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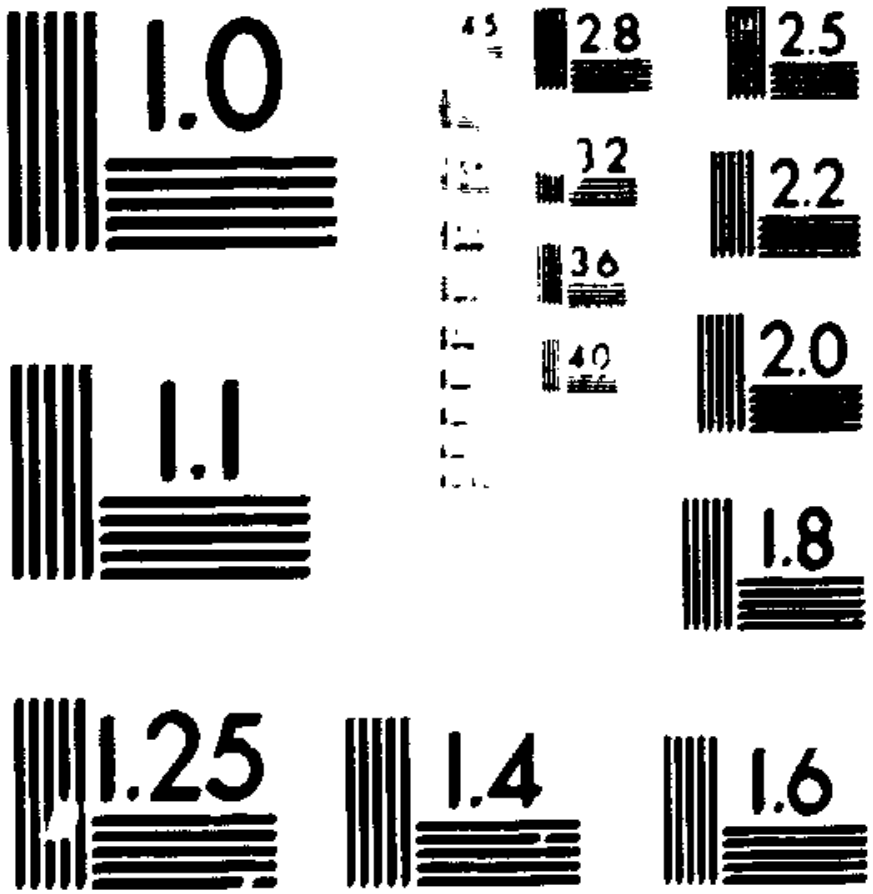

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TECHNICAL AND ECONOMIC ANALYSIS OF THE MANUFACTURE OF CHLOROQUINE PHOSPHATE

Sectoral Studies Series
No.17

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Barna Mezey

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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.

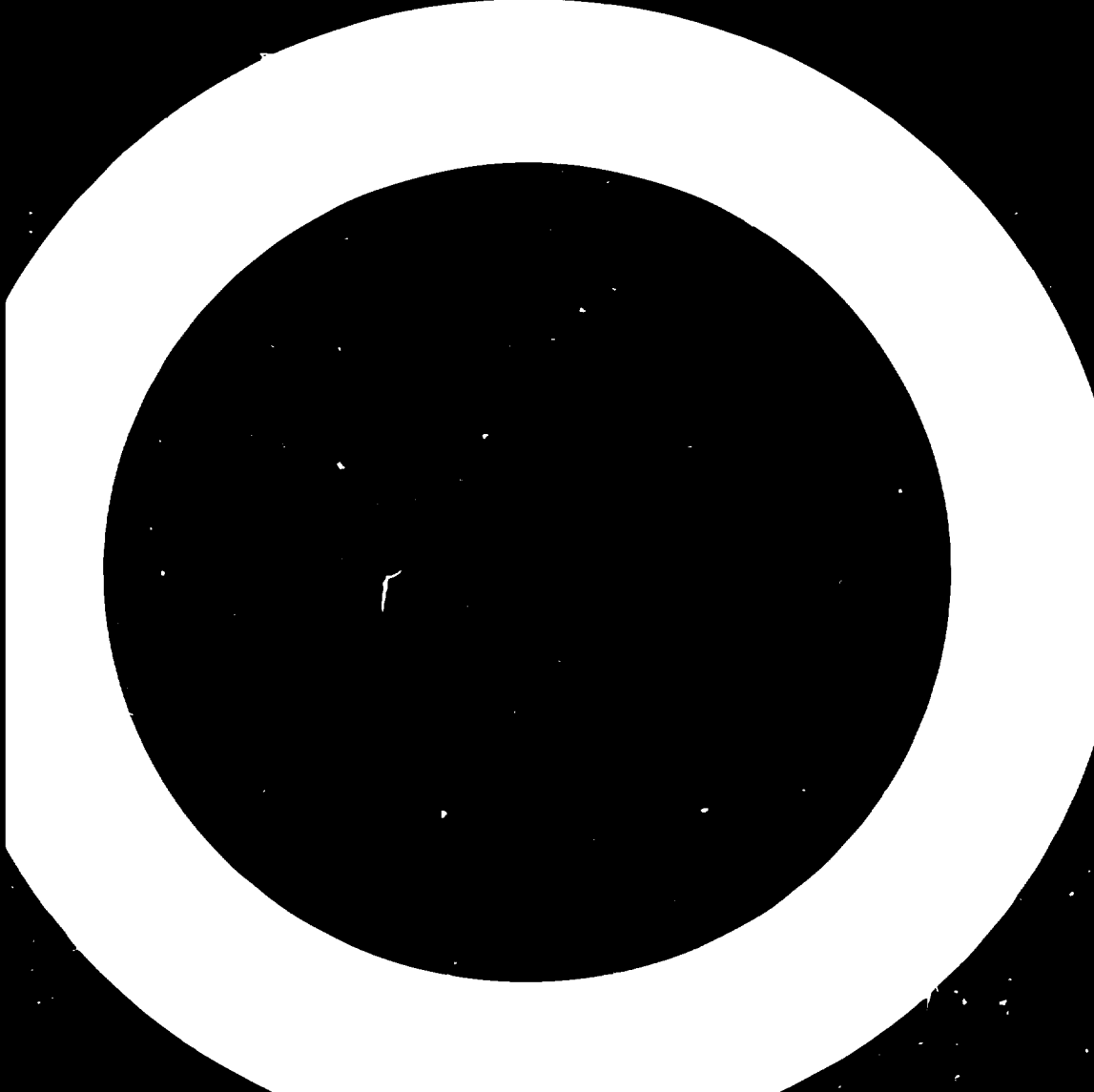
This document presents major results of work under the element Studies on Pharmaceutical Industries in UNIDO's programme of Industrial Studies 1984/85.

Preface

This study addresses the problem of the decision-making in the process development for the manufacture of drugs by organic chemical synthesis. It discusses in detail some of the important factors which must influence the initiation and conduct of a typical development programme as well as the final selection of pharmaceutical chemicals and their intermediates for such programmes. Technical feasibility and economic viability must be carefully evaluated prior to the initiation of such a programme or the purchase of a particular technology.

This subject has been studied because of its industrial importance and social benefits to developing countries. CHLOROQUINE Phosphate was selected as a first case study because of the health importance of the drug in the prophylaxis and therapy of malaria. Research is continued with further case studies on acetylsalicylic acid, ethambutol and isoniazid which, together with this study, will serve as the basis for a generalized decision-making study.

The Sectoral Studies Branch wishes to acknowledge the contribution of Professor Barna Mezey, Budapest Technical University, Hungary, for the provision of essential information and for his comments and criticism in the course of this work.



Contents

Tables

Figures

EXPLANATORY NOTES

Prices and market values are given in United States dollars.

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 financial year.

Use of hyphen between dates (e.g., 1980-2000) indicates the full period involved, including the beginning and end years.

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 have been used in this study:

CAS Chemical Abstracts
WHO World Health Organization
EMME Ethoxy Methylene Malonic acid diEthyl ester
DEM DiEthyl Malonate
TEOF TriEthyl OrthoFormate

KEY WORDS

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

1. Basic patent is the patent which describes first (a) a new process and the product/s/ prepared by this process, or (b) a new product or products prepared by known processes.

2. Chemical input conversion coefficient is the number of units of a chemical input required for the production of 1 unit of a chemical output.

3. Convertible currency saving is the difference between the world-market price of 1 kg of the pharmaceutical chemical and the cost of imported materials to produce the same, both expressed in $US, disregarding the single US dollar expenditure of the investment and those elements of the conversion costs, e.g. energy, that might also have to be paid in United States dollars.

4. Integrated CHLOROQUINE manufacturer is a producer that synthetizes its 4,7-dichloroquinoline starting from DEM, TEOF and m-chloroaniline, or from a more advanced degree of backward integration.

5. Key intermediate is a chemical input which plays a dominant role in the direct material costs.

6. Model is a representation of an actual phenomenon such as an actual system or process.

7. Pharmaceutical chemical is a chemical substance used as the active ingredient of drug products.

8. Yield: is the real quantity of a chemical output, expressed as percentage of the theoretical quantity of the same chemical output with reference to a specified chemical input.

1. INTRODUCTION

UNIDO has drawn up an illustrative list of pharmaceutical chemicals and intermediates for local production in developing countries. This list furnishes a basis for countries to identify their own priorities and to make their own selection. The present case study on CHLOROQUINE Phosphate intends to illustrate some important technical and economic factors, which affect the decision-making process of selecting potential candidates for local production by organic chemical synthesis.[1/]

This study provides basic information that should be taken into account also when operating and expanding a CHLOROQUINE Phosphate production plant, but it should not be interpreted as a feasibility or pre-feasibility study. Plans for actual investment would of course require in-depth engineering and financial studies.

The study has been organized so that the syntheses of chemicals and the relevant patent information as well as the lists of manufacturers and suppliers are given in the annexes, whereas the technical and economic aspects of the production are analysed in chapters 5 to 9.

The technical levels of the studied technologies of CHLOROQUINE Phosphate and key intermediates were estimated by comparing quantitative parameters, such as chemical conversion coefficients and yields and by analysing the brief descriptions of the chemical processes.

The process economics of CHLOROQUINE Phosphate production were assessed taking into account three cost factors:

- Key intermediates,
- Direct material inputs, and
- Conversion costs.

1/ To be followed by similar studies on Acetylsalicylic acid, Ethambutol and Isoniazid.

Costs of key intermediates and direct material inputs were calculated by using the chemical conversion coefficients of the technology studied and annual average import prices of materials in different countries in 1982.

In the analysis, an overall estimate variable has been used for the conversion costs which approximates the real costs of a large producer in a developing country.

2. OBJECTIVES OF THE STUDY

The main objective of the study is to outline a sectoral decision-making model which can be used in the production programme research stage of the pre-investment phase of the project development cycle to generate technically feasible and economically promising, or at least acceptable, ideas and to transform them into broad investment propositions.

To this effect, an attempt has been made to assess available sources of technical and economic microdata for the manufacture of CHLOROQUINE Phosphate and its intermediates, and to illustrate what can be done with the available information. Advantages and disadvantages of alternative strategies as a function of backward integration of the manufacturing process are described.

It is hoped that this work will assist interested developing countries in the evaluation of offers for transfer of technology in the pharmaceutical sector.

3. BACKGROUND AND HISTORY

CHLOROQUINE, synthetized in Germany as early as 1934, was rediscovered and became widely used during World War II. CHLOROQUINE has kept its leading role among the antimalarials ever since, because in the acute malarial attack it rapidly controls parasitemia and clinical symptoms. CHLOROQUINE is well tolerated and no therapeutic or toxic synergism is manifested when it is administered with primaquine.2/

The basic patent and most of the process patents have expired. Only nine patents have been granted for the manufacturing process of CHLOROQUINE and its key intermediates during the past 17 years (annex 3).

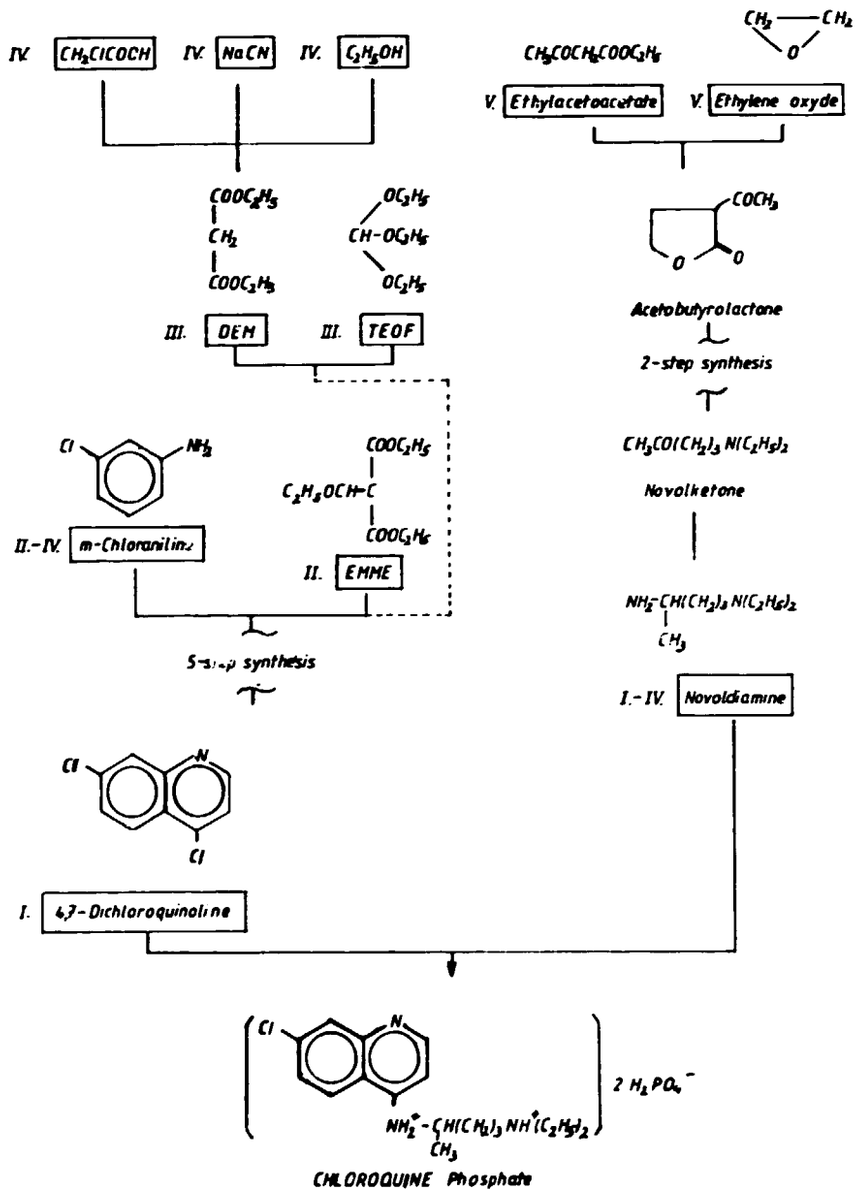
CHLOROQUINE was chosen for a case study because of its health and economic importance to malaria-affected developing countries where demand is not always satisfied due to financial and distributional constraints. About 1,300 tons of CHLOROQUINE are sold annually world wide. The total value to manufacturers is some $US 35 million per year and the total retail value falls in the region of $US 70 million, assuming that manufacturers' price amounts to 50 per cent of the selling price.

2/ Goodman and Gilman, "The Pharmacological Basis of Therapeutics", VIth Edition, Macmillan Publishing Co. Inc., New York (1980), p. 1043.

4. METHODOLOGY OF THE ANALYSIS OF PROCESS ECONOMICS

The manufacturing technology of CHLOROQUINE Phosphate is illustrated in figure `

Figure 1. Schematic illustration of the studied process of CHLOROQUINE Phosphate synthesis



---- Alternative route

The step-by-step technical and economic details were not always available, therefore the manufacturing process under analysis was considered as a single-step chemical reaction.

For example, the optimum degree of backward integration of the chemical synthesis analysed in this study was described by the following equation:

$$C_6H_6ClCN + C_2H_3ClO_2 + NaCN + C_7H_{16}O_3 + H_2O +$$
$$127.57 \qquad 94.50 \qquad 49.01 \qquad 148.20 \qquad 18.02$$

$$POCl_3 + C_9H_{22}N_2 + 2H_3PO_4 =$$
$$153.33 \qquad 158.29 \qquad 196.00$$

$$= C_{18}H_{32}ClN_3O_8P_2 + 3C_2H_6O + CO_2 + HPO_2 +$$
$$515.87 \qquad 138.21 \qquad 44.01 \qquad 63.98$$

$$+ Cl_2 + HCl + NH_3 + NaCl$$
$$70.91 \qquad 36.46 \qquad 17.03 \qquad 58.44$$

which permitted the calculation of overall molecular input conversion coefficients in spite of the fact that such a reaction does not take place in the real manufacturing process.

4.1 Data

The chemical formulae of CHLOROQUINE Phosphate, intermediates and raw materials were taken from different sources. The molecular weights were taken from the United States Pharmacopeia or calculated by using atomic weights recommended by the International Union of Pure and Applied Chemistry in 1978, and the results were rounded up to two decimals (table 1).

Table 1. Definition of important chemicals used in the manufacture of CHLOROQUINE Phosphate

Name	Chemical formula	Molecular weight
CHLOROQUINE Phosphate	$C_{18}H_{32}ClN_3O_8P_2$	515.87
4,7-Dichloroquinoline	$C_9H_5Cl_2N$	198.05
Phosphoric acid	H_3PO_4	98.00
EMME	$C_{10}H_{16}O_5$	216.23
DEM	$C_7H_{12}O_4$	160.17
Chloroacetic acid	$C_2H_3ClO_2$	94.50
Sodium cyanide	NaCN	49.01
Ethanol	C_2H_6O	46.07
TEOF	$C_7H_{16}O_3$	148.20
m-Chloroaniline	C_6H_6ClN	127.57
Novoldiamine	$C_9H_{22}N_2$	158.29
Novolketone	$C_9H_{19}NO$	157.26
Hydrobromic acid	HBr	80.91
Diethylamine	$C_4H_{11}N$	73.14
Acetylbutyrolactone	$C_6H_8O_3$	128.13
Ethylacetoacetate	$C_6H_{10}O_3$	130.14
Ethylene oxide	C_2H_4O	44.05

Table 1 does not contain data of reactants and products which are used in reactions not evaluated separately during the analysis of backward integration of CHLOROQUINE Phosphate production.

The molar input conversion coefficient, F, was calculated by dividing the molecular weights of the chemical with that of CHLOROQUINE Phosphate.

Table 2. Chemical input conversion coefficients and percentage yields of two hypothetical CHLOROQUINE Phosphate producers

Name	F	f_1	y_1	f_2	y_2
4,7-Dichloroquinoline	0.38	0.54	70	0.47	81
Phosphoric acid	0.38	0.66	58	0.58	66
EMME	0.42	0.93	45	0.74	57
DEM	0.31	0.68	46	0.12[a/]	60
Chloroacetic acid	0.18	0.66	27	0.34[a/]	53
Sodium cyanide	0.10	0.25	40	0.18[b/]	56
Ethanol	0.18	1.65	11	0.86[b/]	21
TEOF	0.29	0.67	43	0.51[a/]	57
m-Chloroaniline	0.25	0.53	47	0.40	63
Novoldiamine	0.31	0.51	61	0.41	76
Novolketone	0.30	0.54	56	0.42	71
Hydrobromic acid	0.16	0.42	38	0.33	49
Diethylamine	0.14	0.36	39	0.28	50
Acetobutyrolactone	0.25	0.71	35	0.55	46
Ethylacetoacetate	0.25	1.22	21	0.95	26
Ethylene oxide	0.09	0.73	12	0.57	16

a/ Literature data

b/ Estimated values

Chemical input conversion coefficients and/or yields refer basically to the same technology, hence data from different sources[3/] were pooled and the simple arithmetic average was taken for the average performer (f_1 and y_1 values), whereas the best conversion coefficients achieved in practice (f_2 and y_2 values) were used to describe an ideal performer.

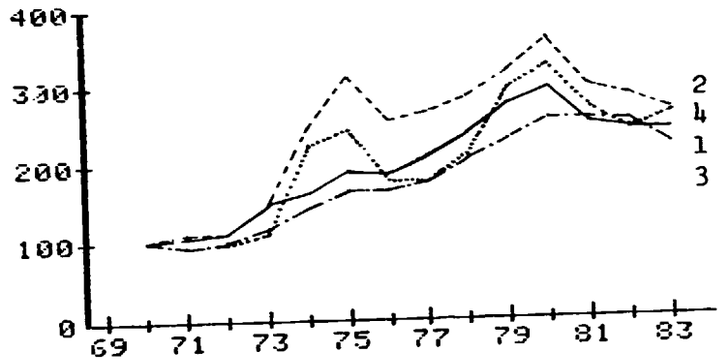
The chemical conversion efficiency was expressed in the literature in different ways. Data were given sometimes as weights of the input and corresponding output, or real input conversion coefficients, or yields. When converting these data into each other, f_1 and f_2 values were rounded up to two decimals whereas yields to integer numbers, because neither the accuracy of the data nor the objectives of the study justify greater precision. F values were also rounded up to two decimals.

The 1981-1982 c.i.f. import and domestic market prices of chemicals were available from different sources[4/] and the following values, converted into $US when necessary, were selected for the techno-economic analysis (table 3). Time-series data for the prices of chemical inputs were rarely available, but annual $US price indices 1970-1983 were received for selected reactants through correspondence with buyers.

3/ Price, Roberts, J. Am. Chem. Soc., 68, 124 (1946), Bruke et al., J. Am. Chem. Soc., 68, 1214 (1946), Gyógyszerek és gyógyszergyártás (Drugs and Drug Manufacturing), Müszaki Könyvkiadó, Budapest, p. 230 (1957), Pharmaceutical Manufacturing Encyclopedia, Noyes Data Corporation, Park Ridge, New Jersey, United States, 1979, p. 116, Hungarian Patent 153500, BIOS Final Report 116, Appendix 9, Process 7, UNIDO documents ID/WG.267/5 of 28 July 1978, IOD.299/Add.1 of 14 August 1978, unpublished project proposal, ID/WG.331/4 of 26 September 1980, PC.14 of August 1981 and PC.52 of 13 September 1982.

4/ Drug Statistics, Ministry of Chemicals and Fertilizers, Government of India, Chemical Marketing Reporter, UNIDO document PC.52 of 13 Sept. 1982 and UNIDO correspondence with buyers and suppliers in 1982.

Figure 2. Price indices of some intermediates for the manufacture of CHLOROQUINE Phosphate, 1970-1983



1. Novoldiamine,
2. m-Chloroaniline,
3. TEOF
4. DEM

Figure 2 shows that $US prices of the studied materials were reasonably stable between 1981 and 1983. These indices were used for the evaluation of the quality of prices from different sources, but raw data were not adjusted, because possible reductions in the price of novoldiamine, 4,7-dichloroquinoline and EMME would not have substantially affected the outcome of the analysis.

In the selection of the prices of chemical inputs, priority was given to those which referred to large-volume purchases. Prices of chemicals sold in a solution of specific strength, e.g. phosphoric acid and hydrobromic acid, were converted to reflect the price of the pure reactant.

Table 3. Prices of important chemical intermediates and raw materials used in the synthesis of CHLOROQUINE Phosphate ($US/kg)

Name	Unit price
4,7-Dichloroquinoline	37.15
Phosphoric acid	0.87
EMME	8.70
DEM	3.17
Chloroacetic acid	1.24
Sodium cyanide	1.22
Ethanol	0.42
TEOF	3.90
m-Chloroaniline	4.20
Novoldiamine	15.78
Novolketone	...
Hydrobromic acid	2.36
Diethylamine	1.48
Acetobutyrolactone	...
Ethylacetoacetate	2.00
Ethylene oxide	1.33

4.2 Brief description of the Model

The molar chemical input conversion coefficients, F, were calculated from the molecular weights given in table 1.

In table 2, the yields, y_1 and y_2, or the real chemical input coefficients, f_1 and f_2, were calculated by using the following formula:

$$y_{ij} = \frac{F}{f_{ij}} \; 100 \qquad (1)$$

and, the unit direct material costs were calculated:

$$C_{ij} = f_{1j}p_1 + f_{2j}p_2 + \ldots\ldots f_{ij}p_i + c_{hj} \qquad (2)$$

taking the unit prices, p_1, $p_2 \ldots p_i$ from table 3. Data for cost of reactants and auxiliary materials of smaller importance, such as phosphorous oxychloride, phenol, organic solvents (benzene, methanol, etc.), inorganic

compounds (ammonia, hydrochloric acid, etc.) and adsorbents (activated carbon), were not available for all degrees of backward integration and a proxy was added for the unit cost of other materials, c_{hj}, to arrive at unit direct material costs, C_{ij}. The proxy was based on published data[5/] and on own estimations taking into account real material input conversion factors and available unit prices. Data were scarce, or not available, for other elements in variable costs such as direct wages and salaries, consumable stores, repairs and maintenance, etc. or in fixed costs such as depreciation, factory and administrative overheads, etc. Since these costs vary according to the size and location of a plant, even within the same country, another proxy, C_c, based on published information in a developing country in 1982 was used.[6/] The unit gross profit or loss was obtained by subtracting the unit total production costs, C_{tp}, from the unit world market price of CHLOROQUINE Phosphate, or vice versa. The world market price of $US 27.10 reflects the arithmetic average of the quotations of seven European trading houses for the delivery of 1 ton of CHLOROQUINE Phosphate in 1982.[7/]

Material costs were based on uniform quality specification of chemical inputs. Adequate power, water and transport facilities were assumed available at the plant site.

Three criteria were used in the evaluation of the different degrees of backward integration: technical feasibility, profitability and convertible currency saving. The methodology does not take into account any additional convertible currency investment costs in new or existing pharmaceutical chemical plants. The methodology will therefore serve as a tool to arrive at a first selection of technically feasible alternatives, which should be studied in closer detail for economic feasibility.

5/ UNIDO PC. 52 of 13 September 1982.

6/ Ibid.

7 Dangschat, Karl O. Helm, K & K Greef, Marsing, Medimpex, Oxyde and Polfa.

Whenever the methodology described is used for decision-making in the selection of potential candidate compounds for domestic production, cost estimation sheets should be completed to conform to local conditions and to improve the reality of estimates in this study.

5. ANALYSIS OF THE PRODUCTION OF CHLOROQUINE PHOSPHATE BULK SUBSTANCE AND KEY INTERMEDIATES

5.1 CHLOROQUINE Phosphate production from imported 4,7-Dichloroquinoline and Novoldiamine

CHLOROQUINE is synthetized by the condensation of 4,7-dichloroquinoline and novoldiamine. The base is converted into phosphate by using phosphoric acid.

The cost and cost structure estimates of the average performer and ideal performer are shown in table 4.

Table 4. Cost and cost structure estimates of CHLOROQUINE Phosphate production. Backward integration I

Cost element	C_1		C_2	
	US$	%	US$	%
Novoldiamine	8.05	23.9	6.47	22.5
4,7-Dichloroquinoline	20.06	59.5	17.46	60.7
Key intermediate costs	28.11	83.4	23.93	83.2
Phosphoric acid	0.57	1.7	0.50	1.7
Other materials	0.35	1.0	0.30	1.0
Direct material costs	29.03	86.1	24.73	86.0
Conversion costs	4.67	13.9	4.04	14.0
Production costs	33.70	100.0	28.77	100.0

C_1 ... unit costs of the average performer
C_2 ... unit costs of the ideal performer

Table 4 shows that 4,7-dichloroquinoline and novoldiamine represent about 83 per cent of the total production costs. The cost structure is practically not affected by the efficiency of the chemical conversion. Due to the technical superiority of the technology, the unit costs of the ideal performer are much lower than those of the average performer.

The unit gross loss is $US 6.60 and $US 1.67 respectively, whereas the unit convertible currency saving is $US 2.37 with the ideal performer and there is a unit convertible currency loss of $US 1.93 with the average performer.

One per cent change in the price of novoldiamine or 4,7-dichloroquinoline will change C_{tp} of the average performer by 0.24 per cent and 0.60 per cent, respectively. The same figures for the ideal performer are 0.23 per cent and 0.61 per cent.

One per cent improvement of the chemical input conversion coefficient of novoldiamine and 4,7-dichloroquinoline will result in the same percentage reduction of C_{tp} as caused by changes in the intermediate price.

To arrive at a break-even point between C_{tp} and the world-market price of CHLOROQUINE Phosphate, the ideal performer should reduce his unit total production costs by about 6 per cent and the average performer by about 20 per cent.

The average performer could achieve this, if key intermediate prices were reduced by about 24 per cent or conversion efficiency improved to values of 0.38 and 0.44 (which would be superior to those of the ideal performer). Such price reductions are improbable and improvement of the conversion efficiency to the indicated level is impossible in commercial-scale practice on the short run, if achievable at all.

The advantages of the synthesis of CHLOROQUINE Phosphate from novoldiamine and 4,7-dichloroquinoline include that (i) the chemical reactions can be carried out in multipurpose batch reactors without additional investment, and (ii) the economic feasibility of the synthesis depends only a little on the scale of production.

The greatest disadvantage is that the influence of the manufacturer on the process economics is very small at this degree of backward integration. Dependence on intermediate suppliers is very high. Only a few companies

supply novoldiamine. 4,7-dichloroquinoline can usually be purchased only in the frame of long-term agreements, although the possibility of custom-synthesis should not entirely be left out of consideration.

5.2 CHLOROQUINE Phosphate production from imported Novoldiamine, EMME and m-Chloroaniline

Since the share of the unit costs of 4,7-dichloroquinoline is about 60 per cent in the C_{tp} of CHLOROQUINE Phosphate, most manufacturers aim at own production. The cost and cost structure estimates of the average and ideal performers synthetizing 4,7-dichloroquinoline from EMME and m-chloroaniline are given in table 5.

Table 5. Cost and cost structure estimates of CHLOROQUINE Phosphate production. Backward integration II

Cost element	C_1 US$	C_1 %	C_2 US$	C_2 %
Novoldiamine	8.05	22.9	6.47	23.0
EMME	8.09	23.0	6.44	22.9
Key intermediate costs	16.14	45.8	12.91	45.8
m-Chloroaniline	2.23	6.3	1.68	6.0
Phosphoric acid	0.57	1.6	0.50	1.8
Other materials	4.61	13.1	3.70	13.1
Direct material costs	23.55	66.9	18.79	66.7
Conversion costs	11.67	33.1	9.37	33.3
Production costs	35.22	100.0	28.16	100.0

C_1 ... unit costs of the average performer
C_2 ... unit costs of the ideal performer

Table 5 shows that novoldiamine and EMME are responsible for about 46 per cent of C_{tp} of CHLOROQUINE Phosphate. The cost structures of the average and ideal performers are similar. The unit gross-loss figures are still US $8.12 and US $1.06, but there is a unit convertible currency saving of US $3.55 and US $8.31, respectively.

One per cent decrease in the price of novoldiamine or EMME and/or one per cent improvement of the chemical input conversion coefficient will decrease C_{tp} of both the average and ideal performers by about 0.23 per cent.

The relative importance of the unit costs of other materials and of the unit conversion costs has increased in comparison to step I of the backward integration.

The advantage of this degree of backward integration is that the condensation, hydrolysis and chlorination steps can be carried out in multipurpose batch reactors, whereas the cyclization and decarboxylation steps require electrically-heated (up to 250-260° C) autoclaves usually available in pharmaceutical chemical plants.

The disadvantages include that (i) the economic feasibility of the synthesis depends on the scale of production to a greater extent than with the first degree of backward integration, particularly in the case of those reactors which are exclusively used for the production of CHLOROQUINE Phosphate, and (ii) dependence on intermediate suppliers is still high, because only a few companies supply novoldiamine and/or EMME.

5.3 CHLOROQUINE Phosphate production from imported Novoldiamine, DEM, TEOF and m-Chloroaniline

DEM and TEOF can be used as an alternative to EMME to produce 4,7-dichloroquinoline. The cost and cost structure estimates of the average and ideal performers are given in table 6.

Table 6 shows that the conversion costs play a dominant role in the C_{tp}. The only key intermediate left is novoldiamine. The average performer has a unit gross loss of $US 4.80, whereas the unit gross profit of the ideal performer is $US 1.74. The unit convertible currency saving is $US 6.87 and $US 11.11, respectively.

Table 6. Cost and cost structure estimates of CHLOROQUINE Phosphate production. Backward integration III

Cost element	C_1 US$	C_1 %	C_2 US$	C_2 %
Novoldiamine	8.05	25.2	6.47	25.5
Key intermediate costs	8.05	25.2	6.47	25.5
DEM	2.16	6.8	1.65	6.5
TEOF	2.61	8.2	1.99	7.8
m-Chloroaniline	2.23	7.0	1.68	6.6
Phosphoric acid	0.57	1.8	0.50	2.0
Other materials	4.61	14.5	3.70	14.6
Direct material costs	20.23	63.4	15.99	63.1
Conversion costs	11.67	36.6	9.37	36.9
Production costs	31.90	100.0	25.36	100.0

C_1 ... unit costs of the average performer

C_2 ... unit costs of the ideal performer

One per cent change in the price of novoldiamine or its conversion efficiency causes C_{tp} to change by about 0.26 per cent, whereas the sensitivity of C_{tp} to the conversion costs is about 0.37 per cent.

The advantages of this process alternative include that the chemical reactions differing from those of the process analysed in section 5.2 can be carried out in multipurpose batch reactors (the subsequent steps are identical with the CHLOROQUINE Phosphate manufacturing process starting from novoldiamine and EMME). The influence of the manufacturer on the process economics has increased, because the share of the unit direct material costs in C_{tp} is reduced to about 63 per cent. Dependence on intermediate suppliers is also smaller, because DEM and TEOF, in contrast to EMME, are used in the synthesis of many other chemicals and are more easily available on the international market.

The disadvantages include the sensitivity of C_{tp} to scale of production and continuing dependence on novoldiamine supply.

5.4 CHLOROQUINE Phosphate production from imported Novoldiamine, m-Chloraniline, TEOF, Chloroacetic acid, Sodium Cyanide and Ethanol

DEM can be synthetized starting from chloroacetic acid, sodium cyanide and ethanol. The cost and cost structure estimates of the average and ideal performers producing CHLOROQUINE Phosphate from own-manufactured DEM, are given in table 7.

Table 7. Cost and cost structure estimates of CHLOROQUINE Phosphate production. Backward integration IV

Cost element	C_1 US$	C_1 %	C_2 US$	C_2 %
Novoldiamine	8.05	25.2	6.47	25.9
Key intermediate costs	8.05	25.2	6.47	25.9
Chloroacetic acid	0.82	2.6	0.42	1.7
Sodium cyanide	0.31	1.0	0.22	0.9
Ethanol	0.69	2.2	0.36	1.4
TEOF	2.61	8.2	1.99	8.0
m-Chloroaniline	2.23	7.0	1.68	6.7
Phosphoric acid	0.57	1.8	0.50	2.0
Other materials	4.61	14.5	3.70	14.8
Direct material costs	19.89	62.4	15.34	61.4
Conversion costs	12.01	37.6	9.64	38.6
Production costs	31.90	100.0	24.98	100.0

C_1 ... unit costs of the average performer

C_2 . unit costs of the ideal performer

Table 7 shows that neither C_{tp}, nor the cost structure has changed significantly as compared to backward-integration degree III. Actually, C_{tp} of the average performer is probably higher than given in table 7, since the

$US 0.34 added to the unit conversion costs hardly compensates for the gain between the unit costs of DEM and the unit cost of chemicals to produce it. The same holds probably true for the ideal performer, although the reduction of the unit direct material costs is US $0.65 in this case.

This alternative is worth consideration principally in those cases where the manufacturer produces malonic acid derivatives also for the synthesis of other pharmaceutical chemicals, such as barbiturates, naphthyridine derivatives, etc.

This degree of backward integration does not have a particular advantage over the former degree and its disadvantages also include the use of sodium cyanide, which is a dangerous chemical both as far as labour safety and environmental aspects are concerned.

5.5 CHLOROQUINE Phosphate production from locally manufactured 4,7-Dichloroquinoline and Novoldiamine

Data were scarce for the analysis of the manufacture of novoldiamine. The chemical input conversion coefficients of the average performer come from a single source, whereas those of the ideal performer were taken from the literature and/or estimated using literature data. The economically best alternative of 4,7-dichloroquinoline manufacture was combined with the above novoldiamine syntheses to give table 8.

Table 8 shows that the share of unit direct-material costs is a little higher than that of the unit conversion costs in the C_{tp}. None of the chemical inputs plays a dominant role in the cost structure.

The average performer has a unit gross loss of $US 6.03, whereas the unit gross profit of the ideal performer is $US 0.86. The respective unit convertible currency savings are $US 8.70 and $US 12.69, respectively.

On the other hand, novoldiamine cannot be produced in multipurpose batch reactors, because the hydrogenation and ammonolysis of novolketone should be carried out in high-pressure autoclaves, and both the high-pressure hydrogen

and the pyrophorous Raney-nickel catalyst are explosion-dangerous chemicals. The unit gross loss of the average performer is higher and the unit gross return of the ideal performer is lower than in the case of backward integration degree III.

Table 8. Cost and cost structure estimates of CHLOROQUINE Phosphate production. Backward integration V

Cost element	C_1 US$	C_1 %	C_2 US$	C_2 %
Ethylacetoacetate	2.44	7.4	1.90	7.2
Ethylene oxide	0.97	2.9	0.76	2.9
Hydrobromic acid	0.99	3.0	0.78	3.0
Diethylamine	0.53	1.6	0.41	1.6
DEM	2.16	6.5	1.65	6.3
TEOF	2.61	7.9	1.99	7.6
m-Chloroaniline	2.23	6.7	1.68	6.4
Phosphoric acid	0.57	1.7	0.50	1.9
Other materials	5.90	17.8	4.74	18.1
Direct material costs	18.40	55.5	14.41	54.9
Conversion costs	14.73	44.5	11.83	45.1
Production costs	33.13	100.0	26.24	100.0

C_1 ... unit costs of the average performer

C_2 ... unit costs of the ideal performer

6. EFFECT OF BACKWARD INTEGRATION ON THE PROCESS ECONOMICS OF CHLOROQUINE PHOSPHATE MANUFACTURE

The cost estimates of the average and ideal performers, given in tables 4-8, were summarized in table 9 to show how the different degrees of backward integration affect the C_{tp}. Costs of chemical inputs representing less than 5 per cent of the C_{tp} were included among the other materials for convenience.

Table 9. Effect of backward integration on the unit total production costs of CHLOROQUINE Phosphate ($US/kg)

Cost element	Degree of backward integration I		II		III		IV		V	
	C_1	C_2	C_1	C_2	C_1	C_2	C_1	C_2	C_1	C_2
Novoldiamine	8.05	6.47	8.05	6.47	8.05	6.47	8.05	6.47	-	-
4,7-Dichloro-quinoline	20.06	17.46	-	-	-	-	-	-	-	-
EMME	-	-	8.09	6.44	-	-	-	-	-	-
Key intermediate costs	28.11	23.93	16.14	12.91	8.05	6.47	8.05	6.47	-	-
m-Chloroaniline	-	-	2.23	1.68	2.23	1.68	2.23	1.68	2.23	1.68
DEM	-	-	-	-	2.16	1.65	-	-	2.16	1.65
TEOF	-	-	-	-	2.61	1.99	2.61	1.99	2.61	1.99
Ethylacetoacetate	-	-	-	-	-	-	-	-	2.44	1.90
Other materials	0.92	0.80	5.18	4.20	5.18	4.20	7.00	5.20	8.96	7.19
Direct material costs	29.03	24.73	23.55	18.79	20.23	15.99	19.89	15.34	18.40	14.41
Conversion costs	4.67	4.04	11.67	9.37	11.67	9.37	12.01	9.64	14.73	11.83
Production costs	33.70	28.77	35.22	28.16	31.90	25.36	31.90	24.98	33.13	26.24
Gross profit	-6.60	-1.67	-8.12	-1.06	-4.80	1.74	-4.80	2.12	-6.03	0.86
Convertible currency saving	-1.93	2.37	3.55	8.31	6.87	11.11	7.21	11.76	8.70	12.69

C_1.. average performer
C_2.. ideal performer

Table 9 shows that the unit cost of the key intermediates decreases as the degree of backward integration decreases. The same holds true for the unit cost of direct materials, but the C_{tp} shows a maximum at degree II and an optimum at degrees III-IV of the average performer, and an optimum at degree IV of the ideal performer. The distinction between degrees III and IV is not justified because the two C_{tp}-s are very close to each other. The average performer has a loss throughout the backward integration studied, whereas the ideal performer makes a profit from backward-integration degree III onwards, showing an optimum at degree IV. Except at degree I, both the average and ideal performers save convertible currency. The higher the degree of backward integration is, the higher the convertible currency saving is. Hence, optimum C_{tp} is observed when CHLOROQUINE Phosphate is produced from purchased novoldiamine, m-chloroaniline, TEOF and DEM, although the latter can also be produced locally. Maximum convertible currency saving is encountered at backward-degree integration V, when also novoldiamine is manufactured domestically.

The cost structure changes significantly as the degree of backward integration increases (table 10).

Table 10 shows that the key intermediates play a dominant role in the cost structures of backward-integration degrees I and II. The share of the unit conversion costs in C_{tp} becomes higher than that of the key intermediates from backward-integration degree III onwards. As the share of the unit conversion costs in the C_{tp} increases, financial and technical management becomes more and more important as a potential source of reducing C_{tp}.

The importance of the cost of other materials reaches that of a key intermediate from backward-integration degree IV onwards.

The average performer makes about a 15-20 per cent unit loss. Neither the improvement of the purchasing efficiency of chemical inputs, nor the development of the technology is probable on the short run to arrive at a break-even point, not talking about profits. The ideal performer is close to

the break-even point at backward-integration degrees I and II, and makes a gross profit of 3 to 8 per cent from degree III onwards, although lower than desirable.

Table 10. Effect of backward integration on the production cost structure of CHLOROQUINE Phosphate (per cent)

Cost element	Degree of backward integration									
	I		II		III		IV		V	
	C_1	C_2	C_1	C_1	C_1	C_2	C_1	C_2	C_1	C_2
Novoldiamine	23.9	22.5	22.8	23.0	25.2	25.5	25.2	25.9	-	-
4,7-Dichloro-quinoline	59.5	60.7	-	-	-	-	-	-	-	-
EMME	-	-	23.0	22.9	-	-	-	-	-	-
Key intermediate costs	83.4	83.2	45.8	45.9	25.2	25.5	25.2	25.9	-	-
m-Chloroaniline	-	-	6.3	6.0	7.0	6.6	7.0	6.7	6.7	6.4
DEM	-	-	-	-	6.8	6.5	-	-	6.5	6.3
TEOF	-	-	-	-	8.2	7.9	8.2	8.0	7.9	7.6
Ethylacetoacetate	-	-	-	-	-	-	-	-	7.4	7.2
Other materials	2.7	2.8	14.8	14.8	16.2	16.6	22.0	20.8	27.0	27.4
Direct material costs	86.1	86.0	66.9	66.7	63.4	63.1	62.4	61.4	55.5	54.9
Conversion costs	13.9	14.0	33.1	33.3	36.6	36.9	37.6	38.6	44.5	45.1
Production costs	100	100	100	100	100	100	100	100	100	100
Gross profit	-19.6	-5.8	-23.0	-3.8	-15.0	6.9%	-15.0	8.5	-18.2	3.3
Convertible currency saving	-7.1	8.7	13.1	30.7	25.4	41.01	26.6	43.4	32.1	46.8

C_1 average performer
C_2 ideal performer

7. AVAILABILITY OF CHLOROQUINE PHOSPHATE, ITS KEY INTERMEDIATES AND THEIR MANUFACTURING TECHNOLOGY

In an attempt to assess the availability of CHLOROQUINE Phosphate, its key intermediates and their manufacturing technology, enquiries were sent to all addresses given in the Chemical Suppliers Directory. Twenty-five positive replies were received, 21 from industrialized and four from developing countries. The information contained in these replies is summarized in annexes 4 and 5.

Although the lists given in this study are based on correspondence with manufacturers and suppliers, they may contain mistakes and be incomplete. They reflect the situation as at the middle of 1984.

CHLOROQUINE Phosphate is one of the relatively few pharmaceutical chemicals which is also sold on the open market by companies usually producing for captive use only. The largest quantities are sold through international trading houses, which keep stocks of the pharmaceutical chemical. Hence, CHLOROQUINE Phosphate is freely available in international trade.

Both novoldiamine and EMME are used in the pharmaceutical industry, mainly but not exclusively, for the production of CHLOROQUINE Phosphate. These key intermediates are produced both in the pharmaceutical and chemical industries. Those manufacturers enjoy comparative advantages who produce or purchase the starting chemicals in large quantities also for the manufacture of other chemical products. The number of novoldiamine and EMME suppliers is few and their market has an oligopolistic character.

4,7-Dichloroquinoline is used only in the pharmaceutical industry, mainly for the production of CHLOROQUINE Phosphate, but also of Amodiaquine Hydrochloride. The integrated 4-aminoquinoline manufacturers produce 4,7-dichloroquinoline. Non-integrated manufacturers, such as affiliates buy their 4,7-dichloroquinoline demand from headquarters, hence this key intermediate is not available in the international trade. If needed, well defined quantities could probably be purchased through long-term agreements or custom synthetized.

DEM, TEOF, m-chloroaniline, ethylacetoacetate, diethylamine, etc., are mainly used for purposes other than the manufacture of CHLOROQUINE Phosphate. They are produced in large quantities by the chemical industries and are freely available on the world market at competitive prices.

With the exception of novoldiamine, CHLOROQUINE Phosphate and its key intermediates are produced both in developing and industrialized countries. Laboratory-scale technology is available from the literature, including alternative processes and routes, both for CHLOROQUINE Phosphate and its key intermediates.

8. OTHER POSSIBLE USES OF THE AVAILABLE INFORMATION AND DESCRIBED METHODOLOGY

Different users have different, sometimes conflicting interests when using the available information for their own purpose. For example, decision-makers concerned about health want to purchase their CHLOROQUINE demand at the lowest possible cost, whereas decision-makers interested in the national balance of payments or in the promotion of domestic industrialization might be satisfied with saving substantial amounts of convertible currency. Potential investors are looking for profits and existing manufacturers spend money to develop their technology and to reduce their production cost in general. The methodology described in this paper serves also as a tool to analyse some aspects of the above objectives.

8.1 Estimation of the quantities and values of materials required for the manufacture of CHLOROQUINE Phosphate

Chemical input conversion coefficients are regularly used for the estimation of direct material demand for the production of a definite quantity of CHLOROQUINE Phosphate in a given period. The same data reflect also the convertible currency saving and the profit or loss for the same quantities and time.

Table 11 shows data for backward-integration degree III of the manufacture of CHLOROQUINE Phosphate. The convertible currency-saving figures imply that the other materials are all imported. The gross profit or loss is encountered in national currency, if domestic consumption of all the CHLOROQUINE Phosphate production is assumed.

Table 11. Material requirements (tons) and some financial aspects (thousand $US) of the annual production of 100 tons of CHLOROQUINE Phosphate

Name	Average performer		Ideal performer	
	quantity	value	quantity	value
Novoldiamine	51	805	41	647
DEM	68	216	52	165
TEOF	67	261	51	199
m-Chloroaniline	53	223	40	168
Other materials	-	518	-	420
Total material requirement		2023		1,599
Convertible currency saving		687		1,111
Gross profit		-480		174

8.2 Estimation of the disaggregated yields and chemical input conversion coefficients

The yields of individual or smaller groups of chemical reactions can be calculated by dividing the overall yield of the reactants with the overall yield of the relevant product (intermediate). The corresponding f value is obtained by dividing the relevant F with the disaggregated yield.

Table 12 shows that there is a significant difference in the 4,7-dichloroquinoline branch of CHLOROQUINE synthesis between the average and ideal performers, while in the novoldiamine branch the difference is practically nil. The better overall yields in table 2 were obtained only because the ideal performer converted novoldiamine into CHLOROQUINE Phosphate with a greater efficiency than the average performer. Such analysis also indicates that data for novoldiamine synthesis were available from one or from the same source. Judged by the disaggregated yields, the studied novoldiamine synthesis is technically not very good, hence the economic conclusions drawn from this process can be considered conservative. Such analysis is useful when evaluating offers for transfer of technology.

Table 12. Estimated disaggregated yields and chemical input conversion coefficients in the manufacture of CHLOROQUINE Phosphate

Name	y a	y i	F	f a	f i
4,7-Dichloroquinoline					
EMME	64	70	1.09	1.70	1.56
DEM	66	74	0.81	1.23	1.09
TEOF	61	70	0.75	1.23	1.07
m-Chloroaniline	67	78	0.64	0.96	0.82
DEM					
Chloroacetic acid	59	88	0.59	1.00	0.67
Sodium cyanide	87	93	0.31	0.36	0.33
Ethanol	24	35	0.29	1.21	0.83
Novoldiamine					
Novolketone	92	93	0.99	1.08	1.06
Novolketone					
Acetobutyrolactone	63	65	0.81	1.29	1.25
Hydrobromic acid	68	69	0.51	0.75	0.74
Diethylamine	70	70	0.47	0.67	0.67
Acetobutyrolactone					
Ethylacetoacetate	60	57	1.02	1.70	1.79
Ethylene oxide	34	35	0.34	1.00	0.97

y... yield of the chemical output with reference to the given chemical input;
f... conversion efficiency of the chemical input with reference to the chemical output under which it is listed;
a... average performer;
i... ideal performer.

8.3 Setting technical development targets

The comparison of the disaggregated chemical yields of the average performer and ideal performer for backward-integration III of the manufacture of CHLOROQUINE Phosphate shows the possibilities of improving conversion efficiency. The obtained figures can be ranked according to decreasing percentage order.

Table 13. Possibilities of improving yields of chemical reactions in the manufacture of CHLOROQUINE Phosphate (percentage)

Product	Reactant	Yield improvement
DEM	Chloroacetic acid	50
DEM	Ethanol	46
CHLOROQUINE Phosphate	Novoldiamine	23
4,7-Dichloroquinoline	m-Chloroaniline	16
CHLOROQUINE Phosphate	4,7-Dichloroquinoline	16
4,7-Dichloroquinoline	TEOF	15
CHLOROQUINE Phosphate	Phosphoric acid	14
4,7-Dichloroquinoline	DEM	13
DEM	Sodium cyanide	7

If only the possibilities of improving the chemical conversion efficiency are taken into account, then the order of the technical development targets will be as follows:

(i) Revision of the technology of DEM, particularly the improvement of the chemical conversion coefficients of chloroacetic acid and ethanol.

(ii) Development of the technology of CHLOROQUINE Phosphate production, particularly the condensation of 4,7-dichloroquinoline with novoldiamine.

(iii) Improvement of 4,7-dichloroquinoline yields with reference to m-chloroaniline, and TEOF and DEM.

The economic aspects of the studied technology (table 7) will modify the order of importance of the technical priorities as follows:

(iv) Development of the condensation reaction of 4,7-dichloroquinoline with novoldiamine, because the first represents 57 per cent, whereas the second 25 per cent in the C_{tp}; the relevant shares in the direct material costs are 55 per cent and 41 per cent, respectively. If the average performer could reach the conversion

efficiency of the ideal performer only in this step, C_{tp} could be reduced by about $US 4.00, which represents about 57 per cent of the ideally achievable reduction of C_{tp}.

(v) The maximum unit cost reduction of the manufacture of 4,7-dichloroquinoline from m-chloroaniline, DEM and TEOF is about $US 2.50.

(vi) Improvement of DEM yield would result in a maximum unit cost reduction of $US 0.90.

Such calculations can also be made the other way around, when the starting point is a desirable CHLOROQUINE price. The proportional difference between the desirable price and C_{tp} is distributed among the intermediates, and the yields to achieve the necessary cost reductions are calculated. These desirable yields can be analysed, whether attainable in commercial-scale production, or not.

8.4 Estimation of the price of chemical intermediates

The cost of 4,7-dichloroquinoline manufacture can be estimated, if the relevant data of table 6 are divided by the chemical input conversion coefficients of 4,7-dichloroquinoline in table 4.

Table 14. Estimation of the production costs of 4,7-dichloroquinoline ($US)

Cost element	C_1	C_2	C_1-C_2
DEM	2.16	1.65	0.51
TEOF	2.61	1.99	0.62
m-Chloroaniline	2.23	1.68	0.55
Other materials	4.26	3.40	0.86
Direct material costs	11.26	8.72	2.54
Conversion costs	7.00	5.33	1.67
Production costs	18.26	14.05	4.21

$US 18.26 and 14.05 represent the costs of 0.54 and 0.47 kg of 4,7-dichloroquinoline, respectively, hence the corresponding unit prices are $US 33.80 and 29.90, in comparison to the import unit price of $US 37.15 given in table 3. Such information is useful when negotiating the price of purchased chemicals.

9. TRENDS AND FORECASTS OF DEMAND FOR CHLOROQUINE PHOSPHATE AND INTERMEDIATES

9.1 The morbidity trend

In 1982, some 6.5 million malaria cases (provisional figure) were reported to WHO, compared to 7.8 million cases in 1981 and 8.1 million in 1980. These figures are still incomplete and do not include data from Africa South of the Sahara. Table 15 shows a time series of WHO data which indicate the trend of global malaria situation 1973-1982.[8/]

Table 15. Number of malaria cases reported by WHO regions, 1973-1982[a/] (in millions)

WHO Region	1973	1976	1977	1978	1979	1980	1981	1982
The Americas	0.3	0.4	0.4	0.5	0.5	0.6	0.6	0.7
South-East Asia	2.7	7.3	5.5	4.8	3.7	3.7	3.5	2.9[d/]
Europe	-	-	0.1	0.1	-	-	0.1	0.1
E. Mediterranean	0.7	0.3	0.2	0.2	0.1	0.1	0.2	0.3
W. Pacific	0.2[c/]	0.2[c/]	4.5	3.4	2.7	3.7	3.5	2.4[d/]
3.9[c/]	8.3[c/]	10.7	8.9	7.0	8.1	7.8	6.5[d/]	
Africa[b/]	6.7	5.5	4.8	7.4	5.8	3.1[d/]	2.0[d/]	...
WORLD	10.6	13.8	15.5	16.3	12.8	11.2[d/]	9.8[d/]	...
World index	100	130	146	154	121	106[d/]	92[d/]	...

a/ The information provided does not cover the total population at risk in some instances.

b/ Mainly clinically diagnosed cases.

c/ Excluding China

d/ Provisional

8/ World Malaria Situation 1982, Wld. Hlth. Statist. Quart., 37, No. 2, pp. 130-161, 1984.

The WHO synopsis of the world malaria situation contains detailed information on most affected countries, with the exception of countries in Africa South of the Sahara. This fact is stressed because sub-Saharan countries are high-risk malarious areas; at the same time, the quality and reliability of observations do not allow an adequate estimation of the situation in this region. The share of Africa in world malaria morbidity is about 28 to 45 per cent. The figures of the African region show oscillations and no clear trend.

Both South-East Asia and the Western Pacific region show a slow declining trend in the prevalence of the disease.

In the region of the Americas, about 50 per cent of the cases were reported in Central America and the balance in South America. The historical trend shows an increase.

The European cases originate mostly from Turkey and the trend shows a tendency to increase.

The number of malaria cases imported to malaria-free zones is not significant as compared to the number of autochthonous cases.

Africa, South-East Asia and the Western Pacific regions play a dominant role in the world malaria morbidity statistics, hence the global trend is expected to decrease slightly in the future.

Malaria mortality also constitutes a serious health problem. In Africa alone, the estimated number of deaths per year is about one million, mainly infants and small children.9/

9/ L. Bruce-Chwatt, "Malaria: from eradication to control", New Scientist, 19 April 1984, p. 18.

9.2 CHLOROQUINE consumption trend

Antimalarial drugs in the last revision of the WHO Model List of Essential Drugs include two 4-aminoquinolines (CHLOROQUINE and amodiaquine), one 8-aminoquinoline (primaquine), a cinchona alkaloid (quinine), and a long-acting sulphonamide plus pyridine derivative combination (sulfadoxine + pyrimethamine). CHLOROQUINE Phosphate is the antimalarial drug selected to exemplify the therapeutic group.10/

Data on CHLOROQUINE Phosphate consumption are scarce and incomplete. A UNIDO document shows 1977 global consumption figures (table 16).11/

Table 16. Geographic distribution of CHLOROQUINE Phosphate consumption 1977 (tons)

Geographic region	CHLOROQUINE Phosphate consumption
North America	2
Latin America	100
Western Europe	3
Asia	600
Africa	340
Oceania	5
WORLD	1050

These figures should be handled with care because time series of data are not available for global CHLOROQUINE Phosphate consumption, hence the morbidity and demand variables cannot be correlated. As an indicator, the 1977 figures of these two variables were divided by each other and an apparent 103 g, 76 g and 250 g of CHLOROQUINE Phosphate consumption per malaria case

10/ The use of essential drugs, Technical Report Series 685, WHO, Geneva, p. 21 (1983).

11/ UNIDO, ID/WG.331/4 of 26 September 1980, The pricing and availability of intermediates and bulk drugs, p. 55.

was obtained for the Asian, African and Latin American regions, respectively, whereas the usual dose for adults is about 3 g per malaria case. This 20 to 93-fold difference between the expected nominal and apparent consumptions indicate that CHLOROQUINE Phosphate is given to patients for other reasons than malaria treatment in many cases when symptoms do not allow for clear distinction between malaria and other diseases.

The WHO has studied antimalarial drugs usage and requirements in 72 countries. Table 17 shows the result of the CHLOROQUINE survey.

Table 17. Estimated world-wide consumption and demand 1978-1985 of CHLOROQUINE Phosphate used in national antimalaria programmes (tons)

WHO Region	1978	1979	1980	1981	1982	1983	1984	1985
AFR	211	211	232	259	286	312	339	339
AMR	8	10	9	13	10	14	12	11
EMR	10	24	43	59	60	54	53	53
EUR	7	6	5	8	7	14	10	7
SEAR	164	116	109	111	113	116	110	110
WPR	22	40	43	[illegible]	44	42	39	41
WORLD	422	407	441	494	520	552	563	561
World index	100	96	105	117	123	131	133	133

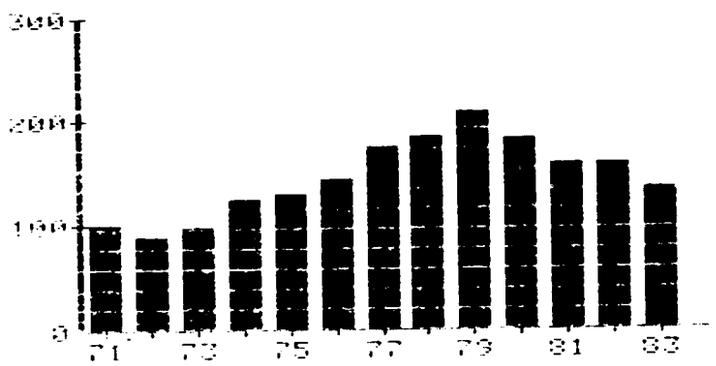
Regions (according to WHO):
AFR... Africa; AMR... Americas; EMR... Eastern Mediterranean;
EUR... Europe; SEAR... South-East Asia; WPR... Western Pacific.

The figures in table 17 are estimates in some cases and do not contain sales through commercial channels, hence the data reflect the trend rather than real consumption. The historical trend shows an increase till 1982 and WHO experts expect stagnation of the demand from 1984 onwards.

9.3 The price trend

Figure 3 shows the changes of the price index of CHLOROQUINE Phosphate in the international free trade.

Figure 3. Price index of CHLOROQUINE Phosphate international market price, 1971-1983



The overall change 1971-1983 shows an increase, but the commodity character of the pharmaceutical chemical is reflected in the transient reductions of the average annual prices in 1972, 1973 and in the decreasing trend of the price curve from 1979 onwards.

A similar trend can be observed with the dosage forms. For instance, the price of 1,000 CHLOROQUINE Phosphate tablets (150 mg. base) was reduced by approx. 21 per cent from Dfl. 27.14 to Dfl. 21.55 between 1979 and 1984. The corresponding figures of $US 13.49 in 1979 and $US 6.55 in 1984 show an even higher decrease of about 51 per cent.

9.4 Assessment of some external factors affecting CHLOROQUINE Phosphate consumption

9.4.1 Economic competition

Safety, effectiveness and other factors being equal, treatment cost is the major consideration in the selection of the drug of choice in a given therapeutic category. Table 18 is an illustrative example of comparing the cost component of drugs in the treatment of acute malaria attacks.

Table 18. Cost of selected essential drugs used in the chemotherapy of acute malaria attacks

Drug	Dose, a/ mg	Cost, b/ $US
Amodiaquine (base)	1,400	0.18
Chloroquine (base)	1,500	0.10
Primaquine (base) + + chloroquine (base)	210 1,500	0.16
Quinine sulphate	9,000	0.84
Sulphadoxine + + pyrimethamine	1,000-1,500 c/ 50-75 c/	0.16-0.24

a/ Goodman and Gilman's The Pharmacological Basis of Therapeutics, 6th Ed. (1980)

b/ Cost of tablets equivalent to Dose a/ at 1982 purchase prices of WHO

c/ Martindale, The Extra Pharmacopoeia, 27th Ed. (1978)

Table 18 shows that CHLOROQUINE is the curative antimalarial drug of short-term economic choice. Hence, competition can be expected on therapeutic rather than economic grounds.

Since both chemotherapy and prices vary from country to country, treatment costs should be assessed at national level taking into account all possible alternatives.

Prevention of malaria attacks is a great concern to international travellers. The recommended chemoprophylaxis depends on conditions which may prejudice the use of certain drugs, hence a physician should be consulted before taking suppressive antimalarials. Unless contraindicated on different grounds, the 4-aminoquinolines are the individual drugs of choice for malaria prophylaxis. The period of suppressive administration is the same for each drug, hence, CHLOROQUINE is also the chemoprophylactic agent of economic choice.[12/]

9.4.2 Resistance of Plasmodium falciparum to CHLOROQUINE Phosphate

CHLOROQUINE-resistant strains of Plasmodium falciparum were reported first from Thailand in 1957, then from Colombia in 1960 and have since spread to other areas of Asia and Latin America. The first confirmed indigenous cases of resistance in Africa were observed in Tanzanians in 1981. The spread of CHLOROQUINE-resistant P. falciparum continues, especially in the South-East Asia and Western Pacific regions; in Latin America, it affects the whole area of distribution of P. falciparum. In Africa, P. falciparum strains are somewhat less sensitive to CHLOROQUINE Phosphate, but they usually still respond to the normal therapeutic regimen.

9.4.3 Therapeutic competition

The P. falciparum treatment in CHLOROQUINE-resistant areas usually consists of the sulfadoxine + pyrimethamine combination. Primaquine is advocated but not always used. In some sulfadoxine + pyrimethamine-resistant areas quinine and tetracycline are administered. Amodiaquine has also been used in CHLOROQUINE resistant cases of P. falciparum.

Mefloquine, a new antimalarial drug, has been used with good results in multidrug-resistant cases but treatment costs are much higher than those with CHLOROQUINE, and mefloquine-resistance of P. falciparum strains has already been detected.

12/ Malaria risk in international travel, WHO Wkly Epidem. Rec., Nos. 29, 30, 31, 1984, pp. 221-227, 229-235, 237-240.

A new antimalarial drug, Quinghaosu (artemisinine), is in clinical trials in China with promising results, through collaboration between various Chinese institutes and the WHO Special Programme.

Extensive research is conducted to find a malaria vaccine comparable in effectiveness and duration of protective action to traditional vaccines. The first product is expected to be available perhaps by 1987.

The resistance and certain acceptable side effect problems apart, CHLROQUINE Phosphate remains the best available drug for the treatment of acute malaria attacks and a valuable preventive drug in many cases. New drugs will not affect significantly CHLOROQUINE Phosphate consumption on the short run. It is difficult to predict, however, the effect of new antimalarials on future CHLOROQUINE Phosphate demand.

9.4.4 Other factors affecting CHLOROQUINE demand

Some important factors positively affecting future consumption are population growth and improving availability of health care in developing countries, as well as increasing resistance of the mosquito to insecticides. CHLOROQUINE Phosphate is also the antiamoebic agent of choice in the WHO model list of essential drugs.[13/] This indication and the malaria prophylactic use of CHLOROQUINE Phosphate before travelling to malaria-zones account mainly for the consumption in North America and Europe.

9.5 Conclusions

The world-wide CHLOROQUINE consumption trend 1978-1982 shows an increasing tendency despite the decreasing malaria morbidity trend 1978-1981. Short-term forecasts of CHLOROQUINE demand, made in 1983, envisaged a declining growth till 1984 and stagnation from 1985 onwards, but there was no argument to substantiate this expectation (table 17).

13/ The use of essential drugs, Technical Report Series 685, WHO, Geneva, p. 18 (1983).

The price of CHLOROQUINE bulk substance has continuously decreased in $US since 1979 and the same holds true for the price of dosage forms both in Dfl. and US$. The price reduction has strengthened the position of CHLOROQUINE as the antimalarial drug of economic choice, but shows a strong price competition on the international market at the same time and constitutes a barrier to entry for new producers. As a matter of fact, prices are close to or even exceeding manufacturing costs and only integrated manufacturers with the best technology can survive such recession periods.

9.6 Short-term forecasts of CHLOROQUINE demand to 1990

Calculated from the figures of table 17, the growth rate 1978-1983 of the world-wide CHLOROQUINE demand is 5.5 per cent. The data are more consistent for the period from 1979 to 1983 and the corresponding growth rate is 7.9 per cent. In practical terms, Africa and the Middle-East are responsible for the increase in volume of CHLOROQUINE demand.

The assumption of a global annual growth rate 1983-1990 of 4 per cent seems to be realistic. A growth rate higher than 4 per cent cannot be argued, whereas a lower growth rate of say 2 per cent would not be surprising.

If the 1980 ratio of 2.4 between the world-wide CHLOROQUINE consumption and consumption of CHLOROQUINE in national antimalaria programmes is used to estimate the 1983 world consumption, then a figure of 1,325 tons is obtained.

The estimates in table 19 show the 1990 demands of CHLOROQUINE Phosphate and intermediates, based on the conversion efficiencies of the average and ideal performers. Intermediate demands in table 19 refer to different degrees of backward integration, hence it is understood that manufacturers that import 4,7-dichloroquinoline will not import EMME, or DEM, etc. It should also be remembered that intermediate demands refer to CHLOROQUINE synthesis only. Use of an intermediate for the production of another pharmaceutical chemical, e.g. 4,7-dichloroquinoline in the synthesis of amodiaquine hydrochloride [69-44-3], has not been taken into account.

Table 19. Current and future world-wide consumption estimates of CHLOROQUINE Phosphate and intermediates (tons)

Chemical	1983 (estimated)	1990 (forecast)
CHLOROQUINE Phosphate	1,325	1,810
Novoldiamine	540-680	740-920
4,7-Dichloroquinoline	620-720	850-980
EMME	980-1,230	1,340-1,680
DEM	690-900	940-1,230
TEOF	680-890	920-1,210
m-Chloroaniline	530-700	720-960

In the Asian region, China is a net exporter of CHLOROQUINE Phosphate and India will probably cover the national demand by local production by 1986. Latin America and Africa are net importers today, although demand would justify local production of CHLOROQUINE Phosphate and key intermediates in Africa.

Integrated CHLOROQUINE Phosphate manufacturers already produce their own 4,7-dichloroquinoline both in industrialized and developing countries.

Novoldiamine is imported/purchased by the majority of CHLOROQUINE producers, but demand for this intermediate will justify consideration of local production in Asia and in Africa by 1990.

m-Chloroaniline, TEOF and DEM are chemical inputs in the production of many pharmaceutical chemicals, hence the figures in table 19 represent only a fraction of the global demands for those products.

9.7 Long-term forecasts of CHLOROQUINE demand to 2000

The environment of the antimalarial market is extremely complex and the circumstances surrounding the situation by the year 2000 cannot be predicted. It can be said with confidence, however, that CHLOROQUINE Phosphate is the most frequently used antimalarial drug at present and its consumption shows a

moderate growth on the global level. This situation is not expected to change during the forthcoming years, because treatment costs with CHLOROQUINE Phosphate are lower than those with other antimalarial drugs and the latter usually do not offer either better therapeutical alternatives or comparative advantages. New drugs under research and development will not become accessible in the near future to the majority of the population in developing countries, hence no turning point is envisaged in the life cycle curve of CHLOROQUINE Phosphate demand before 1990.

10. CONCLUSIONS AND RECOMMENDATIONS

10.1 Major conclusions of the techno-economic analysis

Backward-integration degrees I-IV are technically feasible and all the chemical reactions involved can be carried out in multipurpose batch reactors and by using equipment generally available in pharmaceutical chemical plants. Backward integration degree V is technically feasible in those plants which already have catalytic hydrogenation sections, or are planning to establish one for the production of various chemicals.

Backward integration degrees I-III and V do not cause environmental pollution unusual in pharmaceutical chemical plants. The effluents of the production do not require specific treatment. The air is not polluted. Backward-integration degree IV involves the use of sodium cyanide, a very poisonous chemical, which should be handled with special care and the same applies to effluents containing sodium cyanide. Minimum amounts of hydrogen cyanide, a very poisonous gas, might pollute the air. Backward-integration degree V requires special safety measures in order to avoid fire and explosion in the plant.

No special labour safety regulations need to be observed, except when handling sodium cyanide.

Water, steam, electricity and cold energy requirements are not unusual.

The technical level of the technology of the average performer is not competitive, hence only the best offers should be considered when buying production know-how.

The economic feasibility of CHLOROQUINE Phosphate is equally influenced by the price and conversion efficiency of the key intermediates which are dominant elements of C_{tp} at backward-integration degree I, whereas conversion costs play a gradually increasing role from backward integration III onwards. Measured by the criteria used in this study, only the ideal performer makes a gross profit from backward-integration degreee III onwards,

and this conclusion implies that not even the ideal performer is competitive on the international market. The convertible currency saving is significant at backward-integration degree III.

The global CHLOROQUINE Phosphate market represents a total value of about $US 35 million at manufacturers' price level, and more than 90 per cent of the production is consumed in developing countries. There is no manufacturer in Africa, the share of which in global consumption is more than 30 per cent. A slow growth and no turning point in the life cycle curve of CHLOROQUINE Phosphate consumption is expected until 1990.

10.2 Alternative strategies

10.2.1 Total backward integration

This strategy makes the CHLOROQUINE Phosphate manufacturer completely independent from key intermediates the prices of which can also be influenced by other CHLOROQUINE producers. Total backward integration is a very difficult technical task even in countries or companies with experience in commercial scale organic chemical synthesis. Taking into account that (a) the technical level of the studied novoldiamine technology is lower than desirable, and (b) the novoldiamine production is economic only if the starting chemicals are produced in large quantities by the same manufacturer, the total backward integration is not the optimum economic choice among the strategic alternatives.

Total backward integration cannot be attained without good research and development facilities and efficient management either.

The convertible currency saving is $US 8.70 to $US 12.69 per kg of CHLOROQUINE Phosphate. The unit gross profit of the ideal performer is $US 0.86, whereas the average performer makes a unit loss of $US 6.03.

10.2.2 Advanced backward integration

This alternative assumes that novoldiamine is purchased and 4,7-dichloroquinoline is produced starting from m-chloroaniline, TEOF and DEM.

It is advisable to possess novoldiamine technology with this alternative as well, even if it is not of the best quality because critical demand-supply situations might render such a technology economically feasible on the short run.

This technical alternative offers the best economic feasibility, but it also assumes own R + D basis.

The convertible currency saving is $US 6.87 to $US 11.11/kg of CHLOROQUINE Phosphate production.

A variation of this alternative is when EMME is used for the synthesis of 4,7-dichloroquinoline. This route is clearly less favourable from economic points of view, because EMME is also a key intermediate and its share is about 34 per cent in the direct material costs and about 23 per cent of the total production costs. This is particularly important when the technical level of the production technology is low, because the world-market price of EMME is quite unfavourable for CHLOROQUINE production.

The convertible currency saving is $US 3.55 to $US 8.31/kg of CHLOROQUINE Phosphate.

10.2.3 Minimum backward integration

In this alternative, CHLOROQUINE Phosphate is produced from purchased novoldiamine and 4,7-dichloroquinoline.

The advantage of this alternative is that production is technically easy and practically no investment is required.

The main disadvantage is that the production is unprofitable, and the currency saving of the ideal performer is $US 2.37/kg of CHLOROQUINE Phosphate, whereas the average performer loses hard currency also.

The process economics are very sensitive to the costs of the two key intermediates, whose share represents 97 per cent of the direct material costs and 93 per cent of the total production costs.

Dependence on key intermediate suppliers is very high.

This alternative could be considered as an initial step of advanced backward integration.

10.2.4 Purchase of CHLOROQUINE Phosphate bulk substance

The strategic alternatives would not be complete without considering the continued purchase of CHLOROQUINE Phosphate bulk substance at competitive prices on the world market and to use the investment resources for the production of pharmaceutical bulk substances with limited availability and/or better economic feasibility.

10.2.5 Some factors affecting the alternative strategies

Procurement

There are two possible variations on all the alternative strategies:

(i) Long-term purchasing agreement, or
(ii) Buying at spot prices on the world market of CHLOROQUINE Phosphate and intermediates.

The benefits of variation (i) include the guaranteed supply and independence from increases of the market prices; the main risk is that no profit can be realized from the eventual decreases of the spot prices.

The advantage of variation (ii) is the possibility of making extra profit from the decreased spot prices; the principal risk is that the production costs are very sensitive to the increases of spot prices and there might also be availability problems if the balance of demand and supply is disturbed to an unusual extent.

It must be stressed, however, that the procurement efficiency plays an eminent role in process economics, because direct materials are dominant cost elements and their share in C_{tp} depends on prices and conversion efficiency to the same extent.

Technology

A decision should also be made whether to establish one's own R + D programme, or to buy technical improvements also in the future. At the early stages, co-operation with the technology supplier seems to be the most expedient decision, but the medium-term objective should be the establishment of one's own research apparatus, however modest, capable of developing the existing production technologies.

Management

The more advanced is the vertical integration, the more dominant is the share of conversion costs in the total production costs.

The conversion costs could not be analysed in this study in detail for lack of break-down figures and also because cost components such as depreciation, interest on investment loans and working capital, taxes, insurances, royalties, overheads, etc. vary from country to country and even from manufacturer to manufacturer within the same country.

The reduction of conversion costs needs effective management of all resources and sales activities. Once all practical reserves in technical development have been exhausted, management becomes the only dominant element of the total production costs and the decisive factor of competition.

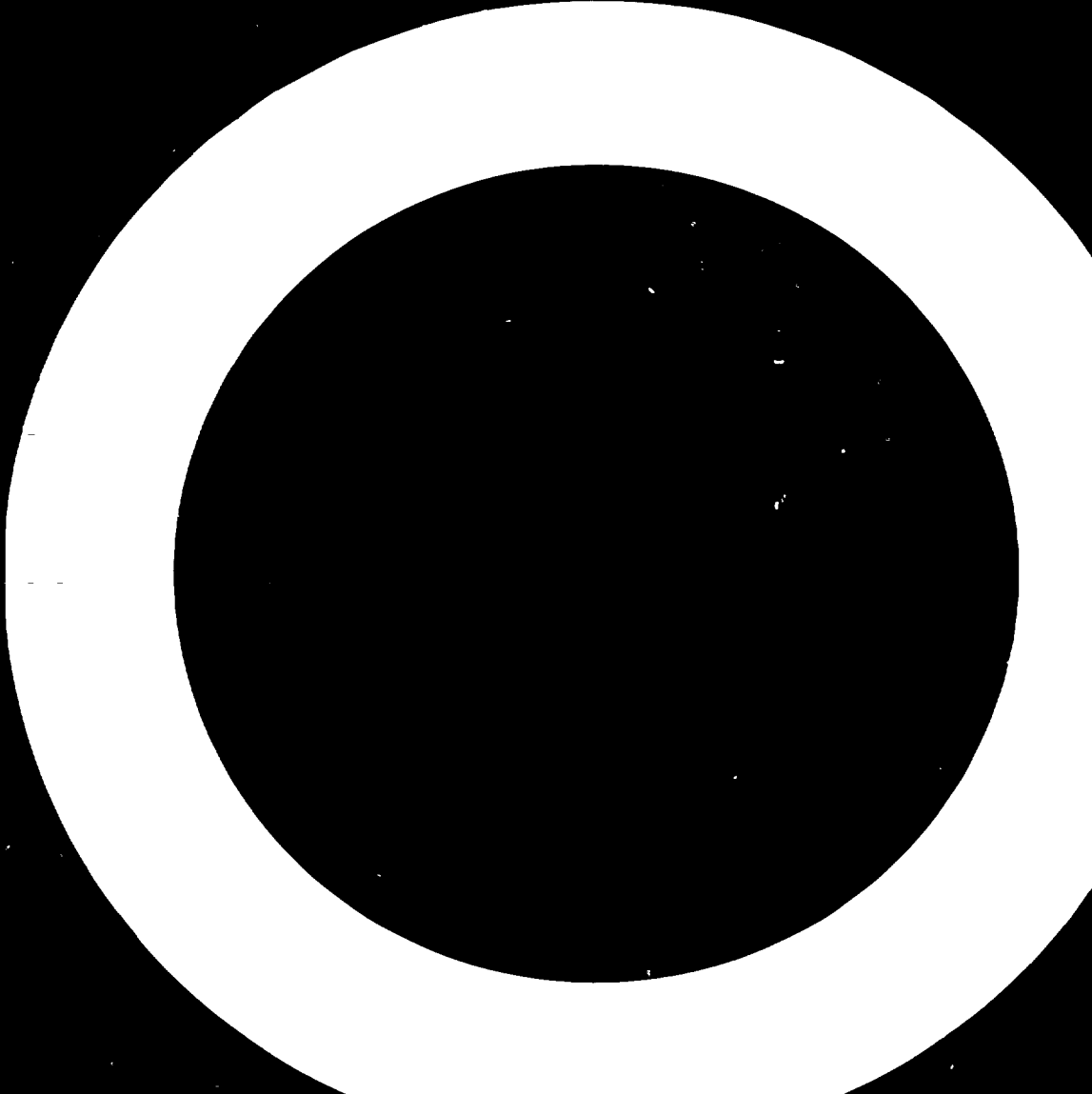
10.3 Recommendations

Developing countries at various stages in the development of the pharmaceutical industry have been summarily reviewed with respect to their possibilities to implement the various degrees of backward integration.

The minimum backward integration is technically feasible, but economically not attractive. Local production can be considered primarily in those countries where the short-term objective is to gain experience in and to train skilled staff for the pharmaceutical chemical industry.

The advanced backward integration of the manufacture of CHLOROQUINE Phosphate is technically feasible and economically acceptable. Therefore, it is worth considering the making of in-depth studies on its marketing, engineering and financial aspects, particularly in African countries with high CHLOROQUINE consumption, aiming at establishing or expanding the production of 4-aminoquinolines and/or of pharmaceutical chemicals and intermediates in general.

Integrated CHLOROQUINE manufacturers, particularly those with high-pressure hydrogenation capacity, might also be interested in studying the investment opportunity for the manufacture of novoldiamine.



Annex 1 to the

Technical and economic analysis of the manufacture

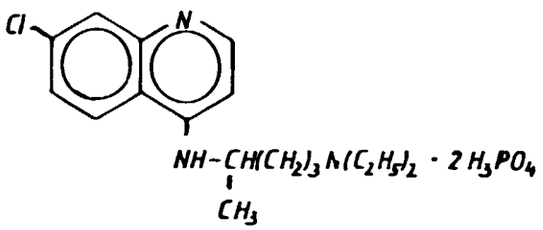
of CHLOROQUINE Phosphate

Chemical synthesis of CHLOROQUINE Phosphate

A. BASIC DATA OF THE PHARMACEUTICAL BULK SUBSTANCE

1. International non-proprietary name: CHLOROQUINE[1/] Phosphate

2. Graphic formula:



3. Chemical formula: $C_{18}H_{26}ClN_3 \cdot 2H_3PO_4$

4. Molecular weight: 518.87

5. Chemical abstracts index name: 1,4-Pentanediamine, N^4-/7-chloro-4-
-quinolinyl/-N',N'-diethyl-,phosphate/1:2

6. CAS registry number: [50-63-5]

7. Other forms: CHLOROQUINE may be used as a base [54-05-7], as a hydrochloride [3545-67-3], as a sulphate [132-73-0] or as sulphate monohydrate [6823-83-2] salt, but commercial CHLOROQUINE is usually the Phosphate. Therapeutic doses are expressed as CHLOROQUINE base, of which 100 mg is approximately equivalent to 160 mg of CHLOROQUINE Phosphate, or to 136 mg of CHLOROQUINE Sulphate monohydrate, or to 123 mg of CHLOROQUINE Hydrochloride. A variety of other salts has been reported[2/] but they offer no advantage over the Phosphate.

1/ The use of essential drugs, Technical Report Series 685, World Health Organization, Geneva (1983), p. 18.

2/ Belg. Pat. 590,165 (1960), French M. Pat. 1258M (1962), Jap. Pat. 7490/62-B-2 (1962), Jap. Pat. 8291/62-B-2(1962), French M. Pat. 2038M (1963).

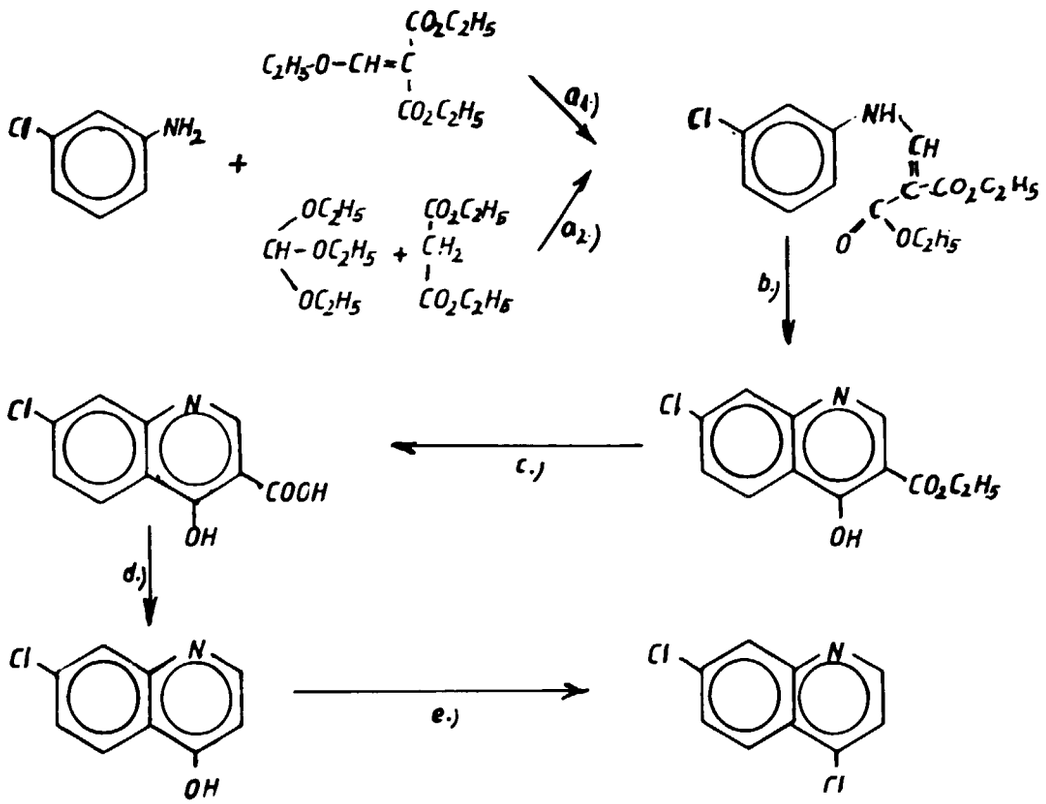
8. Basic patent: H. Andersag. S. Breitner and H. Jung, CA 36 4973, Ger. Pat., 683.692 (to I.G. Farbenindustrie A.G., 1939), and H. Andersag, S. Breitner and H. Jung, CA 35 3771, US Pat. 2,233,970 (to Winthrop Chemical Co., 1941).

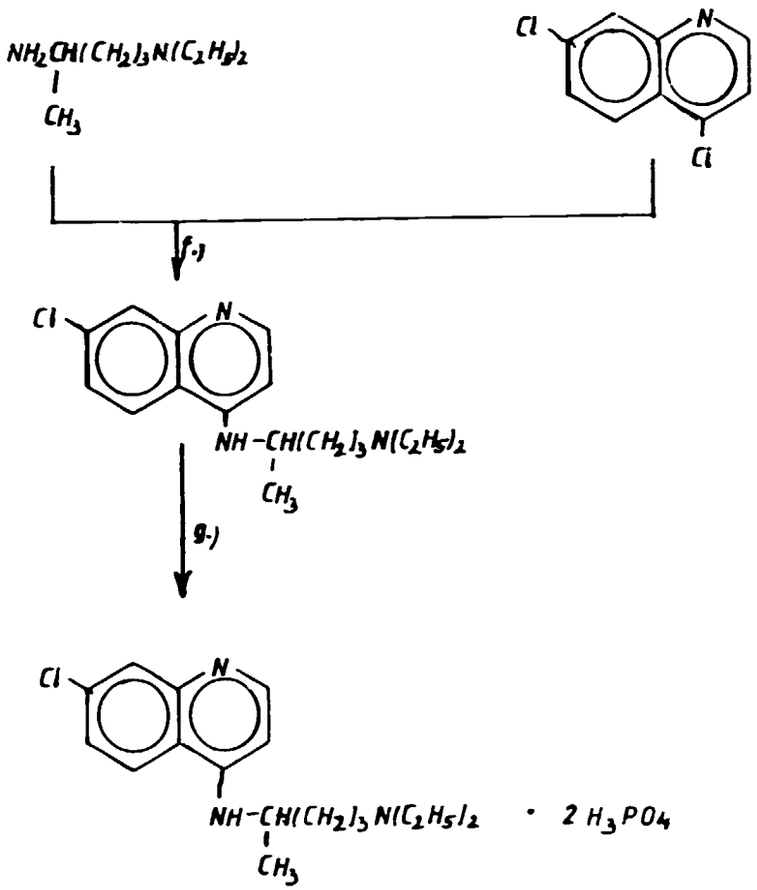
B. BRIEF DESCRIPTION OF THE PRODUCTION PROCESSES

The two key intermediates are 4,7-dichloroquinoline [86-98-6] and novoldiamine [140-80-7]. Most of the manufacturers have their own 4,7-dichloroquinoline production starting from m-chloroaniline [108-42-9] and EMME [87-13-8], or alternatively from DEM [64-17-5] and TEOF [122-51-0], whereas novoldiamine is usually purchased.

1. Chemical synthesis of CHLOROQUINE Phosphate

1.1 Schematic illustration of the synthesis





CHLOROQUINE Phosphate

Backward integration I

According to the patent literature,[3/] 105 g of 4,7-dichloroquinoline (m.p. 93° to 94°) are heated with 200 g of novoldiamine for 7 hours in an oil bath to 180° while stirring until a test portion dissolved in diluted nitric acid does not show a precipitation with sodium acetate solution. The mixture is dissolved in diluted acetic acid and made alkaline by adding sodium hydroxide. The base is extracted with ether, dried with potassium carbonate, the ether removed by distillation and the residue fractionated. CHLOROQUINE

3/ Andersag, H., Breitner, S. and Jung, H.: U.S. Patent 2,333,970; March 4, 1941; (German priority: 1937) assigned to Winthrop Chemical Company, Inc.

(b.p. 212° to 214°C at 0.2 mm) is obtained. On cooling the compound solidifies crystalline. It melts, recrystallized from benzene, at 88°C. The base combines with phosphoric acid to yield a diphosphate salt.

For plant operation,[4/] 4,7-dichloroquinoline is condensed with novoldiamine (reactions f) in molten phenol and diphosphate salt (reaction g) is formed in the same reaction mixture. Advantages of this method also include that the condensation can be carried out at a lower temperature without using a large excess of novoldiamine.

Backward integration II

m-Chloroaniline is condensed with EMME (reaction a_1) and the obtained $C_{14}H_{16}ClNO_4$ is thermally cyclized at 250°C (reaction b). After hydrolysis (reaction c) in the presence of hydrochloric acid and decarboxylation (reaction d) at 230°C, the obtained 4-chloro-7-hydroxy--quinoline is chlorinated to yield 4,7-dichloroquinoline (reaction e).

Backward integration III

Improved routes to intermediate $C_{14}H_{16}ClNO_4$ were reported.[5/] The alternative using m-chloroaniline, DEM and TEOF was reported by Price and Roberts (reaction a_2). Reactions b-c are the same as described under backward integration II.

Backward integration IV

Chloroacetic acid is dissolved in crushed ice and neutralized by sodium hydroxide at a temperature not exceeding 25°C. The solution of sodium

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4/ Bruke et al., J. Am. Chem. Soc., 68, 1214 (1946).

5/ C.C. Price, R.M. Roberts, J. Am. Chem. Soc., 68, 1204 (1946).
U.S. Pat. 2,638,480 (1953),
U.S. Pat. 2,684,976 (1954),
C.C. Wang et al., Yao Hsueh Hsueh Pao, 10, 183 (1963),
G.D.R. Pat. 38,681 (1965), and
Neth. Pat. 6,500,850 (1965).

chloroacetate is added to the concentrated aqueous solution of sodium cyanide at 70°C and the reaction is completed at 95°C. The little hydrogen cyanide liberated during the reaction is exhausted through the ventilation pipe. The sodium cyanoacetate solution is made strongly alkaline by sodium hydroxide and boiled until ammonia is liberated. The water is evaporated, and the residue is dissolved in benzene and esterified by ethanol in the presence of concentrated sulphuric acid. The obtained DEM is washed, dried and vacuum-fractionated.[6/]

1.2 Chemical reactions

a$_1$) $C_6H_6ClN + C_{10}H_{16}O_5 = C_{14}H_{16}ClNO_4 + C_2H_6O$

127.57 216.23 297.74 46.07

a$_2$) $C_6H_6ClN + C_7H_{16}O_3 + C_7H_{12}O_4 = C_{14}H_{16}ClNO_4 + 3C_2H_6O$

127.57 148.20 160.17 297.74 138.21

b) $C_{14}H_{16}ClNO_4 = C_{12}H_{10}ClNO_3 + C_2H_6O$

297.74 251.67 46.07

c) $C_{12}H_{10}ClNO_3 + H_2O = C_{10}H_6ClNO_3 + C_2H_6O$

251.67 18.02 223.61 46.07

d) $C_{10}H_6ClNO_3 = C_9H_6ClNO + CO_2$

223.62 179.61 44.01

e) $C_9H_6ClNO + POCl_3 = C_9H_5Cl_2N + HPO_2 + Cl_2$

179.61 153.33 198.05 63.98 70.91

f) $C_9H_5Cl_2N + C_9H_{22}N_2 = C_{18}H_{26}ClN_3 + HCl$

198.05 158.29 319.88 36.46

g) $C_{18}H_{26}ClN_3 + 2H_3PO_4 = C_{18}H_{32}ClN_3O_8P_2$

319.88 196.00 515.87

6/ Gyógyszerek és gyógyszergyártás, (= Drugs and Drug Manufacturing), Müszaki Könyvkiadó, Budapest (1957), p. 230.

1.3 Combined equation of the synthesis

$$a_1\text{-g)}\ \underset{127.57}{C_6H_6ClN} + \underset{216.23}{C_{10}H_{16}O_5} + \underset{18.02}{H_2O} + \underset{153.33}{POCl_3} + \underset{158.29}{C_9H_{22}N_2} + \underset{196.00}{2H_3PO_4} =$$

$$= \underset{515.87}{C_{18}H_{32}ClN_3O_8P_2} + \underset{138.21}{3C_2H_6O} + \underset{44.01}{CO_2} + \underset{63.98}{HPO_2} + \underset{70.91}{Cl_2} + \underset{36.46}{HCl}$$

$$a_2\text{-g)}\ \underset{127.57}{C_6H_6ClN} + \underset{148.20}{C_7H_{16}O_3} + \underset{160.17}{C_7H_{12}O_4} + \underset{18.02}{H_2O} + \underset{153.33}{POCl_3} + \underset{158.29}{C_9H_{22}N_2} +$$

$$+ \underset{196.00}{2H_3PO_4} = \underset{515.87}{C_{18}H_{32}ClN_3O_8P_2} + \underset{230.35}{5C_2H_6O} + \underset{44.01}{CO_2} \quad \underset{63.98}{HPO_2} + \underset{70.91}{Cl_2} + \underset{36.46}{HCl}$$

1.4 Chemical input conversion coefficients

The various expressions of the conversion efficiency available from the studied sources were converted into chemical input conversion/consumption coefficients to refer to the manufacture of 1 kg of CHLOROQUINE Phosphate and were summarized in table 1. Publications which described the chemical conversion efficiency of different steps of backward integration but came from different sources, were not included in table 1 but they were used for the evaluation of the quality of data from other sources. For example, Bruke and others reported a 76-81 per cent yield of CHLOROQUINE Phosphate to 4,7-dichloroquinoline (column 1 in table 1), and Price and Roberts published[7/] a 90-96 per cent yield of 4,7-dichloroquinoline based on 4-hydroxy-7-chloroquinoline and a 70-77 per cent yield of 4-hydroxy--7-chloroquinoline based on m-chloroaniline. Input conversion coefficients were not given for DEM, TEOF, phosphorous oxychloride, etc., but the conversion of the available data to express yiel s with reference to CHLOROQUINE Phosphate gave useful information:

7/ Price and Roberts, J. Am. Chem. Soc., 68, 124 (1946).

Table A.1. Chemical input conversion coefficients in the manufacture of CHLOROQUINE Phosphate

Name	Source											
	1	2	3	4	5	6	7	8	9	10	11	12
Phosphoric acid		0.64	0.64		0.60		0.66	0.58			0.66	
4,7-Dichloroquinoline	0.47-0.51	0.64	0.50									
EMME				1.10	1.09	0.75	1.09	0.78	0.74			
DEM										0.51-0.68		
Chloroacetic acid											0.66	0.34
Sodium cyanide											0.25	0.18
Ethanol											1.65	0.86
TEOF										0.51-0.54	0.67	
m-Chloroaniline				0.65	0.59	0.40	0.60	0.42	0.59		0.54	
Novoldiamine		0.51	0.67	0.60	0.54	0.41	0.67	0.44	0.42		0.48	
Diphenyl oxide					0.51							
Phosphorous oxychloride					0.79							
Benzene techn.			1.56		1.60							
Benzene dist.					2.39							
Phenol		0.20	0.21		0.21							
Acetic acid					0.64							
Ammonia					0.34							
Kerosene					0.57		0.56					
Ethanol, solv.		13.07			13.00							
Activated carbon			0.33		0.33							
Sodium hydroxide			1.86		1.86							
Hydrochloric acid, techn.					1.13							
Methanol		0.58	1.52		1.52		1.52				1.27	
Toluene											0.80	
Acetone						1.12						

1 Bruke et al., J. Am. Chem. Soc., 68, 1214 (1946)
2 UNIDO/IOD.299/Add.1 of 14 August 1978
3 Unpublished country project proposal, 1982
4 Unpublished UNIDO document, 1977
5 UNIDO/ID/WG.267/5 of 28 July 1978
6 UNIDO/ID/WG.331/4 of 26 September 1980
7-8 UNIDO/PC.14 of 18 August 1981
9 UNIDO/PC.52 of 13 September 1982
10 UNIDO consultant's report 1983
11 same as 7-8
12 Gyógyszerek és gyógyszergyártás (= Drugs and Drug Manufacturing), Müszaki Könyvkiadó, Budapest, 1957, p. 230.

	y	f
4,7-Dichloroquinoline	76-81	0.47-0.51
4-Hydroxy-4-chloroquinoline	68-78	0.45-0.51
m-Chloroaniline	48-60	0.42-0.52

because these calculated limit values confirmed the validity of other m-chloroaniline conversion coefficients and gave quantitative information on the chlorination step within backward integration III, not analysed separately.

With a few exceptions, only the conversion efficiencies of principal reactants were given in the literature and the consumption of less important chemicals and/or auxiliary materials was expressed as a value under the collective term other materials, if at all. The scarce information was included in table 1, because it is qualitatively useful and could be used to estimate roughly the value of other materials.

Those sources were disregarded when quantitative data were available for the inputs but the CHLOROQUINE Phosphate yield was not given.[8/]

1.5 Other information

A chapter was devoted to the wastes and waste water treatment of chemicals[9/] produced by organic synthesis, and a simplified flow sheet for the manufacture of CHLOROQUINE phosphate by a process[10/] similar to that of backward-integration degrees II-III was described in a UNIDO document. The analysis of the described operations concluded that recovery of various

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8/ Pharmaceutical Manufacturing Encyclopedia, Noyes Data Corporation, Park Ridge, New Jersey, U.S.A., (1979), p. 116.

9/ UNIDO/IS.387 of 6 June 1983: Water use and effluent treatment practices for the manufacture of the 26 priority drugs in the UNIDO illustrative list.

10/ A.R. Surrey, H.F. Hammer, J. Am. Chem. Soc. 68, 113 (1946).

solvents was an integral part of the process and the residuum of solvent recovery had to be incinerated. No hazardous waste other than organic solvents was expected.

Similar information was not found for backward-integration degree IV but the analysis of the chemical reactions revealed that hazardous wastes, hydrogen cyanide and/or cyanide ions, might enter the air and waste waters from the manufacture of DEM.

No special labour safety regulations need to be observed, except when handling sodium cyanide at backward-integration degree IV.

Information in the literature and analysis of the process descriptions showed that steam, water, brine, inert gas, process water, distilled water and electricity requirements were not unusual in synthetic pharmaceutical chemical plants.

The principal apparatus used in backward-integration degrees I-IV of the manufacturing process was described in several papers, and none of them listed equipment unusual in pharmaceutical chemical plants.

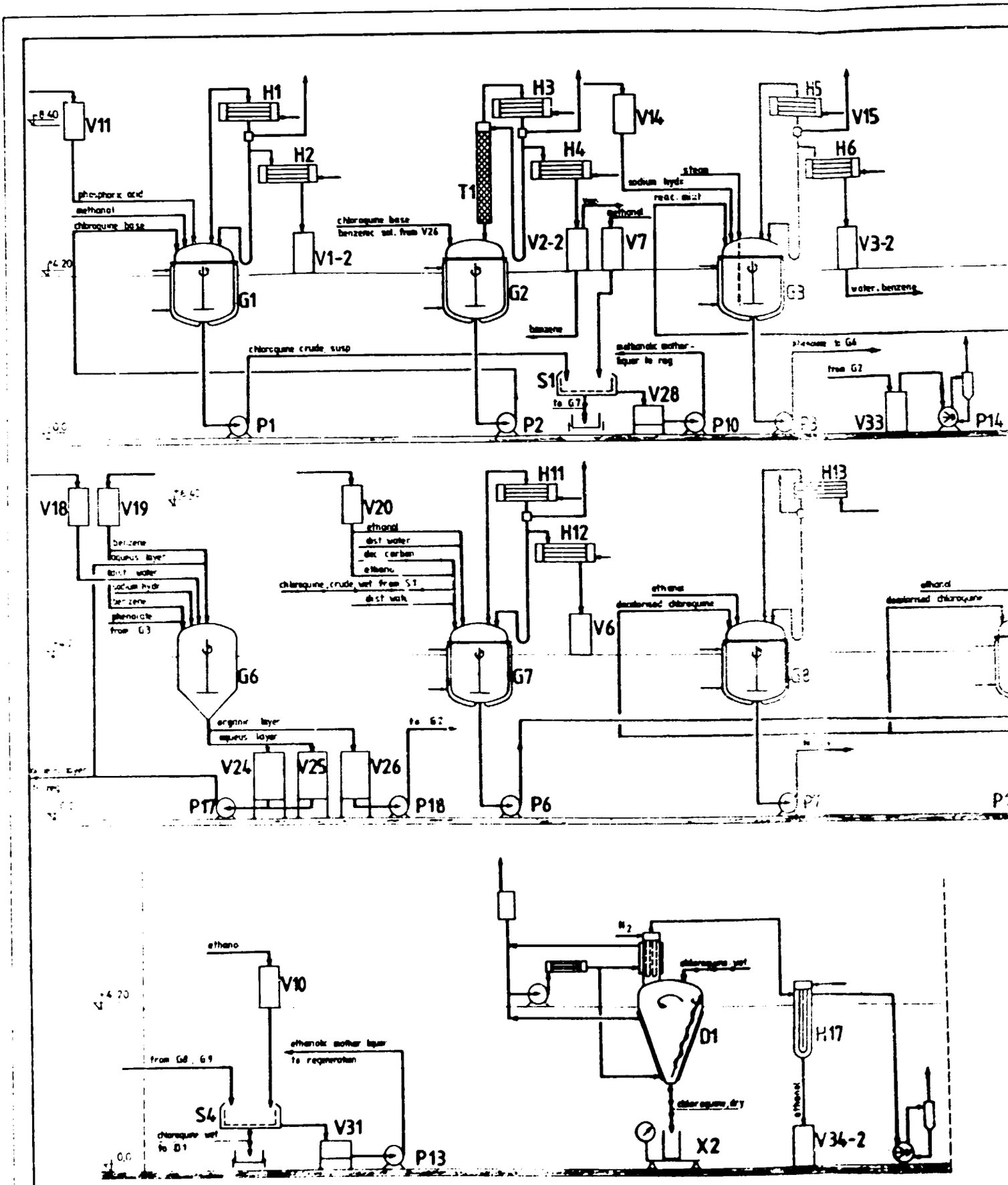
The process flow sheet and the related list of main equipment for backward-integration degree I of CHLOROQUINE Phosphate production is given in pages 60-62.[11/]

The skilled manpower requirement for backward-integration degree III was estimated about 1 hour/kg of CHLOROQUINE Phosphate.

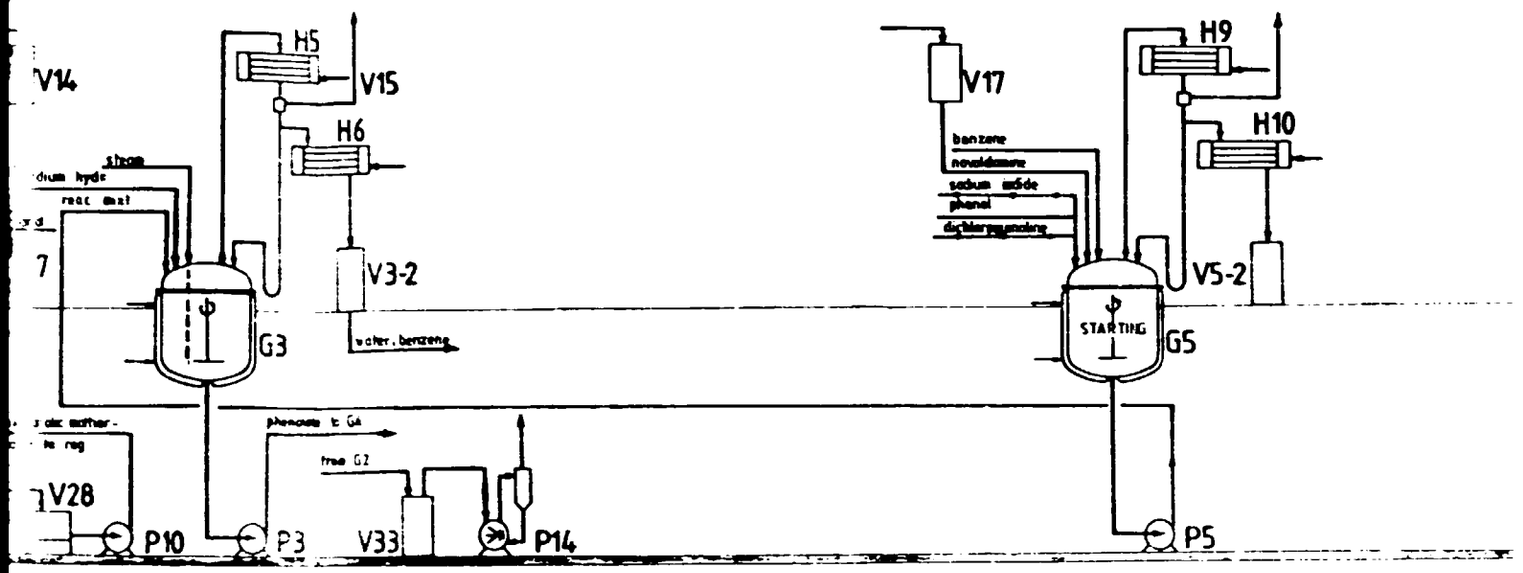
11/ Multipurpose plant, Vegyterv Hungarian Chemical Industries Engineering Centre document (1983).

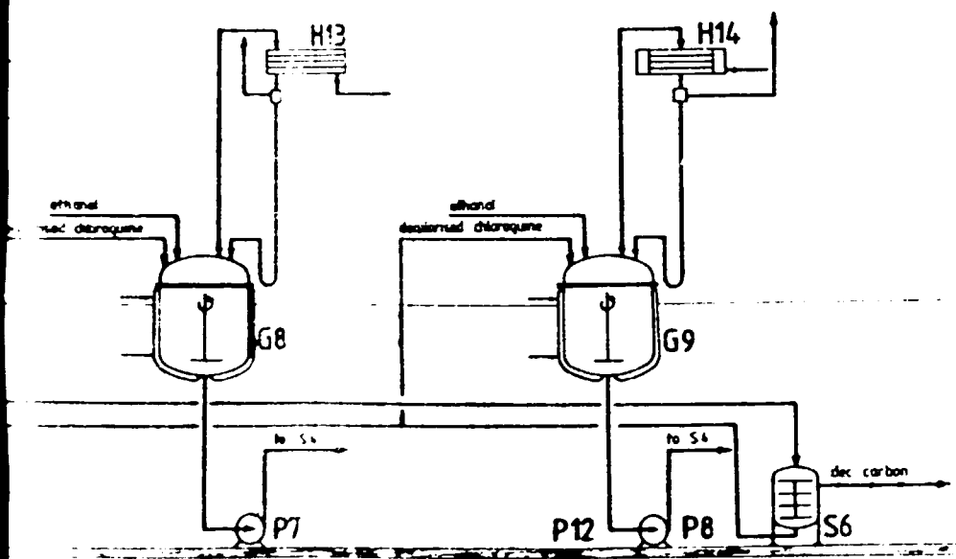
List of main equipment for the production of CHLOROQUINE Phosphate - Backward integration I

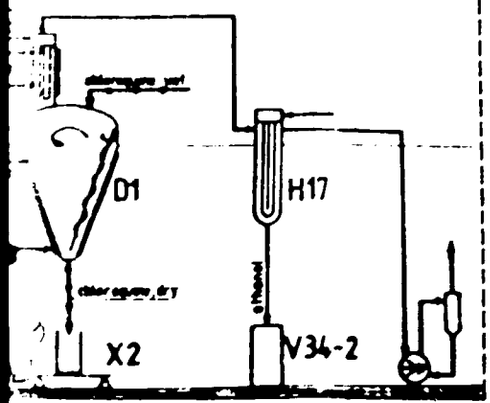
Code	Number	Name	Material
D1	1	2 m^3 vacuum drier	Stainless steel
G1, G2, G3, G7	4	3 m^3 jacketed batch reactor	Enamelled steel
G5	1	1.25 m^3 jacketed batch reactor	Enamelled steel
G6	1	5 m^3 extractor	Stainless steel
G8, G9	2	6.3 m^3 jacketed batch reactor	Enamelled steel
H1, H3, H5, H11	4	16 m^2 condenser	Stainless steel
H2, H4, H6, H12	4	16 m^2 cooler	Stainless steel
H9	1	12.5 m^2 condenser	Stainless steel
H10	1	12.5 m^2 cooler	Stainless steel
H13	1	25 m^2 condenser	Artificial carbon
H14	1	25 m^2 cooler	Stainless steel
P1, P3, P5, P6, P8, P10, P13	7	100 l/min centrifugal pump	Stainless steel
P2, P7, P12	3	As above	Enamelled steel
P14	1	60 m^3/h waterring vacuum pump	Steel
P17, P18	2	200 l/min centrifugal pump	Stainless steel
S1	1	1,000 mm diameter centrifuge	Stainless steel
S4	1	As above	Rubber-coated steel
S6	1	10 m^2 pressfilter	Stainless steel
T1	1	250 mm diameter distillation column	Stainless steel
V1-2, V2-2, V3-2, V5-2	4	0.63 m^3 receiver tank	Stainless steel
V7, V10	2	0.63 m^3 feeding tank	Stainless steel
V11, V14, V20	3	0.63 m^3 feeding tank	Polyester
V24, V25, V26	3	2 m^3 receiver tank	Stainless steel
V28	1	0.5 m^3 filtrate receiver	Stainless steel
V33	1	0.25 m^3 feeding tank	Steel
V34-2	1	0.25 m^3 receiver tank	Steel
X2	1	500 kg balance	Steel


V11
H1
H2
H3
H4
H5
H6
V14
V15
T1
V1-2
V2-2
V7
V3-2
G1
G2
G3
P1
P2
P10
V33
P14
S1
V28
V18
V19
V20
H11
H12
H13
V6
G6
G7
V24
V25
V26
P17
P18
P6
V10
S4
V31
P13
D1
H17
X2
V34-2

SECTION 1



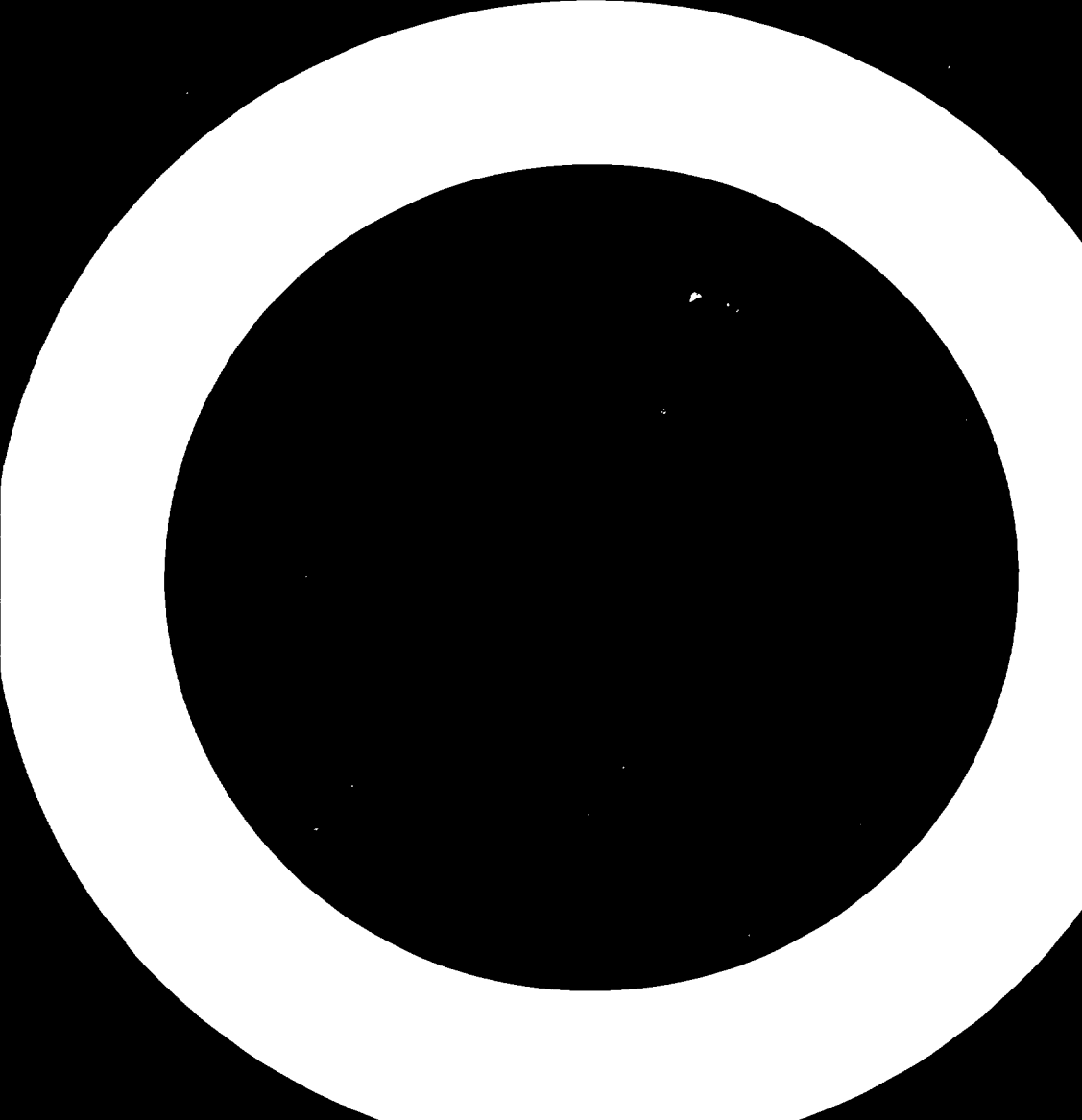




CHLOROQUINE Phosphate production process flow s[illegible]

Backward integration I

SECTION 2



Annex 2 to the

Technical and economic analysis of the manufacture

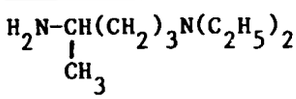
of CHLOROQUINE Phosphate

Chemical synthesis of Novoldiamine

I. BASIC DATA OF THE KEY INTERMEDIATE

1. Common name: Novoldiamine

2. Graphic formula:



3. Chemical formula: $C_9H_{22}N_2$

4. Molecular weight: 158.29

5. Chemical abstracts index name: N',N'-diethyl-1,4-pentanediamine

6. CAS registry number: [140-80-7]

7. Brief history of the product

Novoldiamine is a chemical intermediate used in the production of antimalarial drugs containing a 4-diethylamino-1-methyl-butylamine side chain. The first compound of this group, quinacrine, was marketed in the thirties. Nowadays, novoldiamine is mainly used in the production of CHLOROQUINE.

8. Basic patent: Lucas P. Kyrides, CA 40993, U.S. Pat. 2,365,825 (to Monsanto, 1944)

II. BRIEF DESCRIPTION OF THE PRODUCTION PROCESSES

Several manufacturing processes are described in the literature, of which two will be illustrated. Data for the techno-economic analysis are only available for one process.

1. Synthesis of Novoldiamine. Route A

2-diethylaminoethanol is chlorinated with thionyl chloride and the obtained 2-chlorotriethylamine is condensed with sodium ethylaceto-acetate. The condensation product is first hydrolysed, th... decarboxylated. The obtained novolketone in methanolic solution is catalytically hydrogenated at 100°C, in the presence of ammonia, to yield novoldiamine.

1.1 Schematic illustration of the synthesis

$(C_2H_5)\ N-CH_2-CH_2-OH$ (2-diethylaminoethanol) —a) chlorination→ $(C_2H_5)_2N-CH_2-CH_2-Cl$ + (2-chlorotriethylamine)

+ $CH_3-CO-\overset{Na}{\underset{|}{C}}H-COOC_2H_5$ (sodium ethylacetoacetate) —b) condensation→ $(C_2H_5)_2N-CH_2-CH_2-\overset{CO-CH_3}{\underset{COOC_2H_5}{\underset{|}{\overset{|}{C}}H}}$

—c) hydrolysis→ $(C_2H_5)_2N-CH_2-CH_2-\overset{CO-CH_3}{\underset{COOH}{\underset{|}{\overset{|}{C}}H}}$

—d) decarboxylation→ $(C_2H_5)_2N-CH_2-CH_2-CH_2-CO-CH_3$ (novolketone)

—e) hydroammonolysis→ $(C_2H_5)_2N-CH_2-CH_2-CH_2-\underset{NH_2}{\underset{|}{C}}H-CH_3$ (NOVOLDIAMINE)

1.2 Chemical reactions

a) $C_6H_{15}NO + SOCl_2 = C_6H_{14}ClN + HCl + SO_2$

117.19 118.97 135.64 36.46 64.06

b) $C_6H_{14}ClN + C_6H_{10}O_3 + Na + H_2O + NH_3 + H_2 = C_{12}H_{23}NO_3 + NaCl + 1/2\,H_2$

135.64 130.14 22.99 18.02 17.03 2.02 229.32 58.44 1.01

c) $C_{12}H_{23}NO_3 + H_2O = C_{10}H_{19}NO_3 + C_2H_6O$

229.32 18.02 201.27 46.07

d) $C_{10}H_{19}NO_3$ = $C_9H_{19}NO$ + CO_2

201.27 157.26 44.01

e) $C_9H_{19}NO$ + NH_3 + H_2 = $C_9H_{22}N_2$ + H_2O

157.26 17.03 2.02 = 158.29 + 18.02

1.3 Combined equation of the synthesis

$C_6H_{15}NO$ + $SOCl_2$ + $C_6H_{10}O_3$ + Na + H_2O + NH_3 + H_2 =

117.19 118.97 130.14 22.99 18.02 17.03 2.02

= $C_9H_{22}N_2$ + HCl + SO_2 + NaCl + $1/2H_2$ + C_2H_6O + CO_2 + H_2O

158.29 36.46 64.06 58.44 1.01 46.07 44.01 18.02

1.4 Chemical input conversion coefficients

In the absence of industrial data, only the molar chemical input conversion coefficients are given:

2-diethylaminoethanol	0.74
thionyl chloride	0.75
ethyl acetoacetate	0.82
metallic sodium	0.15

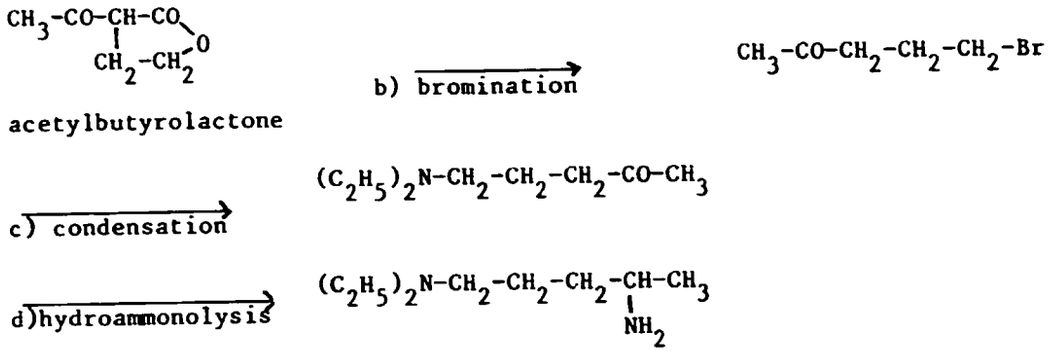
2. Synthesis of novoldiamine. Route B

Ethylacetoacetate is reacted with ethyleneoxide in absolute ethanol to yield acetylbutyrolactone which is brominated with hydrobromic acid and subsequently condensed with diethylamine to produce novolketone. From this step on, the synthesis proceeds as described with route A.

2.1 Schematic illustration of the synthesis

$CH_3-CO-CH_2-COOC_2H_5$ + $(CH_2)O$

ethyl acetoacetate ethylene oxyde a) lactone formation



NOVOLDIAMINE

2.2 Chemical reactions

a) $C_6H_{10}O_3 + C_2H_4O = C_6H_8O_3 + C_2H_6O$

130.14 44.05 128.13 46.07

b) $C_6H_8O_3 + HBr = C_5H_9BrO + CO_2$

128.13 80.91 165.03 44.01

c) $C_5H_9BrO + C_4H_{11}N + NaOH = C_9H_{19}NO + NaBr + H_2O$

165.03 73.14 40.00 157.26 102.89 18.02

d) $C_9H_{19}NO + NH_3 + H_2 = C_9H_{22}N_2 + H_2O$

157.26 17.03 2.02 158.29 18.02

2.3 Combined equation of the synthesis

$C_6H_{10}O_3 + C_2H_4O + HBr + C_4H_{11}N + NaOH + NH_3 +$

130.14 44.05 80.91 73.14 40.00 17.03

$+ H_2 = C_9H_{22}N_2 + C_2H_6O + CO_2 + NaBr + 2H_2O$

2.02 158.29 46.07 44.01 102.89 36.04

2.4 Chemical input conversion coefficients

The synthesis of novoldiamine was included as backward-integration degree V in the manufacture of CHLOROQUINE Phosphate. Chemical input conversion coefficients for the hydroammonolysis of novolketone were available from the literature, whereas data for Route B were described in a patent and obtained from a European manufacturer, which had stopped production of novoldiamine about 10 years ago.

Table A.2. Chemical input conversion coefficients and percentage yields of novoldiamine synthesis

Name	F	f_1	y_1	f_2	y_2
Novolketone	0.99	1.08	92	1.02	97 a/
Hydrobromic acid	0.51	0.75	68	...	...
Diethylamine	0.46	0.66	70	...	...
Acetobutyrolactone	0.81	1.29	63	1.40	58 b/
Ethyl acetoacetate	0.82	2.16	38	...	...
Ethylene oxide	0.28	1.33	21	...	...

a/ BIOS Final Report 116, Appendix 9, Process 7

b/ Hungarian patent 153,500

f_1/y_1 ... commercial-scale production data

f_2/y_2 ... literature data

F, f and y values in table 1 refer to Novoldiamine, but disaggregated yields were also available in this case.

Tables 1 and 2 show that the conversion efficiency of the hydroaminoanalysis is very good, but the syntheses of novolketone and acetobutyrolactone can probably be improved.

Table A.3. Disaggregated chemical input conversion coefficients and yields of novoldiamine synthesis

Name	F	f	y
Novolketone			
Hydrobromic acid	0.51	0.75	68
Diethylamine	0.47	0.67	70
Acetobutyrolactone	0.81	1.29	63
Sodium hydroxide	0.25	0.44	57
Acetobutyrolactone			
Ethylacetoacetate	1.02	1.70	60
Ethylene oxide	0.34	1.00	34

2.5 Estimation of the production costs of Novoldiamine. Route B

The cost estimates of the average performer were based on the f_1 and y_1 values in table 1. The 97 per cent literature conversion efficiency of the hydroaminolysis reaction was taken for the ideal performer, and a general 10 per cent improvement of y values was assumed for the remaining reactions, in the absence of specific data.

Table 3 shows that ethylacetoacetate is a key intermediate and the share of direct materials in C_{tp} is about 64 per cent. The average performer makes a unit gross loss of $US 0.75, and a unit gross profit of $US 0.89 could be made, if the chemical conversion efficiency were improved by 10 per cent.

The unit hard currency saving of the average and ideal performers are $US 5.25 and $US 6.29, respectively.

The cost analysis implies that those Novoldiamine manufacturers enjoy a comparative advantage, who produce or purchase the reactants in large volumes also for the manufacture of other products, because their chemical input prices are competitive and they can employ an automated, modern technology in case of own production.

Table A.4. Estimation of the production costs of novoldiamine

Cost element	C_1 $US	C_1 %	C_2 $US	C_2 %
Ethylacetoacetate	4.32	26.1	3.90	26.2
Key intermediates	4.32	26.1	3.90	26.2
Hydrobromic acid	1.77	10.7	1.58	10.6
Diethylamine	0.98	5.9	0.87	5.8
Ethylene oxide	1.77	10.7	1.62	10.9
Sodium hydroxide	0.09	0.5	0.08	0.5
Other materials	1.60	9.7	1.44	9.7
Direct material costs	10.53	63.7	9.49	63.7
Conversion costs	6.00	36.3	5.40	36.3
Production costs	16.53	100.0	14.89	100.0

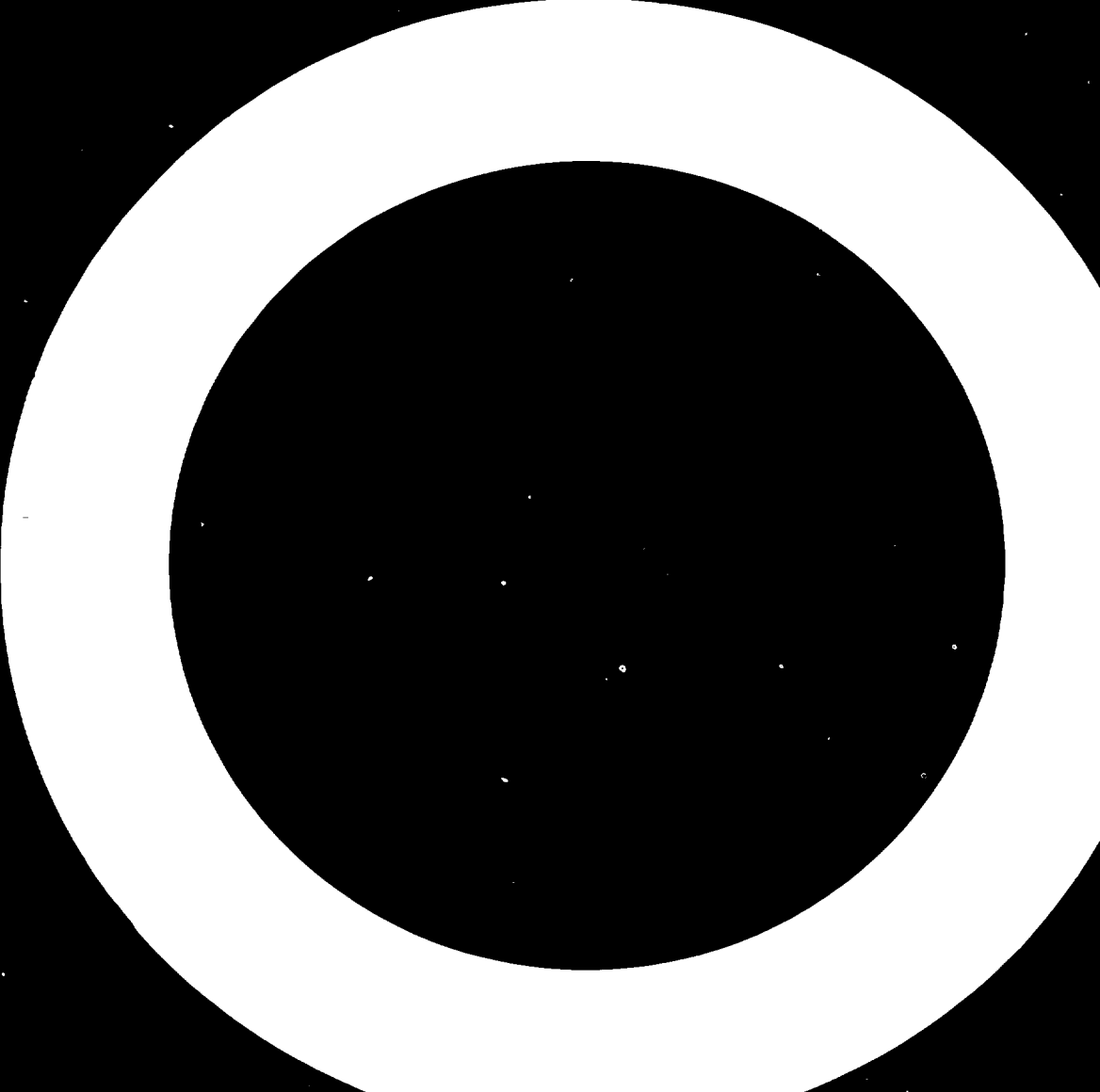
2.6 Other information

Information was not available for environmental pollution, but the chemical reactants and products involved in the synthesis do not indicate problems unusual in pharmaceutical chemical plants.

Novolketone is a toxic, caustic liquid. Pyrophorous Raney-Ni catalyst and high-pressure hydrogen are hazardous chemicals. Fire and explosion might occur during the hydroammonolysis of novolketone, if the safety regulations are not observed.

The requirements for utilities are customary. The production technology is more complex and more sensitive to changes in process parameters than that of 4,7-dichloroquinoline. Reactions a), b) and c) can be carried out in multipurpose batch reactors, but special equipment is needed for reaction d).

The economic feasibility of Novoldiamine synthesis depends to a large extent on the production volume or on the utilization of the capacity of the hydrogenation plant for the manufacture of other chemicals.



Annex 3 to the

Technical and economic analysis of the manufacture

of CHLOROQUINE Phosphate

Patent information on CHLOROQUINE Phosphate and key-intermediates manufacturing processes*/

1. EP 56766, FR 000765/1982/appl. date 810116
   4-aminochloroquinolines
   Rhône-Poulenc Santé
   Baudouin, Michel; Michelet, Daniel;
   CA: 97/25/216029s

2. FR 1514280/1968/appl. date 670110
   Dikloroquinolines
   Roussel-UCLAF
   Joly, Robert; Warnant, Julien; Goffinet, Bernard
   CA 70(15)68195t

3. DD 53065/1967/appl. date 660502
   4,7-dichloroquinoline
   Schwarz, Siegfried; Bohn, Helmut; Schmidt, Dieter, Spakowski, Horst; Becker, Manfred;
   CA 67(5) 21846d

4. Germany offen DE 3112415 ../1982/appl. date 810328
   Chlorination of cyclic amides and cyclic vinylogous amides
   Dynamit Nobel A.G.
   Hofmann, Volker; Peeters, Hermann; Steffen, Klaus Dieter; Vogt, Wilhelm;
   CA 98(9) 71952 W

5. EP 56765, FR000764(1982) appl. date 810116
   4-hydroxyquinolines
   Rhône-Poulenc Santé
   Baudouin, Michel; Michelet, Daniel
   CA 97(25) 216030 K

6. HU 2188/1971/ appl. date 681230
   Continuous production of 1-diethylamino-4-amino-pentane
   HAFKI, VEGYTERV
   Laky, Markó, Csikós, Hetesi, Aszlányi, Reitmann
   CA 75(19) 117 959;

7. G.B. 1157637/1969/appl. date 650701
   2-amino-5-(diethylamino)pentane
   Sterling Drug Inc.
   CA 71(17) 80656;

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*/ Results of the computer search in all issues of Chemical Abstracts published between 1 January 1967 and 31 December 1983.

8. Germany offen DE 2923472/1980/appl. date 790609
Catalysts for the preparation of amines
Bayer A.G.
Hertel, Hoffmann, Boettger, Koernig, Baer, Lebkuecher
CA 94(10) 72304

9. RO 77631/1978/appl. date 74 0212
1-diethylamino-4-aminopentanes
Institutu de Cercetari Chimico-Farmaceutice
Radulescu, Maza, Ambrus, Aftalion, Popescu, Dimofte [illegible]mionovici
CA 92(7) 58214

Annex 4 to the

Technical and economic analysis of the manufacture of CHLOROQUINE Phosphate

Manufacturers and suppliers of CHLOROQUINE Phosphate

1.1 Integrated manufacturers

Bayer AG
Geschäftsbereich Pharma EP, Vertrieb Pharma Chemikalien
D-5090 LEVERKUSEN-Bayerwerk

Telex: 85103-0 by d
Cable: bayer leverkusen
Phone: 0214/30 8415

The Bengal Immunity Co., Ltd*/
Marketing Division
(Management under Govt. of India)
153, Lenin Saranee
CALCUTTA 700 013
India

Telex: 21-4352
Cable: INJECTULE
Phone: 27-4678, 27-2266 & 67

China National Chemicals Corporation
The Ministry of Chemical Industry
Erh-Li-Kon Hsi
Chiao
BEIJING
The People's Republic of China

Alkaloida Chemical Factory
P.O.B. 1
H-444 Tiszavasvári
represented by
Medimpex Hungarian Trading Company for
Pharmaceutical Products
P.O. Box 126
H-1808 BUDAPEST 5

Telex: (861) 225477
Cable: medimpex budapest
Phone: 183 - 955

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*/ Expected to start operations early 1985.

Ranbaxy Laboratories Limited
International Division
78, Nehru Place
NEW DELHI 110 019 India

Telex: 031-2715
Cable: Ranbaxy
Phone: 6415924

Rhône-Poulenc
Dept. Chimie Pharmaceutique
Les Miroirs - Défense 3
F-92400 COURBEVOIE
France

Telex: Rhone X 610 800 F
Cable:
Phone: 768.19.63 Paris

1.2 Non-integrated manufacturers

ICI Bangladesh Manufacturers Ltd
Pharma Sales Department
P.O. Box 48
Water Works Road
NARAYANGANJ
Bangladesh

Telex: 642800 ICI BJ/642848 ICI BJ
Cable: Kemicorp Narayanganj Bangladesh
Phone: 71197, 71466, 71198, 72181, 72949

1.3 International trading houses

Dangschat GmbH
P.O. Box 101224
D-2000 HAMBURG 1
FRG

Telex: 212501 dang d
Cable: "DANGSCHATTRADE"
Phone: 040/233041

Dolder Limited
Immengasse 9
Postfach
Ch-4004 BASEL
Switzerland

Telex: 62306 and 63048
Cable: Dolderag Basel
Phone: 061-576600

FBA Pharmaceuticals
Div. of Mobay Chemical Corporation
425 Park Avenue
NEW YORK, N.Y. 10022
USA

Telex: WU 640562 (METCHEM NYK, answerback)
Cable:
Phone: 212 751-5544

Karl O. Helm
Nordkanalstrasse 28
P.O. Box 103060
D-2000 HAMBURG
BRD

Telex: 2170150
Cable: helmexport
Phone: 040 / 2375-0

K & K Greeff Limited
International Trade
Suffolk House, George Street
CROYDON, CR9 3QL, Surrey
United Kingdom

Telex: 28386
Cable: KIMPEX CROYDON
Phone:01-686 0544

Marsing & Co. Ltd. A/S
Sjaellandsbroen 6
DK-2450 COPENHAGEN SV
Denmark

Oxyde Joba
Postbus 7886
1008 AB AMSTERDAM
The Netherlands

Siemsglüss & Sohn
P.O. Box 105624
D-2000 HAMBURG 1, FRG

Telex: 2162 199/2 162667
Cable: vitachemie
Phone: 040-232121

George Uhe Co. Inc.
76 Ninth Avenue
NEW YORK, N.Y. 10011
U S A

Telex: RCA 236905
Cable: UMENTHOL
Phone: (212) 929-0870

R.W. Unwin & Co. Ltd.
Prospect Place
WELWYN, Herts, AL6 9EW
United Kingdom

Telex: 826371 UNCO G and 24903 UNCO G
Cable: UNCO WELWYN
Phone: 043 871 6441/2/3/4

Annex 5 to the

Technical and economic analysis of the manufacture of CHLOROQUINE Phosphate

Manufacturers and suppliers of intermediates for the production of CHLOROQUINE Phosphate

1. Novoldiamine

BASF Aktiengesellschaft
Carl-Bosch-Strasse 38
D-6700 LUDWIGSHAFEN
B R D

Telex: 4 64 99-0 bas d
Cable: BASF Ludwigshafenrhein
Phone: 06 21 / 60-1

Sterling Organics
Division of Sterling Drug Inc.,
90 Park Ave.
NEW YORK, N.Y. 10016
U.S.A.

Telex: 420512
Cable:
Phone: (212) 972-2632, 33, 527, 550, 555, 676, 729, 890, 943

2. 4,7-Dichloroquinoline

Imperial Chemical Industries PLC
Millbank
LONDON S.W. 1
United Kingdom

Telex: 21324
Cable:
Phone:

And all integrated manufacturers of CHLOROQUINE Phosphate (annex 4, section 1.1).

3. Ethoxymethylenemalonic acid diethyl ester (EMME)

Davos Chemical Corp.
2500 Lemoine Ave.
FORT LEE, N.J. 07024
U.S.A.

Telex: 135-422
Cable: Davoshem FT
Phone: (201) 461-5910

Dynamit Nobel Aktiengesellschaft
Chemicals Division
D-5210 TROISDORF-OBERLAR
Haberstr. 2

Telex: 889401
Cable:
Phone: 02241/180-1

Rhône-Poulenc
Santé Chimie Pharmaceutique
Les Miroirs - Défense 3
F-92400 COURBEVOIE
France

Telex: Rhone X 610 800 F
Cable:
Phone: 768.19.63 Paris

4. Diethyl malonate (DEM)

Dynamit Nobel Aktiengesellschaft
Chemicals Division
D-5210 TROISDORF-OBERLAR
Haberstr. 2

Telex: 889401
Cable:
Phone: 02241/180-1

5. Triethylorthoformate (TEOF)

Dynamit Nobel Aktiengesellschaft
Chemicals Division
D-5210 TROISDORF-OBERLAR
Haberstr. 2

Telex: 889401
Cable:
Phone: 02241/180-1

6. m-Chloroaniline

Aceto Chemical Co., Inc.
126-02 Northern Blvd.
FLUSHING, N.Y. 11368
U.S.A.

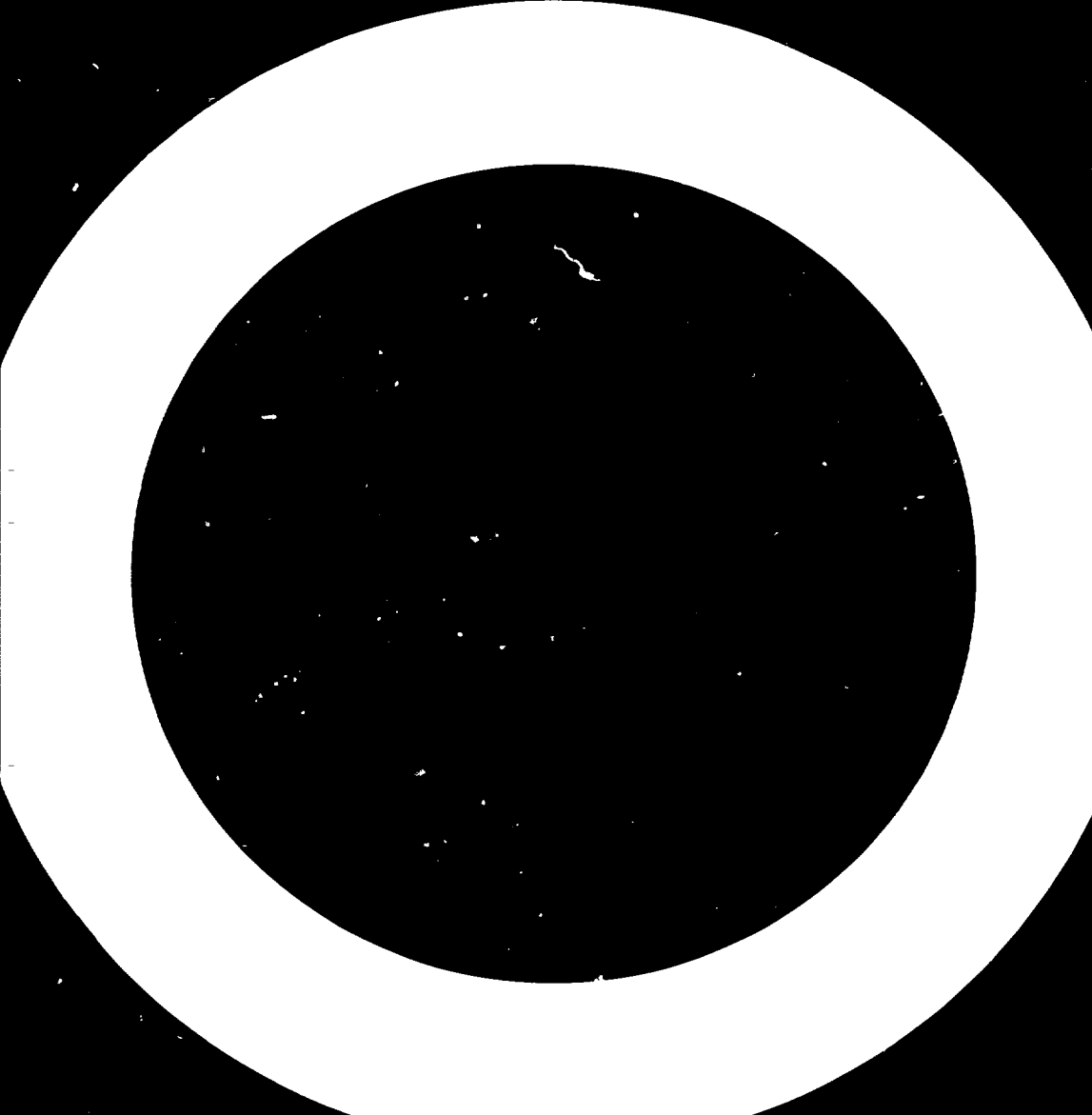
Telex: 62662 INTL.
Cable:
Phone: (212) 898-2300, 2, 426, 486, 743, 871, 893

American Hoechst Corp.
Industrial Chemicals Div.
P.O. Box 2500
SOMMERVILLE, N.J. 08876
U.S.A.

Telex: 833 445, 833 449
Cable:
Phone: (201) 685-2000

Imperial Chemical Industries PLC
Millbank
LONDON S.W. 1
United Kingdom

Telex: 21324
Cable:
Phone:



Résumé

La présente étude de cas a été préparée par le Service des études sectorielles de l'ONUDI comme apport à un modèle sectoriel de prise de décision quant au choix de produits susceptibles d'être fabriqués localement par synthèse chimique organique.

L'économie de procédé dans la fabrication du phosphate de Chloroquine a été évaluée en tenant compte du coût des intermédiaires-clés, des entrées directes de matériel et du coût de conversion. Les données techniques et économiques citées dans l'étude ont été tirées de publications ou obtenues par correspondance auprès des manufacturiers et distributeurs.

On a passé brièvement en revue la situation de pays en développement parvenus à divers stades de développement de leur industrie pharmaceutique et en ce qui a trait aux possibilités de réaliser divers degrés d'intégration verticale.

L'intégration verticale minimum est techniquement réalisable mais peu intéressante au point de vue économique. Une production locale peut être considérée avant tout dans les pays où l'objectif à court-terme serait d'acquérir de l'expérience dans le domaine de l'industrie pharmaceutique chimique et d'y former un personnel qualifié.

L'intégration verticale avancée pour fabriquer le phosphate de Chloroquine est techniquement réalisable et acceptable au point de vue économique. Il vaut donc la peine de songer à en étudier plus avant les aspects de marketing, d'ingénierie et de financement, surtout dans le cas de l'Afrique où la consommation en Chloroquine est élevée et dans les pays qui visent à développer la production des 4-aminoquinolines et des produits chimiques pharmaceutiques et intermédiaires en général.

Pour les fabriquants intégrés de Chloroquine, en particulier ceux qui disposent de capacités d'hydrogénisation à haute pression, il peut être également intéressant de faire des études de perspectives à l'investissement pour la fabrication de novoldiamine.

КРАТКОЕ СОДЕРЖАНИЕ:

Настоящее тематическое исследование подготовлено Отделением секторальных исследований ЮНИДО в качестве вклада в создание секторальной модели принятия решений о выборе вещества, которое потенциально может быть изготовлено на месте методом органического химического синтеза.

В ходе исследования произведена оценка экономических показателей технологии производства хлорохин фосфата с учетом стоимости основных промежуточных соединений, прямых материальных затрат и затрат на конверсию. Технико-экономические данные для исследований получены из литературы или от производителей и поставщиков.

Проведен общий обзор развивающихся стран, имеющих фамацевтическую промышленность на различных этапах развития, для изучения их возможностей обеспечения обратной интеграции различной степени.

Минимальная обратная интеграция является технически целесообразной, но экономически нерентабельной. Возможности местного производства могут быть изучены в первую очередь в тех странах, в которых ближайшей задачей является приобретение опыта и подготовка квалифицированного персонала в области фармацевтической промышленности.

Более высокая обратная интеграция производства хлорохин фосфата является технически целесообразной и экономической проблемой. Поэтому следует рассмотреть вопрос о

проведении углубленных исследований по связанным с его производством вопросам сбыта, технического и финансового обеспечения, особенно в африканских странах с высоким уровнем потребления хлорохина, с целью создания или расширения производства 4-аминохинолинов и/или фармацевтических химических веществ и промежуточных соединений в целом.

Для заводов-изготовителей хлорохина в условиях интегрированного производства, особенно располагающих мощностями для гидрогенезации под высоким давлением, изучение возможностей инвестирования в производство новолдиамина, возможно, также будет представлять интерес.

Resumen

El presente estudio de caso fue realizado por la Sub-división de Estudios Sectoriales de la ONUDI como parte de un modelo sectorial de toma de decisiones adecuado para seleccionar productos potenciales para fabricación local por síntesis química orgánica.

La economía de proceso de producción de Fosfato de Cloroquina se evaluó teniendo en cuenta los costos de intermedios claves, los costos de insumos materiales directos y los costos de conversión. Los datos técnicos y económicos usados en el estudio se tomaron de la literatura disponible o se obtuvieron por correspondencia con casas productoras y proveedoras.

Países en desarrollo en etapas distintas de desarrollo de la industria farmacéutica fueron revisados brevemente con respecto a la implementación de los varios grados de la integración vertical.

El grado mínimo de integración vertical es técnicamente viable, pero no lo es económicamente. Producción local puede considerarse prioritaria en aquellos países donde el objetivo a corto plazo es capacitar y ganar experiencia con personal entrenado para la industria farmacéutica.

El grado avanzado en la integración vertical de la producción de Fosfato de Cloroquina es técnicamente viable y económicamente aceptable. Aspectos más detallados de ingeniería, financieros y de mercado justifican la preparación de estudios de prefactibilidad particularmente en países Africanos con consumo alto de Cloroquina y en aquellos que tienen como meta el establecimiento o expansión de la producción de 4-aminoquinolinas y/o de los productos farmaco-químicos e intermedios en general.

Productores integrados de Cloroquina, particularmente aquellos con capacidad de hidrogenización a presión alta, podrían estar interesados también en estudios de prefactibilidad sobre la producción de novoldiamina.

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