OCCASION

This publication has been made available to the public on the occasion of the 50th anniversary of the United Nations Industrial Development Organisation.

DISCLAIMER

FAIR USE POLICY

CONTACT

Please contact publications@unido.org for further information concerning UNIDO publications.

For more information about UNIDO, please visit us at www.unido.org

UNITED NATIONS INDUSTRIAL DEVELOPMENT ORGANIZATION
Vienna International Centre, P.O. Box 300, 1400 Vienna, Austria
Tel: (+43-1) 26026-0 · www.unido.org · unido@unido.org

Main results of the study work on industrial sectors are presented in the Sectoral Studies Series. In addition a series of Sectoral Working Papers is issued.

This document presents major results of work under the element Pharmaceutical Industries in UNIDO's programme of Studies and Research 1986/87.

Preface

This document is the final output of UNIDO project US/GLO/86/235 originally entitled "Industrial priorities for the production of pharmaceutical chemicals in developing countries" financed through a trust fund arrangement with NOBEL Chematur, Box 430, S-691 27 Karlskoga, Sweden. The study addresses the problem of decision-making in the selection of pharmaceutical chemicals for domestic production and was written with several groups of readers in mind. Primarily, our intention was to provide government decision-makers and industrial managers with an outline of the main considerations and pitfalls involved in the selection of pharmaceutical chemicals for domestic production. Beyond this, the paper reveals immediate and long-term opportunities of technical co-operation projects for UNIDO. We would like to think that the text would promote also international co-operation between developing and industrialized countries.

The Sectoral Studies Branch wishes to acknowledge the contribution of Mr. Ferenc Kováts, Research and Technical Director of CHINOIN Pharmaceutical and Chemical Works Ltd., Hungary, for collecting and organizing the market research data from UNIDO documents and for his involvement in the evaluation of the technical feasibility of alternative production programmes.

Contents

Tables

Figures

EXPLANATORY NOTES

References to dollars ($) are to United States dollars, unless otherwise stated.

A comma (,) is used to distinguish thousands and millions.

A full stop (.) is used to indicate decimals.

A slash between dates (e.g., 1980/81) indicates a crop year, financial year or academic year.

Use of a hyphen between dates (e.g., 1960-1965) indicates the full period involved, including the beginning and end years.

Metric tons have been used throughout.

The following forms have been used in tables:

Three dots (...) indicate that data are not available or are not separately reported.

A dash (-) indicates that the amount is nil or negligible.

A blank indicates that the item is not applicable.

Totals may not add up precisely because of rounding.

Besides the common abbreviations, symbols and terms and those accepted by the International System of Units (SI), the following abbreviations and contractions have been used in this report:

Economic and technical abbreviations

WHO	World Health Organization
CAS	Chemical Abstracts Service
FDA	Food and Drug Administration, USA
CA	Chemical Abstracts
INN	International Nonproprietary Name, published by the WHO

KEY WORDS

For the purpose of this study, certain repeatedly used terms are defined as follows:

ESSENTIAL DRUGS are those included in the official (last revision) WHO Model List of Essential Drugs.

PHARMACEUTICAL PREPARATION (drug preparation, drug product, pharmaceutical drug, pharmaceutical dosage form, pharmaceutical dose form product, pharmaceutical product, dose form, medicine) is the safe and effective finished, or partially finished (e.g., as in the case of a solid to be constituted into a solution for administration) product for use on or for humans, or other end-users, or animals to modify or explore physiological systems or pathological states for the benefit of the recipient.

PHARMACEUTICAL CHEMICAL (therapeutic ingredient, active ingredient, active constituent, active principle, active substance, buik drug, bulk chemical, bulk medicinal, basic medicinal, medicinals, medicinal chemical, pharmaceutical substance etc.) is a chemical substance, or a mixture of such substances the composition of which has not completely been elucidated but the quality of which has been specified in the pharmacopoeias and formularies. Pharmaceutical chemicals are the major inputs for the manufacture of pharmaceutical preparations and their end-user is mostly the pharmaceutical industry, but customers include also the hospitals, wholesalers and pharmacies.

PHARMACEUTICALS is a collective term for pharmaceutical chemicals and pharmaceutical preparations.

PHARMACEUTICAL INTERMEDIATES are organic chemical reactants used exclusively or mainly for the production of pharmaceutical chemicals.

BUILDING BLOCKS (starting materials, educts) are organic chemical reactants used mainly in the synthesis of fine chemicals, including pharmaceutical chemicals and intermediates.

RAW MATERIALS are inorganic chemical reactants and organic petrochemicals used in the production of pharmaceutical chemicals.

UNIT OPERATION is a physical change, e.g., filtration or heat transfer, in chemical industrial processing.

CHEMICAL CONVERSION (unit process, chemical change) is a chemical reaction applied to industrial processing.

MULTIPURPOSE BATCH REACTOR is a reaction vessel readily available from many sources. It usually has the form of a tank, is equipped with some means of agitation and provision for heat transfer to regulate temperature of the reaction mixture between -10° and 300°C, is made of stainless steel and glass- or enamel-lined steel and is connected to steam (less than 25 bar pressure), compressed air (less than 5 bar) and vacuum (higher than 10 mbar pressure). Its nominal capacity varies between 0.5 m^3 and 3 m^3.

1. INTRODUCTION

The report is a first approach to the selection of pharmaceutical chemicals for local production by organic chemical synthesis in multiproduct and multipurpose plants in specific developing countries and regions. The results are intended to guide and support the development programme and technical co-operation project activities of UNIDO but also to indicate opportunities for enterprise-to-enterprise co-operation.

The market environment of the pharmaceutical industry was assessed in specific African and Asian countries and regions. Other developing countries have not been investigated in this study. UNIDO documents (project proposals, feasibility studies, ongoing projects, expert reports, etc.) were summarily reviewed as sources of potential candidate chemicals. The first sample of pharmaceutical chemicals was derived from a country product-demand matrix. The organized information was screened by using health, technical, economic and social criteria to identify 10 substances as the representative sample of the population of all opportunities for the domestic production of pharmaceutical chemicals.

The study has been organized so that the list of studied countries and a directory of suppliers of pharmaceutical chemicals traded on the international open market are given in annexes 1 and 2, whereas the world market, the demand in developing countries, the technical and economic aspects of production are analyzed in chapters 4 to 7. Alternative pharmaceutical chemical industry strategies are described in chapter 8.

The survey of the informative prices of essential pharmaceutical chemicals has revealed that about 17 per cent of the studied 48 substances were scarcely available and that 15 per cent were not available in international trade. About 50 pharmaceutical chemicals, derived mainly from UNIDO documents, offered opportunities for domestic production in developing countries. The analysis of a sample of ten drugs, representative of all types of opportunities, has led to the conclusion that acetylsalicylic acid, chloroquine, paracetamol, pyrimethamine, salicylic acid, sulfonamides and trimethoprim should preferably be manufactured in multiproduct plants. The multipurpose plant was found to be the choice of preference for the manufacture of clotrimazole, pentamidine and praziquantel.

This study illustrates a methodology that could be followed when selecting pharmaceutical chemicals for domestic production but it should not be interpreted as a pre-feasibility of feasibility study. Plans for actual investment would, of course, require in-depth marketing, engineering and financial studies.

2. OBJECTIVES

The immediate objective of the report is to select about ten pharmaceutical chemicals and intermediates for economically promising and technically feasible local production by organic chemical synthesis in multiproduct and multipurpose plants in developing countries in general, and in Kenya, Nigeria, Zimbabwe as well as in the North Africa, West Asia and ASEAN (annex 1) regions in particular.

Opportunities and constraints will be identified for the programme development and technical assistance activities of UNIDO.

The long-term objective is to promote the establishment and expansion of the domestic production of pharmaceutical chemicals by both the public and private sectors in developing countries. Hence, a different set of criteria might be applicable in the two sectors for the evaluation of the economic feasibility of local production.

3. METHODOLOGY OF SELECTION

Pharmaceutical chemicals collected for market analysis were first divided by their method of industrial production into four main categories: organic synthesis, bioconversion, extraction from natural sources and semi-synthesis. Only the substances manufactured by organic chemical synthesis predominantly for human therapeutic use were analysed further.

The availability of pharmacopoeial quality pharmaceutical chemicals in international trade was assessed to identify multisource, oligopolistic (2 and 3 suppliers) and monopolistic situations. Pharmaceutical chemicals in the latter two groups were considered potential candidates for local production.

Informative prices were used to establish industrial priorities on the assumption that the production of expensive fine chemicals is more attractive than that of low-cost commodities.

The volume and value of the present demand for specific pharmaceutical chemicals was analysed worldwide and together with the frequency of demand in the studied developing countries and regions. Drugs used for the treatment of diseases prevailing in developing countries were given special consideration.

The population composed of pharmaceutical chemicals from availability, price and demand screenings were checked for need, effectiveness and safety criteria and only those items were processed further which were included by name or as a therapeutic equivalent in the official WHO model list of essential drugs or in other internationally recognized official compendia. Pharmaceuticals included in the WHO list of drugs for primary health care were given additional importance.

A standard synthesis was selected from reference manuals for each of the pharmaceutical chemicals demanded in developing countries. Preliminary conclusions on the complexity of the process (type and number of unit conversions, process and labour safety, environment pollution, etc.) were drawn on each process and different degrees of backward integration were proposed for their manufacture in multiproduct and/or multipurpose plants.

A representative sample was taken from the demand, non-availability and price groups to identify 10 substances for further analysis. Demand-supply profiles[1/] were prepared for each of the 10 pharmaceutical chemicals to establish pharmaceutical use, other use, preparation exclusivity, manufacturing process exclusivity, market size, therapeutic competition etc., to estimate the demand trend by the year 2000. Active ingredients of fixed combination preparations were all included in the profiles, if one of the components was chosen for future demand analysis. The process analysis was extended to the complementary pharmaceutical chemicals, as well.

Alternative strategies of production in multiproduct and/or multipurpose plants, or by customs synthesis were suggested for pharmaceutical chemicals with significant current demand and good future prospects in the studied developing countries and regions.

1/ Sectoral working paper under publication.

4. THE MARKET FOR PHARMACEUTICAL CHEMICALS

4.1 Overview of the global market

The statistical data on worldwide production, consumption and top pharmaceutical chemicals were taken from Stinson's article "Bulk drug output moves outside U.S.", published in the Chemical and Engineering News, September 16, 1985, pp. 25-59.

Approximately 1,500 to 2,000 pharmaceutical chemicals are used worldwide. World production of pharmaceutical chemicals for human use was about 240,000 tons, worth $US 7.9 billion in 1985. These figures show a 4 per cent growth from the 232,000 tons and a 6 per cent increase over the $US 7.4 billion in 1984. Figures in table 1 include also pharmaceutical chemicals produced by fermentation, extraction and/or semisynthetic methods.

Table 1. Worldwide production and consumption of pharmaceutical chemicals, 1985 (thousand tons)

Geographic region	Production	Consumption
USA	64	82
Western Europe	84	77
Japan	20	10
CMEA + China	73	73

The largest market is the United States (34 per cent) followed by Western Europe (32 per cent), the CMEA countries and the PRC (30 per cent) and Japan (4 per cent). Western Europe (35 per cent) leads the production statistics followed by the CMEA and PRC (30 per cent), the United States (27 per cent) and Japan (8 per cent).

Table 2 shows that developing countries, not included in table 1, would add about $US 1.2 billion to the worldwide consumption figure of $US 7.9 billion in 1985. Argentina, Brazil, the People's Republic of China, Colombia, Egypt, the area of Hong Kong, India, Indonesia, Iran, the Republic of Korea, Mexico, Pakistan, Peru, Saudi Arabia, Singapore, Taiwan Province of China, Turkey, and Venezuela represented each a market of $US 20 million or more in 1985.

UNIDO database has also revealed that developing countries with an annual export value of $US 10 million or more between 1980 and 1985 were Argentina, the Bahamas, Brazil, the People's Republic of China, India, the Republic of Korea, Mexico, Panama, Singapore, and Taiwan Province of China. It should be mentioned that the Bahamas and Panama - like Bermuda, Ireland, Puerto Rico and the Virgin Islands - probably offer substantial advantages for investment and/or production.

The People's Republic of China is practically self-sufficient in pharmaceutical chemical production. The share of the local production is high in the domestic consumption of pharmaceutical chemicals in most of those countries that also export, therefore, the total world consumption of pharmaceutical chemicals is estimated at about $US 10 billion in current dollars in 1985.

Table 2. International trade 1985 of pharmaceutical chemicals in developing countries (current million $US)

Geographic region	Imports	Exports
Africa	126	12
Asia	625	228
Latin America	400	110
Total	1,151	350

Source: UNIDO database.

Table 3 ranks pharmaceutical chemicals by value of sales. The designations in the table are not always clear. The term sulfonamides probably covers a large group of organic compounds with antimicrobial action but excludes diuretics and hypoglycemics of sulfonamide structure. Nicotinic acid and derivatives include nikotinamide, nikethamide, perhaps also isoniazid and other compounds. The top 18 pharmaceutical substances and categories include 10 compounds and groups which are produced by organic chemical total synthesis.

Contrary to the reported values of 82 per cent and 40 per cent, respectively, the 18 pharmaceutical chemicals account for about 50 per cent of the total volume consumed annually and 23 per cent of the overall dollar value of the market. Two thirds of the top 18 chemicals have sales of more than $US 50 million.

Only ampicillin, acetylsalicylic acid, paracetamol and theopylline are exclusively used in the pharmaceutical processing industry which is the principal buyer of pharmaceutical chemicals. The remaining 14 chemicals have other end uses, sometimes to a dominant extent. The hypothetic unit price of the 18 chemicals is $US 15.20/kg. The same value for the synthetics is $US 10.20/kg, whereas the derived unit price of pharmaceutical chemicals produced partially or completely by bio-transformation is $US 21.60/kg. The relative importance of the majority of the top 18 substances is higher in developing than in industrialized countries. The captive use of all pharmaceutical chemicals in table 3 does not affect international availability of these substances.

The ultimate demand for pharmaceutical chemicals depends, however, on the sales of pharmaceutical preparations. The 1986 sales value of the top ten preparations on the prescription market was about $US 3 billion in the United States alone and tne active ingredients in descending order of importance were: cimetidine, ranitidine, naproxen, triamterene + hydrochlorothiazide, cefalexin, atenolol, cefoxitin, piroxicam, alprazolam and nifedipine.[2/]

2/ SCRIP, No. 1171, 16 Jan. 1987, p. 15.

Except for paracetamol (in combination with codeine), the top 10 prescriptions dispensed also do not contain the pharmaceutical chemicals listed in table 3. Most of the top preparations in the United States contain high-value pharmaceutical chemicals which are therapeutically more important in industrialized than in developing countries. The originators sell pharmaceutical chemicals mainly to affiliates and to a limited number of licensees even after the product patent has expired. In fact, the largest companies are directly present on the pharmaceutical preparation market and do not sell pharmaceutical chemicals to competitors unless for continuing a historical tradition or for drugs sold on the non-prescription market. This statement does not apply to chemical producers without or with limited forward integration.

Table 3. Top 18 pharmaceutical chemicals in industrialized market economies

Pharmaceutical chemical	Consumption			Derived unit price
	$ millions	thousand tons		
	total	pharmaceutical	total	$/kg
Ascorbic acid	325	16.5	30.0	10.80
Benzathine benzylpenicillin	240	1.9	8.3	28.90
Vitamin E	230	3.3	6.5	35.40
Ampicillin	150	1.7	1.7	88.20
Acetylsalicylic acid	115	25.3	25.3	4.55
Paracetamol	100	14.2	14.2	7.00
Phenoxymethylpenicillin	100	0.7	3.1	32.30
Riboflavin	90	0.8	2.1	42.90
Sulfonamides	90	3.6	5.0	18.00
Thiamine	85	1.6	2.5	34.00
Nicotinic acid & derivatives	65	2.2	8.8	7.40
Calcium pantothenate	60	0.8	4.0	15.00
Caffeine	45	2.0	4.5	10.00
Chlortetracycline	40	0.1	1.1	36.40
Pyridoxine	40	1.0	1.2	33.30
Tetracycline	35	0.4	1.3	26.90
Oxytetracycline	30	0.7	1.2	25.00
Theophylline	15	1.4	1.4	10.70
TOTAL	1,855	78.2	122.3	15.20

Note: Derived unit price is not included in the source.

It should also be mentioned that generic competition has a tradition in the United States whereas it has become significant in Western Europe only in recent years.

Important factors that affect future demand for pharmaceutical chemicals include establishment and expansion of generic dosage form processing plants worldwide, the continuous expiry of patents mainly in industrialized countries and increasing population and improved access to drugs in developing countries.

Product purity, stable quality and reliability of supply are the principal technical and business criteria of buyers from the pharmaceutical preparation sub-sector. Principal barriers to entry for new producers include preparation and manufacturing process exclusivity, high technology, backward (petrochemical production) and forward (dosage form sales) integration, intense production and sales competition and regulated access to markets in both developing and industrialized countries.

4.2 International trade

Pharmaceutical chemical manufacturers without own international sales organization, particularly in the prescription drug market, sell their substances through international trading houses. These companies keep stock of the regularly demanded pharmaceutical chemicals and supply generic dosage form producers mainly in developing countries.

Questionnaires were sent to 36 international trading houses in order to assess the world-market availability of pharmaceutical chemicals essential in the treatment of diseases[1/] and/or demanded regularly in large quantities in developing countries. Informative, net f.o.b. unit prices were requested for specific amounts of pharmaceutical chemicals, packing included. Irrevocable and confirmed letter of credit was indicated as method of payment and delivery was requested in three months time. The quality had to conform to internationally used pharmacopoeias. Other conditions, such as price reference to dried substance, base or salt, etc. were also specified.

Eighteen replies have been received by the time of writing the study (annex 2), 17 from industrialized countries and one from a developing country. The replies are summarized in tables 4-9. These tables should be used together with annex 2 (pages 42 and 43) which is a directory of suppliers who have replied to our questionnaire. Unit prices quoted in German Marks or Swiss Francs were converted into $US at a rate of 1.9773 and 1.6465, respectively. Unit prices below $US 10 were given with two decimals, whereas those over $US 10 were rounded to one decimal. All unit prices refer to one kilogram of substance except in the case of hydroxocobalamin (cyanocobalamin) where the unit of mass is one gram, and of benzylpenicillin where it is one billion units (BU) approx. equivalent to 1.56 kg (potassium salt) or 1.62 kg (sodium salt) of penicillin G, respectively. All offers were made without patent-guarantee and one supplier stated that pharmaceutical chemicals "protected in a country by valid patent will neither be offered nor supplied to that country".

Table 4 is the most directly related to this study because the listed pharmaceutical chemicals are produced by organic chemical synthesis. No price information has been received so far for:

- clofazimine,
- diloxanide furoate,
- melarsoprol,
- metrifonate,
- oxamniquine,
- pentamidine, isetionate or mesilate, and
- retinol, microencapsulated.

3/ The Use of Essential Drugs, (Model List of Essential Drugs, Fourth Revision), WHO Technical Report Series 722, Geneva, 1985.

Table 4. Informative prices of essential pharmaceutical chemicals manufactured by organic chemical synthesis

Pharmaceutical chemical	No. of offers	FOB unit price, $US minimum	maximum	mean
1. Acetylsalicylic acid, crystalline	10	1.75	2.27	2.04
2. Acetylsalicylic acid, 100% granular	6	2.30	3.30	2.70
3 Ascorbic acid, powder	10	10.10	12.10	11.00
4. Ascorbic acid, film-coated granules	3	10.50	13.10	11.80
5. Caffeine, anhydrous	9	9.00	13.70	10.70
6. Chlorhexidine, digluconate	5	6.60	12.00	9.20
7. Chloroquine, fosfate	11	26.00	31.90	28.00
8. Chloroquine, sulfate	1	42.00	42.00	42.00
9. Chlorphenamine	2	42.00	45.60	43.80
10. Chlorpromazine, hydrochloride	6	38.00	44.50 a/	41.30
11. Cimetidine	7	62.50	80.40	70.30
12. Clofazimine	-			
13. Dapsone	4	17.50	22.00	19.40
14. Diazepam	7	38.30	75.00	50.20
15. Diethylcarbamazine, citrate	2	13.10	17.30	15.20
16. Diloxanide, furoate	-			
17. Ethambutol, hydrochloride	9	27.50	32.00	29.90
18. Furosemide	13	48.00	60.00	53.50
19. Indometacin	7	24.50	45.00	31.50
20. Isoniazid	8	9.90	12.00	10.50
21. Mebendazole	5	45.50	57.00	51.00
22. Melarsoprol	-			
23. Metrifonate	-			
24. Metronidazole	10	17.50	22.30	20.20
25. Methyldopa	7	95.00	123.90	105.70
26. Nicotinamide	3	7.60	8.80	8.20
27. Oxamniquine	-			
28. Paracetamol, powder	12	3.85	5.25	4.30
29. Paracetamol, directly compressible	7	4.40	6.30	5.30
30. Pentamidine, isethionate or mesilate	-			
31. Phthalylsulfathiazole	11	6.30	9.40	8.00
32. Piperazine, adipate	7	3.90	4.90	4.30
33. Piperazine, citrate	6	3.90	4.25	4.10
34. Promethazine, hydrochloride	5	36.00	44.00	41.80
35. Praziquantel	1	380.00	380.00	380.00
36. Primaquine, phosphate	4	56.50	86.00	70.20
37. Propranolol, hydrochloride	4	20.20	23.50 b/	21.90
38. Pyridoxine, hydrochloride	8	36.90	43.00	39.00
39. Riboflavin	8	46.50	65.70	54.80
40. Retinol, microencapsulated	-			
41. Sulfadiazine	9	11.00	13.00	11.90
42. Sulfadimidine	12	9.05	11.10	9.80
43. Sulfamerazine	7	12.60	17.00	15.50
44. Sulfamethoxazole	9	15.90	20.20	17.60
45. Suramin sodium	1	25.30	25.30	25.30
46. Thiamine, hydrochloride	8	32.90	36.00 c/	34.80
47. Thioacetazone	3	15.50	22.30	18.80
48. Trimethoprim	9	25.80	46.50	30.90

One offer of a/ $US 56, b/ $US 42, and c/ $US 43, resp., was disregarded in the statistical analysis because they were considered infrequent variations of the measurement of the same quality.

There are only a few retinol manufacturers and not all of them can produce microcapsules which is required for the production of solid pharmaceutical dosage forms. The remaining chemicals are considered as industrial opportunities that require further investigations.

Substances with three or less than three sources of supply have been classified as oligopolistic:

- ascorbic acid, film-coated granules
- chloroquine sulfate,
- chlorphenamine,
- diethylcarbamazine citrate,
- nicotinamide,
- praziquantel,
- suramin sodium, and
- thioacetazone.

Film-coated ascorbic acid improves the stability of vitamin C in solid pharmaceutical dosage forms but the difference in quality is usually not appreciated in tender evaluations. Nicotinamide is a component of multi-vitamin products and there is no real supply problem. Thioacetazone is a component of antituberculotic combinations and is of interest only in developing countries where the disease prevails. The other pharmaceutical chemicals of the group may offer industrial opportunities for local production.

Only seven suppliers replied to our question whether a given pharmaceutical chemical was traded internationally or not. The negative replies point exactly to the same substances for which no offer was received. It should be mentioned, however, that if a substance was qualified by one responder as a non-trade item but price information from another source was available, such substances were considered among the irregularly demanded chemicals.

The regularity of the demand by customers was also investigated. Five replies could be evaluated and the result of the survey is summarized in table 5. These data complement and facilitate the evaluation of information in table 4, although they do not reveal the cause of the irregular demand. As a result, it is difficult to judge which of the substances offer industrial opportunities for local production in developing countries. E.g., the geographic market orientation of the trading house could be one basic reason why sales of methyldopa or propranolol are much smaller in Africa than in Latin America. Similarly quinine is probably bought from rather than sold to developing countries. Whatever the case is, regular demand should be seen as a prerequisite for easy availability because scarcely sold pharmaceutical chemicals are not kept in stock by international trading houses.

Ampicillin in table 6 represents an opportunity in those countries where the demand for semi-synthetic penicillins is large and crude penicillin is available at competitive prices. The international trade of codeine is controlled by the Division of Narcotic Drugs of the United Nations. The present supply and production capacity of codeine is higher than the demand and this picture is not expected to change soon. The synthetic steps in the prednisolon synthesis offer an opportunity for local production in some developing countries.

Table 5. Pharmaceutical chemicals irregularly demanded in international trade

Pharmaceutical chemical	Supplier				
	1	2	3	4	5
Acetylsalicylic acid, 100% granular	+				
Ascorbic acid, film-coated granules	+	+		+	+
Benzylpenicillin, powder, sterile	+		+		
Chlorhexidine, digluconate		+	+	+	
Chlorphenamine			+	+	+
Chlorpromazine, hydrochloride				+	
Cimetidine				+	+
Codeine, fosfate			+		
Dapsone			+		+
Diazepam				+	
Diethylcarbamazine, citrate	+			+	
Erythromycin, stearate					+
Erythromycin, ethylsuccinate	+				+
Ethambutol, hydrochloride					+
Hydroxocobalamin (cyanocobalamin)			+	+	
Isoniazid				+	
Mebendazole	+				+
Methyldopa			+		+
Nicotinamide	+		+	+	
Paracetamol, directly compressible			+		
Piperazine, adipate				+	
Piperazine, citrate				+	
Praziquantel	+	+	+	+	+
Primaquine, fosfate			+		
Promethazine, hydrochloride				+	
Propanolol, hydrochloride			+	+	+
Pyridoxine, hydrochloride			+		
Quinine, sulfate			+		
Reserpine	+	+	+	+	+
Retinol, microencapsulated	+	+	+	+	+
Riboflavin				+	
Rifampicin					+
Suramin sodium	+	+	+	+	+
Thioacetazone	+	+	+		

Table 6. Informative prices of essential pharmaceutical chemicals manufactured by semi-synthetic methods

Pharmaceutical chemical	No. of offers	FOB unit price, $US minimum	maximum	mean
1. Ampicillin, trihydrate, powder	12	74.00 a/	88.00	77.50
2. Ampicillin, trihydrate, compacted	12	74.00	89.00	78.80
3. Codeine, fosfate	8	212.00	278.00	241.00
4. Prednisolone	8	800.00	1006.00	922.00

a/ One offer of $US 16 was disregarded in the statistical analysis because the discrepancy between this and the other 12 values was very high.

The pharmaceutical chemicals listed in tables 7 and 8 are not further discussed in this study because their total syntheses are not used for commercial production. It is worth mentioning, however, that the pharmaceutical chemicals in table 7 are demanded in large quantities also in developing countries whereas quinine (table 8) is mostly exported to industrialized countries and the demand for reserpine (table 8) has continuously been decreasing during the past decade.

Table 7. Informative prices of essential pharmaceutical chemicals manufactured by fermentation

Pharmaceutical chemical	No. of offers	FOB unit price, $US minimum	maximum	mean
1. Benzylpenicillin	5	36.40 a/	49.80	40.20
2. Erythromycin, stearate	9	70.60	78.00	75.40
3. Erythromycin, ethylsuccinate	7	120.00	140.00	126.60
4. Griseofulvin, micronized	5	56.00	85.00	71.00
5. Hydroxocobalamin (Cyanocobalamin)	4	4.55	5.06	4.84
6. Rifampicin	9	178.00	220.00	199.50
7. Streptomycin, sulfate, powder, sterile	8	25.00	28.20	26.60
8. Tetracycline, hydrochloride	10	23.50	35.00	26.50

a/ One offer of $US 25 was disregarded in the statistical analysis because it was considered an infrequent variation of the measurement of the same quality.

Table 8. Informative prices of essential pharmaceutical chemicals extracted from medicinal plants

Pharmaceutical chemical	No. of offers	FOB unit price, $US minimum	maximum	mean
1. Quinine, sulfate	5	75.00	96.10	86.80
2. Reserpine	1	285.00	285.00	285.00

Table 9 shows information on additional pharmaceutical chemicals kept in stock by international trading houses. The list contains essential and non-essential drugs and also pharmaceutical auxiliary substances which might be of interest to companies manufacturing and selling pharmaceutical preparations in developing countries.

Twelve of the responders were engaged in intermediate trade. Two did not have interest in these goods and four did not reply to this question.

4.3 Other sources of price information on pharmaceutical chemicals

The prices - charged by the producer or importer to the wholesaler or the pharmaceutical industry, excluding packaging, container and value added tax and converted into $US on current exchange rates - in table 10 are figures regularly produced by the Milan Chamber of Commerce and represent the top prices of certain pharmaceutical chemicals traded during November 1986, i.e., approximately at the time when the survey for this study was made. Except for indometacin and riboflavin, other top prices in table 9 are higher than the maximum prices in table 4 possibly because the Italian statistics reflect also purchases of affiliates from headquarters. Nonetheless, this source of information is very useful because it contains also informative prices for pharmaceutical chemicals not listed so far, e.g., allopurinol, doxycycline, gentamicin sulphate, etc. and the price trends of all substances are well reflected in the long-term time series of data.

The Chemical Market Reporter publishes spot prices for pharmaceutical organic chemicals on a weekly basis but these are not comparable with the current international prices and do not show the real price trend either.

The Indian Drug Statistics[4/] contain time series of Indian demand, production and trade data on pharmaceutical chemicals and some intermediates at the product level. As a result, historical trends can be analysed and opportunities for local production can easily be identified. The annual average unit prices can be calculated from these data which is usually an important information for market and sectoral researchers.

4/ Monitoring and Evaluation Drugs Section, Ministry of Chemicals and Fertilizers of the Government of India, New Delhi (annually).

Table 9. Informative prices of pharmaceutical chemicals not included in the survey

Pharmaceutical chemical	f.o.b. unit price DM	f.o.b. unit price $US
Aminophylline	15,-	7.60
Amiodarone	upon request	
Amoxycillin trihydrate, compacted	198,-	100.10
Ampicillin sodium, sterile	218,-	110.30
Calcium panthotenate	26,-	13.10
Chloramphenicol	75,-	37.90
Chloramphenicol palmitate	82,50	41.70
Chloramphenicol sodium succinate, sterile	148,-	74.80
Chlortetracycline hydrochloride	59,50	30.10
Clemizole	upon request	
Cloxacillin sodium, oral	220,-	111.30
Crotamiton	upon request	
Dequalinium chloride	upon request	
Dipyridamole	195,-	98.60
Erythromycine, base	199,50	100.90
Erythromycine estolate	163,-	82.40
Folic acid	250,-	126.40
Haloperidol	110,-	55.60
Iodine	36,-	18.20
Lithium carbonate	19,50	9.90
Mannitol	4,20	2.10
Metamizole (dipyrone)	14,-	7.10
Neomycine sulphate, base	122,-	61.70
Nystatin	60,50/bou	30.60
Oxeladine citrate	upon request	
Oxytetracycline, base	34,50	17.40
Oxytetracycline hydrochloride	37,80	19.10
Papaverine hydrochloride	115,-	58.20
Penicillin V acid	61,-/bou	30.90
Penicillin V potassium	70,-/bou	35.40
Phenolphtalein	14,-	7.10
d,i-Phenylpropanolamine	53,-	26.80
Piperazine, hexahydrate	5,50	2.80
Potassium iodide	28,50	14.40
Procaine hydrochloride	16,-	8.10
Rutin	70,-	35.40
Saccharine sodium	7,80	3.95
Scopolamine N-butylbromide	1.195,-	604.40
Sodium benzoate	1,95	1.00
Sulfadimidine sodium	21,50	10.90
Sulfadoxine	70,-	40.50
Sulfaguanidine	9,50	4.80
Sulfanilamide	8,20	4.15
Thiamine, mononitrate	66,80	33.80
Theophylline, anhydrous	16,30	8.20
Tolbutamide	13,50	6.80
Troxerutin, oral	165,-	83.40

DM ... German mark

Table 10. Italian pharmaceutical chemical prices ($US)

Pharmaceutical chemical	Unit price
Acetylsalicylic acid	6.11
Ampicillin trihydrate	118.41
Ascorbic acid	15.28
Benzylpenicillin	67.23
Hydroxocobalamin (cyanocobalamin)	6.11
Indometacin	42.02
Prednisolone	1,490.00
Pyridoxine hydrochloride	48.51
Riboflavin	62.64
Streptomycin sulphate	50.42
Tetracycline hydrochloride	35.90
Thiamine hydrochloride	41.63

Source: SCRIP No. 1174, 28 January 1987, p. 7

4.4 Conclusions

Publicly available statistical data on the demand and supply of pharmaceutical chemicals do not permit complete assessment of the world market in general, and on substance level in particular. Nevertheless, the general historical trends, the current situation and future prospects can be analyzed and rationally estimated in most cases.

The estimated value of the world market for pharmaceutical chemicals was about $US 10 billion in 1985. The share of the developing countries in the consumption was about 30 per cent whereas their share in production was probably less than 15 per cent.

The pharmaceutical chemical market is international in character and producers with a large domestic market, e.g., the United States, the Federal Republic of Germany, the People's Republic of China, India, etc. are also export-oriented.

The top 18 generic pharmaceutical chemicals contain relatively large volume and low-value synthetics whose therapeutic importance is high both in developing and in industrialized countries.

The active ingredients of expensive pharmaceutical preparations in industrialized countries are different from the top 18 generic pharmaceutical chemicals. Opportunities for the sales of patent-expired commodity pharmaceutical chemicals are limited in industrialized countries. The expensive chemicals are produced for captive use even after the product patent has expired, therefore, the supply of such chemicals to generic preparation manufacturers in industrialized countries is an export opportunity for developing countries.

Export-oriented pharmaceutical chemical manufacturers should also be aware of the industrial property and regulatory barriers of trade in the country of destination.

Many essential pharmaceutical chemicals are easily available on the world market and the price competition is intense, mainly among international trading houses.

A group of essential pharmaceutical chemicals used in the production of drugs required for the treatment of tropical diseases is not or is scarcely available in international trade.

Substances demanded in large quantities and/or having a high unit price, and their intermediates, should form another group of pharmaceutical chemicals for further study of the opportunities for local production.

Several pharmaceutical chemicals which were not included in the questionnaire used for the assessment of availability and prices, are nevertheless important candidates and have been included in the list below for the opportunities of local manufacture in developing countries.

The following pharmaceutical chemicals are scarcely or not available in international trade, or have a unit price higher than $US 25/kg, or are demanded in large quantities worldwide, or meet more than one of these criteria and should be studied in details.

Acetylsalicylic acid
Amiodarone
Chloramphenicol and esters/salts
Chloroquine sulfate
Chlorphenamine
Chlorpromazine hydrochloride
Cimetidine
Clemizole
Clofazimine
Crotamiton
Diazepam
Dequalinium chloride
Diethylcarbamazine citrate
Diloxanide furoate
Dipyridamole
Furosemide
Haloperidol
Indometacin
Mebendazole
Melarsoprol
Metrifonate
Methyldopa
Oxeladine citrate
Papaverine hydrochloride
Paracetamol
d,l-Phenylpropanolamine
Promethazine hydrochloride
Praziquantel
Primaquine fosfate

Pyridoxine hydrochloride
Riboflavin
Retinol, microencapsulated
Rutin
N-Scopolammonium bromide
Sulfonamides
Suramin sodium
Trimethoprim
Troxerutin

The number of substances will diminish after their manufacturing processes have been screened for possible inclusion in multiproduct and/or multipurpose plants.

International trading houses are the best sources of current prices on pharmaceutical chemicals. The public sources of price information contain important data for sectoral studies but they are of little use in the evaluation of the current market situation.

4.5 Recommendations

The international standardization and general breakdown of pharmaceutical production and trade statistics by pharmaceutical chemicals, intermediates, preparations and immunologicals should be considered as an issue for international co-operation.

5. DEMAND FOR PHARMACEUTICAL CHEMICALS IN DEVELOPING COUNTRIES

5.1 The pharmaceutical market in developing countries

The 1975-1986 time-series of data from the UNIDO sectoral database have been analysed by geographic regions[5/] including each country listed in Annex 1. Selected results are displayed in table 11.

Table 11. Pharmaceutical trade 1985 in developing countries

Country	PHC	PHI	PHIC	Consumption per head ($)
	million $			
Algeria	300	200	10	15
Egypt	1,000	160	63	22
Nigeria	700	120	7	8
Iran	800	120	52	18
Iraq	300	185	8	18
Saudi Arabia	410	350	23	33
Indonesia	350	90	70	2
Rep. of Korea	1,100	115	87	26
Philippines	250	50	20	5
Thailand	420	90	40	8

PHC ... pharmaceutical consumption
PHI ... pharmaceutical imports
PHIC .. pharmaceutical chemical imports

Table 11 shows all countries in the studied regions where the annual consumption of drugs was more than $US 250 million in 1985. The PHI/PHC ratio is low, therefore, the pharmaceutical preparation industry is well developed in Egypt, Indonesia, Iran, the Republic of Korea, Nigeria, the Philippines and Thailand. Algeria, Iraq and Saudi Arabia, on the other hand, depend on imports to a large extent.

The consumption trend 1975-1985 showed a continuous growth in Algeria, Egypt, Iran, Iraq, Nigeria, the Republic of Korea and Thailand. Saudi Arabia reached a maximum of $US 430 million in 1983 and has shown a stagnation since that year. The market in Indonesia and the Philippines peaked with $US 540 million and $US 405 million respectively in 1982 and has shown a continuous decrease since then.

The drug consumption per capita values can be considered as general maturity indicators of the market.

The available pharmaceutical production statistics are not broken down into preparations and chemicals but it is described in UNIDO documents that the pharmaceutical chemical production by organic synthesis is significant already in Egypt and the Republic of Korea. Production has been initiated also in Algeria, Indonesia, Iran and the Philippines.

5/ Sectoral working papers under publication.

5.2 Present demand

UNIDO documents[6] were summarily reviewed as potential sources of information on suitable pharmaceutical chemicals for local production by organic chemical synthesis in selected African and Asian developing countries.[7] The effective, estimated and forecast demand figures were extracted from the above documents and presented, in quantity or value terms, for analysis in a country-substance matrix. Values given in local currency were converted into $US at the annual average rate of exchange. International non-proprietary names were used and the anatomical therapeutic chemical (ATC) classification system[8] provided the common basis for the comparison of data. The figures had to be handled with care because the values referred to different years in different countries and reflected ex-factory, wholesale, retail and/or non-specified prices, respectively.

The pharmaceutical chemicals in table 12 meet the principal health criteria - effectiveness, safety and quality - because they are included in the WHO Model List of Essential Drugs and/or in official compendia regularly used in international trade. All these substances have been established in the therapeutical practice for several decades. The synthesis column shows the year in which the method of chemical preparation was first published.[9]

The 64 pharmaceutical chemicals were classified according to demand in two categories. The demand was considered significant when a given pharmaceutical chemical was consumed in more than eight countries, namely, acetylsalicylic acid, chloroquine, chlorpromazine hydrochloride, chlorpropamide, isoniazid, paracetamol, sulfadimidine and sulfamethoxazole. The demand for the following pharmaceutical chemicals fell in the moderate group (4 to 7 countries): acetazolamide, aminosalicylic acid, chloramphenicol, chlorothiazide, clioquinol, dapsone, ethambutol hydrochloride, furosemide, hydralazine, metronidazole, piperazine and its salts, propranolol, thiamine and trimethoprim. The remaining pharmaceutical chemicals were put in the low-demand category and not analysed any further.

Regional country-morbidity/mortality matrices were prepared in an attempt to analyse the spectrum of the drug demands against their therapeutic causes. The tables did not reveal much specific information due to the scarcity and inconsistence of available health statistics.

Demand for pharmaceutical chemicals is an important indicator of the opportunity for local production. Import statistics at substance level, however, show better the opportunity reach areas including the pharmaceutical intermediates (table 13). It should not be excluded in either case, of course, that domestic production exists but cannot satisfy demand and/or a pharma- ceutical chemical or intermediate is imported by a local company which does not wish or contractually cannot change supplier.

6/ Bibliography, pages 44 and 45.

7/ Annex 1, page 41.

8/ Guidelines for ATC classification, Nordic Council on Medicines, Box 607, S-751 25, UPPSALA, Sweden (1985).

9/ The Merck Index, 10th edition, Merck & Co. Inc., Rahway, (1983).

Table 12. Pharmaceutical chemicals produced by organic chemical synthesis and demanded in developing countries

	Substance	CAS Registry No.	Year of synthesis
1.	Acetazolamide	59-66-5	1951
2.	Acetylsalicylic acid	50-78-2	1853
3.	Aminophylline	317-34-0	1909
4.	Aminosalicylic acid	65-49-6	1889
5.	Amitriptyline, hydrochloride	549-18-8	1960
6.	Benzocaine	94-09-7	1895
7.	Bephenium, hydroxynaphthoate	3818-50-6	1959
8.	Calcium benzamidosalicylate	13898-58-3	...
9.	Chloramphenicol	56-75-7	1949
10.	Chlordiazepoxide	58-25-3	1959
11.	Chloroquine, fosfate	50-63-5	1939
12.	Chlorothiazide	58-94-6	1957
13.	Chlorpromazine, hydrochloride	69-09-0	1952
14.	Chlorpropamide	94-20-2	1958
15.	Clioquinol	130-26-7	1899
16.	Clofibrate	637-07-0	1961
17.	Clotrimazole	23593-75-1	1969
18.	Dapsone	80-08-0	1938
19	Diazepam	439-14-5	1961
20.	Diethylcarbamazine citrate	1642-54-2	1948
21.	Ephedrine, hydrochloride	299-42-3	1920
22.	Ethambutol, hydrochloride	1070-11-7	1961
23.	Furosemide	54-31-9	1962
24.	Guaifenesin	93-14-1	1912
25.	Hydralazine, hydrochloride	304-20-1	1949
26.	Hydrochlorothiazide	58-93-5	1958
27.	Indometacin	53-86-1	1963
28.	Isoniazid	53-85-3	1912
29.	Mebendazole	31431-39-7	1971
30.	Meprobamate	57-53-4	1951
31.	Metamizole	5907-38-0	1911
32.	Methyldopa	41372-08-1	1959
33.	Methylsalicylate	119-36-8	...
34.	Metronidazole	443-48-1	1960
35.	Nalidixic acid	389-08-2	1962
36.	Nicotinamide	98-92-0	1959
37.	Nicotinic acid	59-67-6	1925
38.	Nikethamide	59-26-7	1922
39.	Nitrofural	59-87-0	1947
40.	Nitrofurantoin	67-20-9	1952
41.	Oxyphenbutazone	7081-38-1	1956
42.	Paracetamol	103-90-2	1878
43.	Phenobarbital	50-06-6	1911
44.	Phenylbutazone	50-33-9	1951
45.	Phenytoin	57-41-0	1946
46.	Phenytoin sodium	630-93-3	1908
47.	Phthalylsulfathiazole	85-73-4	1943
48.	Piperazine	110-85-0	1893

Table 12. Pharmaceutical chemicals produced by organic chemical synthesis and demanded in developing countries (continued)

Substance	CAS Registry No.	Year of synthesis
49. Primaquine, phosphate	63-45-6	1946
50. Procainamide, hydrochloride	614-39-1	1953
51. Procaine, hydrochloride	51-05-8	1906
52. Propranolol, hydrochloride	318-98-9	1964
53. Propyphenazone	479-92-5	1934
54. Sulfadiazine	68-35-9	1940
55. Sulfaguanidine	57-67-0	1940
56. Sulfamerazine	127-79-7	1940
57. Sulfamethoxazole	723-46-6	1959
58. Sulfanilamide	63-74-1	1908
59. Sulfathiazole	72-14-0	1941
60. Theophylline	5967-84-0	1900
61. Thioacetazone	104-06-3	1946
62. Thiamine, hydrochloride	67-03-8	1926
63. Tolbutamide	64-77-7	1959
64. Trimethoprim	738-70-5	1962

Table 13. Selected pharmaceutical chemical and intermediate imports, Republic of Korea, 1985

Name	Imports		Derived unit price, $
	kg	$1000	
Pharmaceutical chemicals			
Acetylsalicylic acid, coated	63,600	561	8.80
N-Butylscopolammonium bromide a/	925	970	1,048.60
N-Butylscopolammonium bromide b/	594	486	818.20
Chlorpropamide	3,600	162	45.00
Clotrimazole	372	140	376.30
Econazole nitrate	566	113	199.60
Ketoconazole	911	820	900.10
Nalidixic acid	2,550	142	55.70
Pentoxifylline	850	203	238.80
Piroxicam	805	818	1,016.10
Prazosin	17	193	11,352.90
Ranitidine	1,020	1,862	1,825.50
Intermediates			
1-Amino-4-methylpiperazine	9,450	477	50.50
2,4-Dichloro-5-sulfamoylbenzoic acid	2,940	250	85.00
p,alfa-Dimethylbenzyl nicotinate	210	103	490.50

a/ Under the name of hyoscine-N-butyl bromide
b/ Under the name of scopolamine-N-butyl bromide

The selected sample of pharmaceutical chemicals in table 13 reflects a therapeutic demand characteristic of industrialized countries. Except for coated acetylsalicylic acid, derived unit prices extend from $US 45/kg to $US 11,350/kg, most of them being above $US 200/kg. It is interesting to note that N-butylscopolammonium bromide was imported under two different names and at significantly different unit prices.

The three intermediates in table 13 serve only to illustrate industrially attractive opportunities worth of further investigations. The market for pharmaceutical intermediates was valued at $US 3.5 billion in Western Europe in 1984.[10/]

Interesting information can also be found in secondary sources[11/] sometimes. ACDIMA (Arab Company for Drug Industries and Medical Appliances), among others, invited periodical price information from interested companies on sulfachloropyridazine, sulfaquinoxaline and sulfamethizole which are used mainly or exclusively in veterinary medicine but can be produced together with the human sulfonamides both from technical and regulatory points of view.

5.3 Screening by current price

The population of pharmaceutical chemicals in tables 4 and 10 was screened using an arbitrarily set minimum unit price of $US 25/kg as the criterion to yield the following list: chlordiazepoxide ($US 55/kg),[12/] chloroquine fosfate, chlorphenamine, chlorpromazine hydrochloride, cimetidine, clotrimazole ($US 70/kg), diazepam, ethambutol hydrochloride, furosemide, indometacin, mebendazole, methyldopa, nalidixic acid ($US 90/kg), promethazine hydrochloride, praziquantel, primaquine phosphate, pyridoxine hydrochloride, riboflavin, suramin sodium, thiamine hydrochloride, trimethoprim.

Data from table 9 were also taken into account but they were given less weight in the opportunity analysis because the prices originated from a single source. Nevertheless, amiodarone, chloramphenicol and esters/salts, clemizole, crotamiton, dequalinium chloride, dipyridamole, folic acid, haloperidol, oxeladine citrate, papaverine hydrochloride, d,l-phenyl- propanolamine, rutin, sulfadoxine, thiamine mononitrate and troxerutin will have to be further analysed.

Semisynthetic substances such as amoxycillin, ampicillin sodium and N-scopolammonium bromide are also worth consideration because their unit price is between $US 100/kg and $US 600/kg.

5.4 Conclusions

UNIDO's computerized pharmaceutical database and documents have been found an important source of market research information on drugs used in developing countries. Product-specific import lists were the best sources to identify opportunities for local production of pharmaceutical chemicals.

10/ SCRIP No. 905, 13 June 1984, p. 10.

11/ SCRIP No. 935, 26 September 1984, p. 22.

12/ Prices in brackets were obtained through personal communication.

Sixty-four pharmaceutical chemicals were identified as possible candidates for local production by organic chemical synthesis in the studied African and Asian developing countries. Twenty-one drugs were found to have a demand that warrants analysis of production possibilities in multiproduct and multipurpose plants.

Thirty-three synthetic pharmaceutical chemicals had a unit price of $US 25.00/kg, or above.

Interesting complementary information was found in SCRIP World Pharmaceutical News.

5.5 Recommendations

Identified opportunities for the domestic production of pharmaceutical chemicals should be discussed with potential investors in all countries listed in table 11 as well as with ACDIMA which sponsors a number of pharmaceutical plants in various Arab countries to arrive at jointly agreed project proposals for the establishment of multiproduct and multipurpose plants.

6. TECHNICAL FEASIBILITY OF PRODUCTION OF PHARMACEUTICAL CHEMICALS

The manufacturers of pharmaceutical chemicals and intermediates extend from small domestic producers to the largest international chemical companies in the world.

The small producers tend to exploit short-term demand-supply opportunities or concentrate on those segments of the market which are not attractive for large companies, e.g., small volume, relatively large value off-patent pharmaceutical chemicals and/or intermediates.

The strategies of the major pharmaceutical chemical manufacturers contain many elements that help to maintain market dominance even after the product patent has expired. Synthesis routes using starting materials, intermediates or side-chains with limited availability and controlled or no other end use are typical examples. Specialization in dangerous chemistry (e.g., diketene, hydrocyanic acid, or phosgen) and technically difficult chemical conversions (e.g., separation of optical isomers) or both (hydrogenation, nitration, extremely low temperature reactions, etc.) are other examples to support the above statement.

Most processes used in the production of pharmaceutical chemicals are multiconversion syntheses. Warrantees for technical and economic parameters apply only to the plants where the process was scaled up. Any technical modification of the process, including transfer of technology, requires reconsideration of the whole production system. The possible process safety consequences of any change should be given special attention and implemented only after it has been approved at highest management level in order to prevent accidents and to establish liabilities.

Quality, process safety and environmental protection should be built into the production system from plant design stage to everyday operation. The importance of the continuous training of personnel in safety matters cannot be overstressed. Manufacturing documentation should be such as to permit tracing the history of each batch in detail.

All the above statements hold true also for the production of pharmaceutical intermediates.

Investment and operational costs depend to a large extent on the selected production strategy.

Commercial scale production units usually produce several pharmaceutical chemicals in multiproduct and/or multipurpose plants.

6.1 Multiproduct plants

The multiproduct plant is a large scale industrial unit which serves a single purpose: the technically and economically feasible production of pharmaceutical chemicals. The production processes carried out in such plants have a common starting material, and/or common or similar key intermediates, or common basic unit conversions and represent the maximum feasible degree of backward integration and the highest level of chemical engineering. Some conversions, e.g. Kolbe-Schmidt carboxylation, are carried out only in multiproduct plants. Manufacturing technology has been developed on the basis of

several years of own experience or has been purchased at commercial scale level. Machinery and equipment are selected to meet best the requirements of particular processes and may include continuous or special reactors to serve only a single production line which, however, may permit the manufacture of several chemicals. Vessels designed for sophisticated conversions are frequently fully automatic. The established capacities, e.g., nitration or hydrogenation or carboxylation, are convertible only to a limited extent. Concepts such as low-waste or no-waste technologies, e.g. reconversion of acetic acid into acetic anhydride in the synthesis of acetylsalicylic acid apply only to multiproduct plants where the majority of pharmaceutical chemicals is produced.

Some technical data of the multiproduct plant illustrated in figure 1, will indicate selected dimensions of the concept:

Annual capacity

Acetylsalicylic acid	600 tons
Paracetamol	400 tons
Methylsalicylate	180 tons
Methylparaben	30 tons
Propylparaben	10 tons

Operation time: 300 working days, 3 shifts per day

Annual utilities requirement

Steam	5,750 tons
Power	2,600 mWh

Annual material requirement

Phenol	1,120 tons
Sodium hydroxide (100%)	320 tons
Sulphuric acid (96%)	1,010 tons
Acetic anhydride	776 tons
Sodium nitrite	500 tons
Sodium sulphide (60%)	1,140 tons

Estimated total reactor capacity: 120 m^3

Production plant area: 54 m x 36 m

Indoor storage area: 48 m x 24 m

Administration and service facilities: 40 m x 20 m and 40 m x 30 m

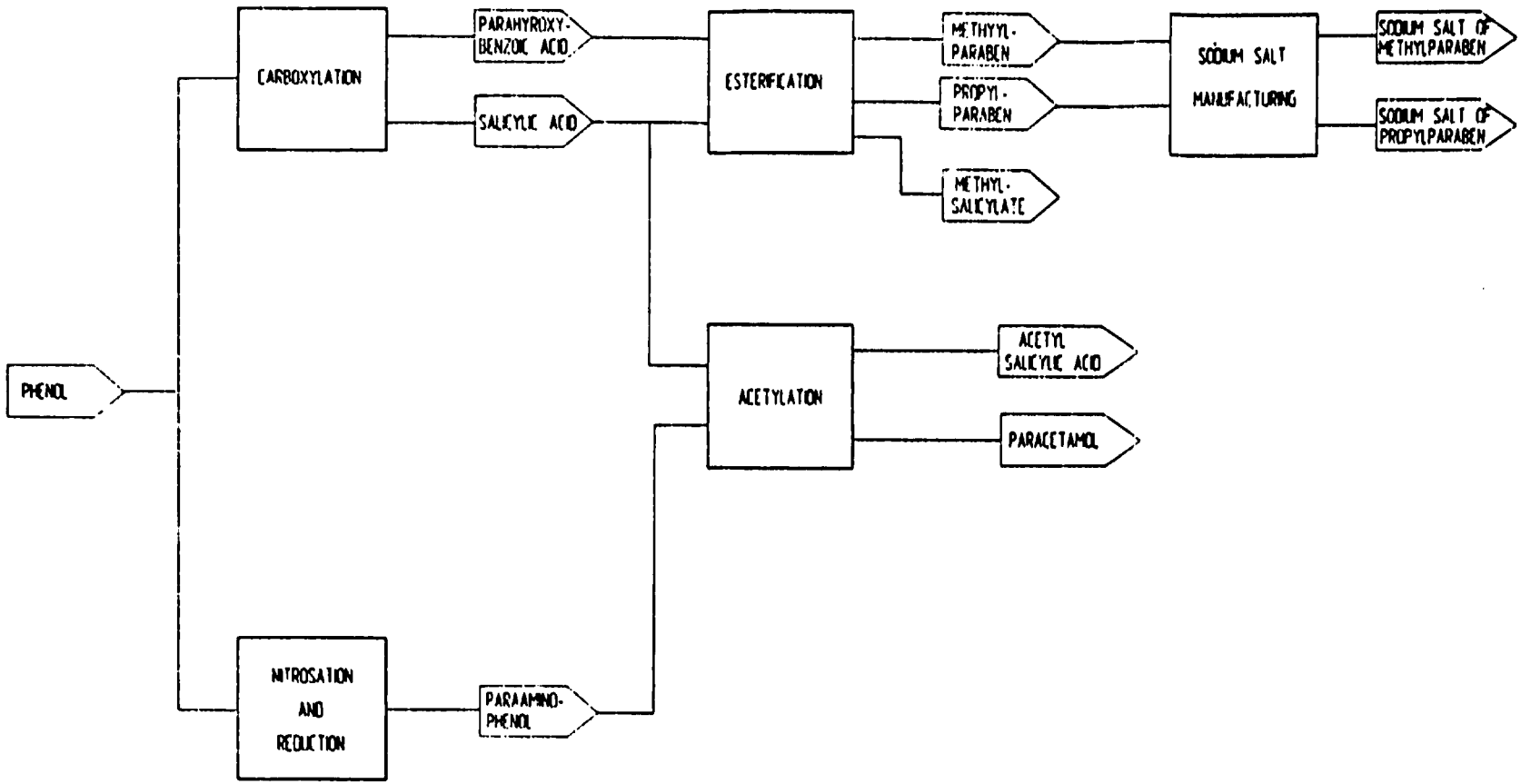
Effluent treatment: 16 m x 16 m

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

Staff requirement

Management	: 5
Production	: 10
Maintenance	: 5
Quality control	: 3

Figure 1. Block diagram of the acetylsalicylic acid and paracetamol multiproduct plant[a/]



a/ Technical information package on multiproduct plant, Nobel Chematur AB, Karlskoga, Sweden (1986).

The multiproduct plant in figure 1 shows the chemical logics of the concept. The manufacture of the two principal end-products, acetylsalicylic acid and paracetamol, are based on phenol as the main starting material and, to a lesser extent, on acetylation as the common unit conversion. The same plant can produce salicylic acid, sodium salicylate, and p-hydroxybenzoic acid -an intermediate for fungicides and dyes- and p-aminophenol, an intermediate for sodium aminosalicylate and dyes, without additional investment. Two anti-fungal agents, methylparaben and propylparaben, their sodium salts and methyl-salicylate can also be produced at minimum additional cost. The experience gained from the carboxylation, nitration and reduction reactions would strongly affect selection of future candidates for local production. Hence, the multiproduct plant concept is based on the similarity of the manufacturing technology of pharmaceutical chemicals, intermediates and auxiliary substances produced on a commercial scale.

6.2 Multipurpose plants

The multipurpose plant is a small-scale production unit which has also research, development and training functions.

The chemical line of the production unit consists of multipurpose batch reactors. They are flexible to produce pharmaceutical chemicals as needed, therefore, plant capacity is not a clear concept.

The multipurpose plant is the choice of preference for the manufacture of expensive pharmaceutical chemicals required in relatively small amounts mainly on the domestic market. This statement is debateable because the analysis of the Indian pharmaceutical statistics reveals that pharmaceutical chemicals such as chlorpropamide, paracetamol, phthalylsulfathiazole, sulfamethoxazole and trimethoprim are manufactured, to a significant and sometimes dominant extent, in small-scale production units. Neither the definition of the small scale is clear nor the degree of backward integration is specified in the original document but the very coexistence of multiproduct and multipurpose plants in the same country is not surprising because this has been the usual structure also in many industrialized countries. It is interesting, however, that about 94 per cent of paracetamol and 64 per cent of trimethoprim are produced on the small scale because both of these pharmaceutical chemicals are usually manufactured in multiproduct plants. Whatever the cause in India may be, it might exist in other developing countries, as well.

Eventual exports are usually destined to the surrounding countries. Low-cost and labor intensive processes are generally given preference to automation and mechanization. The smooth technical operation of the plant and changing over to the manufacture of new pharmaceutical chemicals often depends on the expertise of a few managers and skilled operators.

The multipurpose plant provides material for animal toxicity studies and formulation research and development of pharmaceutical preparations. Impurities arising from the chemical synthesis as well as metabolites produced after administration of the drug for pharmacological tests are also prepared in the multipurpose plant. Pharmaceutical chemicals for clinical trials can also be synthetized in the multipurpose plant provided they will regularly be manufactured there or if the quality standard is identical with that of large-scale production.

Research chemists usually produce relatively small quantities of new compounds for pharmacological screening with little regard to the efficiency and potential hazards of the processes they use. An important target for the process development chemist is therefore the full techno-economic evaluation of the alternative routes of synthesis, e.g., the improvement of efficiency of chemical reactions, the minimization of impurities in the pharmaceutical chemical, and the adaptation of processes to use available equipment. New compounds might result not only from new products but also from new process development, e.g., when the technology is developed from literature descriptions or purchased on a laboratory scale. Eventual production problems are also scaled down here in order to find solutions quickly and in the most economic way.

The multipurpose plant has important techno-economic functions when a chemical process is scaled up or licenced and process parameters are required for the investment feasibility study. Data such as reproducibility of the process, step-by-step yields, conversion cost estimates, etc. can only be obtained from the analysis of own production experience. The assessment of the process is extended, of course, to the whole assembly rather than to individual steps and/or machines and includes environment pollution, solvent recovery, labour safety, regulatory, in-process and quality countrol as well as economic and training aspects of the studied technology.

The multipurpose plant is operated in three shifts hence different cost elements, e.g., manufacturing costs, including overheads, working capital requirement, etc. can accurately be estimated.

Technical staff and skilled workers are also trained in such plants.

All these activities taken together result in the proper documentation of domesticated chemical technologies which on the other hand, is the principal requirement of quality assurance and future exports to many industrialized countries.

The difference between a conventional pharmaceutical pilot plant and a multipurpose plant is that the weight of the production function is dominant in the latter.

6.3 Technical feasibility of the production of pharmaceutical chemicals demanded in developing countries

Reference processes or competitive syntheses[13/] were selected for each pharmaceutical chemical demanded in the studied developing countries. The chemical reactions of each process were analysed to identify potentially hazardous (inflammable, explosive, corrosive or toxic) materials, to establish the different degrees of backward technological integration and to reach the stage where the starting materials are possibly all commodity petrochemicals freely available in international trade. Preliminary conclusions have been drawn from the chemical reactions on the level of complexity of technology, equipment demand, process and labour safety, environment pollution and unusual utility requirements.

13/ Kleemann, A. and Engel, J.: Pharmazeutische Wirkstoffe, Georg Thieme Verlag, Stuttgart - New York (1982).

Starting materials, key intermediates and side chains were also identified during the analysis but their international availability or prices were not surveyed.

The results of the above analysis permitted the classification of the pharmaceutical chemicals into two categories, namely those that should be produced either in multiproduct plants or in multipurpose plants. It should be noted, however, that standard processes for technological analysis were selected from reference manuals and might not represent the best commercially proven synthesis route to-day. Relevant chemical research and development activities were not studied either. Other considerations, e.g., the linkage to a given intermediate, might also affect the choice of process preference in a given country.

Table 14 shows a possible division of pharmaceutical chemicals by production in multipurpose and multiproduct plants. The main criterion was whether in the pharmaceutical industry a given conversion is carried out in multipurpose batch reactors and equipment generally available in chemical plants, or not. Any synthesis consisting of more than five conversions was considered practically non-manageable in a multipurpose plant, even if the chemical reactions could have been carried out in multipurpose batch reactors. Availability of common utilities such as water, steam, electricity and cold energy has been assumed in both cases.

The classification in table 14 depends on the selected reference process, or details thereof, in many cases. For example, Isoniazid[14/] can be manufactured in a multipurpose plant from 4-cyanopyridine by a Pinner-type amide formation. Isoniazid can also be produced in multipurpose plants from 4-picoline via oxidation by potassium permanganate, but the process should be carried out in a multiproduct plant if nitric acid is used as the oxidizing agent or if catalytic or electrolytic oxidation is chosen for the conversion of 4-picoline into isonicotinic acid. This problem is unavoidable as long as there are competing synthesis routes and conversion options. Reactor volume can also be the decisive criterion of multipurpose/multiproduct plant choice.

Table 14. Production options of pharmaceutical chemicals demanded in developing countries

Pharmaceutical chemical	Frequency of demand	Starting material(s) in	
		Multipurpose plant	Multiproduct plant
1. Acetylsalicylic acid	10	Salicylic acid	Phenol
2. Paracetamol	10	4-Amino-phenol	Phenol, Benzene
3. Sulfonamides	10	p-Acetamidobenzene-sulfonyl chloride	Aniline, Acetanilide
4. Chlorpromazine	9	2-Chloro-phenothiazine and 3-Dimethyl-aminopropylchloride	m-Substituted diphenylamine

14/ Technical and economic analysis of the manufacture of Isoniazid, UNIDO/IS.622, Sectoral studies series No. 24, 27 March 1986, p. 60.

Table 14. Production options of pharmaceutical chemicals demanded in developing countries (continued)

Pharmaceutical chemical	Frequency of demand	Starting material(s) in Multipurpose plant	Multiproduct plant
5. Isoniazid	9	(a) 4-Picoline (b) Isonicotinic acid (c) 4-Cyanopyridine	4-Picoline
6. Chloroquine	8	4,7-Dichloroquinoline and Novoldiamine	3-Chloroaniline and Novoldiamine
7. Chlorpropamide	8	4-Chlorobenzene-sulphonamide	Chlorobenzene
8. Propanolol	7	1-Naphthol	Naphthalene
9. Aminosalicylic acid	6	not applicable	3-Amino-phenol
10. Hydralazine	6	1-Chloro-phthalazine	Phthalic anhydride
11. Chloramphenicol	5	2-Aminodiol	4-Nitro-acetophenone
12. Chlorothiazide	5	6-Amino-4-chloroben-zene-1,3-disulfamide	3-Chloroaniline
13. Dapsone	5	4,4'-Bis-[acetamido]-diphenylsulfone	Acetanilide
14. Metronidazole	5	2-Methyl-5-nitro-imidazole	2-Methyl-imidazole
15. Acetazolamide	4	2-Acetylamino--5-mercapto-1,3,4-thiadiazole	2-Amino-5-mercapto-1,3,4-thiadiazole
16. Clioquinol	4	not applicable	2-Aminophenol
17. Ethambutol	4	d,l-2-Amino-1-butanol	
18. Furosemide	4	4,6-Dichloro-3-sulfa-moylbenzoic acid and furfurylamine	2,4-Dichloro-benzoic acid
19. Piperazine salts	4	Piperazine	
20. Thiamine	4	not applicable	Acetonitrile
21. Trimethoprim	4	4-(2-Dimethylamino-ethoxy)-benzylamine and 3,4,5-Trime-thoxybenzoylchloride	4-Hydroxy-benzaldehyde

In practice, the choice might be facilitated by the availability of 4-cyanopyridine or by the generally known high price of potassium permanganate as an oxidizing agent. The main conclusion from this argumentation is that laboratory and literature options and pilot plant level processes should be separated from commercial scale reference syntheses and the latter should be analysed in sufficient details in order to select the alternative which gives the best economic result in a given country. Data for such analysis are made available by the transferor of technology or could be obtained from experiments in the own multipurpose plant.

6.4 Conclusions

Pharmaceutical chemical production is an important element of the business strategy both at the small scale and commercial scale levels.

The various parts of manufacture, e.g., production, technology development, labor and process safety, environment protection, process economics, quality control, etc. sections should be seen as a system. Any change recommended by one section, e.g., adaptation of purchased technology to local conditions, should only be implemented after agreement has been secured from all parts of the system.

Large volume pharmaceutical chemicals should be produced in multiproduct plants which represent the highest technical, economic and social level of art at the time of their establishment. Such plants give the highest degree of self-sufficiency and their operation results in specialization in chemical high technology on the long run. Export-oriented manufacturers should opt for this version.

The multipurpose plant is preferred for the production of small volume chemicals, particularly to fill demand-supply gaps in domestic markets. The technical flexibility is also a technical constraint of the plant. E.g., choice of the manufacturing process and/or economically optimum degree of backward integration might be limited by the practicability of carrying out certain unit conversions in multipurpose batch reactors.

Additional benefits are derived from the chemical research, development and training functions of the multipurpose plants which are particularly important for manufacturers that rely on their own development and/or transfer of technologies for their production.

In some instances, there is no clear borderline between multiproduct and multipurpose plants, e.g., when a multipurpose plant is mainly used for the commercial scale production of a few chemicals in large multipurpose batch reactors.

The choice of the process might also be limited by the (local) availability of starting materials, key intermediates and/or side-chains for a particular process.

6.5 Recommendations

The pharmaceutical chemical production strategies should be studied in more details because this is the largest technical constraint for export-oriented manufacturers in developing countries.

The technical feasibility study of the production of pharmaceutical chemicals in multiproduct and/or multipurpose plants should be extended to all drugs included in the WHO Model List of Essential Drugs and their therapeutic equivalents to establish a database for UNIDO's technical co-operation programme with developing countries.

7. OPPORTUNITIES FOR THE PRODUCTION OF PHARMACEUTICAL CHEMICALS IN DEVELOPING COUNTRIES

7.1 Pharmaceutical chemicals selected for further analysis

Eleven pharmaceutical chemicals essential in the treatment of diseases prevailing in developing countries and not or scarcely available in international trade are listed in pages 7 and 9 of this report. Other compounds included in the list on pages 15 and 16 are also worthy of consideration for various reasons.

Pharmaceutical chemicals with a unit price higher than $US 25/kg at the end of 1986 were listed on page 21.

Table 14 lists 21 pharmaceutical chemicals which are required in many of the studied developing countries. The degree of backward integration of organic chemical synthesis in multiproduct and multipurpose plants is also indicated.

All the above candidates for local production could not be studied within the frame of this report, therefore, a sample was taken to represent the whole population.

Table 15 shows 10 substances identified to meet the most important health, industrial and social criteria. Sulfonamides represent a large group of pharmaceutical chemicals. Two members of the group, sulfadimidine and sulfamethoxazole, showed significant demand, whereas sulfadoxine and salazosulfapyridine have a special therapeutic importance in developing countries. Sulfamethoxazole is official in the WHO model list of essential drugs in combination with trimethoprim and sulfadoxine in combination with pyrimethamine, therefore, the inclusion of sulfonamides in the representative sample automatically meant the selection of their therapeutic partners.

The numbers in table 15 indicate the criteria for selection as follows:

1. Official in the WHO model list of essential drugs
2. Included in the WHO list of drugs for primary health care
3. Significant demand in developing countries
4. Significant demand also in industrialized countries
5. Important therapeutic sub-market in developing countries
6. High unit price
7. Non-availability or limited availability in international trade.

Number in brackets show technical relation to the pharmaceutical chemical in the table to which the number refers.

Table 15. First list of pharmaceutical chemicals for production in developing countries

No.	Pharmaceutical chemical	Reasons for selection
1.	Acetylsalicylic acid	1, 2, 3, 4 (4)
2.	Chloroquine	1, 2, 3, 6, 7a
3.	Clotrimazole	1b, 3, 4, 5, 6, 7
4.	Paracetamol	1, 3, 4, (1)
5.	Pentamidine	1, 3, 6, 7
6.	Praziquantel	1, 3, 6, 7
7.	Pyrimethamine	1, 3, 6, (9)
8.	Salicylic acid	1, 2, 3, 4 (1)
9.	Sulfonamides	1, 3, 4
10.	Trimethoprim	1, 3, 4, 6 (9)

a ... the sulfate salt only
b ... miconazole is the example of the therapeutic group

7.2 Future demand

A demand-supply profile was prepared for each pharmaceutical chemical[15/] included in table 15 to assess the therapeutic prospects of these drugs by the year 2000.

Acetylsalicylic acid, chloroquine, paracetamol, salicylic acid and thimethoprim have been put in the category of large volume commodity chemicals with stable future demand worldwide, but chloroquine mainly in developing countries. Sulfonamides would pertain to this group, however, most single compounds show a decreasing demand trend in industrialized countries and only the antibacterial combination with trimethoprim seems to have a significant but saturated market worldwide. The situation is different in developing countries where the ability of the consumer to pay plays sometimes the most important role. Therefore, a population growth-rate increasing demand seems to be a reasonable assumption in these countries. The antimalarial combination of sulfadoxine with pyrimethamine sells mainly in developing countries. Pyrimethamine is also a commodity chemical but its sales volume is relatively small and unit price is high.

Clotrimazole, a specialty chemical, is one of the leading antifungal drugs both in developing and industrialized countries. Demand is continuously increasing. Unit price is high and the substance is not or scarcely available in international trade.

Pentamidine and praziquantel are specialty chemicals used in the treatment of diseases -leishmaniasis, trypanosomiasis and schistosomiasis- prevailing in developing countries. Pentamidine seems to be less attractive than praziquantel for domestic production but the latter is still under patent protection and in the clinical trial stage in many countries. Demand for praziquantel is high and continuously increasing; its unit price is high and the substance is scarcely available in international trade.

15/ Sectoral working paper under publication.

7.3 Production alternatives

Reference processes were selected for each pharmaceutical chemical not included in table 14 and the same method of analysis was used as the one described in pages 27 to 30. The sulfonamide group was studied at specific product levels. Sulfadimidine and sulfamethoxazole showed a significant demand in developing countries. Salazosulfapyridine, sulfacetamide sodium and sulfadoxine were added to the list because they are official in the WHO model list of essential drugs. The group of antibacterial sulfamides was completed with phthalylsulfathiazole, sulfadiazine, sulfaguanidine, sulfamerazine and sulfathiazole because there is a stable market for these substances in developing countries. Sulfathiazole and particularly sulfaguanidine are also intermediates for other sulfa-drugs. Figure 2 shows the block diagram of the sulfonamide multiproduct plant. The sulfonylurea-type hypoglycemic agents, namely acetohexamide, carbutamide, chlorpropamide, glipizide, glibenclamide, tolazamide and tolbutamide and a group of diuretics, namely chlorothiazide, furosemide and hydrochlorothiazide represent additional options resulting from the availability of production facilities for antimicrobial sulfonamides. Strictly speaking, the world sulfonamide means the $-SO_2NH_2$ group. But pharmaceutical chemicals containing such functions, e.g., acetazolamide, were not considered for manufacture if their synthesis route was not similar to that of the above listed substances.

The possibilities for outlining multiproduct plants have not been exhausted. Chemical structure and conversion similarities suggest the manufacture of ethionamide, isoniazide, nicotinic acid, nicotinamide, nikethamide and prothionamide in another multiproduct plant. Chloroquine could have been considered together with amodiaquine, chlorquinaldol, cinchocaine, dequalinium chloride, hydroxychloroquine, etc. The same side chain, imidazole, is used in the manufacture of clotrimazole, metronidazole and miconazole. Pyrimethamine may conveniently be produced together with pyrantel, sulfadiazine and trimethoprim because of the similarity of side-chain conversions. Another possible approach would be to use aniline as the common starting material to produce, e.g., appropriate sulfonamides, benzocaine, procainamide and practolol in the same plant.

Pentamidine was not analysed technically because of the negative conclusion of future demand. The processes for the manufacture of praziquantel are patent protected in many countries, therefore, their chemical analysis was excluded from the multiproduct plant approach.

The demand versus process analysis can and should be iterated in the preparation of an investment feasibility study but the main purpose of this document was to describe the methodology of selection rather than to arrive at a global chemical production programme. The additional analysis of the remaining 40 opportunities could, however, result in specific multiproduct plants and in a model multipurpose plant that should only be modified to accommodate demand requirements at national level.

Acetylsalicylic acid, chloroquine, paracetamol, salicylic acid, sulfonamides and trimethoprim are usually produced in multiproduct plants.

Figure 2. Block diagram of the sulfonamide multiproduct plant

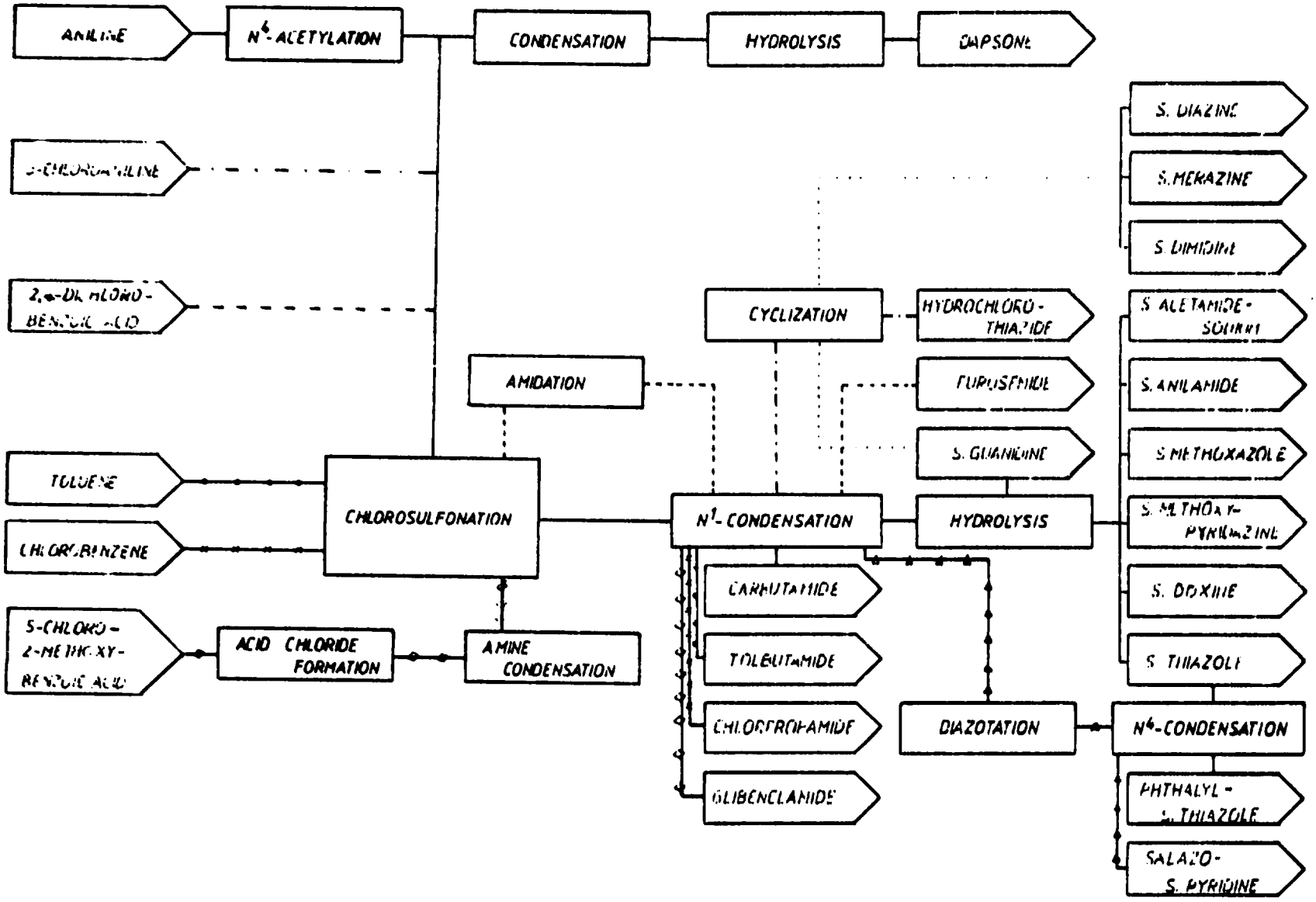


Table 16 shows a technical approach to the production of pharmaceutical chemicals in multipurpose plants. Items given medium and high technical priority should be considered together with other opportunities for domestic production. The economic priority of low technical value syntheses, e.g., clotrimazole, might be high and economic feasibility can only be determined at national level.

Table 16. Production of priority pharmaceutical chemicals in multipurpose plants

Pharmaceutical chemical	Starting material(s)	Technical priority
Acetylsalicylic acid	Salicylic acid	low
Chloroquine	4,7-Dichloroquinoline +Novoldiamine	low
Clotrimazole	2-Chlorotriphenylmethyl chloride + Imidazole	low
Paracetamol	4-Aminophenol	low
Pentamidine	4-Cyanophenol	medium
Praziquantel	1-Aminomethyl-1,2,3,4-tetrahydroisoquinoline and Cyclohexancarbonyl chloride	high
Pyrimethamine	4-Chloro-benzylcyanide	high
Salicylic acid	not applicable	
Antibacterial sulfonamides	sulfonamide intermediate total synthesis	low-medium high
Sulfonylureas	sulfonamide intermediate total synthesis	low-medium high
Sulfonamide-diuretics	sulfonamide-intermediate + side chain total synthesis	low-medium high
Trimethoprim	3,4,5-trimethoxy-benzaldehyde	high

7.4 Conclusions

The first list of pharmaceutical chemicals for production in developing countries has been selected to reflect health, technical, economic and social criteria and to a limited extent, also export possibilities to industrialized countries.

The future demands for the selected 10 pharmaceutical chemicals were estimated significant and stable, except in the case of sulfonamides where individual members of the antibacterial group show decreasing forecasts in industrialized countries and a mature or slowly growing market in the Third World. The therapeutic prospects of the oral diuretic and hypoglycemic sulfonamides are good worldwide and markets in developing countries are gaining importance. This trend is expected to continue.

Large volume commodity chemicals such as acetylsalicylic acid, chloroquine, paracetamol, sulfonamides and trimethoprim affect imports to developing countries also on the long run. Their domestic production should be considered in multiproduct plants and a different set of criteria might be applicable for the evaluation of the economic feasibility of local production.

Clotrimazole and praziquantel are industrially attractive opportunities for production. Clotrimazole has also an export potential to industrialized countries. Praziquantel is used in the treatment of schistosomiasis, therefore, local production would presumably result in a regular supply of an essential drug in developing countries.

7.5 Recommendations

The technical and economic aspects of the manufacture of the 10 selected pharmaceutical chemicals should be analyzed in sufficient details to permit the choice of commercially best synthesis routes, to identify process specific barriers to entry, to analyze process economic consequences of the different degrees of backward integration.[16/] UNIDO projects should be considered for the establishment of multipurpose plants in Algeria, Indonesia, the Philippines and Thailand. Feasibility studies should be prepared for the establishment and/or rehabilitation of multiproduct plants in the Arab and ASEAN countries as well as in Iran, Nigeria and the Republic of Korea.

The opportunity research for the establishment and/or expansion of multipurpose or multiproduct plants for the manufacture of pharmaceutical chemicals should be extended to include other developing countries and additional substances.

Special attention should be paid to pharmaceutical chemicals needed mainly in developing countries and to those which can be exported to generic markets in industrialized countries.

Alternative industrial policies to stimulate and/or support pharmaceutical chemical production in the start up period should be described from the experience of successful developing countries.

16/ A methodology of analysis has been described in the following studies: UNIDO/IS.518 (chloroquine), Sectoral studies series No. 17, UNIDO/IS.588 (ethambutol), Sectoral studies series No. 21, and UNIDO/IS.622 (isoniazid), Sectoral studies series No. 24.

8. ALTERNATIVE STRATEGIES FOR DEVELOPING COUNTRIES

The main criteria for the establishment of a domestic market-oriented pharmaceutical chemical industry include:

(a) A growing pharmaceutical preparation market of $US 250 million per year for multipurpose and $US 1,000 million per year for multiproduct plants.

(b) The share of the domestic production in the local consumption of pharmaceutical preparations should be 70 per cent or higher.

(c) Domestic or regional availability of basic industrial chemicals.

(d) Continuous availability of basic industrial infrastructure such as power, water, sewage, etc. systems.

(e) Availability of highly qualified managers with extensive experience in pharmaceutical and chemical industry marketing.

(f) The quality of the locally produced pharmaceutical chemicals should meet, in all respects, the requirements of the dosage form manufacturers.

(g) An industrial policy which supports domestic production in the first 10 years of operation and stimulates exports to industrialized countries on the long run.

The main strategic goals of pharmaceutical chemical manufacturers without forward integration to the prescription preparation market are to produce pharmaceutical chemical substances and intermediates with a consistent high quality, to introduce quickly new pharmaceutical chemicals to the domestic market, to produce at competitive costs and to build up and maintain the image of a reliable supplier. Profitability is the overall criterion of investment in the private sector, whereas a project is usually considered attractive in the public sector if it is technically feasible, socially desirable and economically acceptable on the short run and profitable on the long run.

Developing countries are becoming more and more important markets for drugs, therefore, new capacities should be established there. This is particularly important in the case of pharmaceutical chemicals which are used in the treatment of diseases prevailing in developing countries such as malaria, schistosomiasis, leprosy, filariasis, etc. An additional strategic objective of pharmaceutical chemical manufacturers in developing countries is to exploit opportunities on the domestic and regional markets to the maximum extent, in particular in the start up period.

8.1 Multiproduct plants

This strategy is the preferred choice in the pharmaceutical industry. It makes the investor most independent from other pharmaceutical chemical manufacturers because the starting materials are commodity chemicals available from multiple sources. Several decades of own experience in commercial-scale organic synthesis or total transfer of technology and continued co-operation with the transferor for a few years is the preliminary condition for the establishment of multiproduct plants. Procurement efficiency as well as process and sales management are the key factors of success. Forward inte-

gration into dosage form production and sales is required rather than desired. Investment costs are the highest with this option; industrial infrastructure requirements are high; labour safety and environment protection needs serious consideration in plant design. In-process control, eventually automated, is a usual feature. Good quality control of inputs, intermediates and outputs is essential. Experience in international sales is very useful.

The multiproduct plant is the recommended strategy in those developing countries where the domestic pharmaceutical market is large, the petrochemical industry has been or is being developed and the current or future demand represents stable and long-term imports for given pharmaceutical chemicals. Among the studied countries, the Arab countries as a group and Nigeria appear to be promising candidates for an acetylsalicylic acid-paracetamol and sulfonamide multiproduct plants. Expansion and/or modernization of the existing production units may also be considered in Egypt.

8.2 Multipurpose plants

The multipurpose plant is frequently the first strategic step in the establishment of a pharmaceutical chemical industry. The main objectives are to gain experience in the management of organic chemical syntheses and to recover operational expenses through the prompt exploitation of domestic market opportunities such as being the first generic supplier of expensive pharmaceutical chemicals required in small quantities. Other important functions include research, development and training.

The flexibility of the plants limits the production volume and possibilities of backward process integration, therefore, dependence on key intermediate suppliers is higher in this case than with the multiproduct plants. On the other hand, investment is considerably smaller.

All countries for multiproduct plants are also candidates for multipurpose plants, particularly as the initial step in the establishment of a pharmaceutical chemical industry. Emphasis on production and training function at the beginning may be changed to research and technical development at a later stage.

The multipurpose plant is the choice of strategy in those developing countries where the preparation-making industry is well developed and the annual domestic market for pharmaceuticals falls in the range of 250 to 1,000 million dollars.

8.3 Custom synthesis

Dosage form manufacturers can secure supply of pharmaceutical chemicals also through customs synthesis, particularly in those cases when a patent-expired specialty chemical is required in small quantities and the substance is not available in international trade. This strategy can also be used with key intermediates of limited sources of supply. Clotrimazole appears to be a good example for customs synthesis to start generic competition on the preparation market in all the studied developing countries.

8.4 Research and development

There is no domestic chemical manufacturing strategy in countries with product patent protection. The discovery of new syntheses, independent from the routes claimed in the registered process patents, is a strategy that had successfully been used also in industrialized countries before the product patent system was adopted.

Opportunities in countries without patent protection include also the domestic development of chemical processes described in the technical literature.

8.5 Purchase of pharmaceutical chemicals

The choice of strategic options would not be complete without considering the continued purchase of pharmaceutical chemicals, particularly those easily available in international trade and at competitive prices and when the prospective long-term domestic demand does not justify the consideration of import substitution as a criterion of economic feasibility.

Annex 1

to the study of

OPPORTUNITIES FOR THE MANUFACTURE OF

PHARMACEUTICAL CHEMICALS IN DEVELOPING COUNTRIES

Selection of developing countries

UNIDO region No. 8: North Africa

Algeria	Morocco
Egypt	Sudan
Libyan Arab Jamahiriya	Tunisia

UNIDO region No. 9: Tropical Africa

Kenya	Zimbabwe
Nigeria	

UNIDO region No. 10: West Asia

Bahrain	Qatar
Iran	Saudi Arabia
Iraq	Syrian Arab Republic
Jordan	Turkey
Kuwait	United Arab Emirates
Lebanon	Yemen Arab Republic
Oman	Democratic Yemen

UNIDO region No. 12: East Asia

Area of Hong Kong	Singapore
Korea, Rep. of	Taiwan Province of China
Philippines	Thailand

UNIDO region No. 13: South East Asia

Brunei	Malaysia
Indonesia	

Annex 2

to the study of

OPPORTUNITIES FOR THE MANUFACTURE OF

PHARMACEUTICAL CHEMICALS IN DEVELOPING COUNTRIES

Directory of suppliers and international trading houses dealing with pharmaceutical chemicals

1.	ALKALOID Chemical Pharmaceutical Cosmetic Industry Bul. E. Kardelja 12 SRM, SFR 91000 SKOPJE P.O.B. 575 Jugoslavija	Telex: YU ALKAID 51-104, 51-440 Cable: ALKALOID Skopje Phone: 63-441
2.	ARCHEMIA S.r.l. Via Pagliano 21 20149 MILAN Italy	Telex: 331238 Cable: ARCHEMIA MILANO Phone: (02) 4988211/2/3
3.	AVRACHEM AG Gartenstrasse 12 6340 BAAR Switzerland	Telex: 864 996 Phone: (042) 31 83 55
5.	CHEMAPOL A.S. Kodanská 46 100 10 PRAHA Czechoslovakia	Cable: CHEMAPOL PRAHA Phone: 715
6.	CHEMEX GmbH Endresstrasse 121 1238 WIEN Austria	Telex: 132863 chex a Phone: 02 22/88 55 91
4.	CIECH - Centrala Importowo-Eksportowa ul. Jasna 12 skr. poczt. 271 (P.O. Box 271) 00-950 WARSZAWA Poland	Telex: 814561 Cable: CIECH WARSZAWA Phone: 26-90-01, 26-90-31
7.	DANGSCHAT AUSSENHANDELS GMBH Frankenstrasse 35 P.O. Box 10 12 24 2000 HAMBURG 1 Federal Republic of Germany	Telex: 2 12 501 dang d Cable: dangschattrade Phone: (040) 23 30 41
8.	DOLDER LIMITED Immengasse 9 P.O. Box CH-4004 BASEL Switzerland	Telex: 62306/63048 Cable: DOLDERAG Basel Phone: (061) 576600

9. FERRO Metal and Chem. Corp. Ltd.
179 Kings Road
READING, RG1 4EX
United Kingdom

Telex: 847295
Phone: 0734-591961

10. ICC HANDELS GMBH
Pharma-Department
Neuer Wall 19
D-2000 HAMBURG 36
Federal Republic of Germany

Telex: 2 163 814 icc d
Cable: Eurochem
Phone: (040) 35 00 17 # 27

11. K & K-GREEFF LIMITED
International Trade
Suffolk House, George Street
CROYDON, CR9 3QL, Surrey
United Kingdom

Telex: 28386 (KKGRF G)
Phone: 01-686 0544

12. KARL O. HELM AKTIENGESELLSCHAFT
Nordkanalstr. 28
P.O. Box 103060
D-2000 HAMBURG 1
Federal Republic of Germany

Telex: 2170150
Cable: HELMEXPORT
Phone: (040) 2375-0

13. MEDIMPEX
Hungarian Trade Co. for
Pharmaceutical Products
Vörösmarty tér 4
P.O. Box 126
H-1808 BUDAPEST 5
Hungary

Telex: 22-6571
Phone: 182-1808

14. PHARMACHIM
16, Illiénsko Chausée
SOFIA
Bulgaria

Telex: 22-097, 22098
Cable: PHARMACHIM
Phone: 38-55-31

15. RANBAXY Laboratories Limited
International Division
Devika Tower, 10th Floor
6, Nehru Place
110019 NEW DELHI
India

Telex: 031 66375
Cable: RANBAXY
Phone: 6437078-81 (4 lines)

16. SIBER HEGNER Raw Materials Ltd.
Wiesenstrasse 8
CH-8022 ZURICH
Switzerland

Telex: 55 84 33
Phone: (01) 2567 349

17. SIEMSGLUSS & Sohn
P.O. Box 10 56 24
D-2000 HAMBURG 1
Fed. Rep. of Germany

Telex: 2 162 199 + 2 162 667
Cable: Vitachemie Hamburg
Phone: (040) 23 21 21-9

18. TOCELO Chemicals BV
Helvoirtseweg 9
5261 Ca VUGHT
The Netherlands

Telex: 50739 tcl nl.
Telefax: 073-568162
Phone: (073) 56 68 34

Bibliography

1. Abstracting and updating services

Chemical Abstracts Service, a Division of the Americal Chemical Society, 2540 Olentangy River Road, P.O. Box 3012, Columbus, Ohio 43210, United States

Specialty Chemicals, continuing multiclient program, SRI (Stanford Research Institute) International (333 Ravenswood Avenue, Menlo Park, California 93025, United States)

Index of Drug Chemicals, a continuing multiclient program, IMS (Intercontinental Medical Statistics), 11-13 Melton Street, London, NW1 2EH, United Kingdom

2. UNIDO documents

Assessment of the pharmaceutical industry 1978-2000. A report for the global preparatory meeting on pharmaceuticals (UNIDO/ICIS/146, 1980)

The availability, terms and conditions for the transfer of technology for the manufacture of essential drugs (ID/WG.331/5, 1980)

Choice and adaptation of appropriate technology in production of drugs and pharmaceuticals in developing countries. Background paper to the International Forum on Appropriate Industrial Technology, New Delhi/Anand, India, November 1978. (ID/WG.282/93)

Etablissement d'un plan directeur de développement de l'industrie pharmaceutique en Algérie (UC/ALG/85/062, 1985)

Feasibility study on local drug manufacture in Zambia by Polytechna-Spofa, Czechoslovakia, (DP/ZAM/78/008, 1980)

Global study of the pharmaceutical industry (ID/WG.331/6, and ID/WG.331/6/Add.1, 1980)

How to conduct a realistic marketing, economic and financial study of the growth potential of a pharmaceutical industry in a developing country (ID/WG.37/10, 1969)

International Report on the Second Consultation on the Pharmaceutical Industry, Vienna, 1982

Issues that might be considered at the First Consultation on the Pharmaceutical Industry. Paper prepared for the Global Preparatory Meeting for Consultations on the Pharmaceutical Industry, Cancun, Mexico (ID/WG.317/1 and ID/WG.317/1/Corr.1, April 1980)

The pricing and availability of intermediates and bulk drugs (ID/WG.331/4, 1980)

Production plan for the Arab pharmaceutical industry in selected Arab countries. Vol. I. General aspects. Vol. II. Drugs and pharmaceuticals (TF/INT/77/017, TF/INT/76/030, VC/INT/76/077, 1978)

Project report for the establishment of a pilot multipurpose plant for the manufacture of pharmaceutical chemicals in Nicaragua (DP/NIC/83/004), prepared by Vishwakarma Process Technik Pvt. Ltd., India

Realization of chemical projects in developing countries. Case study (ID/WG.60/7 and SUMMARY, 1970)

Report. First Consultation on the Pharmaceutical Industry, Lisbon, (ID/WG.331/10/Rev.1 1980)

Report. Second Consultation on the Pharmaceutical Industry, Budapest, (ID/WG.393/19, 1983)

Reports on drugs from the national drug list which because of their essentiality could be produced in the developing countries (ID/WG.267/5, March 1978)

Restrictive clauses in the licensing agreements in the pharmaceutical industry (ID/WG.405/5, 1983)

Some conditions and prerequisites for establishing pharmaceutical industry in developing countries (ID/WG.37/12, 1969)

Technical consultation on the production of drugs in a multipurpose plant. Budapest, 1982 (unpublished)

Technical and economic analysis of the manufacture of chloroquine phosphate. Sectoral studies series No. 17, 1985 (UNIDO/IS.518)

Technical and economic analysis of the manufacture of ethambutol hydrochloride Sectoral studies series No. 21, 1985 (UNIDO/IS.588)

Technical and economic analysis of the manufacture of isoniazid. Sectoral studies series No. 24, 1985 (UNIDO/IS.622)

Technical profiles for the production of dosage forms (ID/WG.393/14/Rev. 1, 1985)

Transfer of technology through the establishment of a multi-purpose pilot plant in Iran, (DP/IRA/83/014, DP/ID/SER.A/600) (restricted)

Water use and effluent treatment practices for the manufacture of the 26 priority drugs in the UNIDO illustrative list, 1983 (UNIDO/IS.387)

Ways of ensuring adequate supplies of chemical intermediates required for the production of drugs in developing countries (ID/WG.267/2, 1978)

Manufacture of paracetamol (project proposal) (BGD/119/V/86-01, 1986)

Several unpublished country reports

3. Other publications

ESCAP (Economic and Social Commission for Asia and the Pacific). The pharmaceutical industry in ASEAN countries. Proceedings of a consultation. Bangkok, May 1980

Leading international generics substances worldwide, IMS, (1985)

The Merck Index, 10th Edition, Merck & Co., Inc., Rahway, N.J., United States (1983)

Future prospects for the fine chemical business, Ecoplan International, 10 rue Joseph Bara, Paris 75006, France

Nordic statistics on medicines 1981-83. Guidelines for ATC classification. Part III. NLN Publication No. 16, Nordic Council on Medicines, UPSALA, Sweden

Kleemann, A. and Engel, J., Pharmazeutische Wirkstoffe (Pharmaceutical active ingredients), 2nd Edition, Georg Thieme Verlag Stuttgart - New York (1982)

For the guidance of our publications programme in order to assist in our publication activities, we would appreciate your completing the questionnaire below and returning it to UNIDO, Studies and Research Division, Sectoral Studies Branch, D-2073, P.O. Box 300, A-1400 Vienna, Austria

---

Q U E S T I O N N A I R E

Opportunities for the manufacture of pharmaceutical chemicals in developing countries

		(please check appropriate box) yes	no
(1)	Were the data contained in the study useful?	/_/	/_/
(2)	Was the analysis sound?	/_/	/_/
(3)	Was the information provided new?	/_/	/_/
(4)	Did you agree with the conclusion?	/_/	/_/
(5)	Did you find the recommendations sound?	/_/	/_/
(6)	Were the format and style easy to read?	/_/	/_/
(7)	Do you wish to be put on our documents mailing list?	/_/	/_/
		If yes, please specify subjects of interest	
(8)	Do you wish to receive the latest list of documents prepared by the Sectoral Studies Branch?	/_/	/_/
(9)	Any other comments?		

Name:
(in capitals) .....

Institution:
(please give full address) .....

Date: .....