commissioning.
- trouble shooting in the event of any production problems.
- monitoring of any new or alternative supplies of critical raw materials or chemicals.
- process improvement.
- development of processes for alternative synthetic routes.
- development of processes leading to 'new' products. The definition of 'new' being products new to production.
- defining for 'new' products or intermediates the analytical control parameters and methods of determination (possibly in conjunction with the Analytical section.)

The Research and Development Department is a most important function and should be responsible to a Research & Development Director (who in early days will probably also function as Manager of the Department.)

The Research function of the Department is somewhat different from the normal function of Academic research, being always commercially orientated, and strict discipline is sometimes needed not to digress from the main object into interesting, purely academic, avenues.

Research and Development will not be directed towards the production of entirely new drugs for this can only be supported by large Multinational organisations or Companies.

To discover a new drug and develop it into a Pharmaceutical speciality can take up to 10 years, involve several disciplines other than chemistry, and cost tens of millions of US dollars. It is not appropriate for Developing Countries nor small Companies.

The areas of interest in Research and Development for the Multi-purpose pilot plant proposed are in (1) process development and (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.

The object of the development of these drugs would not only be for domestic consumption (which might be relatively low until the purchasing power in the Philippines has increased substantially), butto have an opportunity to enter into the World markets. This will generate foreign exchange, not only save it.

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

Another aspect for selection of interesting products, led by a therapeutic need, is to consider products which can be synthesised using techniques or reactions for which experience has been gained.

Another approach, which has already been mentioned, is to utilise specialised equipment which is not so generally available. It is partly for this reason the recommendation has been made to include low pressure hydrogenation facilities. One example of development following this concept could be for the production of terbutaline sulphate.

It has previously been proposed that consideration should be given to the immediate implementation of the use of existing laboratory facilities to set up a Research and Development facility or fund such an organisation as PIPAC to perform directed research projects. This work would be specifically directed at the aspect of developing processes for the

synthesis of selected pharmachemicals of interest whose patent coverage ceased recently or will do so in the coming few years.

9. CONCLUSIONS.

The question is posed :-

"What is the object of the proposal for backward integration and installation of a multi-purpose chemical pilot plant in the Philippines ?"

The prime concern would be to establish a function and facility for :-

(1) gaining experience and training labour in chemical processing methods involved in the production of pharmachemicals. These methods to be supplied by technology transfer.

(2) research and development work in process methods and product synthesis and ability to translate these into profitable production through proper scaling up proceedures.

(3) production, albeit on small scale, to supply some of the important drugs needed in the Philippines and used in the pharmaceutical industry.

The immediate conseouence of setting up such a production unit, which must really be research orientated, will not be to dramatically reduce the price of pharmaceuticals in the Philippines.
Firstly, partly because of scale and partly because of inexperience, it is more likely that the cost of the pharmachemical might even be greater than the price at which it can be imported. As it has been shown earlier this need not have a dramatic effect on increasing the price of the final pharmaceutical, there being other fringe benefits. Conversely though, even a very dramatic cost reduction in a pharmachemical will never reduce the price of any pharmaceutical to an extent that the very poor in the Philippines will be able to buy them.

It is only by subsidy or greatly raising the incomes of the poor that it will be possible to see the appropriate drugs reaching the people who need them most.

After some years experience, successful research and development and increase of production facilities the benefit will be seen ; but still more in terms of foreign exchange benefits than dramatically reduced prices.

It has been muted in some quarters that back integration will be the first move towards self-sufficiency with respect to the Pharmaceutical industry in the Philippines.

This idea must be dispelled at once. There will always be some reliance on importations of chemicals from other Countries. This is not a special case of the Philippines but applicable to virtually every Country in the World. Even with very extensive petrochemical industries and highly developed inorganic, heavy and organic chemical industries very few Countries can provide all internal needs without resorting to importations.

The size of multi-purpose chemical pilot plant unit proposed for the Philippines is considered to be of the appropriate size for the existing and short term future needs of the pharmaceutical industry.

It is considered that the state of the pharmaceutical industry is ready for such back integration and should not now be delayed for any considerable time .

Although there are some problems in infra-structure, none cannot be overcome.

This investigation is considered to have sufficient evidence to warrant a second phase and more detailed examination of the proposition to instal a multi-purpose pilot plant for chemical synthesis in the Philippines.

PART 4. EXECUTIVE SUMMARY.

The object of the mission to the Philippines of the Expert in Chemical synthesis was to assess the situation with respect to making a decision whether it was considered feasible or appropriate to recommend any back integration of the Pharmaceutical Industry.

This involved not only studying the Pharmaceutical Industry, but also the infra-structures (with special attention to Human resources) which would be involved and necessary in implementing any positive proposal.

This involved visiting a wide range of Establishments and sections within these representing :-

- academia covered by both Government and Private Universities.
- research establishments associated with Government, Institutional and Private areas.
- Pharmaceutical Industry. Several production factories were visited covering a wide spectrum from the small private Filipino establishments to a range of Multinational Companies.
- Control Authority which is the Philippine Bureau of Food and Drugs (BFAD).
- other manufacturing facilities in the fields of chemical production and engineering fabrication.
- sections of the Department of Health.
- business organisations.

In the course of these visits a broad spectrum of people were met and varied and representative views on many subjects could be appreciated. This spread of people covered academics from a variety of Government and Private universities; Government scientists; foreign and Filipino senior personnel, middle management and scientists from manufacturing industries; and policy makers of the Philippine Department of Health.

It must be recorded here, that in all instances an excellent reception was experienced. Frank and helpful discussions were held and interest in the project was apparent. A friendly reception was universal.

In addition to meeting people and visiting establishments and offices it was necessary to try to gather factual information and this proved to be a very difficult problem. The level of analysis required by this expert was simply not available for consultation, nor could it be readily abstracted with the degree of definition desired within any reasonable time scale. Some sources of information on importations had to be privately discovered and other statistics rather laboriously abstracted from IMS records of drug sales. Because of this, information on weight consumptions of pharmachemicals (the description used in this report to describe active ingredients and distinguish them from pharmaceuticals which are the drug forms sold) was limited to the last complete year of 1987. In view of the fact that trends of increased consumption of drugs in the Philippines is governed principally by the purchasing power of the people this information can be considered sufficient for initial decision making.

Some of the questions which had to be answered to come to a decision as to what could be proposed for a further development contribution to the pharmaceutical industry of the Philippines are as below.

1. What is the state of the Pharmaceutical Industry in the Philippines - is it ready for any back integration ?
2. Level of consumption of drugs - is it currently sufficiently large to support any level of back integration and, if so, to what degree ?
3. Trends. Is there sufficient expansion potential ?
4. Is there a suitable product mix, at acceptable levels, to support any level of production ?
5. Are infra-structures sufficiently developed to support any facility ?
6. What should be the aim of establishing any facility ? Production orientated to supply immediate needs or research orientated for a more secure and profitable future ?
7. What is the likely cost of any project ?

As a result of all the investigations the answers to these questions are given below.

1. The Pharmaceutical Industry of the Philippines which is engaged in the formulation, compounding and packaging of drugs is of World class and from this point of view the Country is well advanced and ready to consider back integration into the production of Pharmachemicals.

2. The level of sales in 1987 had reached ₱ 9,325 million (US $ 466 million). This is a little lower than might be desired, a 'rule of thumb' annual sales figure of US $ 600 million being considered the guideline for the introduction of a multi-purpose chemical pilot plant.
Other factors must be taken into account and an important one is that the difference between consumed drugs in the Philippines and the truly needed drugs is very large.
Provided other factors are propitious, this level can be considered sufficient.

   Any question of recommendation of either dedicated or multi-product production plants are ruled out, for in these instances sales in excess of US $ 1,000 million are needed together with large individual consumptions.

3. Trends were very difficult to forecast because of the very many factors which may have influence.
It has been mentioned above that there is a very large gap between needs and consumptions. In 1987, while sales consumption was reported at ₱ 9,325 million, the needs were determined at ₱ 51,879, i.e. 5.56 times higher. Any narrowing of this gap could have dramatic effect.
This shortfall is not that there is no facility in the Pharmaceutical industry to make them (in fact there is a considerable excess of capacity which is offered by the manufacturers to the Government for manufacture of additional drugs essentially at cost, but has not been taken up yet).
Rather it is the consequence of the lack of purchasing power, low wages and vast number of people living below the poverty level.

Another factor which can effect sales growth and trends is the rate of population growth. In a satisfied market both might move roughly together, but because of the poverty situation such will not materialise. Indeed the largest population growth rate will probably be observed in poorer families.

The rate of population growth at 2.9% is really too high (and has been for the last twenty years). Responsible parenthood may not be enough to reduce this undesirably high rate. One approach, which might not be yet too acceptable on religious grounds but perhaps worth consideration on ideological grounds, would be to consider promotion of the use of steroid oral contraceptives. The cost is relatively low at ₱ 193 per annum for protection and could possibly be subsidised. The corresponding saving on food consumption would be much more dramatic than the cost of such an exercise.

Overall it not deemed possible to project real factual growth figures over the coming 5 - 10 years, but it can certainly be envisuaged that a minimum growth in real terms of 12% minimum can be expected and considerably more if the general economy improves.

4. It was established that a provisional or preliminary product mix could be identified as a basis for design. This mix satisfied the preference for products which would be of greatest therapeutic use in the Philippines consisting of three anti-bacterial, three anti-tuberculosis, three anti-inflammatory/analgesic drugs and one anti-diarrheal drug. An initial total production level of about 80 tons can be proposed.

   The drug mix proposed would comprise of trimethoprim, sulfamethoxazole, ethambutol, ibuprofen, mefenamic acid, pyrazinamide, furazolidine, glaphenine, isoniazid and metronidazole.

   Technology for these products should be available and they provide a good and varied level of experience.

5. Having established that conditions appear to be met to consider the provision of a multi-purpose chemical pilot plant, the environment must also be suitable for installing and

and sustaining such a facility.
All the various infra-structures were investigated and most aspects found to be acceptable.
The only real problem could be found to exist in the area of human resources. This exists at two levels - the Ph.D. and the tradesman.
The latter could be overcome by appropriate training courses.

There could be a requirement of personnel educated to the level of Ph.D. in chemistry amounting to between 3 and 5 initially.
In the Philippines there are currently resident only a total of 66 such graduates in chemistry, mostly at the University. Of these 3 are graduates of the University of the Philippines. By the end of 1988 the number should have risen to 6.
Even the resident Ph.D. graduates lack in experience in terms of the field of synthesis which would be the basis of a multi-purpose chemical pilot plant. Let it be said though that this is not a reflection on ability, but simply a lack of opportunity due to lack of funds for research. Only 5 research projects were located having any relevance to chemical synthesis.
It might be necessary, and desirable, to try to lure back to the Philippines some ex-patriate chemists and preferably with experience learned abroad in the field of synthesis of pharmachemicals or fine chemicals. The Government could assist in this field by offering some incentives to return to the Philippines to work (as it is understood has been done previously).

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

Training will 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 abroad should be agreed.

6. The aim of installationof a multi-purpose chemical pilot plant is primarily to achieve some backward integration of the pharmaceutical industry together with a source of supply of some pharmachemicals for domestic utilisation.

The decision to be made is whether such a unit should be entirely production orientated or research orientated.

The production orientated unit would tend to be of greater capacity, operate entirely on purchased technology and supply immediate pharmachemical needs.
With such units the opportunity for process improvement, introduction of newly developed products or further backward integration is very limited.
Manufacturing in such a unit, entirely with transferred technology (which is not likely to represent the latest state of the art), profitability will be hard to realise even after several years experience.

The research orientated multi-purpose pilot plant, on the other hand, is a more systematic approach and with more beneficial long term implications. Production levels tend to be lower, but still 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. This contributes to the research function. This unit is equipped with a wider range of reactor sizes. The larger ones are principally used for pharmachemical manufacture, while the range of smaller ones are employed for development and scaling up of improved processes and new products derived from research. They may also, nonetheless be employed to manufacture small quantities of highly priced speciality pharmachemicals.

This type of unit provides a much better long term prospect for the development of a profitable manufacturing industry and one with positive, ultimate, export potential as well as domestic supply.

It is the most appropriate approach for the Philippines to consider the research orientated plant and recommendations are based on this.

7. Based on the function of the multi-purpose chemical plant proposed and the production level of the mix of products proposed to be manufactured in it, a basic preliminary plant and equipment list was prepared. The plant cost of this, including laboratory eouipment, at mid 1987 UK FOB prices and including laboratory and service equipment came to US $ 1,725,000.
The cost of buildings to house the plant and ancilliary facilities (but not including any cost of land) set in a 10,000 m^2 site based on mid 1988 Philippine construction costs amounted to US $ 952,000.

The estimated total installed cost, with fully serviced buildings and site was determined at US $ 5,750,000 including a 10% contingency allowance.
It is estimated that the 1990 figure would amount to about US $ 6,612,500.

These summaries give the answers to the questions posed and give the background to the recommendations which will be given at the end of this report.

Indeed a positive recommendation to consider the installation of a multi-purpose pilot plant will be given and in view of this suggestions were made in the main section that the Laguna area would be a most attractive area, adjacent to Chemfields, Inc. semi-synthetic antibiotics establishment.

One final subject has to be reported on where some minor recommendations can be made.
This is the subject of medicinal plants. The broader aspects of this will be dealt with in the report of another expert, but certain areas are particularly of interest in relationship to pharmachemicals.
Little analytical information was available on plant materials which can give known pharmacologically active ingredients.
As it involves only a little initial work <u>it is recommended</u> that :-
<u>Samples of the following plants should be harvested at the appropriate time and analysed for content of active ingredient</u>.

Plant.	Part.	Analyse for:-
Dioscorea Esculenta (or other species)	Tuber	Diosgenin
Solanum Verbascifolium	Fruits	Solasodine
Solanum Nigrum (or other species)	Fruits	Solasodine
Datura metel	Leaves	Hyoscine & Hyosyamine

The other plant material which it was felt should be investigated further, but could not be looked at during the mission, is Cinchona.
Although it was learned that some analysis work may be done shortly on samples of Cinchona it was felt this product should be looked at in greater depth. It could be an important product for the quinine isolatable from it is desperately needed in the Philippines for malaria treatment and also is a potential export product. Only by inspecting the Mindanao plantations to assess the trees, determine the species , ages and conditions and also to take representative plug samples for analysis, could any proposition be put forward as to whether a worthwhile project exists here.
An idea of cost for development of such a project can be given, although this needs more accurate current analysis. To produce 75 tons quinine per annum an installed plant cost of US $ 8 million might be expected; for 150 tons a cost of US $ 12 million.

It is recommended that :-

A mission be funded for a preliminary assessment of the possibility of processing Cinchona bark in the Philippines for the production of quinine for domestic and export use.
In the event of any positive reaction it would be necessary to follow this with a feasibility study, which could also consider the possibility of manufacturing quinidine by chemical methods from quinine.

Finally it is suggested an investigation should be carried out on the subject of the manufacture of glyceryl guaiacolate. This could be an interesting product being used widely in the pharmaceutical industry and manufactured from one of the main products manufactured in the Philippines, namely glycerine.
The investigation needed is into the consumption in the Philippines (this having been omitted in the analysis) and also a world wide survey of use for this could be a potential export product.

FINAL REMARKS AND RECOMMENDATIONS.

Apart from the minor recommendations made in the preceeding pages, several other suggestions have been voiced on a variety of aspects within the text of the report. Such suggestions referred, for example, to provision of free or subsidised drugs; availing of offers of manufacture of some cheaper drugs utilising spare manufacturing capacity; possible promotion and subsidy of oral contraceptives; Government aids to setting up a multi-purpose pilot plant by means of tariff control, tax concessions or holidays or training grants; and Government incentives to attract certain expatriates back to the Philippines. These are just some ways the Government can show its commitment to progress. As quoted before there is a price to pay for progress.
However, none of these are subjects on which this expert can or should, make recommendations.

There is only one real aspect and that is whether the pharmaceutical industry in the Philippines is ready for backward integration and, if so, to what extent and by what means.

The mission completed did not allow time for a study in any greater depth and it should be pointed out that if the recommendations are accepted a further stage investigation will be necessary to re-confirm preliminary product lists (and perhaps modify them), specify the plant equipment and facilities in greater detail and sufficient to submit for tendering as well as for preparation of proposals for investors.

IT IS RECOMMENDED THAT :-

1. THE PHARMACEUTICAL INDUSTRY OF THE PHILIPPINES IS READY FOR BACKWARD INTEGRATION.
2. CONSIDERATION OF THE INSTALLATION OF DEDICATED OR MULTI-PRODUCT CHEMICAL PLANTS IS NOT APPROPRIATE.
3. CONSIDERATION OF THE INSTALLATION OF A MULTI-PURPOSE CHEMICAL PILOT PLANT IS THE APPROPRIATE MODE OF PROGRESS.
4. THE MULTI-PURPOSE PILOT PLANT SHOULD BE RESEARCH ORIENTATED.
5. ESPECIALLY IN THE EVENT THAT RECOMMENDATIONS 3 & 4 ARE ACCEPTED IMMEDIATE STEPS SHOULD BE TAKEN TO ESTABLISH A RESEARCH FUNCTION UTILISING EXISTING FACILITIES.

ANNEX

CHEMICAL SYNTHESIS.

A verbal request was made for the elaboration of the reasons for the exclusion of several specific products from the first preliminary list of pharmachemicals suggested as possibly suitable for local chemical synthesis in the Philippines.

The products, and Group of products comprise:-

1. ASPIRIN (ACETYLSALICYLIC ACID)
2. ACETAMINOPHEN (PARACETAMOL)
3. VITAMINS

GENERAL.

Both aspirin and acetaminophen and some of the Vitamins fall in the category of large consumption/low cost products which have world-wide demand.

Aspirin and acetaminophen are used exclusively in the Pharmaceutical Industry, but the Vitamins have a market in other areas such as the Food industry and Veterinary use.

The world-wide consumptions of the top 18 pharmachemicals, in order of sales value, was published by Stinson in Chemical & Engineering News, Sept. 16th, 1985. The top 15 of this list contain many of the products under consideration here and this section is reproduced below.

It should be noted that this list is quite different from that of the world-wide top preparations prescribed, these tending to contain high value pharmachemicals. This list of top preparations will vary somewhat from Country to Country and from Industrialised Countries to Developing Countries and is not so relevant in this study. Particularly for Industrialised Countries the pharmachemicals listed would all be high value products.

Top 15 pharmachemicals in major world markets. [a.]

Pharmachemical	Value $ million	Pharmaceutical thousand tons	Total thousand tons
1. Ascorbic acid (Vit. C)	325	16.5	30.0
2. Benzathine benzyl-penicillin (Penicillin G.)	240	1.9	8.3
3. Vitamin E. (∝-tocopherol acet.)	230	3.3	6.5
4. Ampicillin	150	1.7	1.7
5. Aspirin (Acetylsalicylic acid)	115	25.3	25.3
6. Acetaminophen (Paracetamol)	100	14.2	14.2
7. Phenoxymethyl penicillin (Penicillin V)	100	0.7	3.1
8. Riboflavin (Vitamin B_2)	90	0.8	2.1
9. Sulfonamides	90	3.6	5.0
10. Thiamine (Vitamin B_1)	85	1.6	2.5
11. Niacin & derivatives (Nicotinic acid & derivatives - Vitamin B group)	65	2.2	8.8
12. Calcium pantothenate (Vitamin B_5)	60	0.8	4.0
13. Caffeine	45	2.0	4.5
14. Chlortetracycline	40	0.1	1.1
15. Pyridoxine (Vitamin B_6)	40	1.0	1.2

a. Data for U.S., Western Europe and Japan only.
b. Synthetic only
Source: SRI International.

Products of interest are underlined.

Each of the products under consideration will be dealt with individually in the subsequent section.

Exclusion from the primary list proposed can generally be attributed to some combination of lack of information on level of consumption, insufficient volume demand (hence economically adverse), low technology contribution or inclusion in the synthesis of steps not compatible with a multi-purpose chemical pilot plant (fermentation stages or specific chemical reactions).

ANALYSIS OF INDIVIDUAL PRODUCTS.

ASPIRIN (ACETYL SALICYLIC ACID).

This product has the highest consumption of all synthetic pharmachemicals in the industrialised countries and is really a consumer product. Price competition is thus strong. Consumption in the industrialised countries is currently about 30,000 tons and total world consumption about 43,000 tons. Forecasts of world demand are in the order of 45,500 tons in 1990 rising to about 61,400 tons by the year 2000. This corresponds to an average growth rate of 3% per annum, but the growth rate in the developing countries should be higher than the average.
Per capita consumption on the average in developing countries is about 10 gm. per annum, whilst in the industrialised countries the level is about 30 gm. per annum. Closing of this gap with improving economics and population growth rate explain the potentially high future growth rate in developing countries.

Acetylsalicylic acid is freely available on the world market at competitive prices in both crystalline and the preferred directly compressible form most suitable for tableting.
Prices vary with quantity but the average in 1986 was $2.04 per kg. for crystals and $2.70 for the compressible form on the world market.
The price paid for material entering the Philippines in bulk form during 1987 averaged $3.02 C & F or $3.74 landed cost.
Quantities imported varied from 250 kg. lots to 10,000 kg. at C & F prices from $4.1 to $2.0. All the material

would appear to have been in crystal form, apart from a few consignments of 200 - 900 kg. at $6.76 which no doubt were in compressible form.

Production.

Acetylsalicylic acid is mainly produced in the U.S.A., Western Europe, U.S.S.R. and Peoples Republic of China. Most established production capacities are found in the range of 600 to 9,000 tons per annum.
Production usually commences from phenol, the intermediate salicylic acid being produced by a Kolbe-Schmidt reaction with carbon dioxide at elevated temperature and pressure. For this latter reason, i.e. working at 5 - 7 atmospheres this reaction is not compatible with a multi-purpose plant but only with a dedicated plant which is part of a multi-product plant. Such a multi-product plant would also be used for the production of one of the other products under consideration, acetaminophen or paracetamol.
Such high pressure plant, having to be built to high specification is very expensive.

The only alternative synthesis available and suitable for a multi-purpose plant is the one stage synthesis from the intermediate salicylic acid. This can be considered as a quite unsuitable approach for several reasons.
(1) the technology level is very low and would contribute little to the aspect of using a multi-purpose pilot plant to gain experience in production of pharmachemicals by chemical synthesis.
(2) it is impossible to produce acetylsalicylic acid economically. The following calculation illustrates this.

Material costs.

Materials:	Salicylic acid	$3.35	Landed cost
	Acetic anhydride	$1.19	Landed cost

Chemical cost for 100 kg. aspirin.

Material.	Usage.	Unit cost.	Total cost.
Salicylic acid	96 kg.	$ 3.35/kg	$ 321.6
Acetic anhydride	95 kg.	$ 1.19/kg	$ 113.1
Local chemicals	-	-	$ 2.3
Total chemical cost			$ 437.0 per 100 kg.

On top of this all labour & overhead costs have to be added.

The cost must be compared with the landed cost of aspirin of $ 3.74 per kilogram.

(3) There is also a negative contribution towards saving of foreign currency: -

Outlay in US dollars to purchase 1 kg. aspirin final product ..... $ 3.02

Outlay in US dollars to purchase chemicals to produce 1 kg. aspirin ..... $ 3.66

For every kilogram of aspirin product an extra $ 0.64 of foreign exchange would need to be expended if domestic production was employed starting from salicylic acid.

A precise manufacturing cost cannot be determined at this point and is very dependant on works and general overhead level and allocation. Using rough figures it is clear that in a multi-purpose plant the manufacturing cost for aspirin from salicylic acid would not be lower than $ 8 per kg. and might be considerably higher. *

A further illustration of the preparation of aspirin in a multi-product plant together with acetaminophen will be presented after the consideration of producing acetaminophen in a multi-purpose plant.

Volume of aspirin imported and sold.

The volume of aspirin sold through drug stores and hospital pharmacies appears very low at 6,671 kgs. There will be sales through other OTC sources such as Supermarkets although the difference between apparent sales and importations is rather large. The total recorded imported bulk product is in itself also small at 91,760 kgs.

* See appendix for more details.

Even consumption at the imported level is very low corresponding to only 1.63 gms per capita per annum. Even allowing that, perhaps, only 20% Of the population can afford medication of this form the consumption figure would only amount to 8.2 gms per capita per annum against average consumption for developing countries reported at 10 gms. per capita per annum. There is plenty of scope for a substantially increased market.

ACETAMINOPHEN (PARACETAMOL).

The sales value of acetaminophen is only slightly less than aspirin at a quantity volume of about 56% that of aspirin. Consumption in the industrialised countries is currently about 19,750 tons. Forecasts of world demand are in the order of 22,900 tons by 1990 and 32,000 tons by year 2000, correcsponding to a growth rate of 5% until 1990 and thereafter a rate of 3%.

Acetaminophen is freely available in international trade in three forms, fine powder, crystalline and directly compressible forms.

Prices realised at the end of 1986 were $ 4.30/kg. for powder and crystal, while the directly compressible form marketed at $ 5.30/kg. The posted prices at the same time in Chemical Marketing Reporter (29.12.1986) was $ 6.30 and the similar posted prices in 1988 (4.1.1988) were from $ 5.95 to $ 6.60. No product form is indicated in these posted figures and they do not necessarily represent actual sales transactions.

The prices paid for material entering the Philippines in 1987 averaged $ 4.43 C & F or $ 5.49 landed cost. Prices vary considerably with volume, but good prices were obviously obtained for large consignments. For lots up 250 kgs. prices were seen to be from $ 6.3 to $ 5.85; for lots up to 5,000 kgs. from $ 5.85 to $ 4.30 and for large lots up to 35,000 kgs from $ 5.00 to $ 4.00. All these recorded as C & F prices.

Prices in the first half of 1988 were essentially the same as in 1987.

Production.

The main producers operate in the U.S.A., Western Europe; Peoples Republic of China; Republic of Korea; Japan and India. The are also small productions in Argentina, Brazil, Eastern Europe, Mexico and Taiwan.
The range of production scale is much wider than for aspirin, established plants having capacities from 50 tons to 4,000 tons per annum.
There are three possibilities for chemical synthesis which correspond to different degrees of back integration.
The ultimate is to use phenol as basic starting material. Such production is more appropriate to a multi-product plant.
The second possibility is to start from para-nitrophenol. This is feasible in a multi-purpose plant provided it does include the facility of a hydrogenation unit.
The third, and final, possibility is to start from para-aminophenol.
The second and third possibilities only will be studied here, in reverse order.

Starting from para-aminophenol production involves a simple one stage reaction. Such a production scheme is considered quite unacceptable for the following reasons:-

(1) the technology level is very low and would contribute little to the aspect of using a multi-purpose pilot plant to gain experience in production of pharmachemicals by chemical synthesis.
(2) it is impossible to produce acetaminophen economically from purchased para-aminophenol. The following calculation illustrates this.

Material costs.

Materials:	para-aminophenol	$ 8.87	Landed cost.
	Acetic anhydride	$ 1.19	Landed cost.

Chemical cost per 100 kg. acetaminophen.

Material	Usage.	Unit cost.	Total cost.
Para-aminophenol	96 kg.	$ 8.87	$ 851.5
Acetic anhydride	90 kg.	$ 1.19	$ 107.1
Local chemicals	-	-	$ 8.8
Total cost			$ 967.4 per 100 kg.

On top of this all labour and overhead costs have to be added.
The cost must be compared with the landed cost of acetaminophen at the average of $ 5.49/kg.

(3) There is also a negative contribution towards saving of foreign currency:-

Outlay in US dollars to purchase 1 kg. acetaminophen final product ..... $ 4.43

Outlay in US dollars to purchase chemicals, para-aminophenol and acetic anhydride to produce 1 kg. acetaminophen ..... $ 7.73

For every kilogram of acetaminophen product an extra $ 3.30 of foreign exchange would need to be expended if domestic production from para-aminophenol was employed.

A precise manufacturing cost cannot be determined at this point and is very dependant on works and general overhead level and allocation. Using rough figures it is clear that in a multi-purpose plant the manufacturing cost for acetaminophen from para-aminophenol would not be lower than $ 13.2/kg. and might be considerably higher. *

The alternative route for production in a multi-purpose plant, providing that hydrogenation facilities are included in its design, is to start from para-nitrophenol.
In this case the technology level is more interesting giving an introduction to the very useful facility of low pressure hydrogenation.
There are more attractions to this approach, but the production still will prove to be rather un-profitable.

* See appendix for more details.

This route, and production of acetaminophen was not included in the primary list on the basis of the negative profitability although there can be seen to be some small contribution towards the foreign currency balance.

(1) Chemical and manufacturing cost.

Material costs - imported, landed costs.

Para-nitrophenol	$ 2.85
Acetic anhydride	$ 1.19
Catalyst	$ 4.96

Chemical cost per 100 kg. acetaminophen.

Material.	Usage.	Unit cost.	Total cost.
Para-nitrophenol	100 kg.	$ 2.85	$ 285.0
Acetic anhydride	90 kg.	$ 1.19	$ 107.1
Catalyst	18 kg.	$ 4.96	$ 89.3
Local chemicals	-	-	$ 9.7
Total cost			$ 491.1 per 100 kg.

On top of this labour and overheads have to be added. A precise manufacturing cost cannot be determined at this point and is very dependant on works and general overhead level and allocation. Using rough figures it is clear that in a multi-purpose plant the manufacturing cost for acetaminophen from para-nitrophenol would not be lower than $ 9.8 /kg. and might be considerably higher.*

Compared with the average import price there would be an adverse price difference of some $ 4.31/kg.
As limited production would be contemplated it is feasible to expect that only domestic sales of orders up to 2,000 kg. would be satisfied and in this case comparision should be against a landed cost of $ 7.25. There is still an adverse price difference of $ 2.55/kg.

(2) There could be a small/medium positive contribution towards saving of foreign exchange.

Comparing with the average import price of $ 4.43 C & F there is a small positive contribution of $ 0.55/kg. Satisfying the higher price/lower volume market there is a more significant contribution of $ 1.97/kg.

* See appendix for more details.

	Average.	Premium.
Outlay in US dollars to purchase 1 kg. of acetaminophen final product	$ 4.43	$ 5.85
Outlay in US dollars to purchase chemicals, para-nitrophenol, acetic anhydride and catalyst to produce 1 kg. acetaminophen	$ 3.88	$ 3.88
Contribution	+ $ 0.55/kg.	+ $ 1.97/kg.

Volume of acetaminophen imported and sold.

Again a difference was observed, as with aspirin, between the imported volume and the sale volume through drug stores and hospital pharmacies possibly for similar reasons. The difference was not so large.
In the Philippines there is apparently a much higher consumption of acetaminophen than aspirin compared with the general world picture. In the Phillipines, based on the importations there is a ratio of acetamin phen : aspirin of 3.2 : 1 compared with the world ratio in industrialised countries of 0.56 : 1.

Production of aspirin and acetaminophen in a multi-product plant.

Both aspirin and acetaminophen may be produced from the base material phenol. This is available on the world market at a price of $ 0.55 C & F or $ 0.68 landed cost in the Philippines.
In the case of aspirin the synthesis consists of two stages, a Kolbe Schmidt carboxylation followed by the acetylation considered earlier. The Kolbe Schmidt reaction utilises special and expensive equipment as the method involves moderately high pressure.

The production of acetaminophen consists of three stages. Two of these have been referred to earlier. The additional step involves nitration. Such a reaction can be performed in a multi-purpose plant although some advocates prefer not to do so from hazard aspects.

The justification for a multi-product plant lies largely in an adequately high production volume.
Such a high level of consumption does not exist currently in the Philippines for either of the products under consideration and in view of the free availability of these products in the world market it would be hard to justify the installation of a large plant principally for export as it would be very difficult to compete, even if only considering the most obvious market of Asia.

Multi-product plants tend to be much more expensive than multi-purpose plants, partly because of size and partly because (as in this case for aspirin and acetaminophen) some special units are frequently needed.

It has been mentioned earlier that plants operating to produce aspirin mostly start at a capacity of 600 tons per annum. Although some acetaminophen plants are operated at capacity as low as 50 tons per annum, most produce several hundred tons per annum. From world consumption figures an appropriate minimum size of multi-product plant should perhaps be based on a production of 600 tons of aspirin and 336 tons per annum of acetaminophen.

Some figures, essentially for such a capacity are available in a UNIDO Sectoral Studies Publication (No. 36) and will be used here to illustrate the possibilities for this size of unit.

Apart from aspirin and acetaminophen, two other products were included in this production unit. The products, methylparaben (used in foods, beverages and cosmetics as a preservative) and propylparaben (anti-fungal) are of rather low interest. Methyl salicylate is also included which is interesting although the consumption of this product in the Philippines was not established. Salicylic acid itself is used directly in pharmaceuticals but again the Philippine consumption was not identified.

The parameters listed later can be used to determine a rough chemical cost for aspirin and acetaminophen produced in such a plant. The full manufactured cost is more difficult to assess without more information but a minimum can be estimated.

Some technical data of a multi-product plant for products produced from phenol.*

Annual capacity.

Aspirin	600 tons.
Paracetamol	400 tons.
Methyl salicylate	180 tons.
Methylparaben	30 tons.
Propylparaben	10 tons.

Plant operation.: 300 work days; 3 shifts/day.

Annual utilities requirement.

Steam	5,750 tons.
Power	2,600 mWh.

Annual material requirement.

Phenol	1,120 tons.
Sodium hydroxide	320 tons.
Sulphuric acid	1,010 tons.
Acetic anhydride	776 tons.
Sodium nitrite	500 tons.
Sodium sulphide (60%)	1,140 tons.

(Note: This list is obviously not complete omissions being: catalyst, hydrogen, carbon, carbon dioxide, potassium hydroxide.)

Total reactor capacity estimated: 120 m^3.

Production plant area: 1,944 m^2.

Indoor storage area: 1,152 m^2.

Administration & service areas: 2,000 m^2.

Effluent treatment: 256 m^2.

Investment costs: US $ 9.5 million ± 30% (April 1987)

Staff requirements:

Management	5
Production	10
Maintenance	5
Quality control	3

* Reproduced from UNIDO Sectoral Studies Publication No. 36.

Calculation of chemical and manufacturing costs.

This can only be a rough and illustrative costing based on the foregoing information and certain assumptions.

Labour costs:

These are calculated for the labour force listed at rates which are currently considered to be appropriate.

Management	5 x $ 17,400	=	$ 87,000
Production (shift)	10 x $ 10,000	=	$ 100,000
Maintenance	5 x $ 4,800	=	$ 12,000
Quality control	3 x $ 4,800	=	$ 14,400
Total annual salaries (including ins. holiday pay, etc.)			$ 225,400

Building costs:

Total building area	=	5,096 m^2
Estimated average building cost (assumed to include element for site work, roads etc.)	=	$ 500 m^2
Total estimated building cost 5,096 x 500	=	$ 2,548,000

Installed equipment cost:

Determined by difference of stated investment cost less estimated cost of building.

Installed equipment cost = $ 9,500,000
less $ 2,548,000
= $ 6,952,000

Depreciation and Maintenance overheads.

Plant 10% cost	= $	695,200
Plant maintenance	= $	69,520
Buildings 5% cost	= $	127,400
Building maintenance	= $	31,850
Total	= $	962,190

Allocation of labour and overheads.

For simplicity allocations will be made in accordance with production levels and the number of stages employed in the synthesis.
Thus aspirin is allocated 38.5% of all overheads amd acetaminophen 43.5%. The balance would be allocated to the other products.

Material costs. (per kilogram.)

	$
Phenol	0.68
Sodium hydroxide	0.60
Sulphuric acid	0.14
Acetic anhydride	1.19
Sodium nitrite	0.43
Sodium bisulphite	1.20
Active carbon	2.73
Catalyst	4.96
Hydrogen	1.00

Chemical and Manufacturing costs.

ASPIRIN. (600 T. p.a.)

Material.	Volume.	Cost/kg.	Total. ($)
Phenol	550 T	0.68	374,000
Acetic anhydride	475 T	1.19	565,250
Sulphuric acid	314 T	0.14	43,960
Sodium hydroxide	261 T	0.60	156,600
			1,139,810

CHEMICAL COST ASPIRIN $ 1.90 per kg.

Chemical cost (600 T aspirin)	1,139,810
Labour	86,779
Overheads	370,446
	1,597,035

MANUFACTURING COST ASPIRIN $ 2.68 per kg.

This leaves $ 0.3% contribution to profit and any other overheads not included, e.g. interest, sales costs.

Total annual sales	$ 1,812,000
Contribution	$ 215,000

ACETAMINOPHEN. (400 T. p.a.)

Material.	Volume.	Cost/kg.	Total. ($)
Phenol	367 T.	0.68	249,560
Sodium nitrite	500 T.	0.43	215,000
Sulphuric acid	726 T.	0.14	101,640
Acetic anhydride	360 T.	1.19	428,400
Sodium bisulphite	7.2 T.	1.20	8,640
Active carbon	12 T.	2.73	32,760
Catalyst	72 T.	4.96	357,120
Hydrogen	23 T.	1.00	23,000
			1,416,120

CHEMICAL COST ACETAMINOPHEN $ 3.54 per kg.

Chemical cost (400 T acetaminophen)	1,416,120
Labour	98,049
Overheads	418,553
	1,932,723

MANUFACTURING COST ACETAMINOPHEN $ 4.83 per kg.

This leaves $ 1.02 contribution to profit and any other overheads not included, e.g. interest, sales costs.

Total annual sales $ 2,340,000

Contribution $ 408,000

This assumes the selling price of $ 5.85 applicable to sales lots of up to about 2,000 kgs. At this volume of production some larger orders would certainly have to be supplied and kg. selling price would drop below the manufacturing cost.

Although this size of unit shows marginal possible profitability, reducing the production levels would produce a loss making situation.

EXAMPLE OF PRODUCING ACETAMINOPHEN IN A MULTI-PURPOSE PLANT.

To complete the picture the situation can be analysed for the production of acetaminophen from phenol in a multi-purpose plant. This is operationally possible from phenol in the case of acetaminophen (but not so for aspirin). A minimum production level of 50 T. per annum must be considered.
Such production would occupy some 5 m^3 of production equipment and might mean inclusion of additional reactors to those proposed earlier with particular attention directed at the capacity of hydrogenation. Inclusion of such additional items would increase the overall cost of the installation but for calculation purposes this additional expenditure will be ignored.

CHEMICAL COST ESTIMATE.

The chemical cost will be the same as for the multi-product plant as the prices of chemicals in that calculation were taken as general market prices. (In fact in the case of the

multi-product plant the volumes of chemicals which would be used are such that lower prices could be possibly be negotiated under contract purchasing.)

CHEMICAL COST ACETAMINOPHEN $ 3.54 per kg.

MANUFATURING COST. (for 50 T acetaminophen)

Overhead and labour allocation* has been determined on the basis of plant occupancy of the three stages involved. This has been estimated at 25%.

Chemical cost.(50 T. acetaminophen)	$ 177,000
Labour	$ 84,750
Overheads	$ 167,595
Utilities	$ 25,000
Total	$ 454,345

MANUFACTURING COST ACETAMINOPHEN $ 9.09/kg.

This illustrates the fact that essentially the same labour force in production is required more or less independant of the throughput. This alone adds an additional $ 1.5 per kg It is obviously not economic to manufacture in the plant at this level but there is a reasonable contribution towards saving of foreign exchange when considering a purchase price for acetaminophen of $ 5.85.

Expenditure in US dollars for 50 T acetaminophen	.....	$ 292,500
Expenditure in US dollars for the purchase of chemicals to produce 50 T acetaminophen	.....	$ 161,435
		$ 131,065

The loss in manufacture at a minimum of $ 3.24 per kg. and at the volume throughput is considered too great for even the basic manufacture of acetaminophen.

* See appendix for more details.

VITAMINS.

This heading covers a wide range of products covered largely by the following list. Although some are used alone, many preparations contain combinations as also illustrated below.

Vitamin.	Chemical name.	No. preparations.	
		Single	Comb.
Vitamin A	Retinol	5	3
Vitamin B group	Niacin,	-	1
	Niacinamide	1	1
Vitamin B_1	Thiamine	3	4
Vitamin B_2	Riboflavine	-	1
Vitamin B_6	Pyridoxine (HCL)	1	23
Vitamin B_{12}	Cyanocobalamine	1	7
	Hydroxycobalamine	3	1
Vitamin C	Ascorbic acid	12	4
Vitamin D	Alfacalcidol	1	-
Vitamin E	Alfa-tocopherol (acetate)	2	4
	(nicotinate)	1	-
Vitamin K_1	Phytomenadione	2	1
Vitamin K_3	Menadione	2	2
Vitamin K_4	Menadiol	1	-
Vitamin P	Rutin	-	6
Vitamin B_5	Calcium pantothenate	-	1

Apart from prorietary and prescription products, many vitamins are also used in a variety of OTC vitamin and multi-vitamin products. Also veterinary and nutritional feed products.

Each vitamin will now be considered individually in turn.

Vitamin A (Retinol)

The natural source of fish liver oil has been mentioned, but this falls under the report of animal products. It is most likely that the direct value of the oil is greater than considering isolation of vitamin A from it.

From a synthetic point of view, although the price is attractive, production was eliminated for the reasons that it would be difficult to compete against major producers such as Roche & BASF; the synthesis is rather long

for a multi-purpose plant comprising (including preparation of intermediate) some 10 - 11 stages.

Other factors, which might have enhanced interest in the product, such as evidence of a good domestic source of beta-ionone or pre-cursors were not propitious.

The price of Retinol in January 1988 was listed in Chemical & Marketing News at $ 33.00/kg. for synthetic material (pharmaceutical grade, 500,000 A units/gm.) to $ 41.00/kg. for pharmaceutical Liquid in oil (1,000,000 A units/gm.) These were respectively for small lots of 50 kg. and 10 kg. Vitamin A, feed grade (650,000 units/gm.) was listed at $ 31.90.

Vitamin B group: Niacin (Nicotinic acid) & Niacinamide (Nicotinamide).

Although from the operational point of view these products can be considered suitable for production in a multi-purpose plant they were rejected in the first instance as being of very low technology value and low contribution.

Apart from pharmaceutical use, which is low, these products are used as nutritional additives for both humans and animals.

The recorded ethical consumption of niacinamide appeared to be only 16 kg. in 1987 but this will not include OTC vitamin preparations. The consumption of niacin has not been determined.

Importations recorded were :-

Niacin (Jan-Dec.1987)	Not abstracted.		
Niacin (Jan-May.1988)	27,985 kg.	Price average C & F	$ 6.29/kg.
Niacinamide (Jan-Dec.1987)	17,840 kg.	Price average C & F	$ 6.43/kg.
Niacinamide (Jan-May.1988)	6,910 kg.	Price average C & F	$ 6.88

Virtually all importations of each product were of feed grade material.

NOTE: Furazolidone (included in primary list) and having a similar consumption pattern, was chosen in preference as a bulk product for consideration on the basis of slightly higher price and particularly higher technical content and value.

Vitamin B_1 (Thiamine: Aneurine.)

Thiamine (hydrochloride) was not considered in the list for possible synthesis due to lack of abstracted information.

Although thiamine can be produced from rice and some concentrates are marketed it is not an economic source for pure thiamine. All thiamine marketed is produced by synthesis.

Vitamin B_2 (Riboflavine)

This product was not included in the list of possible products for chemical synthesis due to lack of sufficient information on consumption.

Riboflavine for therapeutic use is produced by synthesis, while concentrates for livestock and poultry feed are produced by fermentation.

Vitamin B_6 (Pyridoxine)

This is a product which could be included in the initial list for further study. The reason for non inclusion in the first list was based on the fact that the number of stages in the synthesis, starting either from DL-alanine or alfa-chloroacetylacetic ethyl ester, approach the maximum recommended for a multi-purpose pilot plant in numbering 4/5. It might be more appropriate for established pilot plants.

The price of the product is, on face value, attractive . Importations into the Philippines in 1987 averaged $ 37.2/kg. and in the first half of 1988 were recorded at $ 43.5 (C & F). As with other products a deeper study is necessary to ascertain prices of raw and intermediate chemicals. Several synthetic routes are known to be employed.

Vitamin B_{12} (Cyanocobalamine & Hydroxycobalamine) .

These products were not included in consideration for the multi-purpose pilot plant as the syntheses involve some fermentation stages which are not compatible with the concept.

Vitamin C. (Ascorbic acid).

This product was excluded from consideration of production in the multi-purpose pilot plant as it is not appropriate.

However, it was proposed (Main report 'Raw Materials' section 3.3 para. 3) that an investigation in more detail should be carried out into the production of Ascorbic acid from D-glucose.
This should be considered from the point of view of not only domestic production for home use, but also for export. Such a study is still recommended.

Price indication early 1988 was $ 12.75/kg. for small consignments.

Vitamin D. Alfacalcidol (1α-hydroxycholecalciferol or 1α-hydroxy-Vitamin D_3)

This was rejected from technical considerations (1) synthesis is too long for a multi-purpose plant (7 stages) and also (2) the synthesis involves specialist reaction involving U/V light.

Vitamin E. Alfa-tocopherol (acetate, nicotinate).

Marketed as natural product d-alfa-tocopherol and the racemic dl-tocopherol.

Isolation of natural products alfa-tocopherol from wheat germ, and gamma-tocopherol (one starting material for chemical transformation) from Corn oil were not considered.

The exclusion of dl-tocopherol and salts was based on un-established consumption indications and no evidence of a local advantage of availability of the intermediate isophytol (or its precursors linalool, citral or pseudo-ionone) used for its synthesis.

The dl-alfa-tocopheryl acetate was listed in Jan. 1988 at $ 22.50/kg.

Vitamin K_1. Phytomenadione; phytonadione; phylloquinone; 3-phytyl menadione.

The synthesis of Vitamins K_1, K_3, & K_4 are all inter-related. Menadione (Vitamin K_3) is the prime synthetic product from which Menadiol (Vitamin K_4) is synthesised and this then converted to Vitamin K_1.

Vitamin K_1 was not included for further consideration on the basis of a lack of consumption indications and also that the other Vitamin K products were also not to be selected.

Vitamin K_1 is synthesised from Menadiol diacetate and phytol. Technology content is not high.

Vitamin K_3. Menadione.

This was not considered on the basis of lack of consumption indications and very low technology value.

Vitamin K_4. Menadiol.

Not considered on the basis of lack of consumption indications and also that the synthesis of menadione was not to be considered.

Vitamin P. Rutin.

This Vitamin is not produced by synthesis, but rather by extraction from Sophora japonica or Dimorphandra. There was no indication of abundance of the former and the latter is indigenous to South America.

This was not included as it is not prepared synthetically.

Vitamin B_5. Calcium pantothenate.

The production was not considered on the basis of lack of consumption indications.

The dl- synthetic form is more economic than the natural d- form.

APPENDIX.

This appendix is included to explain the outline calculations used to arrive at estimated manufacturing costs in a multi-purpose pilot plant of the size proposed in the main report.

BASIS FOR COSTING AND ALLOCATION OF LABOUR AND OVERHEADS FOR PROPOSED MULTI-PURPOSE CHEMICAL PILOT PLANT.

Labour cost.

Salary rates have been estimated at the rates given below for operation in the Philippines. They are assumed to be gross rates including element for insurance, holiday etc.

Position.	Production (Direct)		General (Indirect)	
	No.	$ p.a.	No.	$ p.a.
General manager	-	-	1	21,000
Senior managers	2	33,600	2	33,600
Middle managers	3	36,000	2	24,000
Chemists, shift	6	38,400	-	-
Chemists, day	2	9,600	3	14,400
Technicians	6	36,000	-	-
Tradesmen	7	33,600	-	-
Office workers	-	-	7	33,600
Unskilled	7	25,200	-	-
		212,400		126,600

Overheads : Depreciation and maintenance.

Based on the estimated building costs and installed equipment costs given on pages 120 & 121 of the main report.

Installed plant	$ 5,416,220
Building costs	$ 1,196,278
Total :	$ 6,612,498

Depreciation.

Item.	Gross value.	%	Annual charge.
Installed plant	$ 5,416,220	10	$ 541,622
Buildings	$ 1,196,278	5	$ 59,814
Total:			$ 601,436

Maintenance.

Installed plant :	10% annual depreciation	$ 54,162
Buildings:	25% annual depreciation	$ 14,953
		$ 69,115

Total fixed overheads.

Depreciation	$ 601,436
Maintenance	$ 69,115
General admin, R & D labour	$ 126,600
Total fixed overheads	$ 797,151

Overheads: Variable.

For this exercise only utilities are being considered. Here only a rough estimate of costs/kg. product are being used and are based on general knowledge or experience of process and likely use of steam, power, refrigerant, packing material etc.

Allocation of labour and overheads.

Allocation of labour and overheads are based on the basis of the plant occupancy of the total stages for the synthesis of the final product. It may be determined fairly accurately by a concept known as 'litre-hours' when full process details are to hand. It is not sufficient to allocate by the weight volume production as different products utilise various number of stages, different unit weight charge per unit volume and times of occupancy within plants.

As indicated only accurate allocations can be made when full process details are available, but rough estimates can be made from experience and general knowledge of the processes. This is what has been applied to the following examples.

(1) Production of aspirin (acetylsalicylic acid) at 50 T. level in a multi-purpose plant from salicylic acid.

Allocation of overheads & labour estimated at 16%

For production of 50,000 kgs. aspirin per annum.

	Total	Cost per kg. product.	
	$	$	
Chemical cost	218,500	4.37	(see A-5)
Utilities	20,000	0.40	
Direct labour	33,984	0.68	
Fixed overheads	127,544	2.55	
Total cost	400,028	8.00	

(2) Production of acetaminophen (paracetamol) at 50 T. level in a multi-purpose plant, from para-aminophenol.

Allocation of overheads & labour estimated at 16%

For production of 50,000 kgs. acetaminophen per annum.

	Total.	Cost per kg. product.	
	$	$	
Chemical cost	483,700	9.67	(see A-8)
Utilities	15,000	0.30	
Direct labour	33,984	0.68	
Fixed overheads	127,544	2.55	
		13.20	

(3) Production of acetaminophen (paracetamol) at 50 T. level in a multi-purpose plant, from para-nitrophenol.

Allocation of overheads & labour estimated at 22%.

For production of 50,000 kgs. acetaminophen per annum.

(3) Production of acetaminopher (paracetamol) at 50 T. level in a multi-purpose plant, from para-nitrophenol.

Allocation of overheads & labour estimated at 22%.

For production of 50,000 kgs. per annum.

	Total.	Cost per kg. product.
	$	$
Chemical cost	245,550	4.91 (see A-9)
Utilities	22,000	0.44
Direct labour	46,728	0.93
Fixed overheads	175,373	3.51
		9.79

NOTE: These are considered minimum manufactured prices as no element has been included in the fixed overheads for any interest or insurance charges.

SUMMARY.

Individual and various reasons which were taken into account have been presented to illustrate why the specific products of aspirin (acetylsalicylic acid), acetaminophen (paracetamol) and Vitamins did not appear in the primary list proposed for bulk manufacture in the Philippines.

Aspirin and acetaminophen have been considered both separately and together.

Vitamins covers a large range of products and the most important have been dealt with individually.

Aspirin and acetaminophen, both large volume/low value consumer products are readily available on the world market. Philippine consumption is too low to consider production of both in a multi-product plant.

Aspirin is of too low technical value and too expensive to produce at a limited level in a multi-purpose pilot plant.

Acetaminophen (Paracetamol), although of more technically acceptable value when prepared from phenol, is too expensive to produce at a limited level in a multi-purpose pilot plant.

Vitamins may be divided into groups.

(1) Vitamins A, B_{12}, D and P were rejected on technological grounds.

Vitamin A (Retinol) rejection was based on too long a synthesis (10-11 stages) for a multi-purpose plant and no advantage of locally available starting material.

Vitamin B_{12} (Cyanocobalamine & Hydroxycobalamine) were rejected as the sythesis is not compatible with the concept of a multi-purpose pilot plant, fermentation steps being involved.

Vitamin D (Alfacalcidol) was rejected because too many stages are involved in the chemical synthesis and also some specialist stage involving a light reaction is also included.

Vitamin P (Rutin) was rejected as it is not prepared by chemical synthesis and also there was no evidence of significant plant raw material to consider extraction.

(2) Vitamins B_1, B_2, E and B_5 were not proposed principally on the basis of a lack of consumption information.

Vitamin B_1 (Thiamine) synthesis is also rather long (5 stages) for a multi-purpose pilot plant and later intermediates would be difficult to obtain.

Vitamin B_2 (Riboflavine) synthesis is also rather too long for a multi-purpose pilot plant (4/5 stages) due to the fact that basic intermediates have to be sythesised.

Vitamin E (alfa-tocopherol) synthesis from either 2,3,5-trimethyl hydroquinone and isophytol nor partial synthesis from gamma-tocopherol is of special technological interest. Respectively only two or three simple stages are involved. A cheap local source of raw material, either isophytol or gamma-tocopherol are considered very important to consider production of this product.

Vitamin B_5 (Calcium pantothenate) synthesis is not very compatible with a multi-purpose pilot plant comprising some 5 stages, although most are involved in making the intermediates.

(3) Vitamins K_1, K_2 and K_3 are all inter-related. They were not proposed for synthesis partly due to a lack of consumption information, but also because of the low technology content.

Vitamin K_1 (Phytomenadione: phytonadione.) This is synthesised from menadiol by a simple one step reaction. Mendiol itself is not proposed for synthesis and so preparation of Vitamin K_1 is inappropriate.

Vitamin K_3 (Menadione). This is the basic starting material for the K vitamins. It is not represented in PIMS as such but only as the sodium bisulphite derivative (known as water soluble vitamin K_3.) The synthesis is very basic and of too low technology content to warrant inclusion.

Vitamin K_4 (Menadiol diacetate). Synthesis from menadione is a simple one step reaction, also of low technology content.

(4) Vitamins B_6 and C.

Vitamin B_6 (Pyridoxine hydrochloride)

This product was a borderline case for inclusion in the preliminary list and only left off as it was thought to be a rather long synthesis (4/5 stages) for initial inclusion. It may have an attractive price structure depending on raw material costs and could still be considered as a candidate when a more detailed study is carried out.

Vitamin C (Ascorbic acid)

Although excluded from consideration for production in a multi-purpose plant it was recommended in the main report (under 'Raw materials', section 3.3 para 3) that investigation of this product should be carried out in more detail because of the benefit of D-glucose being the principal raw material. This recommendation still stands.

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