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TECHNICAL AND ECONOMIC ANALYSIS OF THE MANUFACTURE OF ISONIAZID

Sectoral Studies Series
No.24

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DIVISION FOR INDUSTRIAL STUDIES

V.86-53898

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 the Pharmaceutical Industry in UNIDO's programme of Industrial Studies 1984/1985.

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Preface

This study addresses the problem of the decision-making in the process development for the manufacture of pharmaceutical chemicals and intermediates by organic chemical synthesis. It discusses in detail some of the important factors (e.g., available plant facilities, profitability, convertible currency savings, availability of starting materials and commercial-scale technology) which must influence the initiation and conduct of a typical development programme as well as the final selection of pharmaceutical chemicals and intermediates for such programmes. Nevertheless, further detailed and definitive studies of technical feasibility and economic viability are strongly recommended prior to the actual initiation of such programmes or the purchase of a particular technology for use in a specific geographical area.

The subject has been studied because of its industrial importance and social benefits to developing countries. This particular study deals with ISONIAZID, a drug which is specifically effective against most strains of actively growing Mycobacterium tuberculosis. The three other reports in the series are concerned with Chloroquine Phosphate,[1/] used widely in the therapy and prophylaxis of malaria; with Ethambutol Hydrochloride,[2/] sometimes administered concurrently with ISONIAZID for the treatment of tuberculosis; and with Acetylsalicylic Acid, a common analgesic. Collectively, these four documents will serve as the basis for a preliminary, 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.

1/ UNIDO/IS.518: Technical and economic analysis of the manufacture of Chloroquine Phosphate.

2/ UNIDO/IS.588: Technical and economic analysis of the manufacture of Ethambutol Hydrochloride.

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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.

ISONIAZID was typed in capital letters to highlight that it is the chemical subject of the study.

First letters of important reactants and intermediate products were also capitalized to facilitate the distinction from compounds less relevant in the analysis of the manufacture of ISONIAZID.

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
INA	Isonicotinic Acid
CMR	Chemical Market Reporter
C_{tp}	Total production costs
C_{ij}	Direct material costs

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. Priority is determined by the date of application and not by the date of approval/publication of the patent.

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

3. Material input consumption coefficient is the number of units of a material input required for the production of one unit of chemical output. The material input consumption coefficient differs from the chemical input conversion coefficient in that it accounts also for the material loss occurring during physical operations, such as crystallization, drying, etc.

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

5. Integrated ISONIAZID manufacturer is a producer that synthetizes its INA starting from 4-Picoline, or 4-Cyanopyridine, or from a more advanced degree of backward integration.

6. Key intermediate is an organic chemical input that plays a dominant role in the direct material costs.

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

8. Pharmaceutical chemical is a chemical substance used as the active ingredient of pharmaceutical preparations.

9. 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. This case study on ISONIAZID is one of four intended 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.[3/]

This study provides basic information that should be taken into account also when operating and expanding an ISONIAZID 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 marketing, engineering and financial studies.

The study has been organized so that the detailed 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 analyzed in chapters 5 to 10.

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

The process economics of ISONIAZID production were assessed, taking into account three cost factors:

- Key intermediate),
- Direct material inputs, and
- Conversion costs.

3/ The other studies in the series concern Chloroquine Phosphate, Ethambutol Hydrochloride and Acetylsalicylic Acid.

Costs of key intermediates and direct material inputs were calculated by using the material input consumption 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 in 1982.

Profitability and convertible currency savings were estimated by subtracting the total production costs and direct material costs, respectively, from the world-market price of ISONIAZID to conclude the economic feasibility of the process alternative studied.

The patent information given in this study shows the result of the computer search in all issues of the Chemical Abstracts published between 1 January 1967 and 31 December 1985. This patent information should not be construed as a guarantee that other process patents of ISONIAZID or its intermediates do not exist and/or are not valid in a given 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 ISONIAZID and its intermediates, and to illustrate what can be done with the available information. Advantages and disadvantages of alternative manufacturing processes 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

ISONIAZID was first synthesized in 1912,[4/] however, its activity as an antitubercular drug was not recognized until almost four decades later.

In 1945 it was reported that nicotinamide possessed tuberculostatic action. Examination of compounds related to nicotinamide subsequently revealed that ISONIAZID was also tuberculostatic.[5/] Such findings were discovered almost simultaneously and published by several authors in 1952, the same year in which the drug was first made commercially available in the pharmaceutical market. Since that time, it has achieved and maintained a leading position as an antitubercular agent. However, as will be discussed later in section 10.4, it is rarely used alone, except for prophylaxis.

ISONIAZID is generally used as a tablet and as a fixed-ratio combination product with thioacetazone, another antitubercular drug.[6/]

The basic patents and most process patents for ISONIAZID have expired and the technology for ISONIAZID preparation is now far advanced so that, very probably, some manufacturers have achieved optimum levels of production.

ISONIAZID was chosen as one of the four products to be studied in this series because of its health and economic importance in developing countries where tuberculosis is a problem and where therapeutic needs are not always satisfied because of financial and distributional constraints.

According to UNIDO estimates, about 1,600 tons of ISONIAZID are sold annually worldwide. The total value of the market for manufacturers is some $US 16 million per year, and the total retail value falls in the region of $US 32 million, assuming that the manufacturers' price amounts to 50 per cent of the price to the consumer.

4/ The Merck Index, 10th edition, 1983, p. 745.

5/ Goodman and Gilman's The Pharmacological Basis of Therapeutics, 6th edition, 1980, p. 1200.

6/ WHO Technical Report Series 722: The use of essential drugs, 1985, p. 19.

4. METHODOLOGY OF THE ANALYSIS OF PROCESS ECONOMICS

The processes selected to discuss the manufacturing technology of ISONIAZID are illustrated in figures 1 and 2.

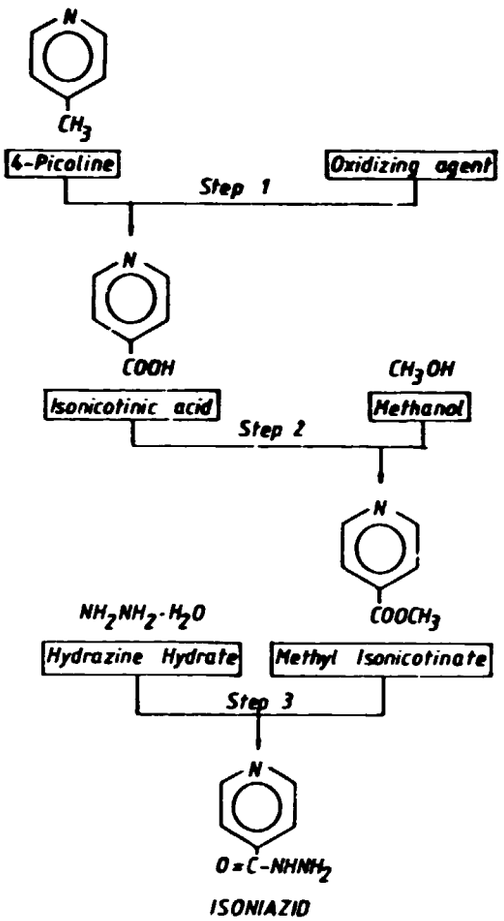


Figure 1. Schematic illustration of the studied processes of ISONIAZID synthesis from 4-Picoline

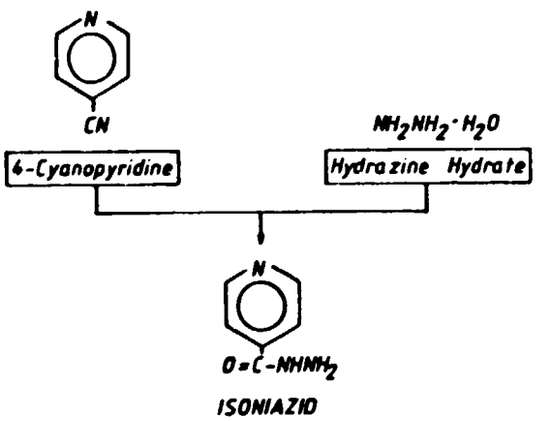
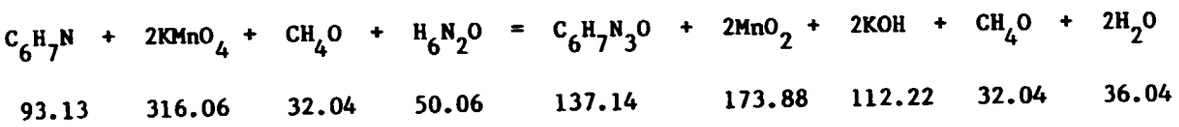


Figure 2. Schematic illustration of the studied process of ISONIAZID synthesis from 4-Cyanopyridine

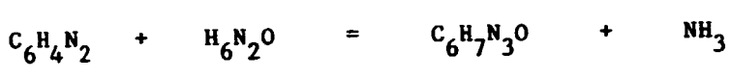
The step-by-step technical and economic details are not all immediately available. However, at this preliminary level in the decision-making, these are generally not necessary so, here, the alternative manufacturing processes have been considered as single step chemical reactions. Thus, they may be described by the following two equations.

Synthesis from 4-Picoline by oxidation with Potassium Permanganate



C_6H_7N	+ $2KMnO_4$	+ CH_4O	+ H_6N_2O	= $C_6H_7N_3O$	+ $2MnO_2$	+ $2KOH$	+ CH_4O	+ $2H_2O$
93.13	316.06	32.04	50.06	137.14	173.88	112.22	32.04	36.04

Synthesis from 4-Cyanopyridine



$C_6H_4N_2$	+ H_6N_2O	= $C_6H_7N_3O$	+ NH_3
104.11	50.06	137.14	17.03

These 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

In table 1, the chemical formulae of ISONIAZID, its intermediates and raw materials were taken from different sources. The molecular weights were obtained 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 does not contain data concerning reactants and products which are used in reactions not evaluated separately during the analysis of ISONIAZID production.

Table 1. Definition of important chemical inputs and outputs in the manufacture of ISONIAZID

Name	CAS Registry Number	Chemical formula	Molecular weight
ISONIAZID	[54-85-3]	$C_6H_7N_3O$	137.14
Isonicotinic Acid Methylester	[2459-09-8]	$C_7H_7NO_2$	137.14
Hydrazine Hydrate	[7803-57-8]	H_6N_2O	50.06
Isonicotinic Acid	[55-22-1]	$C_6H_5NO_2$	123.11
4-Picoline	[108-89-4]	C_6H_7N	93.13
Potassium Permanganate	[7722-64-7]	$KMnO_4$	158.03
Manganese dioxide	[1313-13-9]	MnO_2	86.94
Methanol	[67-56-1]	CH_4O	32.04
Nitric Acid	[7697-37-2]	HNO_3	63.01
4-Cyanopyridine	[100-48-1]	$C_6H_4N_2$	104.11
Potassium hydroxide	[1310-58-3]	KOH	56.11
Water	[7732-18-5]	H_2O	18.02
Ammonia	[7664-41-7]	NH_3	17.03

In table 2, the molar chemical input conversion coefficient, F, was calculated by dividing the molecular weight of the chemical on hand with that of ISONIAZID.

Material input consumption coefficients and/or yields for each oxidation method refer basically to the same technology, hence data from different sources[7/] 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.

Table 2. Material input consumption coefficients and percentage yields of two hypothetical average and ideal ISONIAZID producers

Name	F	f_1	y_1	f_2	y_2
1. 4-Picoline route					
a. oxidizing agent: Potassium Permanganate					
4-Picoline	0.68	1.00	68	0.90	76
Hydrazine Hydrate	0.37	0.63	59	0.43	86
Potassium Permanganate	2.30	4.00	58	3.60	64
b. oxiding agent: Nitric Acid					
4-Picoline	0.68	1.11	61	1.05[a/]	65
Hydrazine Hydrate	0.37	0.63	59	0.43	86
Nitric Acid	1.38	4.44	31	3.45	40
c. other oxidizing agent					
4-Picoline	0.68	1.00	68	0.90	76
Hydrazine Hydrate	0.37	0.63	59	0.43	86
2. 4-Cyanopyridine route					
4-Cyanopyridine	0.76	1.14	67	0.95[a/]	80
Hydrazine Hydrate	0.37	0.86	43	0.69	54

a/ Estimated value.

7/ UNIDO document ID/WG.267/5 (1978); unpublished document; UNIDO document ID/WG.331/4 (1980); UNIDO document PC.14 (1981); UNIDO document PC.52 (1982); commercial-scale technology, F. Hoffman-La Roche & Cie, S.A., Basel (1981); Marshall Sittig; Pharmaceutical Manufacturing Encyclopedia, Noyes Data Corporation, Park Ridge, NJ, United States (1979).

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 but yields only 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[8/] and the following values, converted into $US when necessary, were selected for the techno-economic analysis (table 3).

Table 3. Prices of important chemical intermediates, raw and auxiliary materials used in the manufacture of ISONIAZID ($US/kg)

Name	Unit price
4-Picoline	2.50
Hydrazine Hydrate	2.40
Potassium Permanganate	1.13
Sulphuric acid	0.08
Hydrochloric acid, 36%	0.07
Methanol	0.20
Ammonia solution, 25%	0.12
4-Cyanopyridine	4.04
Ethanol	0.45
Resin IRA-402	3.30
Manganese dioxide	0.31
Nitric Acid	0.20
Sodium carbonate	0.09
Methylene chloride	0.77
Carbon, activated	2.53

8/ 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.

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:

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

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 were not available for all processes 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[9/] and on own estimates 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.[10/] The unit gross profit or loss was obtained by subtracting the unit total production costs, C_{tp}, from the unit world market price of ISONIAZID, or vice versa. The world market price of $US 10 has been derived from the f.o.b. quotations of three European trading houses for the delivery of 2,500 kg of ISONIAZID in 1982 and from the 1982 c.i.f. import prices of two developing countries, taking into account the $US price trend of the CMR.

9/ UNIDO PC. 52 of 13 September 1982.

10/ Ibid.

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 alternate processes: technical feasibility, profitability and convertible currency saving. The method does not take into account any additional convertible currency investment costs in new or existing pharmaceutical chemical plants. The model 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.

Whenever the method 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 ISONIAZID BULK SUBSTANCE AND KEY INTERMEDIATES

There are two basic processes in use for producing ISONIAZID. One is a two-step synthesis in which Isonicotinic Acid is esterified and then the ester reacts with Hydrazine Hydrate;[11/] in the other, Isonicotinic Acid produced in situ from 4-Cyanopyridine is directly reacted with Hydrazine Hydrate.[12/]

The former route has been more widely adopted because there are several alternative methods by which the Isonicotinic Acid may be prepared and, generally, the starting chemicals are readily available and relatively inexpensive. Additionally, there may be ongoing opportunities for the further development of new processes which would afford more economical preparation of Isonicotinic Acid, itself.

The most popular method for the manufacture of Isonicotinic Acid appears to be that involving the oxidation of 4-Picoline (4-methylpyridine); which, in turn, is either derived from coal tar or may be totally synthesized from acetylene or acetaldehyde and ammonia.

Other alternative processes for obtaining Isonicotinic Acid include the:

(a) Oxidation of 4-ethylpyridine, synthesized by reacting pyridine with acetic anhydride and zinc or iron powder.[13/] This involves an extra step and has proven more costly than starting from 4-Picoline, unless 4-ethyl-pyridine is available as the by-product of another manufacturing process, or the pyridine price is not more than $US 1.80/kg.

(b) Decarboxylation of cinchomeronic acid, obtained by oxidation of isoquinoline,[14/] does not seem to be an economically feasible alternative

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11/ H.H. Fox, U.S. patent 2,596,069 assigned to Hoffman La Roche (1952).

12/ E.J. Gasson, U.S. patent 2,830,994 assigned to the Distillers Co. (1958).

13/ U.S. patent 2,712,019 to Napera Chemical (1955), German patent 390,333 to Schering AG (1924).

14/ U.S. patent 2,436,660 to Allied Chemical (1946).

because the starting material itself is not readily available and Isonicotinic Acid has to be separated from nicotinic acid.

(c) The transformation of citric acid in a five-step synthesis[15/] involves a reaction in 70 per cent sulphuric acid at 130°C, a chlorination with phosphorous oxichloride under overpressure, and a catalytic hydrogenation. Hence, this route is technically not feasible.

Several agents have been employed in the oxidation of 4-Picoline. Oxidation with Potassium Permanganate[16/] is nearly complete and the quality of ISONIAZID is very good. The disadvantage on a commercial scale is the high price of Potassium Permanganate; among the other oxidizing agents are Nitric Acid, sulphuric acid plus selenium,[17/] or air with vanadium pentoxide as the catalyst.[18/] The disadvantages of the latter method include the large operating volume, the long reaction cycle (equipment use) and low yields.

The majority of these syntheses do not require any special equipment and they may be carried out in multipurpose batch reactors without additional investment, possibly utilizing excess capacity. Consequently, the economic feasibility of the production is not heavily dependent upon its scale. This conclusion does not of course apply to oxidation of 4-Picoline by Nitric Acid or to special unit operations such as catalytic hydrogenation in the citric acid route.

Although dangers are minimal in the process of oxidation of 4-Picoline by Potassium Permanganate, if the protocol is followed correctly, caution must be used: the methanolic solution of hydrazine hydrate is inflammable; explosions could occur if the distillations are carried out at reduced pressure; and the concentrated acids can have a corrosive effect and/or cause explosion. There

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15/ U.S. patent 2,729,647 and 2,738,352 to Pfizer (1956).

16/ U.S. patent 2,946,801 to Standard Oil (1960).

17/ Spanish patent 202,450 to Magrave (1952).

18/ U.S. patent 2,946,801 to Standard Oil (1960).

are no unusual energy requirements nor potentional environmental problems. However, the solvents used are potential sources of pollution and should be recovered and reused. Residuals from solvent recovery should be incinerated.[19/] Additionally, nitrous oxide vapours from heated 4-Picoline and Hydrazine Hydrate should be absorbed.

5.1 ISONIAZID production using imported 4-Picoline

5.1.1 Oxidizing agent: Potassium Permanganate, method A

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

Table 4. Cost and cost structure estimates of ISONIAZID production. 4-Picoline route. Oxidizing agent: Potassium Permanganate

Cost element	C_1		C_2	
	$US	%	$US	%
4-Picoline	2.50	19.6	2.25	20.6
Key intermediate costs	2.50	19.6	2.25	20.6
Potassium Permanganate	4.52	35.4	4.07	37.3
Hydrazine Hydrate	1.51	11.8	1.03	9.4
Methylene Chloride	0.98	7.7	0.82	7.5
Other materials	0.67	5.3	0.57	5.2
Manganese Dioxide, recovered	-0.72	-5.6	-0.61	-5.6
Direct material costs	9.46	74.1	8.13	74.5
Conversion costs	3.30	25.9	2.78	25.5
Production costs	12.76	100.0	10.91	100.0
Gross profit	-2.76	-21.6	-0.91	-8.3
Convertible currency saving	0.54		1.87	

C_1 ... unit costs of the average performer

C_2 ... unit costs of the ideal performer

19/ UNIDO/IS.387, 6 June 1983, p. 22.

Table 4 indicates that Potassium Permanganate accounts for about 48 to 50 per cent of direct material costs and about 35 to 37 per cent of total production cost while the key intermediate, 4-Picoline, accounts only for about 20 per cent. Some economies may be realized by the recovery of Manganese dioxide.

Conversion costs of over 25 per cent are also a very notable segment of the total production costs.

Inspection of these data reveals that the total production cost (C_{tp}) of the average performer, $US 12.76, is over 27 per cent above the world market price of $US 10 for ISONIAZID quoted in section 4.2; that of the ideal performer, $US 10.91, although considerably better, is still about 9 per cent higher. However, based on direct material costs, both realize convertible currency savings. Those of the average producer, $US 0.54, are marginal but those of the ideal producer, $US 1.87, are much more significant.

A one per cent increase in the price of Potassium Permanganate would increase the direct material costs of both producers by about 0.5 per cent (disregarding subsequent recovery of the Manganese dioxide); a similar increase for 4-Picoline would increase these costs by about 0.2-0.3 per cent.

Thus, such an increase in the price of one of the chemicals would raise the monetary gross loss of both producers by $US 0.02-0.05 and the resulting percentage change of the loss for the average performer would be 0.9 to 1.6 per cent. For the ideal performer, the percentage change of the loss would be 2.4 to 4.9 per cent.

A one per cent improvement in the chemical input conversion coefficient for one of the chemicals, likewise, would be reflected in a $US 0.02-0.05 reduction in direct material costs with a corresponding marginal decrease in gross losses for both producers. However, assuming a decrease of $US 0.05 in the price of Potassium Permanganate, this could increase convertible currency savings for the average performer by about 9.3 per cent; for the ideal performer, the increase would represent only about 3 per cent.

5.1.2 Oxidizing agent: Nitric Acid, method B

The data in table 5 show that both direct material and total production costs may be reduced by using Nitric Acid as the oxidizing agent. Although the share of 4-Picoline increases in both, the overall values are reduced substantially.

Table 5. Cost and cost structure estimates of ISONIAZID production. 4-Picoline route. Oxidizing agent: Nitric Acid

Cost element	C_1 $US	C_1 %	C_2 $US	C_2 %
4-Picoline	2.78	27.3	2.63	28.7
Key intermediate costs	2.78	27.3	2.63	28.7
Hydrazine Hydrate	1.51	14.8	1.03	11.3
Methylene chloride	0.92	9.0	0.92	10.1
Nitric Acid	0.89	8.7	0.69	7.5
Other materials	0.79	7.8	0.78	8.5
Direct material costs	6.89	67.6	6.05	66.1
Conversion costs	3.30	32.4	3.10	33.9
Production costs	10.19	100.0	9.15	100.0
Gross profit	-0.19	-1.9	0.85	9.3
Convertible currency saving	3.11		3.95	

C_1 ... unit costs of the average performer

C_2 ... unit costs of the ideal performer

For the average performer the same conversion costs in $US were taken as in the previous method, but in terms of percentage over C_{tp} they are about 6 per cent higher for the average and over 8 per cent higher for the ideal producer; this seems to be justified because oxidation with Nitric Acid is carried out in a special reactor and environment protection from nitrous oxides is also more expensive than in the Potassium Permanganate route.

C_{tp} for the average producer is $US 10.19, or about 80 per cent of that incurred in the Potassium Permanganate procedure; it is $US 9.15, or about 84 per cent of the previous method for the ideal operator. These differences

between the average and ideal performer cannot be considered as significant. Despite these reductions, the average performer still shows a gross (but very marginal) loss of $US 0.19 while the ideal producer has a gross profit of $US 0.85 per kilo.

The lower direct material costs result in more sizable convertible currency savings for both, about 6 times greater than the preceding method for the average and double for the ideal performer. However, as noted earlier, the key intermediate, 4-Picoline, assumes a more significant role here, representing about 40-44 per cent of all direct material costs and about 27-29 per cent of C_{tp} for the two operators. Thus, price changes for this chemical can impact more heavily upon the economics of the method. It should again be noted that the differences in the conversion efficiencies of the two manufacturers, with the exception of Hydrazine Hydrate, are relatively small.

Consequently, monetary amounts involved are modest and a one per cent increase in the price of 4-Picoline would increase the direct material costs of both producers by less than 0.5 per cent. However, this would result in an almost 15 per cent increase in the amount of the gross loss of the average producer and a decrease of 3 per cent in the gross profit of the ideal operator.

Conversely, a one per cent improvement in the chemical input conversion coefficient would result in not only a fractional decrease in direct material costs and C_{tp}, but would represent increased convertible currency savings of almost one per cent for each producer.

5.1.3 Unknown oxidizing agent, method C

As illustrated in table 6, this particular method - which presumably does not employ either Potassium Permanganate or Nitric Acid - delivers the highest gross profits and convertible currency savings. Once again, the saving is realized principally from overall lowering of direct material costs; conversion costs remain the same for the average and about the same for the ideal performer, although their share of C_{tp} is higher than in either of the two preceding syntheses.

4-Picoline has a similar share in direct material costs, for both the average and ideal performer (43 or 45 per cent), and of C_{tp} (about 28 per cent). However, as has been pointed out in the two preceding examples, a one per cent increase in its price or, conversely, a one per cent improvement of the chemical input conversion coefficient, would have a very insignificant effect upon either gross profit or convertible currency savings.

Table 6. Cost and cost structure estimates of ISONIAZID production. 4-Picoline route: unknown oxidizing agent

Cost element	C_1 $US	C_1 %	C_2 $US	C_2 %
4-Picoline	2.50	27.2	2.25	27.9
Key intermediate costs	2.50	27.2	2.25	27.9
Hydrazine Hydrate	1.51	16.4	1.03	12.8
Other materials	1.87	20.4	1.73	21.4
Direct material costs	5.88	64.0	5.01	62.1
Conversion costs	3.30	35.9	3.06	37.9
Production costs	9.18	100.0	8.07	100.0
Gross profit	0.82	8.9	1.93	23.9
Convertible currency saving	4.12		4.99	

C_1 ... unit costs of the average performer

C_2 ... unit costs of the ideal performer

5.2 ISONIAZID production using imported 4-Cyanopyridine, method D

In this process, 4-Cyanopyridine is reacted with at least an equimolecular proportion of Hydrazine Hydrate in an aqueous medium in the presence of a strong base. The hydrolysis and the formation of acid hydrazide proceed in one step. Although the route beginning with 4-Picoline has usually gained wider acceptance, the technology involved in this alternate method is technically less complex. Consequently, when the starting raw material is available, it is worthy of consideration.

Data provided in table 7 indicate that the price of the key intermediate can very notably affect the economics of this process, since the chemical accounts for over 60 per cent of the direct material costs and about half of the total production cost for both producers. It should be noted that Hydrazine Hydrate is taken as a key intermediate in this process, since its share in C_{tp} is above 20 per cent.

Table 7. Cost and cost structure estimates of ISONIAZID production. 4-Cyanopyridine route

Cost element	C_1 $US	C_1 %	C_2 $US	C_2 %
4-Cyanopyridine	4.61	48.2	3.84	49.0
Hydrazine Hydrate	2.06	21.5	1.66	21.2
Key intermediate costs	6.67	69.7	5.50	70.2
Other materials	1.03	10.8	0.60	7.7
Direct material costs	7.70	80.5	6.10	77.9
Conversion costs	1.87	19.5	1.73	22.1
Production costs	9.57	100.0	7.83	100.0
Gross profit	0.43	4.5	2.17	27.7
Convertible currency saving	2.30		3.90	

C_1 ... unit costs of the average performer

C_2 ... unit costs of the ideal performer

However, as illustrated, the gross profit of $US 0.43 for the average and $US 2.17 for the ideal performer are higher than any of the three previously discussed methods.

The same does not hold true of the convertible currency savings. The $US 2.30 realized by the average producer is better than that utilizing the Potassium Permanganate oxidation but not as favourable as either of the other two oxidation processes. The $US 3.90 realized by the ideal performer is better than the Potassium Permanganate oxidation, about the same as the Nitric Acid process but not as favourable as the one employing the unknown oxidizing agent.

A one per cent increase in the cost of 4-Cyanopyridine will raise the direct material costs of both producers by about 0.8 per cent and the corresponding total production costs by about 0.5 per cent.

Conversely, a one per cent improvement in the chemical input conversion coefficient would be reflected in a 0.5 per cent reduction of C_{tp} for both producers; however, it would also result in an elevation of the convertible currency savings of 2.0 per cent for the average and about 1.0 per cent for the ideal performer.

The technology and equipment required for this method are less complex than those for the oxidation processes, and this is reflected in the lower conversion costs.

The major disadvantage of this route lies in the key-intermediate, 4-Cyanopyridine; the chemical, itself, is an intermediate which is incidental to other unrelated synthesis; as such, its availability in the open market is limited and not dependable.

6. EFFECT OF THE VARIOUS PRODUCTION METHODS ON THE PROCESS ECONOMICS OF ISONIAZID MANUFACTURE

The cost estimates of the average and ideal performers provided in tables 4, 5, 6 and 7 may be more closely compared in tables 8 and 9 which illustrate how the use of each method affects the C_{tp}, the gross profit/loss and the convertible currency savings. Costs shown for Potassium Permanganate here have been reduced from those originally shown by the value of manganese dioxide recovered during the process.

All of the studied technologies are carried out by integrated manufacturers, i.e. none of them starts production from INA. Hence, the effect of backward integration on process economics is not analyzed here.

Despite the observations made in the introduction to chapter 5 concerning the preferences for the isonicotinic acid route, it is apparent that those potential producers whose primary objective is gross profit as well as more simplified technology should at least explore the possibilities of utilizing 4-Cyanopyridine as the starting material. For both the average and the ideal producers, the gross profit is about in the same order of magnitude as that of the only other profitable oxidation procedure which utilizes an unidentified oxidizing agent. Conversion costs of the 4-Cyanopyridine route are around 40 per cent lower than those of the various oxidation processes.

For those potential producers whose primary concern is the saving of convertible currency, the best choice appears to be method C, utilizing an undisclosed oxidizing agent.

Some of these points may become clearer by reviewing the percentage presentation provided in table 9.

Here it can be seen that direct material costs are most dominant in methods A and D and that one of the key intermediates plays a dominant role in the latter; hence, its availability and price are very important.

Further, the complexity of the technology - as judged by the percentage share of conversion costs - is greatest for B and C; therefore, they may require more qualified and experienced technical and administrative management, not only to carry out the tasks involved but also to explore ways in which efficiencies may be improved and costs possibly may be reduced.

Nevertheless, based on the C_{tp} shown for each method, gross profits are most signficant for method D while the most favourable convertible currency savings emanate from C, using the unknown agent.

Table 8. Comparison of four alternative processes for the manufacture of ISONIAZID ($US)

Cost element	A		B		C		D	
	C_1	C_2	C_1	C_2	C_1	C_2	C_1	C_2
4-Picoline	2.50	2.25	2.78	2.63	2.50	2.25		
4-Cyanopyridine							4.61	3.84
Hydrazine Hydrate							2.06	1.66
Key intermediate costs	2.50	2.25	2.78	2.63	2.50	2.25	6.67	5.50
Hydrazine Hydrate	1.51	1.03	1.51	1.03	1.51	1.03		
Potassium Permanganate	3.80	3.46						
Methylene chloride	0.98	0.82	0.92	0.92	...	...	...	...
Nitric Acid			0.89	0.69				
Other materials	0.67	0.57	0.79	0.78	1.87	1.73	1.03	0.60
Direct material costs	9.46	8.13	6.89	6.05	5.88	5.01	7.70	6.10
Conversion costs	3.30	2.78	3.30	3.10	3.30	3.06	1.87	1.73
Production costs	12.76	10.91	10.19	9.15	9.18	8.07	9.57	7.83
Gross profit	-2.76	-0.91	-0.19	0.85	0.82	1.93	0.43	2.17
Convertible currency savings	0.54	1.87	3.11	3.95	4.12	4.99	2.30	3.90

C_1 ... average performer

C_2 ... ideal performer

Table 9. Comparison of the production cost structures of four alternative processes for the manufacture of ISONIAZID (per cent)

Cost element	A		B		C		D	
	C_1	C_2	C_1	C_2	C_1	C_2	C_1	C_2
4-Picoline	19.6	20.6	27.3	28.7	27.2	27.9		
4-Cyanopyridine							48.2	49.0
Hydrazine Hydrate							21.5	21.2
Key intermediate costs	19.6	20.6	27.3	28.7	27.2	27.9	69.7	70.2
Hydrazine Hydrate	11.8	9.4	14.8	11.3	16.4	12.8		
Potassium Permanganate	29.8	31.7						
Methylene chloride	7.7	7.5	9.0	10.1	...	...	...	...
Nitric Acid			8.7	7.5				
Other materials	5.3	5.2	7.8	8.5	20.4	21.4	10.8	7.7
Direct material costs	74.1	74.5	67.6	66.1	64.0	62.1	80.5	77.9
Conversion costs	25.9	25.5	32.4	33.9	35.9	37.9	19.5	22.1
Production costs	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Gross profit	-21.6	-8.3	-1.9	9.3	8.9	23.9	4.5	27.7

C_1 ... average performer
C_2 ... ideal performer

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

In an attempt to assess the availability of ISONIAZID, its key intermediates and their manufacturing technology, inquiries were sent to 88 addresses given in various directories.[20/]

Twenty-two positive replies were received, 20 from industrialized countries and two from developing countries. The information contained in these replies is given in annexes 4 and 5.

Although the lists given in this study are based on correspondence with manufacturers and suppliers, they may contain errors. They are not complete because a few companies known to produce ISONIAZID and intermediates have not replied. Important companies have stopped the chemical production of ISONIAZID and either buy their requirements or have it contract manufactured. Suppliers that sell ISONIAZID only sporadically and in very small quantities, e.g. about 100 kg per year, have not been included in the list either. Annexes 4 and 5 reflect the situation as at the end of 1985.

In addition to direct transactions between headquarters and affiliates, large quantities of ISONIAZID are sold on the open market through international trading houses, which keep stocks of the pharmaceutical chemical. Hence, ISONIAZID is freely available in international trade.

The important starting materials - 4-Picoline and 4-Cyanopyridine - are manufactured in the petrochemical industry. The pharmaceutical industry is an important consumer of these chemicals, but no correlation could be established between their prices and that of ISONIAZID due to the lack of reliable and consistent time series of their prices. It is assumed, however, that these compounds are used more outside than by the pharmaceutical industry and their prices may only slightly be influenced by the demand of this industry.

20/ Directory of Chemical Producers, Western Europe, SRI International; CHEM Sources - United States, 1983; Pharmaceutical Technology: Chemical Raw Materials and Pharmaceutical Ingredients, July 1982; UNIDO: Directory of Pharmaceutical Chemicals and Intermediates, 1984.

Methanol, ethanol, methylene chloride, Hydrazine Hydrate, Potassium Permanganate, Nitric Acid, etc. are primary petrochemicals, petrochemical intermediates or basic inorganic chemicals, respectively, and they are mainly used for purposes other than the manufacture of ISONIAZID. 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 4-Cyanopyridine, ISONIAZID and the chemical inputs for its production are manufactured both in industrialized and developing countries. Commercial scale technology is available for the 4-Picoline route by oxidation with Potassium Permanganate and laboratory scale technology for the manufacture of ISONIAZID is described in the literature, including alternative processes and routes, although some of them are still patent protected.

8. EVALUATION OF OFFERS FOR TRANSFER OF TECHNOLOGY

Commercial scale chemical coefficients and yields for various intermediates in the production of pure ISONIAZID have been made available by a leading international manufacturer.[21/]

Table 10. Chemical input conversion coefficients and percentage yields of ISONIAZID synthesis

Name	F	f	y
ISONIAZID, crude	1.00	1.05	95
Isonicotinic Acid Methylester	1.00	1.11	90
Isonicotinic Acid	0.90	1.10	82
4-Picoline	0.68	1.00	68
Potassium Permanganate	2.30	4.00	58
Hydrazine Hydrate	0.37	0.43	86

When receiving offers of process technology, a developing country should find it informative to compare these with data which may be received from potential technology suppliers. Thus, a preliminary evaluation may be made of the efficiency and the economic aspects of various steps involved.

For example, a developing country receives offers for the transfer of technology from two competing suppliers and the values provided are similar to those expressed in table 2 for the average and ideal producers, using Potassium Permanganate as an oxidizing agent. Comparing these with the industrial data in table 10, the technology of the ideal producer as it concerns 4-Picoline and Potassium Permanganate shows better results than the coefficients and yields in table 10, while that of the average producer is identical; for Hydrazine Hydrate, the ideal producer matches the real value.

21/ F. Hoffmann-La Roche & Cie, Société Anonyme, Basel, Switzerland.

Generally, technologies offering a lower conversion coefficient reflect higher convertible currency savings; those offering a higher yield provide greater profits. Consequently, it would appear that the ideal producer is the obvious choice to supply the technology.

However, other relevant aspects should also be explored.

Among them, the chemical coefficients of mutual reactants should be examined in relation to each other. Although it is not so in the above case, if the chemical coefficient for Hydrazine Hydrate should appear to be unusally high, the one for 4-Picoline would have to be regarded with caution; either an error may have been made or the technology may demonstrate economies in the use of one chemical at the expense of another. E.g. the use in excess of one reactant to increase the yield is a commmon practice in organic syntheses. If this excess is not recovered or if the recovery is not efficient or not reflected in the material consumption coefficient, false process economic conclusions might be drawn. It is very desirable that offers reflecting unusually low chemical coefficients or unusually high yields be controlled by own laboratory tests or supported by other literature (such as that provided in annex 1 of this report).

An additional approach, depending upon the amount of detail provided initially by potential suppliers, would be to review and cost individual steps and materials in the manufacturing process. Utilizing the information shown in table 11 (which is based upon prices provided in table 3) or substituting more current values, various competitive technologies can be compared more effectively. For example, even though one technology may have a distinctly better yield than the one shown in table 10 for Isonicotinic Acid, if its direct material costs should be significantly higher, it may not be worth buying or it may offer opportunities for improvement in technology and possible cost reductions. Availability of costs of each material input improves the accuracy of assessment, since there is no need of a proxy for other materials.

Breakdowns for succeeding steps in the process, using the 4-Picoline route with Potassium Permanganate as the oxidizing agent, to produce pure ISONIAZID, are illustrated in tables 11 through 15. The progression through these will serve not only to evaluate the individual steps more thoroughly but also to weigh potential convertible currency savings.

Table 11. Direct material costs of ISONIAZID manufacture ($US, per cent)
Step 2: Isonicotinic Acid Methylester

Name	f	c	Per cent
Isocotinic Acid	1.00	5.86	83.2
Methylene chloride	1.08	0.83	11.8
Methanol	0.77	0.15	2.1
Ammonia solution, 25%	0.90	0.11	1.6
Sulphuric acid 100%	1.08	0.09	1.3
Direct material costs		7.04	100.0

Table 12. Direct material costs of ISONIAZID manufacture ($US, per cent).
Steps 1 and 2 combined: Isonicotinic Acid Methylester

Name	f	c	per cent
4-Picoline	0.91	2.28	32.4
Potassium Permanganate	3.62	4.09	58.1
Methylene chloride	1.08	0.83	11.8
Methanol	0.77	0.15	2.1
Ammonia solution, 25%	0.90	0.11	1.6
Hydrochloric acid, 36%	1.63	0.11	1.6
Sulphuric acid	1.08	0.09	1.2
Manganese dioxide, recovered	-1.99	-0.62	-8.8
Direct material costs		7.04	100.0

Table 13. Direct material costs of ISONIAZID manufacture ($US, per cent). Step 3: ISONIAZID crude

Name	f	c	per cent
Isocotinic Acid Methylester	1.05	7.39	88.6
Hydrazine Hydrate	0.41	0.98	11.8
Methanol, recovered	-0.17	-0.03	-0.4
Direct material costs		8.34	100.0

Table 14. Direct material costs of ISONIAZID manufacture ($US, per cent). Steps 1, 2 and 3 combined: ISONIAZID crude

Name	f	c	per cent
4-Picoline	0.96	2.40	29.0
Potassium Permanganate	3.80	4.29	51.8
Hydrazine Hydrate	0.41	0.98	11.8
Methylene Chloride	1.13	0.87	10.5
Methanol	0.64	0.13	1.6
Hydrochloric Acid, 36%	1.71	0.12	1.4
Ammonia solution, 25%	0.95	0.11	1.3
Sulphuric Acid	1.13	0.09	1.1
Manganese Dioxide, recovered	-2.09	-0.65	-7.9
Methanol, recovered	-0.18	-0.06	-0.7
Direct material costs		8.28	100.0

Table 15. Direct material costs of ISONIAZID manufacture ($US, per cent). Step 4: ISONIAZID

Name	f	c	Per cent
ISONIAZID crude	1.05	8.76	98.2
Methanol	0.58	0.12	1.3
Carbon, activated	0.01	0.03	0.3
Speedex[a/]	0.01	0.01	0.1
Direct material costs		8.92	100.0

a/ Auxiliary material to aid filtration.

Table 16 summarizes the overall synthesis, showing the percentage share of each ingredient, both in direct material costs (C_{ij}) and total production costs (C_{tp}), as well as the contribution of conversion costs to the total production costs.

Table 16. Direct material costs and total production costs of ISONIAZID manufacture ($US, per cent)

Name	f	c	C_{ij} per cent	C_{tp} per cent
4-Picoline	1.00	2.50	28.0	20.4
Potassium Permanganate	4.00	4.52	50.6	37.0
Hydrazine Hydrate	0.43	1.03	11.5	8.4
Methylene Chloride	1.20	0.92	10.3	7.5
Methanol	1.25	0.25	2.8	2.0
Hydrochloric Acid, 36%	1.80	0.13	1.5	1.1
Ammonia solution, 25%	0.99	0.12	1.3	1.0
Sulphuric Acid	1.20	0.10	1.1	0.8
Carbon, activated	0.01	0.03	0.3	0.2
Speedex a/	0.01	0.01	1	0.1
Manganese dioxide, recovered	-2.20	-0.68	- 0	-5.6
Direct material costs		8.93	100.0	73.0
Conversion costs		3.30		27.0
Production costs		12.23		100.0

a/ Auxiliary material to aid filtration.

Other material costs, if at all given, are not detailed in the literature. Figures from different sources or those derived from detailed information should be handled with care because such costs may differ from manufacturer to manufacturer, hence an accurate comparison is impossible. Here, for example, the percentage of other materials (i.e., methanol, hydrochloric acid, ammonia, sulphuric acid, activated carbon, Speedex) in C_{tp} is 5.2, the same as for the ideal producer but lower than the 5.3 for the average performer cited in table 4. Although the difference is fractional, it can be due to various factors: the process of the average producer may use less of several minor inexpensive materials, leading to

higher coefficients for more expensive ones, a possibility suggested earlier; or, there may be opportunities to further refine individual processes and reduce costs through recycling mother liquor or better recovery and re-use of solvents.

Comparisons or reviews of this nature, substituting updated world market and, depending upon availability, local market prices can provide more realistic values for both gross profit (or loss) and convertible currency savings, employing various proprietary technologies offered for transfer.

Among other patterns which may be revealed by such exercises are high convertible currency savings but very low profits or even losses. Such situations could result from an apparently excessive price for one or more locally produced chemicals. This premise could lead to the examination of prices and/or production of other locally produced components as well as an examination of the conversion into dollars of their prices as expressed in the local currency. Therefore, it might prove more advantageous to purchase selected items on the world market.

This is particularly true in regard to key intermediates; their probable cost is usually decisive in judging/accepting/rejecting technology as well as in constructing local facilities.

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

Chemical input conversion coefficients are regularly used to estimate direct material requirements for the production of a specific quantity of a given chemical in a given period. The same data reflect also the overall convertible currency saving and the profit or loss for the same quantities and time.

Table 17 shows data for manufacture of ISONIAZID by oxidation of 4-Picoline with Potassium Permanganate.

Table 17. Material requirements (tons) and some financial aspects (thousand $US) of 100 tons of ISONIAZID

Name	Average performer		Ideal performer	
	quantity	value	quantity	value
4-Picoline	100	250	90	225
Potassium Permanganate	400	452	360	407
Hydrazine Hydrate	63	151	43	103
Methylene chloride	120	98	106	82
Other materials		67		57
		1,018		874
Manganese dioxide, recovered		- 72		- 61
Total material requirements		946		813
Convertible currency saving		54		187
Gross loss		276		91

It can be seen that if 100 tons of ISONIAZID were produced locally by the Potassium Permanganate oxidation route, an average performer would realize a negligible convertible currency saving and a substantial gross loss. The figures of the ideal performer are much better but still unattractive. These figures assume that all materials are imported. The picture would change if Potassium Permanganate could be purchased locally because convertible currency savings could then be as high as $US 500,000 with the average and $US 600,000 with the ideal performer, respectively. Any credit from the recovery of

manganese dioxide can be realized only if there is a domestic company that needs the material. Additionally, the gross loss will be taken in local currency if the total output is finished and consumed domestically.

Hence, no significant economies can be realized at national level unless the project is assessed together with the local production of Potassium Permanganate. At the enterprise level, desk research has shown a gross loss that cannot be changed to profit by technical development of the same route, but only by using an alternative process that is technically feasible and economically much more attractive.

10. TRENDS AND FORECASTS OF DEMAND FOR ISONIAZID AND ITS INTERMEDIATES

10.1 Morbidity trends for tuberculosis

In 1982, almost 1.6 million cases of tuberculosis were reported to WHO, down from a total of almost 2.2 million in the preceding year; however, rather than showing an actual decrease, this simply means that returns from member countries are incomplete. Totals for 1983 are even further from being complete.

Table 18. Number of tuberculosis cases reported in WHO regions 1967-1983 (in thousands)[a/]

	1967	1971	1975	1979	1980	1981	1982[a/]	1983[b/]
World total	1,160	1,038	1,862	2,109	2,101	2,183	1,596	825
South-East Asia	481	495	727	752	757	894	747	750
E. Mediteranean	...	...	392	491	525	500	422	48
Africa	212	98	30	117	110	193	205	3
W. Pacific	8	11	160	326	278	353	175	1
Americas	168	207	187	213	218	66	32	24
Europe	291	227	306	210	213	175	15	-

a/ Incomplete returns, particularly from the Western Pacific, Americas and European regions.

b/ Incomplete returns from all regions except South-East Asia.

Source: World Health Statistics 1984, WHO, Geneva (1984).

Consequently, judging by the returns from the preceding three years (1979/1981), it appears that the overall number of annually-reported cases may be plateauing, even though there may be significant yearly variations within the individual countries themselves.

The actual number of cases worldwide is unknown but previously published WHO extrapolations from the registered cases to the total population[22/] suggest that in 1981 there could have been as many as 7.3 million. Other estimates have placed the annual figure of occurrence in developing countries alone as high as ten million, including four to five million highly infectious cases of smear-positive tuberculosis and an equal number of less infectious cases; the latter include those positive by culture only as well as culture-negative cases, the most frequent form of pulmonary disease in children.[23/] At least three million people (30 per cent) are believed to die from the infection every year.[24/]

Although the WHO global target envisages that some communicable diseases in the developing countries will be of no greater public health significance in the year 2000 than they were in technically advanced countries in 1980, the current high incidence and the natural history of tuberculosis in man suggest that such a level of control would be extremely difficult to achieve during so short a span, although it is hoped that a substantial reduction in the magnitude of the problem may be achieved.

It should be realized that the decline in tuberculosis cases in the industrialized countries started in the early years of the twentieth century as a result of improved socio-economic and public health conditions. This was long before the advent of chemotherapy, which began with the introduction of streptomycin in 1947.[25/] Consequently, improvement of the quality and the rate of development of primary health-care services as well as the degree of integration of case-finding and treatment in developing countries will aid but will not provide the ultimate solution to the problem. The combination of

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22/ A. Bulla, Tuberculosis Patients - how many now?. WHO Chronicle, 31: 279-286 (1977), Geneva, Switzerland.

23/ Tuberculosis Control, Technical Report Series 671, WHO, Geneva, p. 10 (1982).

24/ Ibid.

25/ H.B. Simon, M.D., Tuberculosis: Update on Drug Therapy, Consultant, April 1984, p. 63.

case-finding and chemotherapy can be a powerful weapon in eliminating sources of infection as well as suffering and death. However, in areas where poor socio-economic conditions such as overcrowding, poor hygiene and sanitation, malnutrition and illiteracy continue to exist, effective control will be difficult to attain.

The fact that treatment is often long-term (i.e., 12 to 18 months) increases the significance of further problems, most notably the development of microbacterial resistance, drug toxicity and patient non-compliance with the therapeutic regimen.

Even if the effectiveness of the BCG vaccine - developed in the 1950s and most frequently used to protect children against tuberculosis - should be proven in more widespread populations, it can have only a relatively small epidemiological effect in that it will not contribute signficiantly to the reduction in the overall risk of infection in the community as a whole.[26/]

Furthermore, preventive treatment (chemoprophylaxis) with ISONIAZID can prevent the development of tuberculosis in infected individuals but its impact upon the community will be minimal because it cannot be applied on a mass scale, even in technically advanced countries.[27/] It is best used alone for patients who have positive tuberculin skin tests but no active disease. The rationale for this use rests upon three postulates. First, if the patient has not received chemotherapy, a positive reaction reflects the persistence of viable, if dormant, bacilli within host macrophages. Second, the risk of reactivation of these dormant bacilli is always present, but is greatest in patients within the first two years after infection, in children and adolescents, and in impaired hosts. These are the groups most likely to benefit from chemoprophylaxis. Third, ISONIAZID substantially reduces the risk of reactivation of tuberculosis in persons with positive skin tests.[28/]

26/ Tuberculosis Control, Technical Report Series 671, WHO, Geneva, p. 11 (1982).

27/ Ibid.

28/ H.B. Simon, M.D., Tuberculosis: Update on Drug Therapy, Consultant, April 1984, p. 75.

Not only would its more widespread use be unecessary for many people who, as adults, have long since built up an immunity to the disease but it would also be costly and would foster even greater bacterial resistance which is already a problem with the drug.

Up to 12 per cent of patients from certain population groups, such as Hispanic people and (United States) immigrants from Asia and Haiti, harbour microorganisms which are resistant to at least one antituberculosis drug. Resistance to ISONIAZID or streptomycin or both is common among these groups, and resistance to rifampin and ethambutol remains also quite common.29/

Consequently, in the majority of the developing countries there has been little, if any, improvement in the epidemiological situation. In fact, there has been an overall increase in the absolute number of tuberculosis cases in these countries during the last three decades because the population has doubled during the period.30/ These increases are most notable within the African, South-East Asian and Eastern Mediterranean regions.

Data from the African region, even with fewer countries reporting, suggest a recent sharp acceleration in the number of identified cases, most notably in Ethiopia. However, this increase more probably reflects improved and/or expanded identification of infected patients and/or more reliable reporting rather than a dramatic increase in the incidence of the disease.

Data from the Eastern Mediterranean region indicate a similar pattern. Within this area, Pakistan has accounted for an increasing share of the cases, reaching 77 per cent in 1982.

On the other hand, figures from South-East Asia, where around 85 per cent of the identified patients are found in India, continue to oscillate around the ten-year average of about 740,000 reported cases a year.

29/ Op. cit.

30/ Tuberculosis Control, Technical Report Series 671, WHO, Geneva, p. 11 (1982).

The Western Pacific nations also show an oscillating trend, even though Japan and the Philippines - two of the three countries where the problem has been most acute (the Republic of Korea is the other) - appear to be successfully reducing local incidence.

The Americas also suggest rather a status quo situation with North America (i.e., Canada and the United States) registering about 14 per cent of all cases; Central America, about ten per cent; the Caribbean about three per cent; and the South American continent upwards of 70 per cent. Brazil alone, with an increasing number of identified cases, accounts for about one-third of the Americas' total.

A similar profile is evident in the WHO European region where three diverse countries - Morocco, Poland and Turkey - collectively present between 40 and 50 per cent of all yearly cases.

Despite the fact that the technically advanced countries have achieved very substantial results in the control of tuberculosis through a combination of improved socio-economic conditions and advances in health care and therapy, the disease will occur in these areas - though at a decreasing rate - for many years to come. Specific problems, such as indigenous high-risk groups, refugees and immigrants from high-prevalence areas will continue to require special attention, even though they are unlikely to have a significant long-term effect on the overall tuberculosis situation.[31/]

10.2 ISONIAZID consumption

The WHO model list of essential drugs contains six pharmaceuticals specifically for use against tuberculosis: ethambutol, ISONIAZID, pyrazinamide, rifampicin, streptomycin and a combination of thiacetazone plus ISONIAZID.[32/]

31/ Global media-term programme 13.8: Tuberculosis, WHO, Geneva (1983), p. 2.

32/ The use of essential drugs, WHO Technical Report Series 722, Geneva, 1985, p. 19.

ISONIAZID, thioacetazone and streptomycin are the drugs most commonly used, followed by rifampicin, ethambutol and pyrazinamide. These latter are used only on a limited scale in developing countries, generally being reserved for retreatment because of high cost. Thioacetazone, normally not used alone, is rarely used in industrialized countries. In both industrialized and developing countries, rifampicin and pyrazinamide are used for short-term chemotherapy where it has been introduced.[33/]

For the initial regimen of therapy, a multi-drug approach is usually taken. This is because some may prove bactericidal against the causative bacteria population, some may be only bacteriostatic and some may be completely ineffective.

In the ninth report of the WHO Expert Committee on tuberculosis, two regimens are recommended for use in developing countries: (a) ISONIAZID plus thioacetazone, often supplemented by streptomycin in the initial intensive daily treatment phase, and (b) a twice-weekly, fully supervised regimen of streptomycin plus ISONIAZID, preceded wherever possible, by an initial intensive daily treatment phase. The recommended duration of both regimens is 12 months.

Assuming that - based upon the number of identified cases[34/] - patients in those countries included in table 19 represent about 45 per cent and that those in all developing countries represent about 85 per cent of the worldwide potential for antitubercular drugs, the estimated annual consumption of 841 metric tons may be projected to almost 1,600 metric tons for all developing countries.

Further, assuming that - based upon the afore-mentioned world market price of $US 10 per kilo - each metric ton has a value of $US 10,000 - the total market for ISONIAZID in all developing countries may be about $US 16 million a year.

33/ World Health Statistics 1984, WHO, Geneva (1984).

34/ Recent advances in the chemotherapy of tuberculosis, WHO Chronicle, 34:101-103 (1980).

Table 19. Estimated annual consumption of ISONIAZID, 1977/1982 (metric tons)

ASEAN countries	100
India	375
Bangladesh	29
Arab countries including Egypt	100
ANDEAN countries	237
Total, selected countries	841

Source: UNIDO, ID/WG.331/4 of 26 September 1980, The pricing and availability of intermediates and bulk drugs, annex vi, p. 64.

10.3 Pharmaceutical price trends

Time series data for the prices of chemical inputs were available from the Chemical Market Reporter (CMR) and annual $US price indices were received for a few pharmaceutical intermediates through correspondence with buyers.

Figure 3 shows that the price index 1970-1984 of Hydrazine Hydrate grew between 1970 and 1979 with unusual market conditions in the years 1974-1975. Since 1979, the price of this chemical has gradually declined. Absolute values were also available for some years and they were significantly lower than those quoted in the CMR.

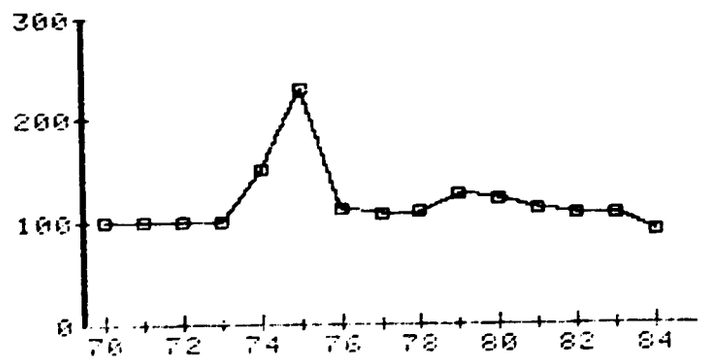

FIG. 3: $US PRICE INDEX 1970-1984
HYDRAZINE HYDRATE

Unusual changes in the price index trend of Potassium Permanganate (figure 4) in the years 1980 and 1981 were due to changing quality from DAB6 (outdated German Pharmacopeia, edition 6) to British Pharmacopeia official in those years. This meant also change of supplier. As regards the manufacture of ISONIAZID, the quality of DAB6 is satisfactory. Significant differences were observed again between the absolute values of two available sources. Usually, again the prices quoted in the CMR were higher. It should also be mentioned that quality in the latter source is indicated as bulk.

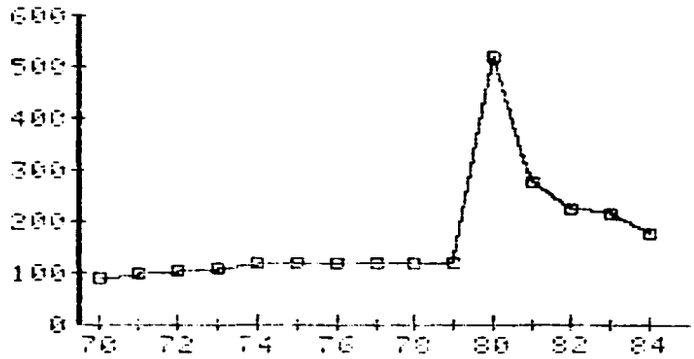

FIG.4 $US PRICE INDEX 1970-1984
POTASSIUM PERMANGANATE

Figure 5 shows that the price of ISONIAZID bulk substance increased sharply in the years 1973 and 1975, and remained at $US 12 since 1976. The latter information should be handled with care, because ISONIAZID is the first pharmaceutical commodity chemical, the price of which does not seem to be affected by supply and demand over a decade.

The $US price of Hydrazine Hydrate (85 per cent) was converted into 100 per cent chemical activity and the obtained figures were plotted against time. The unit price of Hydrazine Hydrate in about 200-litre drums was used for the time series and this was about $US 2.40 higher than the price/kg of the chemical delivered in tankers. Figure 6 shows a sharp increase in the $US price of Hydrazine Hydrate in the years 1974-1975 and a constant section between 1975 and 1984, an unusual and improbable phenomenon in commodity chemical trade.

In the absence of a complete time series for 4-Picoline, figure 7 plots the changes in the $US/kg price of mixed, refined picolines. In the early 1970s, prices of 2-, 3- and 4-picolines showed an approximate proportion of 1:1.5:1. In the years 1975-1978, the CMR quoted $US 1.70 for a kg of 4-Picoline and $US 1.65 for refined, mixed picolines. Based on these facts, the price of 4-Picoline has been taken as practically equal to that of mixed picolines. Figure 7 shows that the price of 4-Picoline doubled between 1973 and 1975, and increased by about 55 per cent from 1982 to 1983.

The unit price of a truckload of Potassium Permanganate equalled the price of the bulk substance in 150-kg drums. The pharmacopeial quality was about $US 0.60/kg more expensive than the free flowing Potassium Permanganate in bulk, which was chosen for price analysis. Figure 8 shows three significant increases in the $US/kg price of this chemical in 1974, 1977 and 1979, whereas a sharp decrease can be observed in 1983.

The last chemical that plays an important role in the cost structure of ISONIAZID is Methylene Chloride, the $US/kg price of which has continously increased and quadrupled between the years 1970 and 1985.

Time series for the price of 4-Cyanopyridine have not been available. The kg price of this chemical was about $US 6 in 1970 and $US 4 in 1982. It should be mentioned, however, that these prices were given for the supply of relatively small quanitities of 4-Cyanopyridine and larger quantities could probably be purchased at much better prices.

Nitric Acid has been analyzed as a reactant in the oxidation of 4-Picoline into Isonicotinic Acid. Its $US/ton price trend (figure 9) shows a sharp increase in the years 1973 and 1974, and a continuous, albeit moderate growth since 1975.

The other commodity chemicals, taken individually, do not contribute significantly to the C_{tp}. Nevertheless, their price trends (figures 10, 11, 12, 13, 14 and 15) are worth considering, particularly in years of sudden, high increases.

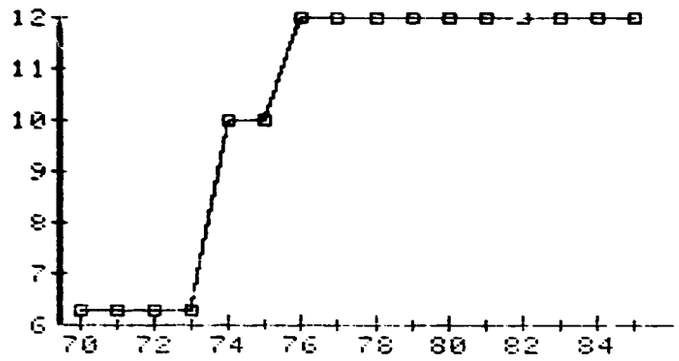

FIG.5: ISONIAZID
$US/KG PRICE TREND 1970-1985

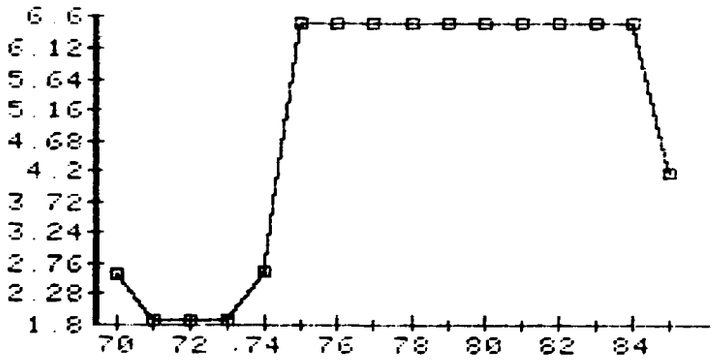

FIG.6:HYDRAZINE HYDRATE 85%,100% BASIS
$US/KG PRICE TREND 1970-1985

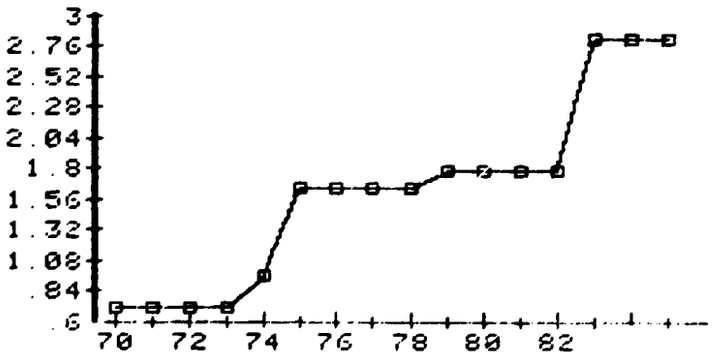

FIG.7: MIXED, REFINED PICOL.
$US/KG PRICE TREND 1970-19

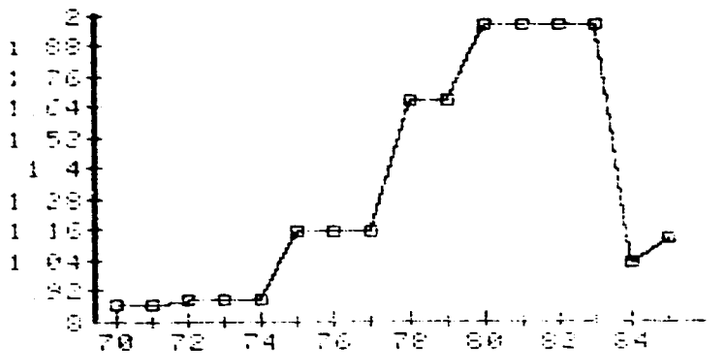

FIG.8 POTASSIUM PERMANGANATE
$US/KG PRICE TREND 1970-1985

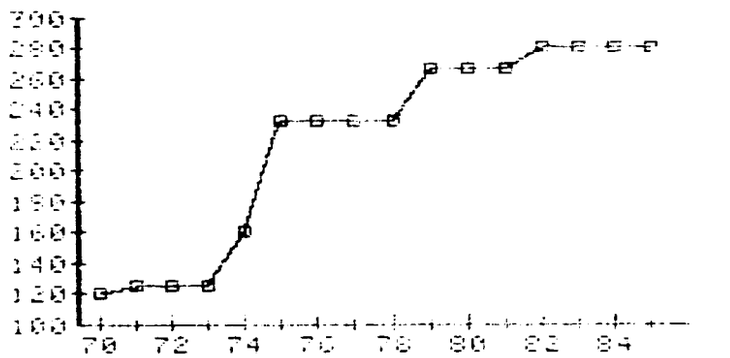

FIG.9 NITRIC ACID 94-98%, 100% BASIS
$US/TON PRICE TREND 1970-1985

FIG.10 SULFURIC ACID, VIRGIN, 100%
$US/TON PRICE TREND 1970-1985

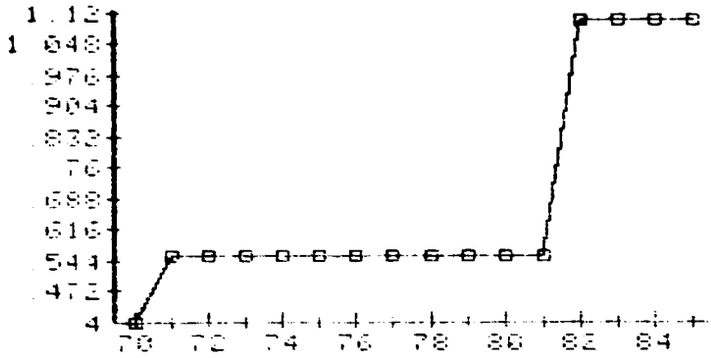

FIG 11 MANGANESE DIOXIDE, FERRIT GRADE
$US/TON PRICE TREND 1970-1985

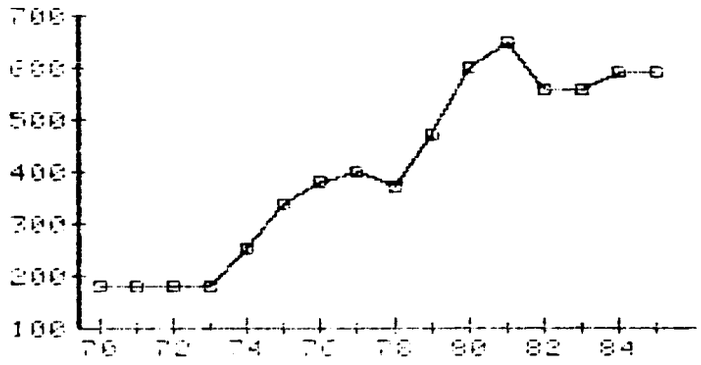

FIG 12 SYNTHETIC ETHANOL 95%
$US/TON PRICE TREND 1970-1985

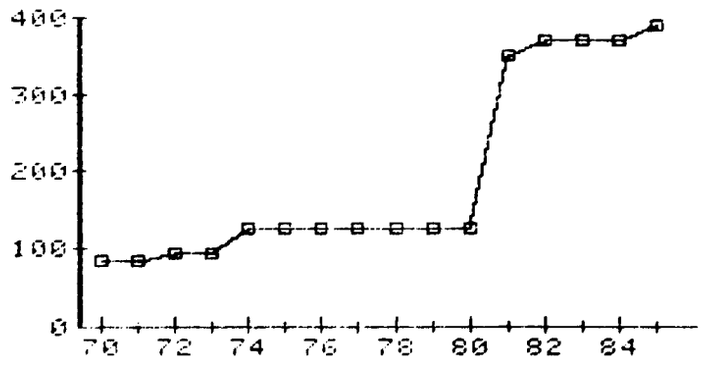

FIG 13: SODIUM CARBONATE, MONOHYDRATE
$US/TON PRICE TREND 1970-1985

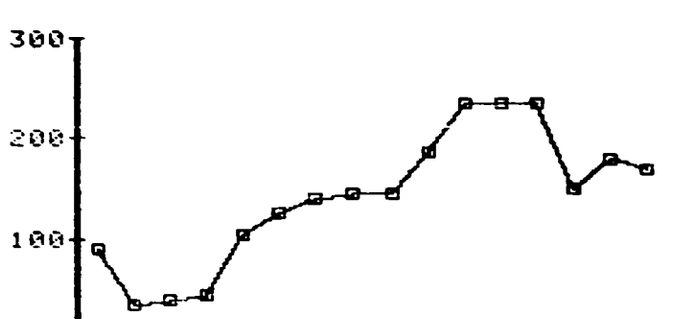

FIG.14: SYNTHETIC METHANOL
$US/TON PRICE TREND 1970-1985

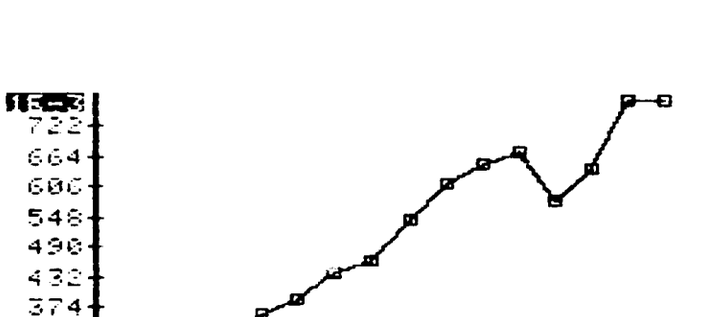

FIG.15: METHYLENE CHLORIDE
$US/KG PRICE TREND 1970-1985

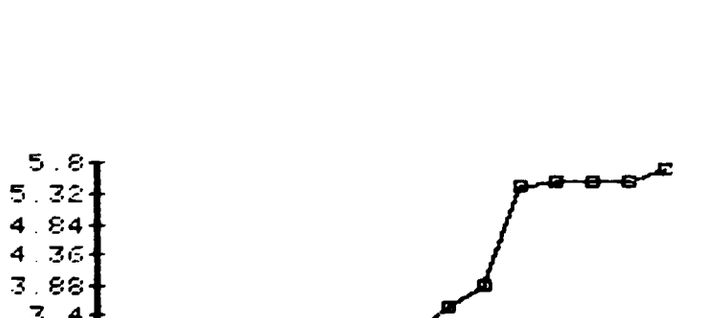

FIG.16: REFINED PYRIDINE
$US/KG PRICE TREND 1970-1985

Figure 16 has been included in the selection to show that pyridine was a competitor to 4-Picoline in the early 1970s, but could not be considered as a starting material to-day.

The price trend of ISONIAZID cannot be correlated with those of the reactants playing a dominant role in the cost structure of the pharmaceutical chemcal. This can be explained by the fact that ISONIAZID production is not the major consumer for these reactants, not even in case of 4-Picoline.

Table 20 provides prices[35/] over the past six years for ISONIAZID tablets 100 mg.

Table 20. Annual average prices for 1,000 ISONIAZID tablets of 100 mg available in international trade

Year	Dfl - $US index	Price	
		Dfl	$US
1980	100	4.25	2.14
1981	126	4.48	1.79
1982	134	5.75	2.16
1983	144	7.30	2.56
1984	161	7.50	2.34
1985	160	8.60	2.84

It should be noted that the 1984 average Dfl-$US index was taken during an upward trend of the $US against the Dfl. The June 1984 index of 155, for example, grew to 176 in December 1984 and peaked at 188 in March 1985, when the declining trend of the $US started which reached a yearly minimum of 140 in December 1985. Hence, the annual average prices both in Dfl and $US should be handled with care in the years 1984-1985.

35/ Price Indicators 1980-1985 of IDA International Dispensary Association, P.O. Box 3098, Amsterdam.

The overall change over the period 1980-1985 shows a continuous increase both in the Dfl and $US prices of 1,000 ISONIAZID tablets 100 mg. Current $US price decreased only in 1981. The prices in table 20 can be considered competitive, because the 1981 value was close to the best price in an international comparison.[36/]

Table 21. Price analysis of ISONIAZID tablets sold on the US generic market

Price	Tablets 100 mg		Tablets 300 mg	
	1982	1984	1982	1984
Average	5.96	7.00	9.89	11.54
Minimum	3.25	3.25	7.50	7.50
Maximum	14.27	17.95	14.95	25.95

Source: Red Book 1982 and 1984, Medical Economics Co. Inc., Oradell, N.J. 07649.

The current $US selling prices to the consumer of 31 and 21 suppliers of ISONIAZID tablets, 100 mg and 300 mg, respectively, are given in table 21. The minimum retail price of 100 mg tablets in 1982 compares well with the duty- and tax-free price of $US 2.16 on the international market.

Assuming a 100 per cent mark-up between the manufacturers' and retail sales prices, the cost shares of the active ingredient in the sales price are 56 per cent and 61 per cent, respectively, in the most competitive prices of ISONIAZID tablets 100 mg. The same figures for 100 mg and 300 mg tablets suggest a mark-up of about 60 per cent and 30 per cent for producers that can realize the average price. Two general conclusions can be drawn from these statements: (a) the production of tablets is economically promising for manufacturers buying the pharmaceutical chemical and selling their product even on a competitive market, and (b) the competition is relatively higher on the 300 mg than on the 100 mg tablet market, probably because the

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36/ Price Indicator on International Low-Price Sources for Essential Drugs (WHO), 2nd ed., medico international and A.T.I. Arzneimittel Information Berlin GmbH, 1982.

manufacturing costs, with the exception of the cost of the active ingredient, do not differ significantly for the 100 mg and 300 mg tablets. Fluctuations in other costs and overheads can better be dealt with in 300 mg tablet production, where a smaller percentage might still mean higher profit in absolute values.

10.4 Assessment of some external factors affecting ISONIAZID consumption

10.4.1 Economic competition

Safety, effectiveness and other factors being equal, cost is the major consideration in the selection of the drug of choice in a given therapeutic category. Table 22 illustrates the comparative costs of some of the primary drugs used for tuberculosis.

Admittedly, price relationships of different drugs will vary depending on a variety of factors including quantity purchased, source from which obtained, import duties and country in which acquired. A further factor is the dependence of the dosis on the weight of the patient. For example, one study revealed that the $US price of ISONIAZID tablets sold to the health service in one developing country was over 18 times as much as that in another.[37/]

Nevertheless, from the data presented here, it is evident that, on a daily basis, ISONIAZID or the popular ISONIAZID plus thioacetazone combination appear to afford the most economical therapies, bearing in mind that Streptomycin is not administered alone in the treatment of tuberculosis. Rifampin costs about five times as much, Ethambutol ten times as much, and Pyrazinamide about 26 times as much as the treatment with ISONIAZID.

37/ Results of the international co-operative inquiry into the cost of antituberculosis drugs. Bulletin of the International Union against Tuberculosis, vol. 53, no. 4, December 1978, p. 249.

Table 22. Indices of relative cost/day of standard dosage of antitubercular drugs

Drug	Dose,[a] mg	Cost,[b] $US/100	Cost,[b] Index
ISONIAZID	300	6.5[c]	2
ISONIAZID and thioacetazone	300+150	9.8	3
Streptomycin	286	3.3[d]	1
Ethambutol hydrochloride	900[e]	67.0	20
Pyrazinamide	2,100[e]	175.0	53
Rifampicin	600[e]	33.0	10

a/ Expert Commitee on Essential Drugs, Information sheets: Section 7.9, antituberculosis drugs, WHO, Geneva, 1982.

b/ Employing the closest standard dosage sizes and average $US prices calculated from the Dfl prices listed in the International Dispensary Association (IDA) Price Indicator for 1982.

c/ 3 x 100 mg tablet.

d/ The weekly dose of 2 g was divided by seven and the relevant fraction of water for injection was added to the costs.

e/ Assuming 60 kg of body weight.

10.4.2 Therapeutic competition

ISONIAZID has been categorized as the most effective antitubercular drug available; it is not only the most potent bactericidal agent against actively growing bacilli but it is also the only one effective for prophylaxis.

Nevertheless, resistant strains of tubercular bacilli can emerge rapidly and may become dominant unless the drug is used in combination with other agents. It has been reported that naturally occurring drug resistant mutants are produced at the rate of one in 10^5 bacilli for ISONIAZID, one in 10^6 bacilli for streptomycin, and one in 10^7 bacilli for rifampin.[38] With single agent administration, the resistant mutants multiply until the total population becomes resistant. However, if the patient receives two

38/ J.L. LeFrock, M.D., and B.R. Smith, M.D., Tuberculosis therapy, American Family Physician, March 1983, p. 261.

agents, the bacilli that are resistant to one of the drugs are destroyed by the other. The incidence of mutants simultaneously resistant to both drugs is approximately one in 10^{11} bacilli. Therefore, concomitant use of two effective drugs is essential to prevent the development of drug resistance.39/

In the United States, in view of current judgements of efficacy and toxicity, antituberculous drugs now fall into one of three classifications:

Primary - ISONIAZID, rifampin

Secondary - ethambutol, streptomycin, pyrazinamide (a derivative of nicotinic acid)

Tertiary - para-aminosalicylic acid (PAS), ethionamide, cycloserine, kanamycin, capreomycin.

The secondary drugs are less effective than either ISONIAZID or rifampicin. The tertiary drugs are the least efficacious and most toxic.40/

In programming an effective therapy, ideally the drugs should be chosen for their specific activity against various types of bacterial population present in lesions. On large populations of bacilli actively multiplying at neutral pH on the walk of pulmonary caverns, the effect of ISONIAZID, streptomycin and rifampicin is bactericidal; ethambutol is bacteriostatic; and pyrazinamide is inactive. Against the small bacterial population that multiplies slowly in an acid medium inside macrophages (phagocytes), pyrazinamide is most effective followed by ISONIAZID plus rifampicin; streptomycin is inactive. Against bacilli in solid caseous lesions which multiply intermittently, only rifampicin is bactericidal, all others being inactive.

39/ Ibid.

40/ H.B. Simon, M.D., Tuberculosis: update on drug therapy, Consultant, April 1984, p. 64.

From the bacteriological standpoint, the short-term use of ISONIAZID and rifampicin in combination in both the initial and continuation phases[41] has been strongly recommended as the optimum therapy for all forms of the disease including those caused by more sensitive strains. These drugs are usually supplemented - at least, in the initial phases - with one or two others, such as ethambutol or streptomycin. Overall, courses of short-term therapy usually run from six to nine months.

Short-course chemotherapy regimens (6-months duration) are gradually being introduced as standard treatment in control programmes. In the region of the Americas, they are already given to almost 50 per cent of the newly reported cases. However, the regimens of one year (or more) duration will remain the basic chemotherapy for the tuberculosis programmes in many countries unless further substantial reductions are made in the cost of the drugs for short-term use, particularly rifampicin and pyrazinamide.[42]

In fact, for mild to moderate cases, some physicians still prefer the older (and longer) regimen of ISONIAZID and ethambutol. It is of proven efficacy and it avoids the potentially overlapping hepatotoxicity of ISONIAZID and rifampicin. Additionally, this approach permits holding rifampicin in reserve should drug intolerance, microbial resistance or treatment failure come about.[43]

Generally speaking, however, all of the major antitubercular agents discussed in this report are well tolerated and notable adverse effects will occur in less than five per cent of all patients; reportedly, these may vary

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41/ Recent advances in the chemotherapy of tuberculosis, WHO Chronicle, 34:101-103 (1980).

42/ Global medium-term programme 13.8: Tuberculosis, WHO, Geneva, p. 3.

43/ H.B. Simon, M.D., Tuberculosis: update on drug therapy, Consultant, April 1984, p. 71.

from country to country and patient to patient. However, the number of patients in which treatment has to be discontinued permanently is usually under three per cent.[44/]

In addition to its potential hepatotoxicity - which, reportedly, was not widely recognized until about 17 years after its introduction - other potentially serious effects occasionally encountered with ISONIAZID are peripheral neuritis and, in patients with epilepsy, convulsions. All may be avoided by carefully exploring a patient's medical history, by frequent observation and, for peripheral neuritis, by the concurrent administration of pyridoxine.

The most notable side effects of the other principal antitubercular drugs are loss of visual acuity from ethambutol; ototoxicity from streptomycin; and hepatotoxicity from pyrazinamide and, as mentioned earlier, rifampicin.

10.4.3 Other factors affecting ISONIAZID use

Although, worldwide, the overall total number of tuberculosis cases reported appears to be plateauing, it has been recognized that the majority of those existing now go unreported, either because they are unidentified orbecause of deficiencies in reporting systems. Programmes are underway aimed at improving both of these situations.

Nevertheless, poor socio-economic conditions in some countries, further aggravated by population growth, lack of availability of adequate health-care facilities, poor attendance at these facilities and various financial constraints cannot only foster further spread of the condition but also impede the progress of the proper diagnosis and treatment.

44/ Recent advances in the chemotherapy of tuberculosis, WHO Chronicle, 34:101-103 (1980).

10.5 Short-term forecasts of ISONIAZID demand to 1990

Time series of worldwide ISONIAZID consumption have not been available, hence the historical growth cannot be calculated.

The market for developing countries, which can be taken equal to the world market in practical terms, was estimated at about 1,600 tons in 1982.

In the absence of a better method, it is assumed that the growth rate of ISONIAZID consumption for the period 1982-1990 will be 2.2 per cent, i.e. equal to the estimated average annual percentage change for population growth in all developing countries.

Table 23 shows the estimated demand for ISONIAZID and intermediates based on the conversion efficiencies of the average and ideal performers. Intermediates in table 23 refer to different processes and/or routes of oxidation, hence manufacturers that import 4-Picoline will not import 4-Cyanopyridine. It should also be remembered that intermediate demands refer to ISONIAZID synthesis only, which might represent only a small fraction of the total demand for such intermediates, e.g., in the case of Hydrazine Hydrate.

In the Asian region, Chinese and Indian manufacturers cover the national demand by local production. Latin America and Africa are net importers today, although, demand, as judged by morbidity figures, would justify domestic manufacture of ISONIAZID in both regions.

Table 23. Current and future worldwide consumption estimates of ISONIAZID and intermediates (tons)

Chemical	1982 (estimated)	1990 (forecast)
ISONIAZID	1,600	1,950
4-Picoline	1,440-1,780	1,750-2,170
4-Cyanopyridine	1,520-1,820	1,850-2,210
Hydrazine Hydrate	690-1,380	840-1,680

10.6 Long-term forecasts of ISONIAZID demand to 2000

The antituberculosis drug market is very complex and the circumstances surrounding the situation by the year 2000 cannot be predicted.

At the time of writing, there appears to be only one possible new antitubercular drug on the horizon, a long way from commercial marketing. This is LM-427, generically known as rifabutine, which is a rifampicin-like drug in the ansamycin class; it has been experimentally used in atypical cases of tuberculosis (such as in AIDS patients) but has yet to be widely tested clinically for other cases. Farmitalia Carlo Erba is pursuing the research.

Therefore, the focus among available drugs is unlikely to change significantly over the next few years.

ISONIAZID is regarded as the most potent and selective of the known tuberculostatic antibacterial agents and it is regarded as the most effective in the therapy of tuberculosis. It is the central drug around which various combinations are formulated.[45/] These attributes combined with the favourable price among major antitubercular products assure its continuing widespread use for both propylaxis and therapy for many years to come.

45/ Remington Pharmaceutical Sciences, 16th ed., Mack Publishing Co., Easton, PA 18042 (1980), p. 1159.

11. CONCLUSIONS AND RECOMMENDATIONS

Various aspects (i.e., sourcing, technology, safety, economical, etc.) of the production of ISONIAZID by the two basic routes have been discussed in some detail in chapters 5 and 6. Both reference routes appear to be technically feasible and all chemical reactions involved can be carried out in a multipurpose batch reactor, utilizing equipment generally available for the production of pharmaceuticals. The reactor for the oxidation of 4-Picoline by Nitric Acid should be specially designed and can only be used for this type of chemical unit operation. The method with the unknown oxidizing agent cannot be assessed properly.

Consequently, technical preference is given to the 4-Cyanopyride route and the oxidation of 4-Picoline by Potassium Permanganate, whereas the oxidation by Nitric Acid should be considered as a choice of preference where this unit operation is carried out regularly and there is capacity left for new products. Different potential users will have different, sometimes conflicting, interests when considering this information for their own purposes and objectives. For example, decision-makers concerned with health may want to purchase their supplies of ISONIAZID at the lowest possible cost, without regard to source, whereas decision-makers more concerned with international balance-of-payments may be more interested in saving substantial amounts of convertible currency. For others still, the benefits of increased domestic industrialization may be the governing factor. Superimposed overall, potential investors are seeking profits and existing manufacturers are spending money to further develop their technology as well as to reduce production costs in general. The data provided in this paper should aid in analyzing the various aspects related to the above or other objectives.

11.1 Major conclusions of the techno-economic analysis

Based upon the assumption that the two primary considerations for establishing a new pharmaceutical operation are the availability of a continuing supply of necessary raw materials and the availability of facilities/personnel to carry out the synthesis involved, the ISONIAZID production route beginning with 4-Picoline is the choice. There are

alternative methods for producing the Isonicotinic Acid Methylester, affording latitude in the procurement of various components needed, and the technology involved is relatively simple so that production may probably be accommodated in an existing pharmaceutical plant, using existing personnel.

The selection of the particular method and oxidizing agent to be employed is more a local one, based upon the availability and price of the alternative chemicals. Although, reportedly, Potassium Permanganate is the one which has been most widely used, it does not appear to be either profitable or deliver the most significant convertible currency savings.

As noted in chapter 6, the unknown oxidizing agent (and, as such, difficult to evaluate) appears to afford the greatest profit with the largest convertible currency savings, with Nitric Acid in second place.

11.2 Alternative strategies

11.2.1 Alternative production route

For those potential producers whose primary objective is gross profit, it could be extremely advantageous to explore the possiblity of regularly obtaining anticipated requirements of 4-Cyanopyridine; not only is this particular synthesis less complex than those involving 4-Picoline but both the profitability and the convertible currency savings appear to be attractive. Supply of the starting material is the major problem.

11.2.2 Purchase of ISONIAZID bulk substance

The strategic alternatives would not be complete without considering the purchase of ISONIAZID bulk substance on the world market for finishing and packaging locally and to use such investment resources as may be available towards the production of a pharmaceutical bulk substance which may have greater local demand and/or more limited availability and/or better economic facility.

11.2.3 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 ISONIAZID and its 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 an eventual decrease of the spot prices.

The advantage of variation (ii) is the possibility of making extra profit from decreased spot prices; the principal risk is that the production costs may be very sensitive to the increases of spot prices and that there may also be availability problems if the balance of demand and supply is disturbed to an unusual extent. In the oxidation route with Potassium Permanganate, e.g., this single chemical represents 43.6 per cent of direct materials costs and 31.4 per cent of C_{tp}, if the credit from the recovered and sold Manganese Dioxide is taken into account. Hence, the price of Potassium Permanganate is a decisive factor in the process economics of ISONIAZID manufacture.

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 the particular synthesis is, the more dominant the share of conversion costs in the total production costs can be.

The conversion costs could not be analyzed in this study in detail due to lack of breakdown 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. 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.

11.3 Market analysis

One of the major attributes of ISONIAZID is that it can be produced in multipurpose batch reactors and, consequently, in relatively small quantities if there is little demand. Unfortunately, the economies of scale would have to be carefully considered since the intermittent production of small quanitities may add significantly to the cost of the product.

Rough calculations suggest that - predicated upon a daily dosage of three 100 mg tablets - one metric ton would provide enough chemical to treat about 9,100 people for one year. Consequently, 100 tons could provide enough medication for about 913,000 patients or more than 40 per cent of all of the cases which have been reported to the WHO annually over the last few years.

However, it is acknowledged that the number of cases reported to the WHO represents only a fraction of the actual number worldwide and projections of recent consumption suggest that the developing countries could consume as much as 1,600 metric tons of the chemical a year, not only for treatment but also for prophylaxis. Thus, there should be opportunities for ISONIAZID production

in developing countries, particularly in Africa, where no such facilities are known to exist currently and where undoubtedly a largely unquantified need does exist.

11.4 Recommendations

Developing countries in various stages in the development of the pharmaceutical industry have been summarily reviewed with respect to their possibilities to implement the various routes of ISONIAZID production.

The 4-Cyanopyridine route is technically feasible and economically acceptable for producers better than the average performer. This process is the preferred choice in countries where the starting material is available at a competitive price.

Of the studied oxidation processes, route A (Potassium Permanganate) is technically feasible but economically not viable. Hence, 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.

Route B, oxidation by Nitric Acid, cannot be carried out in multipurpose batch reactors and is, therefore, technically not feasible. It is not attractive economically either, thus this route should only be considered as a contribution to the rational utilization of existing oxidation (by Nitric Acid) capacities.

Further research is necessary for route C to conclude the technical feasibility of the probable catalytic or electrolytic oxidation process. This route is the preferred economic choice.

The prospects for establishing a new manufacturing plant solely for the production of ISONIAZID does not appear to be economically feasible enough.

Annex 1 to the

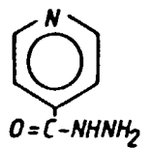
Technical and Economic Analysis of the Manufacture of ISONIAZID

Chemical Synthesis ISONIAZID

A. BASIC DATA OF THE PHARMACEUTICAL CHEMICAL

1. International non-proprietary name: ISONIAZID[45/]

2. Graphic formula:



3. Chemical formula: $C_6H_7N_3O$

4. Molecular weight: 137.14

5. Chemical abstracts index name: 4-Pyridinecarboxylic acid hydrazide

6. Cas registry number: [54-85-3]

7. Other forms: Iproniazid (isonicotinic acid 2-isopropylhydrazide)[46/] has been shown to have antitubercular activity but, because of its toxicity, is no longer employed for treatment.

45/ The use of essential drugs, WHO Technical Report Series 722, Geneva (1985), p. 19.

46/ U.S. Pat.

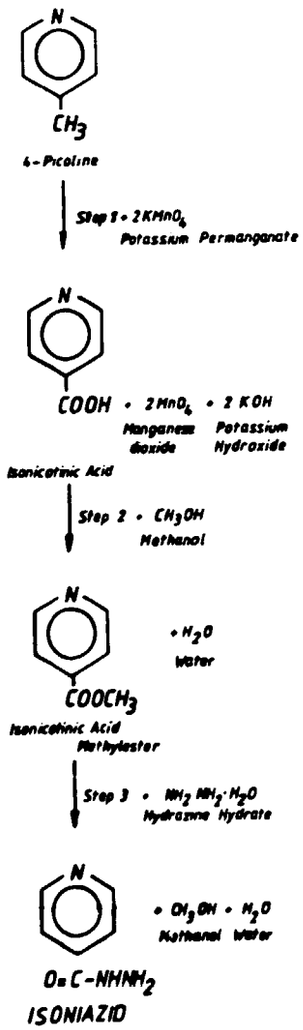
8. Basic patent: U.S. Pat. 2,596,069, H.H. Fox: Compositions for combatting tuberculosis (1952 to Hoffmann-LaRoche), and U.S. Pat. 2,830,994, E.J. Gasson: Process for the manufacture of isonicotinic acid hydrazide from pyridine nitrile (1958 to the Distillers Co.)

B. BRIEF DESCRIPTION OF THE PRODUCTION PROCESSES

Most bulk substance manufacturers in the pharmaceutical industry produce ISONIAZID starting from 4-Picoline, which is oxidized to INA. Subsequent steps consist of esterification and conversion into INA hydrazide, i.e., ISONIAZID. The alternative process beginning with 4-Cyanopyridine, although apparently simpler and more profitable, is applied only by a few manufacturers.

1. Chemical synthesis of ISONIAZID from 4-Picoline

1.1 Schematic illustration and description of the synthesis



The available information exceptionally included the commercial scale manufacturing instructions of the original patent holder, F. Hoffmann-LaRoche & Cie., for the production of 50 kg/day (10 tons in 200 days, equipment used in 2x8-hour shifts) and 100 kg/day (20 tons in 200 days, equipment in 3x8-hours shifts) of ISONIAZID, respectively.

The major economic parameters of the process are given below.

Figure A.1. Step-by-step yields in the production of 50 kg ISONIAZID/day

Overall yield 67.8 per cent	50.0 kg	4-Picoline	0.536 kmole
	55.2 kg	INA	0.448 kmole
	55.3 kg	Methyl Isonicotinate	0.403 kmole
	52.5 kg	ISONIAZID crude	0.383 kmole
	50.0 kg	ISONIAZID pure	0.364 kmole

The quality of all reactants and step-by-step products is controlled.

1.1.1 Oxidation of 4-Picoline to INA with Potassium Permanganate

Step 1

50 kg of 4-Picoline is mixed with 150 l of water and 400 l of mother liquor recycled from the former batch. The mixture is heated to 80°C and agitated throughout the oxidation. 200 kg of Potassium Permanganate are added at a rate of about 1 kg/min, meanwhile the temperature is kept at 85°C by cooling. The reaction is completed when the colour of Potassium Permanganate has disappeared.

The excess of 4-Picoline is recovered by steam distillation until the volume of the distillate reaches 400 l in about 3 hours.

The suspension in the reactor is filtered to separate manganese dioxide from the INA solution. The filtrate is neutralized with hydrochloric acid to a pH = 6.6, and concentrated to 250 l by evaporation of the solvent at a

temperature of 50-55°C and a pressure of 90 mmHg. INA is then precipitated by hydrochloric acid at pH = 3.6 and 70°C, the mixture cooled down to 15°C and kept at that temperature overnight. INA is centrifuged, washed and dried at 100-110°C.

Step 2

55.2 kg of INA prepared in step 1 and 4.8 kg of INA recovered from a former batch are mixed with 136 l of methanol for 40 minutes and 60 kg of 100 per cent sulphuric acid is added while the temperature is kept at 50°C by cooling. The mixture is refluxed for 5 hours, then its temperature is cooled down from 70-71°C to 20°C. 160 kg of crushed ice is added to keep the temperature below 10°C during the following neutralization to pH = 3.6 with 45 kg of 25 per cent ammonia solution. A large part of the non-esterified INA, about 4.8 kg, is precipitated and removed by filtration.

The pH of the filtrate is adjusted to 6.6 by 4.5 kg of 25 per cent ammonia solution. The temperature is kept below 10°C during neutralization by adding 20 kg of crushed ice and the solution is extracted with 100 l and subsequently 3 x 50 l of methylene chloride. The organic phases are collected, filtered and washed with 10 l of demineralized water. From the organic mixture, first the excess methylene chloride is distilled off at 90°C. The second fraction (methylene chloride and Methyl Isonicotinate) is distilled off at 20 mmHg until the temperature reaches 100°C, when the pure Methyl Isoniconate starts to distillate. Fraction I is used for extraction, fraction II is recycled and fraction III - 55.3 kg of Methyl Isonicotinate - is processed further.

Step 3

67 l of demineralized water, 43.4 kg of Hydrazine Hydrate and 110.6 kg of Methyl Isonicotinate obtained from two former batches are mixed and the temperature is kept at 50°C by cooling for 1 hour. The temperature is reduced to 15°C, and the mixture is kept at this temperature overnight. The suspension is centrifuged, the crystals are washed with demineralized water to yield about 94 kg of crude ISONIAZID (with reference to dried substance).

The aqueous mixtures of the former operations are concentrated to 50 l by distilling of a water-methanol mixture at 60°C. The methanol is recovered, whereas the concentrate is cooled down to and kept at 15°C for 1 hour, when it is centrifuged to yield a second generation of 11 kg crude ISONIAZID (with reference to dried substance).

The 105 kg of crude ISONIAZID and 16 kg of ISONIAZID remnants from recrystallization of former batches is mixed with 180 l of water and the temperature is elevated to 60°C. 1.2 kg active carbon and 1.2 kg of filtration aid Speedex are added and the temperature is elevated to 70°C. The mixture is filtered. The filtrate is cooled down to 15°C and kept at that value for 12 hours. The mixture is centrifuged and the crystals are washed with methanol and dried at 50°C and 20 mmHg for 24 hours to yield 100 kg of pure ISONIAZID.

A second generation of 14 kg and a third generation of 2 kg crude ISONIAZID is recovered from the mother liquor.

1.1.2 Other information

Operation of the plant requires 1 plant manager and 10 operators in 2 shifts.

The following utilities are needed for the production of each kg of ISONIAZID:

Cooling water	8.5 m^3
Demineralized water	0.9 m^3
Steam	0.14 tons
Electricity	5.8 kWh
Cold energy	2.5 kWh

Methanol and methylene chloride are recovered with 65 per cent and 82 per cent efficiency, respectively. This is important both from economic and environment pollution points of view.

1.2 Chemical reactions

(1) $C_6H_7N + 2KMnO_4 = C_6H_5NO_2 + 2MnO_2 + 2KOH$

93.13 316.06 123.11 173.88 112.22

(2) $C_6H_5NO_2 + CH_4O = C_7H_7NO_2 + H_2O$

123.11 32.04 137.14 18.02

(3) $C_7H_7NO_2 + H_6N_2O = C_6H_7N_3O + CH_4O + H_2O$

137.14 50.06 137.14 32.04 18.02

1.3 Combined equation of the synthesis

$C_6H_7N + 2KMnO_4 + CH_4O + H_6N_2O =$

93.13 316.06 32.04 50.06

$C_6H_7N_3O + 2MnO_2 + 2KOH + CH_4O + 2H_2O$

137.14 173.88 112.22 32.04 36.04

1.4 Chemical input conversion coefficients

The various expressions of the conversion efficiency available from the studied sources were converted to chemical input conversion/consumption coefficients to refer to the manufacture of one kg of ISONIAZID from 4-Picoline, utilizing various oxidizing agents. These have been summarized in table A.1. If the material input consumption coefficients in the literature were given with reference to an intermediate, such as Methyl Isonicotinate, the original figures were given in brackets behind the derived overall consumption coefficient. Publications which described the chemical conversion efficiency of different steps of the synthesis but came from different sources were not included in table A.1; they were only used for the evaluation of the quality of data from other sources. Those sources were disregarded where quantitative data were available for the inputs but the ISONIAZID yield was not given, or vice versa. On the other hand, real values reflecting the statistical average of hundreds of batches were given with three-decimal accuracy (column 8).

Table A.1. Chemical input conversion coefficients in the manufacture of ISONIAZID from 4-Picoline

Name	Source 1	2	3	4	5	6	7	8
4-Picoline	1.11 (1.0)[a]	1.0	0.90	1.00	1.08	0.89	1.08	1.000
Isonicotinic Acid	1.11							
Hydrazine Hydrate	...	0.8	2.27	0.54 (0.43)[b]	0.66 (0.53)[b]	2.83 (2.26)[b]	0.55	0.434
Potassium Permanganate	-		-	4.00	...	...	-	4.000
Nitric Acid, 55%	4.44 (4.0)[a]		-					
Sulphuric Acid	1.67 (1.5)[a]		...					1.200
Sodium Carbonate	1.67 (1.50)[a]		4.01					
Hydrochloric Acid, 36%								1.800
Ethanol		2.0						
Methanol				.25	1.82	...		1.248
Methylene Chloride								1.200
Ammonia solution, 25%				0.99	0.70	...		0.990
Carbon, activated								0.012
Filtrating agent, Speedex								0.012
Other materials, $US/kg	1.77	0.72					1.87	

[a] Values in brackets refer to Isonicotinic Acid
[b] Figure in brackets refers to an 80 per cent reactant

1 UNIDO/ID/WG.267/5 (1978)
2 Unpublished UNIDO document
3 UNIDO/ID/WG.331/4 (1980)
4,5,6 UNIDO/PC.14 (1981)
7 UNIDO/PC.52 (1982), first draft
8 Commercial scale technology, F. Hoffmann La-Roche & Cie, Société Anonyme, Basle (1981).

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. This information was included in table A.1, because it was used as such to estimate direct material costs and C_{tp}, furthermore it was qualitatively useful in the technical assessment of other data.

1.5 Other information

A chapter was devoted to the wastes and waste water treatment of chemicals produced by organic synthesis, and a simplified flow sheet for the manufacture of ISONIAZID from 4-Picoline was described in a UNIDO document.[47/] The analysis of the described operations concluded that the major pollution from these processes are the solvents, which should be recovered and re-used. Residual from solvent recovery should be incinerated.

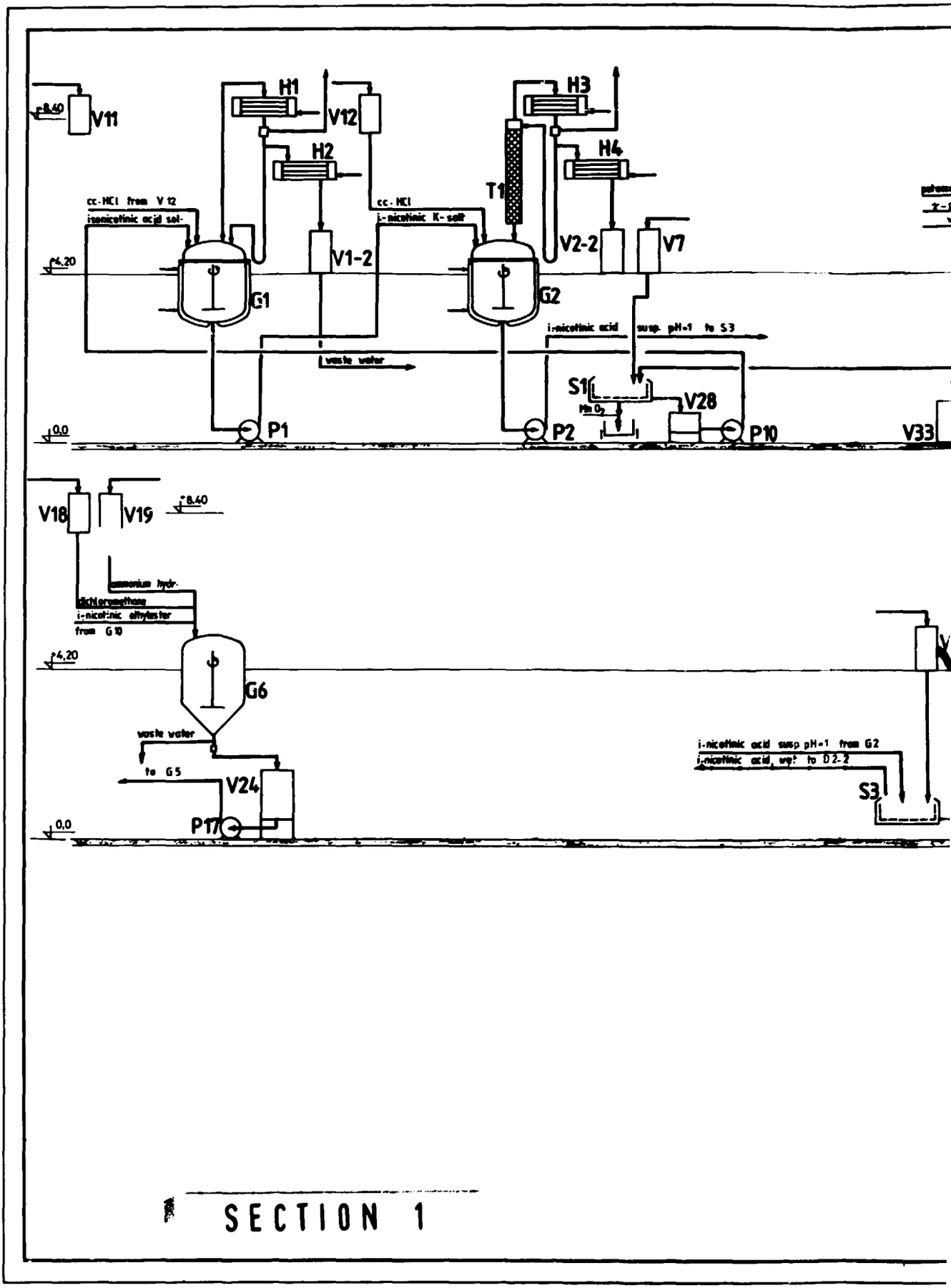
Additionally, nitrous oxide vapours from heated 4-Picoline and Hydrazine Hydrate should be absorbed.

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

The flow sheets for a process similar to that described in section 1.1 are provided in figures A.3 and A.4.[48/] The main equipment used in this process is listed in table A.2.

47/ 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, p. 22.

48/ Multipurpose plant, VEGYTERV Hungarian Chemical Industries Engineering Centre document (1983).


V11
H1
V12
H2
H3
H4
T1
cc.-HCl from V 12
isonicotinic acid sal-
cc.-HCl
i-nicotinic K-salt
V1-2
V2-2
V7
G1
G2
i-nicotinic acid
susp. pH=1 to S3
waste water
S1
V28
P1
P2
P10
V33
V18
V19
ammonium hydr-
dichloromethane
i-nicotinic ethylester
from G10
G6
waste water
to G5
V24
P17
i-nicotinic acid susp pH=1 from G2
i-nicotinic acid, wet to D2-2
S3
8,40
4,20
0,0

SECTION 1

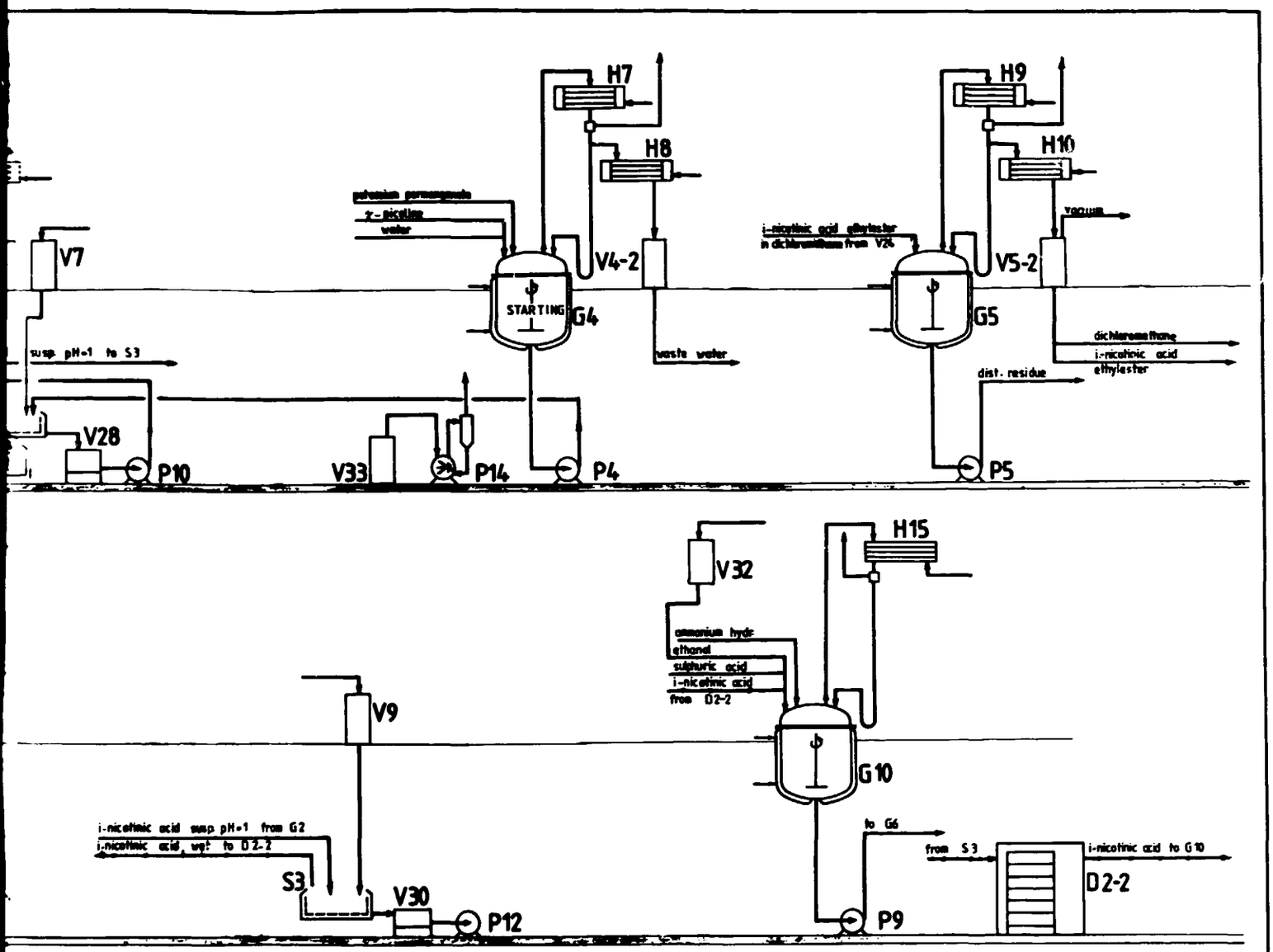
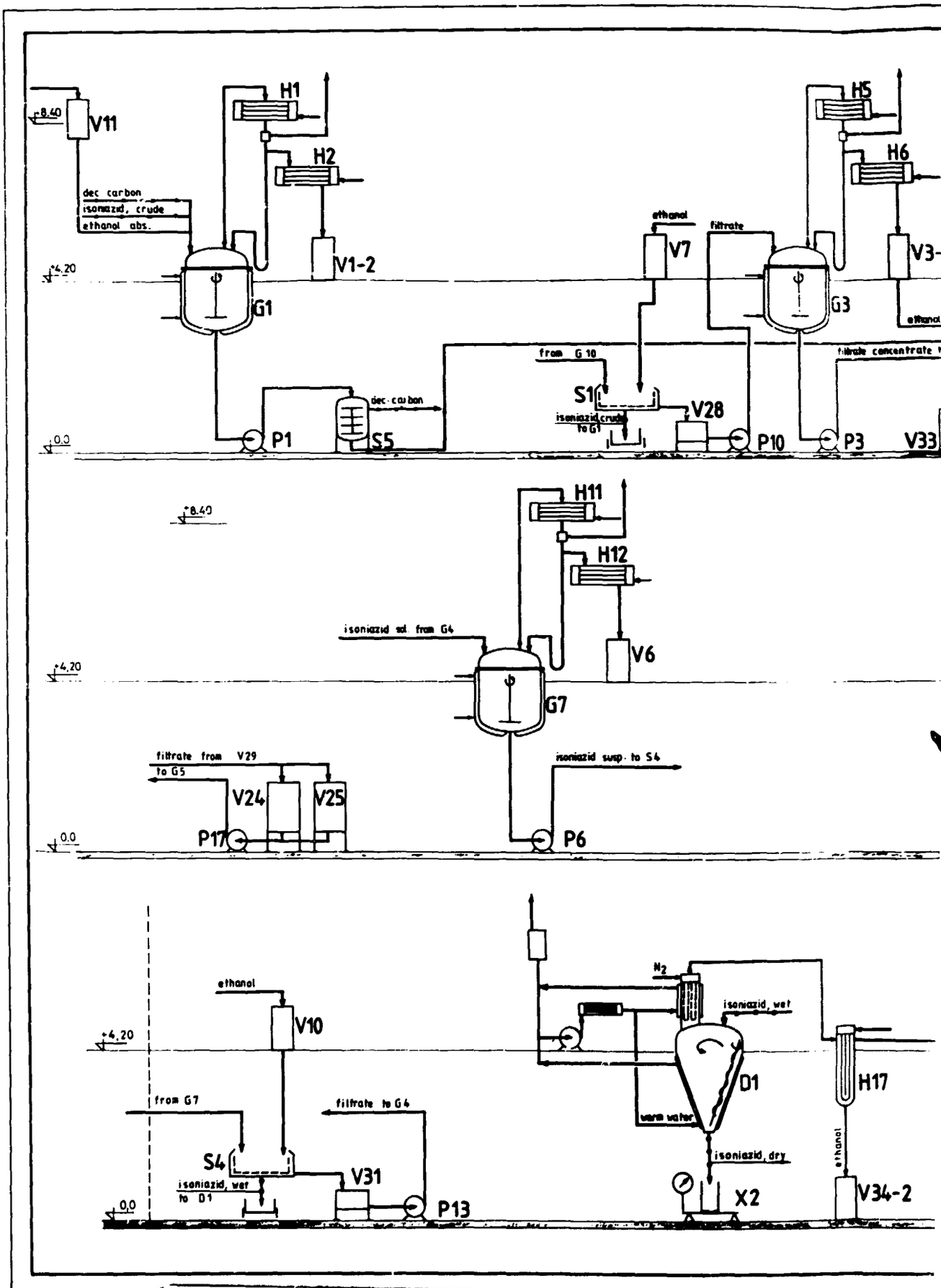


Figure A.2

ISONIAZID production process flow sheet - 4-Picoline route

page 1

SECTION 2


+8.40
V11
H1
H2
dec carbon
isoniazid, crude
ethanol abs.
+4.20
V1-2
G1
P1
dec. carbon
S5
0.0
ethanol
V7
filtrate
H5
H6
V3-
G3
from G 10
S1
isoniazid crude to G1
V28
P10
P3
V33
filtrate concentrate
+8.40
H11
H12
isoniazid sol. from G4
V6
+4.20
G7
filtrate from V29 to G5
V24
V25
P17
isoniazid susp. to S4
P6
0.0
ethanol
V10
+4.20
from G7
filtrate to G4
S4
isoniazid, wet to D1
V31
P13
0.0
N2
isoniazid, wet
D1
warm water
isoniazid, dry
X2
H17
ethanol
V34-2

SECTION 1

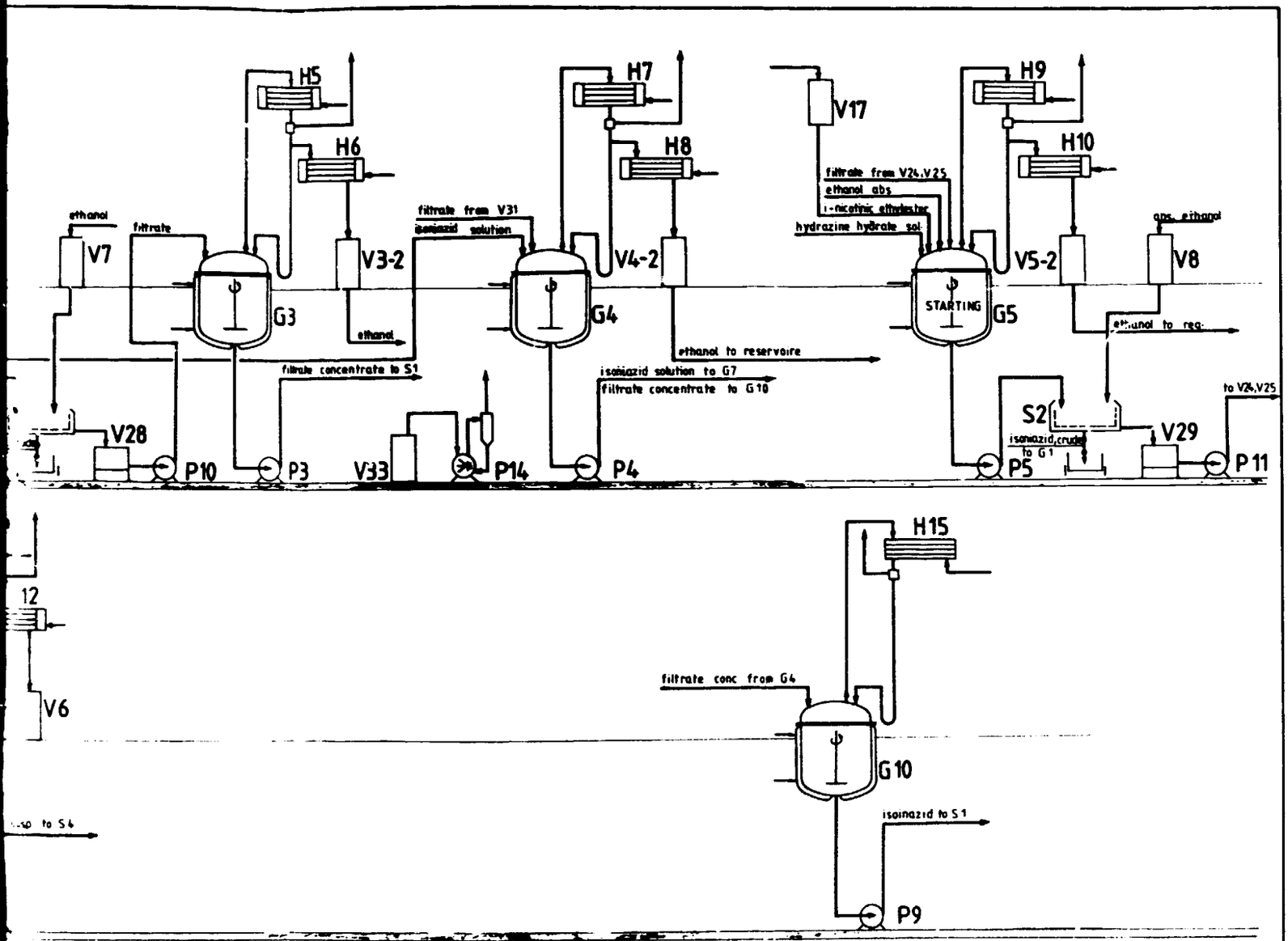


Figure A.2

ISONIAZID production process flow sheet
4-Picoline route

page 2

Table A.2. List of main equipment for the production of IONIAZID from 4-Picoline - esterification and hydrazide-formation steps

Code	Number	Name	Material
D1	1	2 m^3 vacuum dryer with agitator	stainless steel
G1, G2, G3, G7	4	3 m^3 jacketed batch reactor with agitator	enamelled steel
G4	1	3 m^3 jacketed batch reactor with agitator	stainless steel
G5	1	1.25 m^3 jacketed batch reactor with agitator	enamelled steel
G6	1	5 m^3 extractor	stainless steel
G10	1	1.25 m^3 jacketed vessel with agitator	enamelled steel
H1, H3, H5, H7, H11	5	16 m^2 condenser	stainless steel
H2, H4, H6, H8,H12	5	16 m^2 cooler	stainless steel
H9	1	12.5 m^2 condenser	stainless steel
H10	1	12.5 m^2 cooler	stainless steel
H15	1	12.5 m^2 condenser	artificial carbon
H17	1	4 m^2 vacuum condenser	stainless steel
P1. P3, P4, P5, P6, P10, P11, P13	8	100 l/min centrifugal pump	stainless steel
P2, P9, P12	3	100 l/min centrifugal pump	enamelled steel
P14	1	60 m^3/h watering vacuum pump	steel
P17	1	200 l/min centrifugal pump	stainless steel
S1, S2, S3	3	1000-mm diameter centrifuge	stainless steel
S4	1	1000-mm diameter centrifuge	rubber-coated steel
S5	1	6.3 m^2 pressfilter	stainless steel

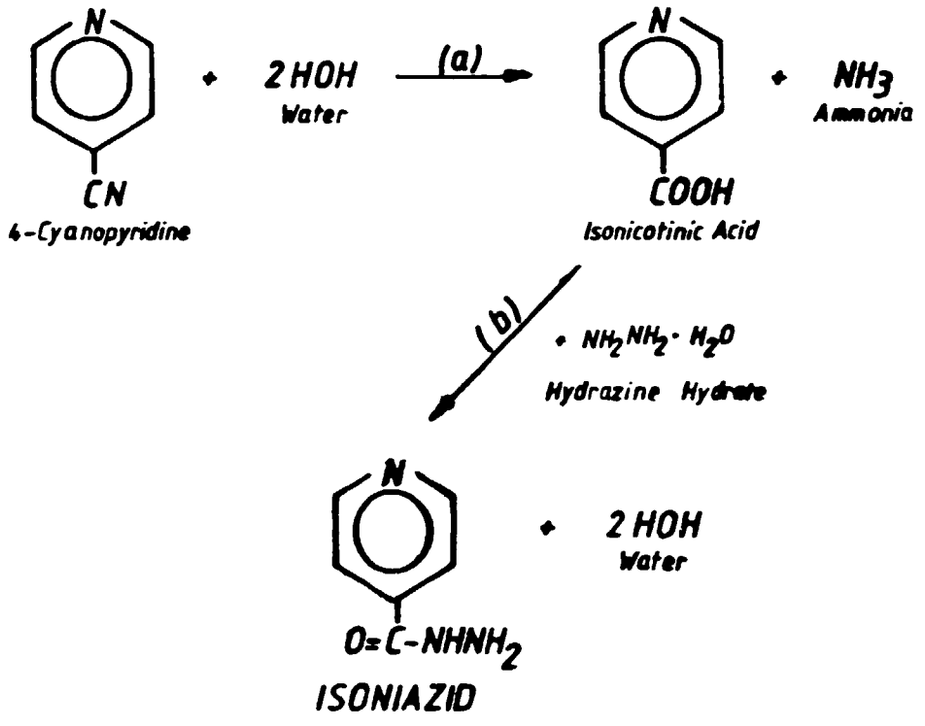
Table A.2. List of main equipment for the production of IONIAZID from 4-Picoline - esterification and hydrazide-formation steps (cont'd)

Code	Number	Name	Material
T1	1	250-mm diameter distillation column	stainless steel
V1/2, V2/2, V3/2, V4/2, V4/2, V5/2			
V6	7	0.63 m^3 receiver tank	stainless steel
V7, V8, V9		0.63 m^3 washing medium	
V10	4	feeding tank	stainless steel
V11, V12, V17, V19, V22, V23	7	0.63 m^3 feeding tank	stainless steel
V24, V25	2	2 m^3 receiver tank	stainless steel
V28, V29, V31	3	0.5 m^3 filtrate receiver tank	stainless steel
V30	1	0.5 m^3 filtrate receiver	rubber-coated steel
V32	1	0.25 m^3 feeding tank	stainless steel
V33	1	0.25 m^3 feeding tank	steel
V31,2	1	0.25^3 receiver tank	steel
X1, X2	2	500-kg balance	steel

2. Chemical synthesis of ISONIAZID from 4-Cyanopyridine

2.1 Schematic illustration and description of the synthesis

By this route, 4-Cyanopyridine is hydrolyzed in the presence of an anion-exchange resin at 60-80°C and reacted directly with Hydrazine Hydrate in the presence of ethanol to yield ISONIAZID.



2.2 Chemical reactions

(a)	$C_6H_4N_2$	+	$2H_2O$	=	$C_6H_5NO_2$	+	NH_3
	104.11		36.04		123.11		17.03
(b)	$C_6H_5NO_2$	+	H_6N_2O	=	$C_6H_7N_3O$	+	$2H_2O$
	123.11		50.06		137.14		36.04

2.3 Combined equation of the synthesis

$C_6H_4N_2$	+	H_6N_2O	=	$C_6H_7N_3O$	+	NH_3
104.11		50.06		137.14		17.03

2.4 Chemical input conversion coefficients

The various expressions of the conversion efficiency available from studied sources were converted into chemical input/consumption coefficients to refer to the manufacture of 1 kg of ISONIAZID from 4-Cyanopyridine.

Table A.3 Chemical input conversion coefficients in the manufacture of ISONIAZID from 4-Cyanopyridine

Name	Source 1	2	3
4-Cyanopyridine	1.00	1.22	1.20
Ethanol	...	...	1.60
Hydrazine hydrate	0.70	1.22	0.55
Resin IRA-402	...	...	0.20
Sodium hydroxide	...	0.22	...
Other chemicals, $US/kg	0.60	...	...

1. UNIDO/ID/WG.267/5 (1978)
2. Marshall, Sittig: Pharmaceutical Manufacturing Encyclopedia
3. UNIDO/PC.14 (1981).

2.5 Other information

The technology of this synthesis is simpler than that beginning with 4-Picoline. Consequently, if 4-Cyanopyridine is available at a favourable price, production of ISONIAZID utilizing this route should be considered.

Annex 2 to the

Technical and Economic Analysis of the Manufacture of ISONIAZID

Patent Information on ISONIAZID and intermediates manufacturing processes[49/]

German 396,333 1924[50/]

Synthesis of pyridine to 4-ethylpyridine
Schering AG

US 2,436,660 1946

Oxidation of heterocyclic aromatic nitrogen compounts
Allied Chemical & Dye Corp.
Mueller, M.B.
CA 42:4203e

US 2,596,069 1952.03.07

Composition for combatting tuberculosis
Hoffmann-LaRoche Inc.
Fox, H.H.
CA 46:7294d

Spanish 202,450

Relates to US 2,946,801

Japan 7472 1954

Acid hydrazides
Takizawa, S.
CA 50:9447c

Japan 3482 1954.06.15

Isonicotinic acid
Tanabe Drug Manufacturing Co.
Utsumi, I.
CA 50:1039e

Japan 8285 1954.12.15

Simultaneous preparation of isonicotinic acid and pyridine
Tanabe Drug Manufacturing Co.
Utsumi, I.
CA 50:14001f

49/ Collection from secondary sources.

50/ The date might show the time of either the application or the publication of this and following patents.

US 3,712,019 1952.07.16

Relates to German 396,333

Japan 974 1955.02.17

Pyridine-carboxylic acid and its ester
Shionogi Drug Manufacturing Co.
Ishikawa, M.
CA 51:2877f

British 725,774 1955.03.09

n-Isonicotinohyrazones
Hoechst AG
Lucius, M.; Bruning
CA 50:4235h

Japan 2628 1955.04.21

Nicotinic and isonicotinic acids from coal-tar base
Chugai Drug Manufacturing Co.
Tajika Y.; Sano, H.; Nakano, T.
CA 51:15599h

US 2,733,246 1956

Isonicotinic acid
American Cyanamid Co.
Hultquist, M.E.
CA 50:5999e

US 2,738,352 1956

Citric acid to isonicotinic acid
Charles Pfizer & Co.
CA 50:9447c

US 2,748,137 1956

Isonicotinic acid
American Cyanamid Co.
Hultquist, M.E.; Barker, R.S.
CA 51:496d

USSR 106,220 1957.07.25

Isonicotinic acid hyrazide
Pavlov, L.N.; Gangrskii, P.A.
CA 51:16563b

US 2,793,213 1957

Pyridinecarboxylic acids
Allied Chemical & Dye Corp.
Mueller, M.B.
CA 51:16564b

US 2,830,994 1956.06.11

Process for the manufacture of isonicotinic acid hydrazide from pyridine nitrile
The Distillers Co.
Gasson, E.J.
CA 50:12336c
Relates to British 787,282, CA 52(?):6729h

Danish 87,228 1959.07.27

Organic hydrazides or amides
Dumex Ltd.
Thomasen, H.B.

US 2,946,800 1957.06.05

Process for the preparation of isonicotinic acid
Standard Oil Co.
Fields, E.K.

US 2,946,801 1957.06.05

Production of pyridine carboxylic acid
Standard Oil Co.
Fields, E.K.
CA 55:1662b

German 1,116,667 1958.04.26

Sulfur-containing isonicotinic acid hydrazides
E. Merck
Zima, O.; von Werder, F.
CA 63:8325h

Annex 3 to the

Technical and Economic Analysis of the Manufacture of ISONIAZID

Patent information on Isonicotinic Acid and ISONIAZID manufacturing processes[51/]

CA: 70(9)37658s
Nicotinic acid and isonicotinic acid
Assignee: Ruetgerswerke und Teeverwertung A.-G.
Patent: Britain GB 1132746 Date: 1968.11.06
Application: Germany Date: 1965.06.25

CA: 72(9)43469p
Separation of a eutectic mixture of nicorinic and isonicotinic acids
Inventor (author): Jerzy Bialek; Slawomira Porada
Assignee: Instytut Chemii Ogolnej
Patent: Poland PL 57343 Date: 1969.06.30
Application: Poland Date: 1966.12.29

CA: 70(1)3842g
Separation of nicotinic and isonicotinic acid
Inventor (author): Wilhelm Hoefling; Hans D. Eilhauer; Gerd Krautschik; Rolf Mohrhauer
Patent: Germany (East) DD 58090 Date: 1967.10.05
Application: Germany (East) Date: 1967.01.26

CA: 70(10)40629p
Recovery of nicotinic and isonicotinic acid
Inventor (author): Hans D. Eilhauer; Gerd Krautschick; Gerhard Kurtschinkski
Patent: Germany (East) DD 61544 Date: 1968.05.05
Application: Germany (East) Date: 1967.08.28

CA: 74(21)111921y
Pyridinecarboxylic acids
Inventor (author): Mitsuo Azumi; Yoshio Ichikawa
Assignee: Japan Gas-Chemical Co., Inc.
Patent: Japan Tokkyo Koho JP 7103978 Date: 1971.01.30
Application: Japan Date: 1967.11.14

CA: 75(5)35763b
Isonicotinic acid
Inventor (author): Ryoichi Yokoyama; Katsumi Sawada
Assignee: Teijin Ltd.
Patent: Japan Tokkyo Koho JP 7107253 Date: 1971.02.23
Application: Japan Date: 1968.01.17

51/ Results of the computer search in all issues of Chemical Abstracts published between 1 January 1967 and 31 December 1985.

CA: 76(3)14348a
Pyridine carboxylic acid
Inventor (author): Teodor Gostea; Constantin Camarasu
Assignee: Institutul de Cercetari Chimico-Farmaceutice
Patent: Romania RO 53589 Date: 1971.08.25
Application: Romania Date: 1968.02.05

CA: 72(9)43476p
Nicotinic and isonicotinic acid
Inventor (author): Dieter Eilhauer; Wilhelm Hoefling; Gerhard Reckling; Karl H. Meinicke; Peter Fahrig
Patent: Germany (East) DD 68229 Date: 1969.08.05
Application: Germany (East) Date: 1968.07.15

CA: 84(13)90014u
Isonicotinic acid
Inventor (author): V.A. Yakobi; L.A. Kozorez; P.A. Gangrskii; A.A. Nikiforov; N.F. Tyupalo
Assignee: Khar'kov Polytechnic Institute, Rubezhnoe
Patent: USSR SU 338099 Date: 1975.12.05
Application: USSR SU 1319848 Date: 1969.04.08

CA: 75(7)48914b
Catalytic manufacture of pyridine carboxylic acids
Inventor (author): Ryoichi Yokoyama; Katsumi Sawada
Assignee: Teijin Ltd.
Patent: Germany Offen. DE 1940320 Date: 1971.02.25
Application: Germany Date: 1969.08.07

CA: 79(25)146416t
Pyridinecarboxylic acids
Inventor (author): Ryoichi Yokoyama; Katsumi Sawada
Assignee: Teijin Chemicals Ltd.
Patent: Britain GB 1330135 Date: 1973.09.12
Application: Britain GB 4774370 Date: 1970.10.07

CA: 78(5)29627f
Catalytic manufacture of pyridinecarboxylic acids
Assignee: Teijin Chemicals Ltd.
Patent: France FR 2110607 Date: 1972.07.07
Application: France FR 7038300 Date: 1970.10.23

CA: 77(9)61822f
Pyridinecarboxylic acids
Inventor (author): Dieter Dieterich
Assignee: Farbenfabriken Bayer A.-G.
Patent: Germany Offen. DE 2055102 Date: 1972.05.18
Application: Germany DE P20551024 Date: 1970.11.10

CA: 77(9)126435d
Pyridinecarboxylic acids
Inventor (author): Masayoshi Kubo; Takeshi Horikawa
Assignee: Daicell Co., Ltd.
Patent: Germany Offen. DE 2165035 Date: 1972.07.13
Application: Japan JP 70122247 Date: 1970.12.30

CA: 86(17)121171r
Nicotinic or isonicotinic acid from 3- or 4-picolines
Inventor (author): Edward Treszczanowicz; Barbara Lipka; Barbara Burzynska; Jerzy Musierowicz; Lech Stefaniak; Antoni Wawer; Maria Grzybowska
Assignee: Instytut Chemii Przemyslowej
Patent: Poland PL 75604 Date: 1975.12.20
Application: Poland PL 155466 Date: 1972.05.19

CA: 80(21)120789n
Pyridinecarboxylic acids
Inventor (author): Jacques D.V. Hanotier; Monique G.S. Hanotier-Bridoux
Assignee: Labofina S.A.
Patent: Germany Offen. DE 2242386 Date: 1974.02.07
Application: France FR 7226867 Date: 1972.07.26

CA: 81(19)120493g
Pyridinecarboxylic acids from alkylpyridines
Inventor (author): Kazuhisa Nakajima; Tsuneo Sato
Assignee: Japan Synthetic Chemical Industry Co., Ltd.
Patent: Japan Kokai Tokkyo Koho JP 7461173 Date: 1974.06.13
Application: Japan JP 72102566 Date: 1972.10.12

CA: 92(4)31033s
Electrolytic production of isonicotinic acid from gamma picoline
Inventor (author): Handady Venkatakrishna Udupa; Mysore Seshaiyer Venkatachalapathy; Sankaranarayanaiyer Chidambaram; Karaikudi Sanakaranarayana Sasirigal Laliiha; Alamelun Hamamoorthy
Assignee: Council of Scientific and Industrial Research (India)
Patent: India IN 144132 Date: 1978.03.25
Application: India IN 75CA1946 Date: 1975.10.09

CA: 90(11)87294d
Highly selective oxidation for manufacturing pyridine carboxylic acids
Assignee: Luigi Stoppani S.p.A.
Patent: Belgium BE 868261 Date: 1978.10.16
Application: Italy IT 7725812 Date: 1977.07.18

CA: 94(1)3929m
Carboxylic acid and esters
Inventor (author): Ken Hiiro; Hideki Sakurai
Assignee: Kawaken Fine Chemicals Co., Ltd.
Patent: Japan Kokai Tokkyo Koho JP 8033423 Date: 1980.03.08
Application: Japan JP 78105997 Date: 1978.08.30

CA: 98(25)215329y
Simultaneous preparation of carboxylic acids and N-tert-alkyl amines
Inventor (author): Gerhard Bonse; Gerhard Marzolph; Heinz Ulrich Blank
Assignee: Bayer A.-G.
Patent: European Pat. Appl.; EP 68219 A1 Date: 1983.01.05
Application: EP 82105100 Date: 1982.06.11
DE 3124652 Date: 1981.06.23
DE 3211326 Date: 1982.03.27

CA: 101(23)210993f
Isonicotinic acid
Inventor (author): G.A. Artamkina; A.A. Grinfel'd; I.P. Beletskava
Assignee: Moscow State University 19
Patent: USSR SU 1092154 A1 Date: 1984.05.15
Application: USSR SU 3469308 Date: 1982.07.14

CA: 102(12)102453s
Electrochemical oxidation of pyridine bases
Inventor (author): Joseph E. Toomey, Jr.
Assignee: Reilly Tar and Chemical Corp.
Patent: United States US 4482439 A Date: 1984.11.13
Application: United States US 597014 Date: 1984.04.05

CA: 90(11)86723f
2-Aminobutanol
Inventor (author): Czeslaw Belzecki, Witold Tomasik, Jerzy Trojnar
Assignee: Instytut Chemii Organicznej
Patent: Poland; PL 86547 Date: 1977.12.31
Application: Poland; PL 161371 Date: 1973.03.20

CA: 88(25)190067q
2-Amino-1-butanol
Inventor (author): Iustin Alexandru Mihai Pihuleac, Ioan Bradescu, Thea Panaitescu, Steliana Cilianu, Mariana Ionescu
Assignee: Institutul de Cercetari Chimico-Farmaceutice
Patent: Romania; RO 60029 Date: 1976.02.16
Application: Romania; RO 71101 Date: 1972.06.01

CA: 88(13)89089y
Resolution of racemic organic amines
Inventor (author): Masahiko Saito, Yoshiki Kato, Kenzo Watanabe, Toshio Wakabayashi
Assignee: Teijin Ltd.
Patent: Japan Kokai Tokkyo Koho; JP 77139001 Date: 1977.11.19
Application: Japan; JP 7655279 Date: 1976.05.17

CA: 88(3)22136t
Synthesis of dl-2-amino-1-butanol
Assignee: American Cyanamid Co.
Patent: Belgium; BE 838764 Date: 1976.08.20
Application: Belgium; BE 838764 Date: 1976.02.20

CA: 87(23)183977n
Synthesis of D-2-amino-1-butanol
Inventor (author): Balwant Singh
Assignee: American Cyanamid Co.
Patent: South Africa; ZA 7600577 Date: 1976.11.24
Application: South Africa; ZA 76577 Date: 1976.02.02

CA: 87(9)67960c
2,6-Dinitroaniline herbicides
Inventor (author): Albert William Lutz, Robert Eugene Diehl
Assignee: American Cyanamid Co.
Patent: United States; US 4025538 Date: 1977.05.24
Application: United States; US 174938 Date: 1971.08.25

CA: 95(11)97030g
Optically active 2-aminobutanol and its salts with acids
Inventor (author): László Magdányi, Lajos Kovács
Assignee: Finomvegyszer Szövetkezet
Patent: Hungary Teljes; HU 19369 Date: 1981.01.28
Application: Hungary; HU 79FI695 Date: 1979.01.31

CA: 94(11)82201u
Amino alcohols
Assignee: Denki Kagaku Kogyo K.K.
Patent: Japan Kokai Tokkyo Koho; JP 80138389 Date: 1980.10.29
Application: Japan; JP 7945899 Date: 1979.04.14

CA: 99(1)5191s
(+)-2-Amino-1-butanol by resolution of racemic aminobutanol
Inventor (author): Alois Krajicek, Eduard Spicak, Adolf Immr, Antonin Xerny, Miroslav Semonsky
Patent: Czechoslovakia; CS 208913 B Date: 1982.11.01
Application: CS 718822 Date: 1971.12.20

CA: 97(21)181716j
d-2-Amino-1-butanol
Inventor (author): Péter Lónyai
Patent: Hungary Teljes; HU 21828 0 Date: 1982.02.27
Application: HU 79LO430 Date: 1979.01.27

CA: 100(15)119354s
Microbial production of d-2-aminobutanol
Assignee: Chisso Corp.
Patent: Japan Kokai Tokkyo Koho; JP 58/198296 A2 Date: 1983.11.18
Application: Japan; JP 82/79699 Date: 1982.05.12

Annex 4 to the

Technical and Economic Analysis of the Manufacture of ISONIAZID

Manufacturers and Suppliers of ISONIAZID

1.1 Manufacturers

AMERICAN ROLAND CHEMICAL CORP.
91 Carolyn Blvd.
Farmingdale
NY 11735-1527
United States of America

Telex: 232771
Cable: AMRO UR
Phone: (516) 694-9090

BAYER AG
GB-Organica/V-Z2
D-5090 Leverkusen-Bayerwerk
Federal Republic of Germany

Telex: 85103-216 by d
Cable: bayer leverkusen
Phone: 0214/30-8735

BIOLOGICAL E. LIMITED
18/1&3 Azamabad
Hyderabad 500 020
India

Telex: 0155-343
Cable: BIOLOGICAL
Phone: 60 131

GERARDO RAMON & CIA. S.A.I.C.
Int. Amaro Avalos 4208
Munro-Pcia.
Buenos Aires (1605)
Argentina

PFALTZ + BAUER, INC.
172 East Aurora Street
Waterbury
CT 06708
United States of America

Telex: 996 471
Cable: PFALTHEN WBY
Phone: (203) 574-0075

RHONE-POULENC
Santé Chimie Pharmaceutique
Les Miroirs - Défense 3
F-92400 Courbevoie
France

Telex: Rhone X 610 800 F
Phone: (Paris) 768.19.63

1.2 International trading houses

AVRACHEM AG
Gartenstrasse 12
6340 Baar
Switzerland

Telex: 864996
Phone: (042) 318355

DANGSCHAT AUSSENHANDELS GMBH
Frankenstrasse 35
P.O. Box 101224
2000 Hamburg 1
Federal Republic of Germany

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

DOLDER LTD.
Immengasse 9
P.O. box 4004
Basel
Switzerland

Telex: 62306/63048
Cable: DOLDERAG
Phone: (061) 576600

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

Telex: 2163814
Phone: 40-3500170

KARL O. HELM AKTIENGESELLSCHAFT
Nordkavalstr. 28
P.O. Box 103060
D-2000 Hamburg 1
Federal Republic of Germany

Telex: 2170150
Cable: HELMPHARMA
Phone: (040) 2375-1422

MARSING AND CO. LTD. A/S
Export Department
6, 3rd Floor
Sjaellandsbroen 6
DK-2450 Copenhagen SV
Denmark

Telex: 19925 marco dk
Cable: MARSINGCO
Phone: (01) 164444

MEDIMPEX
Hungarian Trading Company for Pharmaceuticals
Vörösmarty tér 4
P.O. Box 126
H-1808 Budapest
Hungary

Telex: 22-6571
Cable: MEDIMPEX
Phone: 183-955

Annex 5 to the

Technical and Economic Analysis of the Manufacture of ISONIAZID

Manufacturers and Suppliers of Intermediates for the Production of ISONIAZID

1. 4-Cyanopyridine

ATOMERGIC CHEMETALS CORP.
91 Carolyn Blvd.
Farmingdale
NY 11735-1527
United States of America

Telex: 6852289 or 144612
Cable: ATOMERG
Phone: (516) 694-9000

BIOLOGICAL E. LIMITED
18/1&3 Azamabad
Hyderabad 500 020
India

Telex: 0155-343
Cable: BIOLOGICAL
Phone: 60131

CHEMICAL DYNAMICS CORPORATION
Post Office Box 345
South Plainfield, NJ 07080
United States of America

Telex: 833-447
Phone: (202) 753-5000

DANGSCHAT AUSSENHANDELS GMBH
Frankenstrasse 35
P.O. Box 101224
2000 Hamburg 1
Federal Republic of Germany

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

MAYPRO
11 Penn Plaza
New York, NY 10001
United States of America

Telex: 425160
Cable: Maypro NY
Phone: (212) 239-1462

PFALTZ & BAUER, INC.
172 East Aurora Street
Waterbury, CT 06708
United States of America

Telex: 996-471
Cable: PFALTHEN
Phone: 574-0075

REILLY TAR & CHEMICAL
151 N. Delaware
Indianapolis, In 46204
United States of America

Telex: 27-404 Retar Ind
Phone: 317-248-6411

2. Hydrazine Hydrate

ACETO CHEMICAL COMPANY
126-02 Northern Boulevard
Flushing, NY 11368
United States of America
South Plainfield, NJ 07080

Telex: 62662 Intl
Phone: (718) 898-2300

CROMPTON & KNOWLES CORPORATION
1701 Nevins Road
Fairlawn, NJ 07410
United States of America

Telex: 710-988-2240
Phone: (201) 791-7100

ERLANGER & CO.
One Bridge Plaza North
Fort Lee, NJ 07024
United States of America

Telex: 64-2106
Phone: (201) 947-7300

GALLARD-SCHLESINGER CHEMICAL MANUFACTURING CORPORATION
584 Mineola Avenue
Carle Place, NY 11514
United States of America

Telex: 967792
Phone: (516) 333-5600

MALLINCKRODT, INC.
2nd & Mallinckrodt Streets
St. Louis, MO 63167
United States of America

Telex: 44-7282/44-853
Phone: (314) 694-1000

PFALTZ & BAUER, INC.
172 East Aurora Street
Waterbury, CT 06708
United States of America

Telex: 996-471
Cable: PFALTHEN
Phone: 574-0075

TOYOMENKA (AMERICA), INC.
One World Trade Center
Suite 4011
New York, NY 10048
United States of America

Telex: 127-095
Phone: (212) 466-4600

3. 4-Picoline

CHEMICAL DYNAMICS CORPORATION
Post Office Box 345
South Plainfield, NJ 07080
United States of America

Telex: 833-447
Phone: (202) 753-5000

DANGSCHAT AUSSENHANDELS GMBH
Frankenstrasse 35
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2000 Hamburg 1
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PFALTZ + BAUER, INC.
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SOMMAIRE

Cette étude a été préparée par le Service des études sectorielles comme apport au modèle général de prise de décision dans le choix de produits pharmaceutiques et intermédiaires susceptibles d'être fabriqués localement par synthèse chimique organique.

Les niveaux techniques de procédés chimiques qui entrent dans la fabrication de l'ISONIAZIDE ont été évalués en analysant de brèves descriptions des variantes technologiques et en comparant leurs coefficients de consomption de produits chimiques avec leurs taux de rendement.

L'évaluation de l'économie de procédé a tenu compte du prix des intermédiaires-clés, des entrées directes de matériel et du coût de conversion chimique.

L'oxydation de la 4-Picoline par Permanganate de potassium et la synthèse à partir de la 4-Cyanopyridine ont été trouvées techniquement réalisables. Toutefois, une viabilité économique qui justifierait l'utilité d'études plus approfondies ne put être établie que dans le second cas. L'oxydation de la 4-Picoline par l'acide nitrique ne s'est pas avérée techniquement réalisable dans des usines polyvalentes. Les résultats économiques les plus intéressants se rapportent à un procédé qu'on ne pouvait pas évaluer techniquement faute d'une description détaillée de ses opérations. Des recherches se poursuivent sur l'oxydation de la 4-Picoline par procédés catalytique ou électrolytique.

Par ailleurs, l'analyse par étapes de la voie d'oxydation par le Permanganate de potassium a souligné la place importante qu'occupent les opérations de régénération et de recyclage dans l'économie de procédé.

EXTRACTO

El presente estudio fue realizado por la Subdivisión de Estudios Sectoriales de la ONUDI como parte de un modelo sectorial de toma de decisiones adecuado para seleccionar productos químicos e intermedios para fabricación local por síntesis orgánica.

Los niveles técnicos de las tecnologías estudiadas en la producción de ISONIAZID se evaluaron analizando las breves descripciones de los procesos químicos alternativos y comparando sus coeficientes químicos de consumo y/o rendimiento.

La economía del proceso se evaluó teniendo en cuenta los costos de intermedios claves, los costos de insumos materiales directos y los costos de conversión.

La oxidación de 4-Picolina por Permanganato de Potasio y la síntesis a partir de 4-Cianopiridina fueron evaluados técnicamente viables, pero sólo el último demostró viabilidad económica que merece consideración de estudios detallados adicionales. La oxidación de 4-Picolina por Acido Nítrico no se encontró técnicamente viable en una planta multipropósito. Los mejores resultados económicos se observaron con un proceso que no pudo ser técnicamente evaluado por falta de una descripción detallada del proceso. Las investigaciones continúan sobre la oxidación de 4-Picolina por procesos catalíticos y electrolíticos.

El análisis de las etapas químicas individuales del proceso de oxidación por Permanganato de Potasio reveló que la regeneración y recirculación de productos intermedios y solventes orgánicos desempeña un papel importante en la economía del proceso.

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

Technical and economic analysis of the manufacture of ISONIAZID

		(please check appropriate box) yes	no
(1)	Were the data contained in the study useful?	☐	☐
(2)	Was the analysis sound?	☐	☐
(3)	Was the information provided new?	☐	☐
(4)	Did you agree with the conclusion?	☐	☐
(5)	Did you find the recommendations sound?	☐	☐
(6)	Were the format and style easy tc read?	☐	☐
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(please give full address) .....

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