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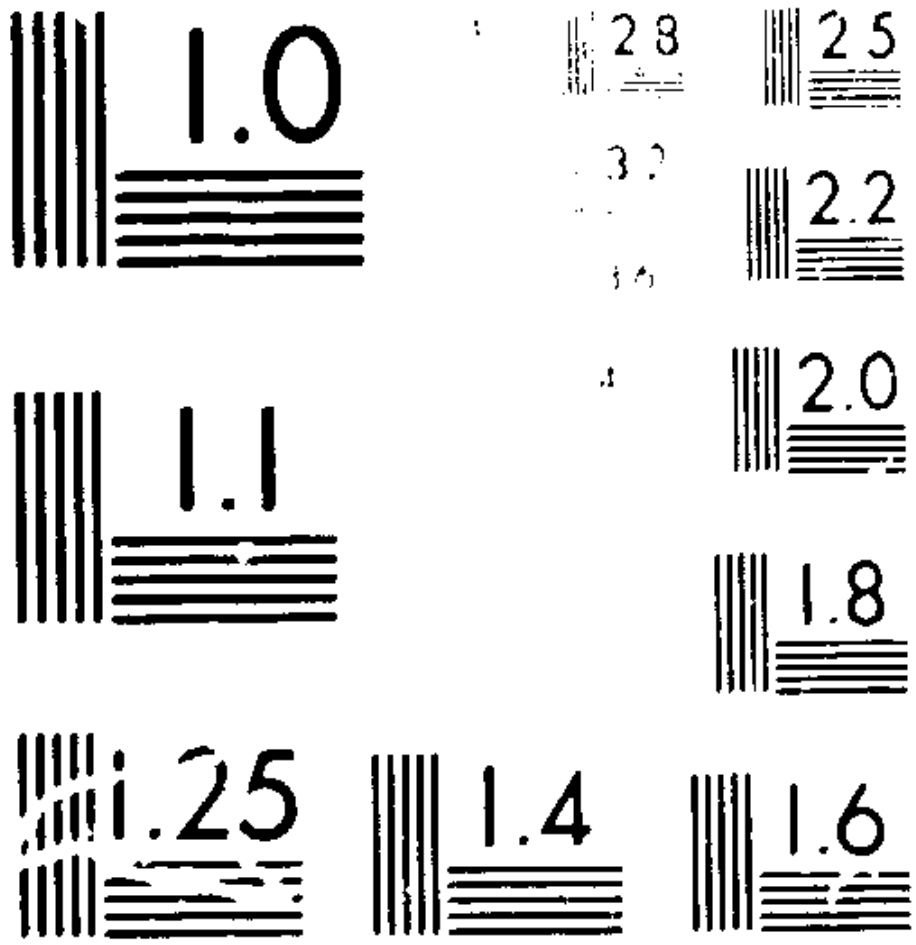
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Round Table Meeting of Experts
on Pharmaceuticals, 1981
Vienna

BACKGROUND PAPER FOR DISCUSSION ON AVAILABILITY, PRICING AND TECHNOLOGY OF ESSENTIAL DRUGS *

prepared by

the UNIDO secretariat

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81-28756

C O N T E N T S

Introduction:

1. The Second General Conference of the United Nations Industrial Development Organization (UNIDO) held at Lima, Peru in March 1975 recommended that UNIDO should include among its activities a system of continuing consultations between developing and developed countries with the objective of raising the developing countries' share in the world industrial output through increased international co-operation. That recommendation was endorsed by the General Assembly at its seventh special session in September 1975.

2. The System of Consultation is being implemented under the guidance of the Industrial Development Board, the policy making organ of UNIDO. The Board decided at its fourteenth session in May 1980, to establish the system on a permanent basis with the following main characteristics, including those described in its past decisions:

(a) The System of Consultations should be an instrument through which the United Nations Industrial Development Organization (UNIDO) would serve as a forum for developed and developing countries in their contacts and consultations directed towards the industrialization of developing countries;

(b) Consultation would also permit negotiations among interested parties at their request, at the same time as or after Consultations;

(c) Participants of each member country should include officials of Governments as well as representatives of industry, labour, consumer groups and others, as deemed appropriate by each Government.

3. To prepare for consultations on the Pharmaceutical Industry, two panels of experts from developing and developed countries were convened in June 1977 and February 1978. An Interregional Meeting to prepare for consultations on the Pharmaceutical Industry was held in January 1979 at Cairo, Egypt. Through these meetings UNIDO secretariat identified the issues that might be suitable for consultations on this industry.

4. The Global Preparatory Meeting which was held in Cancun, Mexico, from 24 - 27 April 1980, recommended that the First Consultation Meeting on the Pharmaceutical Industry should consider the following three issues:

- The pricing and availability of intermediate and bulk drugs.

- Contractual arrangements for the production of drugs. Part 1: Relevant issues to be taken into account when negotiating a transfer of technology agreement: Part 2: Preparation of guidelines.

- The availability, terms and conditions for transfer of technology for manufacture of essential drugs included in the illustrative list prepared by UNIDO in consultation with WHO.

5. The First Consultation on the Pharmaceutical Industry was held in Estoril, Portugal, from 1 to 5 December 1980. The consultation was attended by 217 participants representing governments, industry, labour and consumer groups from 68 countries and 13 international organisations.

6. The conclusions and recommendations of the First Consultation on 3 issues were as follows:

Issue I: The First Consultation recommended the setting up of a UNIDO committee of Experts on Pharmaceuticals composed of members from developing and developed countries, under the auspices of UNIDO, to discuss the technical and economic aspects of the availability of intermediates and bulk drugs.

a) The committee will be dedicated to the concept of and committed to high-lighting the need for evolving a better understanding of matters relating to the availability of those bulk drugs (and the necessary intermediates) included in the UNIDO illustrative list of 26 essential drugs, and to assisting developing countries in the production of these intermediates and bulk drugs.

b) The members of the committee, which would be a reasonable and small number, would be experts with professional experience selected by UNIDO secretariat giving preference to maximum possible extent of experts having participated in the First Consultation and representing all geographical groups, including countries with a major pharmaceutical industry.

c) The committee will complete its work in due time for the second consultation on the Pharmaceutical Industry planned for 1983.

Issue II: The First Consultation recommended that the UNIDO secretariat, in co-operation with an ad hoc panel of experts, selected on the basis of equitable geographical distribution, prepare a document, complete with the necessary background notes, on various terms, conditions and variations thereof that could be included in contractual agreements. In addition, the UNIDO secretariat should undertake a detailed study on relevant issues to be taken into account when negotiating transfer of technology agreements taking into account the experience of developed countries.

Issue III: The First Consultation arrived at the following conclusions:

a) The 26 essential drugs identified by UNIDO and essential and well-defined products based on medicinal plants constitute an illustration list for undertaking basic manufacture in developing countries.

b) The developing countries as a group constitute large markets for these drugs where in certain cases patents have lapsed.

c) There is willingness expressed by developed countries, centrally planned economies and transnational corporations to enable the transfer of technology to developing countries, bearing in mind the human health needs aspects of such transfers of technology.

d) Transfer of technology has to take place on mutually acceptable and equitable terms.

e) Manufacture to be based on maximum feasible backwards integration to raw materials.

f) Such mutually acceptable transfers of technology should be facilitated through UNIDO providing reference information relevant to the transfer of technology, including technical aspects such as level of production, magnitude of investments, inputs, infrastructure, etc., which could be a significant aid to individual developing countries in bilateral negotiations for transfer of technology, the result of such transfer, and experience should be brought to the attention of second consultation on the Pharmaceutical Industry.

7. In order to have better understanding of matters relating to Issue I and Issue III information has been collected from the available sources and projected in this paper for discussion.

- Issue I - The pricing and availability of intermediates and bulk drugs.

(i) Availability and Price of Bulk Drugs.

A. Background

8. Developing countries are large consumers of many essential drugs which are needed to treat diseases widely prevalent in these countries. Some of these countries with facilities to formulate, import the bulk drugs. In a survey conducted by UNIDO, consultants identified that one of the constraints in the growth of pharmaceutical industry in these countries is the wide disparity in prices at which bulk drugs were supplied to different countries.[1] Such a variation in prices was found to exist even within the same country depending on the source of supply and licence tie ups. With wide disparity in the prices it is not feasible to sustain viable manufacturing activities. The variation in prices of bulk drgus has direct impact on the prices of pharmaceutical formulations, which in turn adversely affect the ability of the developing countries to make available the essential formulations at reasonable prices to the vast majority of the population.[2]

B. Availability of bulk drugs.

9. Out of the 26 essential drugs identified by UNIDO and approved by WHO, UNIDO selected nine drugs as priority for this study. A review from the available sources has indicated that these drugs

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1) Preparatory Meeting for the First Consultation on the Pharmaceutical Industry, UNIDO ID/WG/317.

2) First Consultation Meeting on the Pharmaceutical Industry, UNIDO ID/WG.331/4.

have been in existence for several years. In most cases patents have expired and some developing countries also have technologies for manufacture of these nine drugs, in some cases from late intermediates. But the restricted availability of some of these drugs hinders the development of pharmaceutical industry in the developing countries which have facilities to formulate these drugs. A list of manufacturers/suppliers of the 9 essential drugs have been compiled and put at appendix I . This would help developing countries in knowing the alternate sources of supplies. However, this list does not ensure that these 9 drugs would be available at the reasonable prices and of right quality. Among the list, there are manufacturers, which are the subsidiaries of large transnational pharmaceutical corporations and may not be in a position to make supplies without consulting their parent organisations. In some cases, particularly in the developing countries, the manufacturers may not have surplus quantities to offer.

C. Pricing scheme to solve the disparity in prices.

10. In order to solve the problem of wide variation in the bulk drug prices, UNIDO secretariat presented a scheme based on escalatory formula in First Consultation Meeting.[1] This pricing scheme for bulk drugs was based on the idea that arrangements would become feasible if the suppliers of bulk drugs could agree upon bench mark prices for the bulk drugs based on the yearly average price preceding the contract. For example Acetyl Salicylic acid is manufactured in two stages. In the first stage phenol is converted to salicylic acid and in the second stage salicylic acid is subjected to acylation with acetic anhydride to produce acetyl salicylic acid. The pricing of this drug is linked to the prices of phenol and acetic anhydride. The bench mark price (CIF) was taken as US$1.88 per kg. The suggested esclation formula was given as - for 50% increase in phenol price, bulk drug price could increase by 15% and for 40% increase in acetic anhydride price, bulk drug price could increase by 15%.

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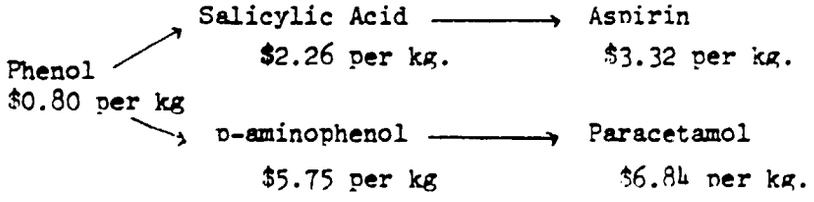
1) First Consultation Meeting on the Pharmaceutical Industry, UNIDO ID/WG.331/4

11. In the pricing scheme mentioned above, the main principles have been outlined. Although the relative price of raw materials, intermediates and bulk drugs and the conversion costs may undergo changes from time to time, the principles hold good and can be used for discussion to find out a mechanism for deciding fair prices for bulk drugs.

D - Alternate approach for working out fair prices

12. There is definite relationship of prices of bulk drugs with their intermediates and prices of intermediates with the starting chemical/agricultural raw materials. Aspirin price is based on salicylic acid, and salicylic acid price is based on phenol, and phenol price is based on cumene, and cumene price is based on benzene, and benzene price is based on crude naptha. With the help of willing partners and co-operation between developed countries and developing countries, it would be possible to work out factors which can be used for esclation of prices of intermediate and bulk drugs based on the increase of prices in crude naptha or any of intermediate chemical. This has to be mutually agreed by the suppliers from the developed countries, willing to enter into contracts with the potential buyers from the developing countries. Since the phenol is the basic chemical used for the manufacture of acetyl salicylic acid and paracetamol, its price can be taken as bench mark price or base price and factors developed for calculating the reasonable price for salicylic acid, aminophenol, aspirin and paracetamol. Based on US market prices (CMR Jan. 19, 1981) of these two products, their intermediates and the starting chemicals, the factors have been worked out.



The price of salicylic acid can be taken as 2.825 times of phenol price and that of acetyl salicylic acid as 4.15 times of phenol price or 1.47 times of salicylic acid price. Similarly, the price of p-aminophenol can be taken as 7.18 times of phenol price and that of paracetamol as 8.55 times of phenol price or 1.19 times of p-amino phenol price.. The point made here in this scheme can be extended to any number of drugs. The starting sources of the 9 essential drugs are traced on the chart given in the Appendix II . It may be noted that for almost all the 9 essential drugs, the basic source is petroleum.

E. Analysis

13. The pricing scheme based on the esclation formula of important chemical inputs and the alternate scheme based on the mutually agreed factors depending on the cost of starting chemicals as described, could form a basis of discussion for working out a mechanism by which essential bulk drugs could be made available at reasonable prices. The other factors such as purchase lot size, period of purchase contract, the quality of the product, the liability of supplier, patent situation etc., which affect the price of bulk drugs can also be taken into account. The directory of manufacturers of 9 essential drugs (Appendix I) would serve as a useful source of information for the developing countries.

(ii) Availability and price of intermediates

A. Background.

14. Out of the 26 essential drugs identified by UNIDO and approved by WHO, UNIDO again selected nine drugs as priority for establishment of production facilities in the developing countries where these drugs have large markets and are used widely. These drugs have been in existence for several years and in most cases patents have expired.

Many of the developing countries are already engaged in the manufacture of these drugs but in the majority of cases, the manufacture is based on imported early or late intermediates. Some of the developing countries are in a position to obtain the technology but the technology available is often based on the use of imported intermediates. The limited availability and the high cost of intermediates in relation to the price of bulk drugs adversely affects the economics of their manufacture. This is a major constraint to the development of pharmaceutical industry in the developing countries.

B. Availability of intermediates

15. The technical and ecnomic analysis of the manufacture of 9 essential drugs have been carried out based on the available data. The important key raw materials and intermediates have been identified. (Appendix III). A list of manufacturers/suppliers of the important raw materials and intermediates have been compiled and put at Appendix I . It may be seen from this list that there are limited sources of supply of some of the important intermediates like 6-amino penicillinic acid, N-Methyl piprazine, 4, 7 - dichloroquinoline, novaldiamine and D-2-aminobutanol. The majority of these sources are with transnational pharmaceutical corporations or their affiliates. These intermediates are not available to manufacturers in the developing countries at reasonable prices.

C. Impact of high cost of intermediates on the cost of production of bulk drugs

16. The production cost of a drug depends on various inputs. These cost elements are detailed in Appendix IV . The most important input in the cost of production of a bulk drug is the cost of raw materials/ intermediates. An analysis of cost of production involving chemical analysis has revealed that the raw material cost is the major input (65 to 85 percent of the total cost of production). In a case study of production of eight products, the average cost input of raw materials/

intermediates has worked out to 74.48 percent (Appendix V). For antibiotics production, the cost input of raw materials is about 45 to 50 percent. The analysis given in Appendix V has further confirmed that in cases where production is carried out using late intermediates, the cost of intermediates constitutes the most significant component of bulk drug cost. Therefore, availability of intermediates at reasonable price becomes of vital importance to those manufacturers who are doing synthesis from the early or late intermediate stages. The other factor which is directly involved in the raw material cost element is the consumption of key intermediates/ chemicals per kilo of the finished drug. The soncumption depends on the efficiency of the technology. This is discussed in the technical and economic analysis of the manufacturing processes (Appendix III).

D. Pricing scheme for intermediates presented at the First Consultation Meeting.

17. In the First Consultation Meeting, UNIDO Secretariat presented a pricing scheme for intermediates, the high price of which is a major limitation on the development of the pharmaceutical industry in the developing countries.[1)]

18. This scheme is based on the various cost elements going into the cost of production. The major component of cost of production is the cost of imported intermediates which was taken as the basis of the pricing scheme. The residual value obtained by deducting the conversion cost from the imported CIF price of the product was apportioned between the important imported intermediates in the ratio these are utilized in the process. The resulting figure showed at what prices these intermediates should be available. The scheme is explained below. In a particular case study CIF price of Ampicillin Trihydrate is US$77.92 per Kg. The conversion cost starting from 6APA and D-X-phenylglycine chloride hydrochloride in the ratio of 74:26 based on their consumption coefficient per kg of Ampicillin Trihydrate (cons. coefficient of 6-APA is 0.7kg/kg and of phenyl glycine chloride hydrochloride is 0.64 kg/kg of Ampicillin Trihydrate. Thus, the desir-

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1) The Pricing and availability of intermediates and bulk drugs. UNIDO, ID/WG.331/4.

able price of 6APA was arrived at US $ 64.05 per kg and that of D-Y-phenyl glycine chloride hydrochloride at US$24.63. The desirable prices arrived at by using this pricing scheme for imported intermediates were lower than the prices on which these intermediates were made available. This scheme is based on the data available from the developing countries and has been verified and confirmed. In case members from developed countries wish to revise the scheme, it would be desirable to obtain conversion cost data based on the experience of developed countries.

E. Alternate approach for working out fair prices

19. An analysis based on U.S. market prices of chemicals, intermediate and bulk drugs has confirmed that if the cost of raw materials/intermediates is reasonable and the technology is efficient, it is possible to produce the bulk drug at reasonable cost. For example, in January 1981 p-Amino phenol price was US$5.75 per kg and that of acetic anhydride was US$0.79 per kg in U.S. market. Taking the consumption coefficient from a technology used in one of the developing countries the cost of production of paracetamol works out as US$6.54 per kg. as explained below:

cost of p-aminophenol	0.8x5.75 = 4.60
cost of acetic anhydride	0.8x0.79 = 0.63
conversion cost including other local chemicals etc. as 20% of cost of production	= 1.31
	Total US$6.54

Prevailing price for paracetamol in the same market was US$6.84 per kg. Thus there is a margin of US$0.30 per kg for selling expenses and return on the capital. (All prices taken from CMR - Jan. 19, 1981. Therefore the factor to determine the price of intermediate (p-aminophenol) in this case could be arrived at by taking the prevailing price of the bulk drug or by taking the price of the basic chemical

required for the production of this intermediate. Based on paracetamol price, the factor works out to be 0.88. In other words if the market price for paracetamol is US$6.54, then p-aminophenol should be made available at US$5.75. Alternately, the factor based on phenol price of US$0.80 per kg (see alternate approach for bulk drugs) would work out to be 7.18. The scheme to work out factors to determine the desirable price of intermediates can be extended to any number of intermediates.

F. Analysis

24. The effort required is to find a mechanism by which the intermediates are made available at reasonable prices to enable developing countries to sustain viable bulk production manufacturing activity. It would be desirable to request the members/companies from developed countries to provide sufficient data based on their experience to determine the conversion cost factor so that the desirable and reasonable price for identified intermediates is determined. The prices thus worked out by the experts then could form the basis of negotiation for purchase of key intermediates by the developing countries.

25. The pricing scheme based on the esclation formula described for the bulk drugs can also be extended to intermediates by identifying the factors which could mutually be agreed by the experts from developed countries and developing countries in determining the desired prices of intermediates.

26. It is also necessary to determine the steps required to ensure the consistant and reliable quality of purchased raw materials and intermediates.

27. The directory of manufacturers of intermediates and key chemicals required for the manufacture of the 9 essential drugs (Appendix I) would serve as a useful source of information for the developing countries engaged in the production of these drugs and also for the developing countries which intend to start production in the near future. However, this does not ensure the availability of intermediates at reasonable prices. This

would only increase the bargaining power of developing countries.

G. Importance of quality of raw materials and intermediates

21. Rigid quality of purchased raw materials and intermediates is critical. If such purchased materials fail to meet the analytical specifications and are used in production, the yield in drug synthesis may fall significantly, thus increasing the unit cost of production. The finished drug itself may not meet the required specification leading to batch rejections and batch reprocessings. Analytical specifications for raw materials and intermediates are available from various sources like pharmacopoeias, national standard institutes and along with transferred technology package. It becomes essential that "package" of process technology transferred includes full and detailed analytical specifications and methods of assay.

22. Development of purchasing system to ensure that all purchased materials meet the specifications is important. Supplier should be asked to ensure the quality before shipment and each batch should be tested by the purchaser locally before its use. The analysis of smaples locally can be carried out either by analytical laboratory attached to the drug plant or any outside analytical laboratory of repute. The purchase contracts should be drawn up in such a way that in the event of a delivered batch failing to meet analytical specifications, it will be returned to the supplier at no cost to purchaser. The procedure should be applied without exception to all purchased materials, even in case of suppliers with a high international reputation for quality.

Issue III - The availability, terms and conditions for the transfer of technology for the manufacture of essential drugs.

A. Background

23. Developing countries are at various stages of development of pharmaceutical industry ranging from simple formulation and packaging based on imported bulk drugs to the manufacture of bulk drugs based on local raw materials.[1] The technology involved in the formulation and packaging is well known and fairly well defused. Moreover, the nine essential drugs selected by UNIDO as priority for establishment of production facilities are being used in most countries under generic name and do not require any licence agreements. Most developing countries already have the technology of formulations and are in a position to transfer to other developing countries. Therefore the technology transfer of formulations is not discussed here.

24. The technology involved in the manufacture of bulk drugs is relatively more sophisticated than that involved in the formulation and packaging of drugs. Such a technology is available in developed countries, countries with centrally planned economies as well as in some of the developing countries. A survey carried out in selected countries in Africa, Asia, and Latin America about the production of 26 essential drugs has indicated that only few countries have facilities for the manufacture of some of the 26 essential drugs in varying degrees.[2] Even in the countries where they have facilities to manufacture these drugs, the technology is often based on the early or late intermediates and not on the raw materials. These countries have to depend on the import

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1) Issues that might be considered at the First Consultation UNIDO/ID/WG.317/1

2) Op. cit. UNIDO/ID/WG.317/1

of intermediates, cost of which makes the local manufacture uneconomical as compared to the cost of bulk drug. The non-availability of suitable technology for the manufacture of bulk drugs is perhaps the largest single constraint to the development of indigenous production of bulk drugs. 1)

It is observed that developing countries experience considerable difficulty in obtaining access to suitable technology at a reasonable price.

B. Present status of technology of 9 essential drugs

25. The production status of 9 essential bulk drugs in developing countries and countries with centrally planned economics is given in Appendix VI. It may be seen that few developing countries are manufacturing these 9 most essential drugs mostly from early or late intermediates. This shows that there has virtually been no transfer of technology to manufacture of these drugs based on raw materials. Even in cases where manufacturing is done by subsidiaries of transnational companies, the technology is based on intermediates which are supplied by the parent company.

26. In the First Consultation on the Pharmaceutical Industry at Estoril, Portugal, some participants from developed countries, centrally planned economies and industry expressed their willingness to promote the transfer of technology to developing countries. Participants from a few countries gave written preliminary information concerning the drugs for which technology could be offered. An international trade association gave a list of international companies which would consider transfer of technology for the 9 priority drugs in the illustrative list produced by UNIDO. The consensus at the First Consultation was that the transfer of technology has to take place on mutually acceptable and equitable terms.

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

The manufacture to be based on maximum feasible backward integration to raw materials.

C. Technologies available for transfer

27. In order to facilitate transfer of technology on mutually acceptable terms and to determine the techno-economical suitability, which could lead to decide appropriate technology for any particular developing country, UNIDO has requested the manufacturers of these nine priority drugs, including the international companies (the list of which was provided by one international trade association) to provide basic information and to confirm their willingness to negotiate for the transfer of technology. Based on the information provided by the participants at the First Consultation Meeting and based on the replies received in response to UNIDO's request, the availability of technology for the manufacture of nine drugs is indicated in the Appendix VII. This tabulation of available sources of technology is at the time of compilation of this report and not yet complete.

28. It may be seen from the Appendix VII that technology for acetyl salicylic acid, ampicillin, tetracycline, sulphadimidine, diethyl carbazine citrate, dapsone, ethambutol and isoniazid is available for transfer to developing countries. The technology for the manufacture of chloroquine phosphate, an antimalarial drug, is not available at present for transfer to developing countries. There are four major producers of this drug in the developed countries. 99 percent of the market for this drug is in the developing countries.[1)] The technology for ethambutol is only available starting from the late intermediate stage of D-2-aminobutanol.

29. The information received does not contain sufficient details for UNIDO to determine technoeconomical suitability of different technologies available. In order to prepare pre-feasibility reports, which could lead to tentative invitation for developing countries

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

to bilateral negotiations for transfer of technology, additional information is required by UNIDO. Some of the companies from developed countries are willing to provide the required information, subject to contracts and other secrecy agreements with the recipient organisations in the developing countries. It would be desirable that the required information is made available so that UNIDO is able to carry out pre-feasibility studies. Such pre-feasibility studies then could form the basis for calling the developing countries for bilateral negotiations. Therefore the information required by UNIDO has to be provided. UNIDO has been in correspondecne with some of the financial institutions and once the prefeasibility studies are completed, it may be possible to approach for financial assistance.

D. Method for Transfer of Technology

30. Different methods for the transfer of technology are described in UNIDO Report.[1] The following methods are widely used:

1. Establishment of subsidiaries by foreign companies.
2. Joint ventures.
3. Transfer of technology under licence.
4. Sale of technology.

The establishment of joint venture is considered most desirable in the interest of both the recipient of technology and the supplier of technology. Even limited equity participation by the foreign company will give that company a sense of involvement without making them the sole owner of the new venture. The technology based on manufacture of drugs from raw materials would be desirable in many cases since it would not be sensitive to disparity of prices of intermediates in the international market. Freedom to purchase intermediates, raw materials, equipment and

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1) Second Panel Meeting of Industrial Experts on the Pharmaceutical Industry, UNIDO/ID/WG.267/4/Rev.1.

machinery by recipient of technology would give more confidence in the supplier of technology. Contractual agreement covering transmission of improvements in technology to the recipient of the technology would remove the fear that the technology being purchased would become obsolete after some time. In some cases arrangements to buy back part of the production by the supplier of technology for export and assistance in the development of export market in the region would help the recipient of technology to set up economic scale production. Transfer of technology to third parties with mutual consent would be beneficial to both the parties as well as help in the development of pharmaceutical industry in other countries. For these purposes, the terms and conditions of the licensing agreements entered into between the recipient and the supplier of technology becomes the most essential part of transfer of technology.

E. Analysis

31. The technology for production of formulations is fairly well known to developing countries and is not needed. However, the issues concerning contractual arrangements and licensing agreements in transfer of technology of formulations are discussed in the paper on Issue II.

32. Few developing countries are manufacturing the nine most essential drugs needed to treat diseases widely prevalent in the developing world. In most cases production is carried out from imported intermediates and the high cost and limited availability of these intermediates hinder economic viability of production. In view of this, it is essential that the developing countries should have access to the appropriate technology for those nine essential drugs from raw materials to overcome this problem.

33. Technical and economic analysis (Appendix III) of the manufacturing processes of these nine essential drugs have indicated that it is possible to set up small scale production units for most of these drugs without significantly affecting the economics of production provided the efficient technology and key intermediates/raw materials are available at reasonable prices. However,

in cases where there is difficulty in obtaining the intermediates, it would be desirable to get a technology which makes use of basic raw materials; in some cases, it would be necessary to set up multiproduct plants. In case the availability of infrastructure and demand of a particular country does not permit establishment of economic size production facilities, it would be desirable to set up a plant for meeting the needs of a region, one country of the region having basic infrastructure can be selected for establishment of economic scale production thus meeting the demand of countries of region through exports.

3.4 A number of companies based in the developing countries and few companies based in the developed countries are in a position to negotiate the transfer of production know how of eight out of the nine essential drugs. These offers could be considered after getting more details from the countries/companies who are willing to co-operate in the development of the pharmaceutical industry in the developing countries.

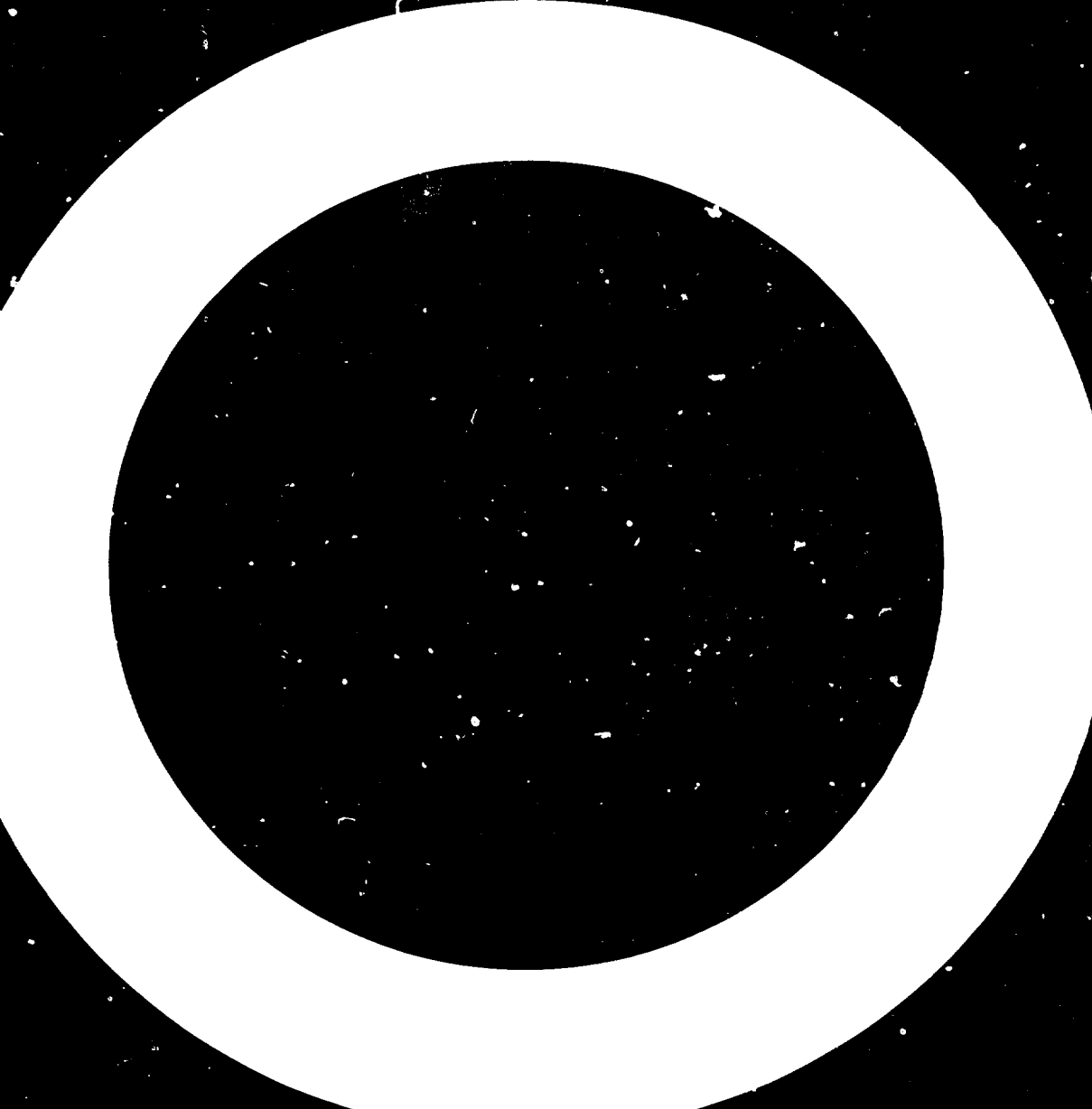
3.5 The terms and conditions of transfer of technology for these drugs are not available to UNIDO as most suppliers of technology would prefer to negotiate directly with the countries/companies who wish to acquire the technology. Since UNIDO is committed to provide assistance to the developing countries for development of pharmaceutical industry, it is important for UNIDO to determine the appropriate stage of chemical synthesis, appropriate capacity and capital cost of the plant suitable for each country or region. To undertake the pre-feasibility studies, UNIDO requires the relevant data including basic process data on raw material inputs, chemical yields at various stages and the terms and conditions of transfer of technology.

3.6 The formation of joint venture between the supplier of technology and the recipient of technology is considered as one of the best methods of transfer of technology provided the other terms and conditions of licensing agreement protect the interest of both parties.

37. The development of technological capabilities of developing countries would help the effective transfer of technology. Protection from the local Government in the initial stages would promote the development of the industry.

F. Export Restrictions in Transfer of Technology Agreements

38. It has been observed that condition restricting the export of intermediates and finished drugs is generally put in the agreements in the transfer of technology to developing countries. The export restriction is one of the main concerns of developing countries who wish to be the recipient of technology since the impact of restriction prevents the achievement of economic scale of production. Moreover, it does not allow the recipient of technology to meet the needs of the countries of the region for that particular product. In many cases, freedom to export to its own regional market is of basic concern of the recipient country. The elimination of export restrictions from the terms and conditions of transfer of technology would lead to setting up of economic scale production facilities, would give opportunity to explore the markets of the region and regional development of the pharmaceutical industry.



List of Manufacturers of bulk drugs and their intermediates

Appendix I

Manufacture of Acetyl Salicylic Acid

Australia:
1. Monsanto Australia Ltd.
P.O. Box 4507
Melbourne, Vic 3001
Australia

Argentina:
2. Quim. Farm. Platense S.A. (P)
Jose Barros Pazos 5531
Buenos Aires, Argentina.

Brazil:
3. Sydney Ross Co.,
Av. Rio Branco 251-11e
Andar. Caixa Postal 1363
Rio de Janeiro

China:
4. China National Chemicals
Import and Export Corporation
Erh-Li-Kon, Hsi, Chiao
Peking, China

Colombia:
5. Sydney Ross

6. Industria Química Andina
Carrera 12, 15-95 Piso 1o.
Bogota, Colombia.

Czechoslovakia:
7. SPOFA
Husinecka 11a
Prague, Czechoslovakia

France:
8. Rhone-Poulenc Industries S.A.
21 rue Jean Goujon
75360 Paris cédex 08
France

Federal Republic of Germany:

9. Bayer A.G.
5090 Leverkusen Bayer Werk
F.R.G.

10. Hoecht Aktiengesellschaft
Postfach 800 320
6230 Frankfurt Main 80
FRG

11. E. Merck
Postfach 4119
6100 Darmstadt
FRG

12. Chemische Fabrik Aubing
Dr. Kurt Block Nachf
Industriestrasse 18-22
8000 Munich 60
FRG

German Democratic Republic:

13. Veb Chem. Pharm. Werke
c/o Chemie Export-Import
Volkseigner Aussenhandelsbetrieb
DDR 1055, Berlin
Storkower Strasse 133, G.D.R.

India:

14. Alta Laboratories Pvt. Ltd.
P.O. Box 7019
Dadar, Bombay - 400028
India

Italy:

15. Farmitalia - Societá Farmaceutici
Italia S.p.A.
Casella postale 3075
20100, Milano
Italy

Japan:

16. Iwaki and Co.
4-1 Nihonbashi Honcho
Chuo-ku, Tokyo 103
Japan

17. Mitsui Toatsu Chemicals Inc.
Kasumigaseki Bldg.
3-2-5 Kasumigaseki
Chiyoda-ku
Tokyo-100, Japan

Mexico:

19. Salicilatos de México, S.A.
Avenida Oriente 171
No. 435
Mexico 14, DF
Mexico.

20. Dow Quimica Mexicana S.A. de C.V.
Apartado postal 77-330
Mexico 10, DF
Mexico.

Poland:

21. Polfa
00-926 Warszawa
Ulica Wspolna Nr. 4
Poland

Rumania:

22. Uzina de Medicamente
c/o Chimimport Export
Blvd. Republicii Nr 10
Sector 4, Bucharest, Rumania.

Spain:

23. Products Pyre
Daniel Mangrañe, S.A.
Apartado 224
Barcelona
Spain

24. Quim. Farm;

Turkey:

25. Bayer Türk Kimya Sanayü

U.K.

26. Albright and Wilson Ltd.
Industrial Chemicals Div.
P.O. Box 3 Oldbury
Warley, Worcs. B694 NL
U.K.

27. Graesser Salicylates Ltd.
Sandy craft, Deeside
Frinltshire CH5 2PX
U.K.

28. Laporate Industries Ltd.
P.O. Box 8
Luton, Beds. LU4 8EW
U.K.

29. Monsanto Limited
10-18 Victoria Street
London SW1H ONQ
U.K.

U.S.A.

30. Norwich Pharmacal Co.
13-27, Eaton Avenue
Norwich, N.Y. - 13815
U.S.A.

31. DOW Chemical Corporation
Midland, MI-48640
U.S.A.

32. Mallinckrodt Inc.
Industrial Chemicals Div.
P.O. Box 5439
St. Louis
MO-63160, U.S.A.

33. Monsanto Company
800 North Lindbergh Boulevard
St. Louis
MO-63166, U.S.A.

34. Sterling Drug Inc.
Glenbrook Labs Div.
90 Park Avenue
New York -10016
U.S.A.

Yugoslavia:

35. Bayer Pharma Yugoslavija
61001 Ljubljana
Celovska Cesta
135, Yugoslavia

Manufacturers of Salicylic Acid

Australia:

1. Monsanto Australia Ltd.

France:

2. Rhone Poulenc Industries

F.R.G.

3. Bayer AG
Chemische Fabrik Aubing
Kepec Chemische Fabrik GmbH
Postfach 90
5200 Siegburg (Rheinland)
F.R.G.

India:

4. Alta Laboratories

Italy:

5. Farmitalia- Societa Farmaceutici
Italia S.r.l.

6. AINA - Aziende Colori Nationali
Affini S.p.A.
Casella postale 3484
20100 Milano
Italy.

7. Mineralchimica S.r.l.
Casella postale 4300
20 100, Milano
Italy.

Japan:

8. Iwaki and Co.

9. Mitsui Toatsu

10. Kamaguchi Chemical Co. Ltd.
3-8 Nihonbashi Honcho
Chuo-ku, Tokyo 103
Japan

11. Daici Kakok. K.
Kitawara, Itami city
Hyogo Pref. 664
Japan

12. Yoshitomi Pharmaceutical Ind. Ltd.
    Hiranomachi Showa Building
    3-25 Hirano-machi
    Higashi-ku, Osaka 540-91
    Japan

Mexico:

13. Salicilatos de Mexico
14. DOW Quimica Mexicana

Poland:

15. Polfa

Spain:

16. Products Pyre

U.K.:

17. Albright Wilson Ltd.
18. Graesser Salicylates
19. Monsanto Ltd.
20. Imperial Chemical Industries
    Millbank
    London SW1P 3JF
    U.K.
21. Lunevale Products Ltd.
    Low Mill Halton
    Lancaster LA2 6NE
    U.K.

U.S.A.:

22. DOW Chemical Co.
23. Mallinckrodt Inc.
24. Monsanto company
25. Teneco Chemicals Inc.
    P.O. Box 365, Tuener place
    Piscataway NJ 08854
    U.S.A.
26. Hilton Davis Chemical Co.
    2235 Langdon Farm Road
    Cincinnati, OH 45237
    U.S.A.
27. E.I. Du Pont de Nemours and Co.
    Elastomer Department
    Wilmington, DE - 19898
    U.S.A.

Note: Wherever the name of a company is repeated, its address is not repeated in this list.

Manufacturers of Ampicillin

Argentina:

1. Squibb

Brazil:

2. Bayer Do Brazil Indus. Quimicas
R. Domingos Jorge 1000
Santo Amaro, CEP 04761, Sao Paulo
Brazil.

3. Quimasa-Bristol

Belgium:

4. Beecham Pharmaceuticals
4, Leuvensesteenweg
1380 Tervuren, Belgium

Finland:

5. Fermion OY
P.O. Box 28
02101 Tapiola
Finland

F.R.G.:

6. Bayer AG
5090 Leverkusen Bayerwerk
F.R.G.

Italy:

7. Instituto Biochemico Italiano S.a.S.
2 via G. Lorenzini
20139 Milano
Italy

8. Farmitalia Societa Farmaceutici
Italia S.p.A.
Casella postale 3075
20100 Milano
Italy

9. Flamma S.a.S.
13 via Boccaleone
24100 Bergamo
Italy

10. Pro-chim-Re S.p.A.
2 via Sereso
20100 Milano
Italy

11. Ankerfarm S.p.A.
Casella postale 42
2s092 Cinisello Balsamo, Italy

12. Archifar-Industrie Chimiche del Trentino S.p.A.
18 via Trivulzio
20146 Milano
Italy

13. Co. Farmaceutica Milanese S.r.L.
37 via Gallarati
20151 Milano
Italy

14. I.S.F. S.p.A.
1 Via Leonardo da Vinci
20090 Trezzano sul Naviglio
Italy

15. Bristol Italiana S.p.a.
Via del Murillo, km 2.8, 04010 Sermoneta
(Latina) Italy

16. Glaxo S.p.A.
via A. Fleming 2
37100, Verona, Italy

Israel:

17. Ikapharm Ltd.
P.O. Box 31, Ramat Gan, Israel

18. Plantex
P.O. Box 160
Netanya, Israel

India:

20. Indian Drugs and Pharmaceuticals Ltd.
P.O. Box 3816
New Delhi - 49, India

21. Hindustan Antibiotics Ltd.
Pimpi, Prona - 410018, India

22. Alembic Chemical Works Ltd.
Alembic Road, Baroda 390003
India

23. Ranbaxy Laboratories Ltd.
78 Nehsu Place
New Delhi - 110019, India

Japan:

24. Banyu Pharmaceuticals Co.
2-7 Nihonhashi, Honcho-2 chome
Chuo-ku, Tokyo 104, Japan

25. Meizi-Seika Kaisha
4-16 Kyobasli - 2 chome
Chuo-ku, Tokyo 104, Japan

26. Takeda chemicals, 2-27 Doshomachin
Highshiky, Osaka 541, Japan

27. Toyama Chemicals
2-27 Doshomachin
Highshiku, Osaka 541, Japan
28. Toyo Jozo
29. Yamanouchi

Mexico:

30. Eurolatin Pharmaceuticals S.A.
Jrbina 18, Naucalpan
Mexico DF, Mexico.

31. Fermic S.A. de C.V.
Reforma 300
Iztapalapa, Mexico 13 DF
Mexico.

32. Fermentaciones y Síntesis SA
Apartado postal 301
Col. del Valle, N.L., Mexico

33. Products Gedon Richter (America) S.A.
Apartado postal 21-957
Mexico-21, DF, Mexico.

34. Kemika Industrial S.A.
Apartado postal 34-004
Mexico 10, DF, Mexico.

35. Orsabe S.A.
Apartado postal 430
Cuernavaca, Mor. Mexico

36. Quinonas de Mexico S.A.
Apartado 75-504
Mexico 14, DF, Mexico.

37. Benvenides

38. Laboratorios Sanfor

South Korea:

39. Chong kun Dang. Corp.
410 Shindorim Dong
Kuru-ku, Seoul, South Korea.

40. Dong Wha Pharm. Ind. Co. Ltd.
5 Sunwha - Dong
Chung-ku, Seoul, South Korea

41. Seoul Pharmaceuticals.

42. Dong Shin

Netherlands:

43. Gist-Brocades
Industrial Products Division
P.O. Box 1, Delft, Netherlands

Portugal:

44. Cipan SARL
Av. Gomes Pereira 74
Lisbon, Portugal

Peru:

45. Sinquisa

Singapore:

46. Beecham (Manufacturing) Singapore Ltd.
Jalan Tukang, Jurang Tchen
Singapore-22

Spain:

47. Antibioticos
38 Bravo Murillo
Madrid 3, Spain

48. Lisac S.A.
Calle Rosario s/n, San Fausto
de Campocentellas, Barcelona, Spain

Sweden:

49. A.B. Astra
15185 Södertälje, Sweden

Turkey:

50. Mustfa Nevzat
Meridiyikoy yeni yol sokak No. 8
istanbul, Turkey.

U.K.:

51. Beecham Group
Great West Road
Brentford, Middlesex, U.K.

U.S.A.

52. Beecham Inc.
65 Industrial South
Clifton, N.J. -07012, U.S.A.

53. E.R. Squibb and Sons, Inc.
P.O. Box 4000
Princeton, N.J. 08540, U.S.A.

54. Bristol Laboratories
P.O. Box 657, Syracuse
N.Y. - 13201, U.S.A.

55. Wyeth Laboratories Inc.
P.O. Box 831
Paoli, PA - 19301, U.S.A.

56. Biocraft Laboratories Inc.
12, Industrial Way
Waldwick, N.J. - 07463, U.S.A.

Rumania:

57. Ehim Import Export

'Manufacturers of 6-amino penicillanic acid. (Most of the manufacturers of ampicillin also manufacture 6 APA, therefore the above list is not repeated).

Austria:

1. H. Bergmann KG
Postfach 102
1041, Vienna, Austria

U.S.A.:

2. Aldrich Chemicals Co. Inc.
940 West Street
Paul Avenue
Milwaukee, WI 53233
U.S.A.

U.S.S.R.

3. U. S. S. R.

Manufacture of D-X-Phenylglycyl chloride, HCL

Japan:

1. Tanabe Seiyaku Co. Ltd.
3-21 Dosho-machi
Higashi-ku
Osaka-541, Japan

2. Nippon Kayaku Co. Ltd.
New Kaijo Building
1-2-1 Marunouchi
Chiyoda-ku
Tokyo-100, Japan

3. Daiichi Pure Chemicals Co. Ltd.
3-13-5 Nihonbashi
Chuo-ku, Tokyo 103, Japan

4. Hamasi Pharmaceuticals Industries Ltd.
Yamaguchi Building
2-19, Doshomachi
Higashi ku, Osaka 541, Japan.

Netherlands:

5. Oce Andeno B.V.
P.O. Box 81
Venlo, Netherlands

Switzerland:

6. ICN-Arco S.A.
9 rue Boissonnas
1211 Geneva 24
Switzerland

U.K.:

7. Sterling organics Ltd.
Dudley, Cramlington
Northumberland NE2372G
U.K.

U.S.A.:

8. Kay Fries Chemicals Inc.
60 Craig Road
Montvale, NJ 07645, USA.

9. Upjohn Company
Kalamazoo
MI 49001, USA

10. Story chemical corporation
500 Agard Road
Muskegon, MI 49445, U.S.A.

Manufacturers of Dimethyl dichloro silane

U.S.A.:

1. DOW Corning Corporation
   Midland, MI 48640
   U.S.A.

2. Pierce chemical Co.
   P.O. Box 117
   Rockford, IL 61105, USA

3. Union Carbide Corporation
   270, Park Avenue
   New York, NY - 10017, USA

Manufacturers of sulphadimidine

Belgium:

1. Cosima P.V.B.A.
   P.O. Box 14
   2610 Wilrijk
   Belium

Bulgaria:

2. Pharmachim
   16 Iliensko Chausee
   Sofia, Bulgaria

Canada:

3. Cyanamid of Canada Ltd.
   635 Dorchester Boulevard W.
   Montreal, P2 H3P1rG

China:

4. China National Chemicals Import
   Export Corporation
   Erh-Li-Kou
   Hsichio, Peking, China.

Denmark:

5. A/5 Synthetic
   53 Jens Baggesens Vej
   8200 Aarhus N.
   Denmark

Egypt:

6. El Nasr Co. for Pharmaceuticals
   Abou-Zaabal, Cairo, Egypt

Hungary:

7. Medimpex
   P.O. Box 126
   H-1808 Budapest
   Hungary

India:

8. Indian Drugs and Pharmaceuticals Ltd.
P.O. Box 3816
New Delhi - 49
India

Italy:

9. Istituto Chemioterapico Italiano S.p.A.
Casella postale 1052
20100, Milano, Italy.

Israel:

10. Abic Ltd.
P.O. Box 2077
Ramat Gan 52100, Israel

Mexico:

11. Laboratorios Julian de Mexico S.A.
Apartado postal 154
Suc. A, Cuernavaca, Mor. Mexico.

Netherlands:

12. ACF Chemiefarma N.V.
P.O. Box 5
Maarssen, Netherlands.

Poland:

13. Polfa
00-927 Warszawa
Ulica Wspolna No. 4, Poland

U.K.:

14. Imperial Chemical Industries Ltd.
Imperial Chemical House
Millbank, London SW1P 3JF
U.K.

15. May and Baker Ltd.
Dagenham, Essex RM10 7XS
U.K.

U.S.A.:

16. American cyanamid Co.
Fine chemicals dept.
Middle town Road
Pearl River, NY 10965, USA

17. Rachelle Laboratories, Inc.
P.O. Box 2029
Long Beach, CA 90801, U.S.A.

18. Salsbury Laboratories
2000 Rockford Road
Charles city IO 50616, USA

19. Napp Chemicals Inc.
199 Main Street
Lodi, NJ 07644, U.S.A.

20. Beecham Research Laboratories

Manufacturers of Acetanilide

Austria:

1. Shell Austria AG
   Postfach 174
   1011 Vienna, Austria.

France:

2. Rhone-Poulenc Ind. S.A.
   21 rue Jean Goujon
   75360 Paris, Cedex 08, France

F.R.G.:

3. Bayer AG
   5090 Leverkusen Bayerwerk
   F.R. Germany

4. E. Merck
   Postfach 4119
   6100 Darmstadt, F.R.G.

5. Dr. Theodor Shuchardt and Co.
   Postfach 801 549
   8000, Munich 80, F.R.G.

India:

6. Hindustan Organic Chemicals Ltd.
   Harchandri House
   81 Queen's Road
   Bombay 400 002, India.

Italy:

7. Carbo Erba S.p.A.
   Casella postale 3996
   20100 Milano, Italy

Japan:

8. Daiwa Chemical Co. Ltd.
   6-1-106 Minami Tsumori
   Nishinari-ku, Osaka 557, Japan.

9. Honshu Chemical Industries Co. Ltd.
   Fuji Bldg., 1-5-3 Yaesu
   Chuo-ku, Tokyo 103
   Japan

10. Iwaki and Co. Ltd.
    4-1 Nihonbashi Honcho
    Chuo-ku, Tokyo 103
    Japan

11. Yamanouchi Pharmaceutical Co. Ltd.
    2-5 Nihonbashi Honcho
    Chuo-ku, Tokyo 103, Japan

Mexico:

12. Promotora Tecnica Industrial S.A.
    Calle del Esfuerzo 19
    Col. Lazaro Cardenas
    Naucalpan
    Mex., Mexico

Netherlands:

13. B.V. Frado
P.O. Box 543
Tilburg, Netherlands

Spain:

14. Industrias GMB S.L.
24 Virgili
Barcelona 16, Spain

Taiwan:

15. Cheng Fong Chemicals Co. Ltd.
P.O. Box 2, Tu Cheng
Taipei Hsein
Taiwan

U.K.:

16. Albright and Wilson Ltd.
Industrial Chemicals Div.
P.O. Box 3, Oldbury
Warley, Worcs. B69 4NL
U.K.

17. Ciba¡Geigy (U.K.) Ltd.
30 Buckingham gate
London SW1E 6LH
U.K.

18. Hopkin and Williams
P.O. Box 1, Romford
Essex RM1 1HA, U.K.

U.S.A.:

19. Arapqhoe Chemicals Inc.
P.O. Box 511
Boulder, CO 80302, U/S.A.

20. Merck and Co. Inc.
Merck Chemicals Division
Rahway, N. J. 07065, U.S.A.

21. Salsbury Laboratories
2000 Rochford Road
Charles City, IO 50616
U.S.A.

Manufacturers of Acetyl acetone:

F.R.G.:

1. Walker-chemie GmbH
Postfach 8000
Munich 22, FRG.

Japan:

2. Daicel Ltd.
Osaka Kokusai Building
2-30 Azuchimachi
Higashi-ku, Osaka 541, Japan

U.K.:

3. British Celanese Ltd.
P.O. Box 5
Spondon
Derby DE2 7BP, U.K.

4. Hopkin and Williams
P.O. Box 1, Romford
Essex RM 1 1HA, U.K.

U.S.A.:

5. Mackenzie Chemical Works Inc.
1 Cordello Avenue
Central Islip, N.Y. - 11722
U.S.A.

6. Union Carbide Corp.
270 Park Avenue, New York
N.Y. - 10017, U.S.A.

7. Strem Chemicals Inc.
P.O. Box 212
Danvers, MA 01923, USA

Manufactuers of Guanidine Nitrate

Canada:

1. Cyanamid of Canada Ltd.
635 Dorchester Boulevard W
Montreal, P.Q. H3B 1R6, Canada

France:

2. Produits chimiques Ugine-Kuhlmann
B.P. 175-16
75782 Paris Cédex 16, France

F.R.G.:

3. Suddeutsche Kalkstickstoffwerke A.G.
Postfach 1150/1160
8223 Trostberg, FRG

4. Dr. Theodor Schuchardt and Co.
Postfach 801 549
8000 Munich, 80,
FRG

Japan:

5. Nippon Carbide Industries Co. Inc.
New Tokyo Bldg.
3-3-1 Marunouchi
Chiyoda-ku, Tokyo 00,

U.K.:

6. Imperial Chemical Industries Ltd.
Imperial Chemical House
Millbank, London SW1P 3JF, U.K.

U.S.A.:

7. Hummel Chemical Co.
P.O. Box 250
South Plainfield
NJ 07080, U.S.A.

Manufacturers of Tetracycline

Argentina:

1. Pfizer
   Minones 2177, Buenos Aires, Argentina

Belgium:

2. Cosima P.V.B.A.
   P.O. Box 14
   2610 Wilrijk
   Belgium

Brazil:

3. Cyanamid Quimica do Brasil Ltd.
   Caixa Postal 1039, Rio de Janeiro, Brazil.

4. Pfizer Quimica Ltd.
   Caixa Postal 143, 07000 Guarulhos, Sao Paulo, Brazil.

5. Quimica Industrial Santo Amaro (Quimasa)
   Rua Ignatirga, 337, Santo Amaro
   Sao Paulo, Caixa Postal 2240, Brazil.

China:

6. China National Chemicals Import Export Corporation
   Erh-Li-Kou
   Hsichio, Peking, China

France:

7. Pfizer-France
   B.P. 60
   91401 Orsay - Cédex
   France

8. Société chimique Pointet Girard S.A.
   16 Boulevard du General Leclerc
   92115 Chinchy, France

9. S.A. des Establishments Rouse-Bertrand Fils and Justin Dupont
   17 bis rue Legendre
   75017, Paris, France

10. Rhone-Poulenc Industries S.A.
    21 rue Jean-Goujon
    75360 Paris cédex 08,France

11. Roussel-uclaf S.A.
    Tour Rousell-Nobel, Cedex No. 3
    92080 Paris La Defense, France

F.R.G.

12. Boehringer Mannheim GmbH
    Postfach 51
    6800 Mannheim 31, F.R. Germany

13. Hoechst Aktiengesellschaft
    Postfach 800320, 6230 Frankfurt Main 80,
    F.R. Germany

13. Hoechst Aktiengesellschaft
Postfach 800 320
6230 Frankfurt Main 80
F.R. Germany

Ireland:

14. Squibb

15. Proter (A and D) Ltd.

Italy:

16. Istituto Biochemico Italiano S.a.S.
2 via G. Lorenzini
20139 Milano, Italy

17. Carlo Erba S.p.A.
Casella postale 3996
20100 Milano, Italy

18. Farmitalia Societa Farmaceutici
Italiana S.p.A.
Casella postale 3075
20100 Milano, Italy

19. Gruppo Lepetit S.p.A.
Casella postale 3698
20100 Milano, Italy

20. Pro-Chim-Re S.p.A.
2 via Seveso
20091, Bresso, Italy.

21. Societe Prodotti Antibiotici, S.p.A.
8 via Biella
20143, Milano, Italy

22. Archifar - Industrie Chimiche
del Trentino S.p.A.
18 via Trivulzio
20146 Milano, Italy

23. Rachelle Laboratories Italia S.p.A.
5 via del Mulino
20094 Buccinasco, Italy.

24. Co. Farmaceutica Milanese S.r.L.
37 via Gallarati
20151 Milano, Italy.

25. Iniziative Terapeutiche Panther
16 via Doberdo
20100, Milano, Italy.

26. Laboratori Pro-Ter S.p.A.
38 via Lambro
20 100 Milano, Italy

27. Cyanamid Italia S.p.A.
via S. Sofia 21, Milan, Italy

28. Diaspa

29. Pierrel S.p.A.
30 via Turati
20100, Milano, Italy

30. Ankerfarm S.p.A.
Casella postale 42
20092 cinisello Balsamo, Italy

India:

31. Indian Drugs and Pharmaceuticals Ltd.
P.O. Box 3816
New Delhi - 49, India

32. Cyanamid India,
254 Dr. Annil Besant Road
P.O. Box 9109, Bombay

33. Synbiotics Ltd.
P.O. Box 139
Wadi wadi, Baroda
India

Japan:

34. Pfizer Taito Ltd., 1-1 Nishi-Shingjuku, 2-chome
Shinjuku-ku, Tokyo 160, Japan

35. Meizi-Seika Kaisha Ltd.
2-8 Kyobashi-2-chome
chuo-ku, Tokyo 104, Japan

36. Mitsui Toatsu chemicals Co.
Kasumigaseki Bldg, 3-2-5 Kasumigaseki
Chiyoda-ku, Tokyo 100, Japan.

37. Lederle (Japan) Ltd.
P.O. Box 957
Tokyo central, Japan

38. Takeda Chemicals
2-27 Doshomachi
Higashiku, Osaka 541, Japan

S. Korea:

39. Chong Kung Dang Co. Ltd.
410 Shindorim-Dong
Kuru-ku, Seoul, S. Korea

40. Korea Pfizer Ltd.
427 Kwanjang-Dong
Sungdong-ku, Seoul, S. Korea

Mexico:

41. Fermic S.A. de C.V.
Reforma No. 300
Istapalapa, Mexico 13, D.F., Mexico.

42. Cyanamid de Mexico, Calzada de Tlalpan 3092
Mexico 22, D.F. Mexico.

Spain:

43. Periberica S.A.
Apartado 197
Pamplona, Spain

44. Union Explosivos Río Tinto S.A.
Apartado 66
Madrid-1, Spain

45. Antibioticos S.A.
38 Bravo Murillo
Madrid 3, Spain

46. Compañía Española de la Penicilina
y Antibióticos S.A.
15-17 Avenida del Generalísimo
Madrid 16, Spain

47. Iberica S.A.
Apartado 471
Madrid, Spain

Switzerland:

48. ICN-Arco S.A.
9 rue Boissonnas
1211 Geneva, Switzerland

U.K.:

49. Pfizer Ltd., Ramasgate Road
Sandwich, Kent CT13 9NJ, U.K.

U.S.A.:

50. Pfizer Inc.
Chemicals Division
235 East 42nd St.
N.Y. - 10017, U.S.A.

51. Bristol Laboratories
P.O. Box 657
Syracuse NY 13201, U.S.A.

52. American Cyanamid Co.
Fine Chemicals Division
Middle Town Road
Pearl River, N.Y. - 10965, U.S.A.

53. Upjohn Company
Kalamazoo, MI 49001, U.S.A.

54. Rachelle Laboratories Inc.
P.O. Box 2029
Long Beach, CA
90801 U.S.A.

Manufacturers of Diethyl Carhamazine citrate

India:

1. Burrows Wellcome (India) Ltd.
16 Bank St, P.O. Box 290
Bombay 400023, India

2. Indian Drugs and Pharmaceuticals Ltd.
P.O. Box 3816
New Delhi 110049, India

3. UNI-UCB Ltd.
22, Bhulabhai Desai Road
Bombay 400026, India

France:

4. Rhone-Poulenc Industries S.A.
21 rue Jean-Goujon
75360, Paris cedex 08
France

5. Roussel Uclaf
35 Bvd. des Invalides, F75007, Paris ,France

Sweden:

6. Rexolin Chemicals A.B.
Box 622
25106 Helsingborg, Sweden

Switzerland:

7. Organol, S.A.
1902 Evionnaz
Switzerland

8. Sandoz AG
Fine Chemicals Dept.
35 Lichtstrasse
4002 Basel 13, Switzerland

9. Siegfried AG
4800 Zofingen
Switzerland

10. Wanderchemie AG
via Serafino Balestra
ch-6601, Locarno, Switzerland.

U.K.:

11. Wellcome Foundation Ltd.
Temple Hill, Dartford
Kent DA1 5AH
U.K.

12. Ward Blenkinsop and Co.
Fulton House, Empire Way
Wembley, Middlesex, U.K.

U.S.A.:

13. American Cyanamid Co.
Fine Chemicals Div.
Middle town Road
Pearl River, NY - 10965, U.S.A.

14. Acetochemical Co. Inc.

Manufacturers of N-Methyl piprazine

F.R.G.:

1. BASF A.G.
6700 Ludwingshafen
Rhein. F.R.G.

2. E. Merck
Postfach 4119
6100 Darmstadt, F.R.G.

3. Dr. Theodor Schuchardt and Co.
Postfach 801 549
8000 Munich 80, Germany

Sweden:

4. Rexolin Chemicals AB, Sweden.

U.S.A.:

5. Aldwich Chemicals Co. Inc.
940 West St.
Paul Avenue
Milwaukee, W153233, U.S.A.

6. Jefferson chemicals Co. Inc.
P.O. Box 430
Bellaire, Tx. -77401, U.S.A.

7. Union Carbide Corporation
270, Park Avenue
New York, N.Y. - 10017, U.S.A.

8. R.S.A. Corporation
690 Saw Mill River Road
Ardsley, N.Y. - 10502, U.S.A.

Manufacturers of Diethylamine

France:

1. Produits chimiques
   Ugine-Kuhlmann
   B.P. 175-16
   75782 Paris cedex 16, France

2. Rhone Poulenc Industries S.A.

F.R.G.:

3. BASF AG

4. E. Merck

5. Dr. Theodor Schuchardt and Co.

India:

6. Indian Drugs and Pharmaceuticals Ltd.

Italy:

7. Carlo Erba S.p.A.
   Casella postale 3996
   20100, Milano, Italy.

Japan:

8. Daicel Ltd.
   Osaka Kokusai Bldg.
   2-30 Azuchimachi
   Higashi-ku
   Osaka 541, Japan

9. Mitsibishi Gas Chemical Co. Ltd.
   Mitsubishi Bldg.
   2-5-2 Marunouchi
   Chiyoda-ku, Tokyo 100, Japan

10. Sugai Chemical Industries Co. Ltd.
    Toyota Building
    4-18 Shiomachidori
    Minami-ku, Osaka 542, Japan

Switzerland:

11. Metako S.A.
    Case postale 13
    1920 Martingny, Switzerland

U.K.:

12. Esso Chemical Ltd.
    Arundel Towers
    Portland Terrace
    Southampton 509 2GW, U.K.

U.S.A.:

13. Air Products and Chemicals Inc.
    P.O. Box 538, Allentown
    P.A. 18105, U.S.A.

14. Pennwalt Corporation
    Chemical Division
    Three Parkway
    Philadelphia, PA 19102, U.S.A.

15. Union Carbide Corporation.

16. Virginia Chemicals Inc.
3340 West Norfolk Road
Portsmouth, VA 23703, U.S.A.

Manufacturers of Dapsone

China:
1. China National Chemicals Import and Export Corp.
Erh-Li-Kou, Hsi Chiao
Peking, China

France:
2. Roussel-Uclaf S.A.
Tour Roussel-Nobel
Cédex No. 3, 92080 Paris La Défense
France

F.R.G.:
3. Dr. Theodor Schuchardt and Co.
Postfach 801 549
8000 Munich 80, F.R.G.

India:
4. Bengal Immunity Co., Immunity House
153, Lenin Saranee, Calcutta 700013, India.

U.K.:
5. Imperial Chemical Industries
Imperial Chemical House
Millbank, London SW1P 3JF, U.K.

U.S.A.:
6. R.S.A. Corporation
690 Sawmill River Road
Ardsley, N.Y. - 10502, U.S.A.

U.S.S.R.:
7.

Manufacturers of chloroquine:

Bangladesh:
1. Imperial Chemical Industries (Bangladesh) Ltd.
9 Motijheel Commercial Area
Dacca, Bangladesh.

China:
2. China National Chemicals Import and Export Corporation
Erh-Li-Kou, Hsi-chiao
Peking, China

France:
3. Rhone Poulenc Industries S.A.
21 Rue Jean-Goujon
75360 Paris Cedex 08
France

F.R.G.: 4. Bayer AG
D-5090 Leverkusen-Bayerwerk
Federal Republic of Germany

Hungary: 5. Medimpex
P.O. Box 126
H-1808 Budapest, Hungary

India: 6. Suneeta Laboratories (Pvt) Ltd
502 Arunchambers
J. Dadajee Road
Bombay - 400034, India

7. Bengal Immunity Co., Immunity House
153 Lenin Saranee, Calcutta 7000, India

8. Bayers (India) Ltd.
Express Towers, Nariman Point,
Bombay, 400021, India.

U.K.: 9. Imperial Chemical Industries Ltd.
Imperial Chemical House
Millbank, London SW1P 3JF
U.K.

10. Sterling organics Ltd.
Dudley, Cramlington
Northumberland NE23 7QG, U.K.

U.S.A.: 11. Sterling Organics Division
90 Park Avenue
New York 10016, U.S.A.

Manufacturers of metachloroaniline

France: 1. SPCM - Societe des Produits et
Matieres Colorantes de Mulhouse S.A.
21 Rue Henri-Rochefort
75017 Paris, France

F.R.G.: 2. Bayer AG
5090 Leverkusen Bayerwerk
F.R.G.

3. Hoecht Aktiengesellschaft
Postfach 800 320
6230 Frankfurt Main 80
F.R.G.

4. E. Merck
Postfach 4119
6100, Darmstadt, F.R.C.

5. Dr. Theodor Schuchardt and Co.
Postfach 801 549
8000 Munich 80, FRG

India:

6. Amar Dye-chem Ltd.
P.O. Box 6471, Mahim
Bombay 400016, India

Italy:

7. ACNA-Aziende colori Nazionali Affini 3484
Casella postale 3434
20100, Milano, Italy

8. Carlo Erba S.p.A.
Casella postale 3996
20 100, Milano, Italy

Japan:

9. Sanyo color works Ltd.
3rd Floor 13th Chuo Bldg.
4-4 Moncho Nihonbashi
Chuo-ku , Tokyo, Japan

10. Mitsubishi Chemical Industries Ltd.
Mitsubishi Building
2-5-2, Marunouchi
Chiyoda-ku, Tokyo 100, Japan

U.K.:

11. B.D. H. Chemicals Ltd.
Poole, Dorset BH124NN, U.K.

12. Hickson and Welch Ltd.
Castelford, Yorks. WF10 2JT
U.K.

13. Hopkin and Williams
P.O. Box 1, Romford
Essex RM1 1HA, U.K.

U.S.A.:

14. E.I. Du Pont de Nemours and Co. Inc.
Organic Chemicals Department
Wilmington, DE 19898, U.S.A.

Manufacturers of Novaldiamine

France:

1. Rhone Poulenc Industries S.A.

F.R.G.:

2. BASF AG.

Manufacturers of Ethoxy methylene malonic ester

France:
1. Rhone Poulenc Industries S.A.

F.R.G.:
2. Bayer AG
3. Dr. Theodor Schuchardt and Co.
4. Dynamit Nobel AG
   Postfach 1209
   5210 Troidorf, FRG
5. Riedel-de-Haën AG
   Postfach 1180
   3016 Seelze, F.R.G.

Switzerland:
6. Fluka A.G.
   9476 Buchs
   Switzerland

U.S.A.:
7. Kay Fries Chemicals Inc.
   60 Craig Road
   Montvale, NJ07645

Manufacturers of Ethambutol

Brazil:
1. Cyanamid Quimica do Brazil

France:
2. Lederle - Novalis

Hungary:
3. Medimpex
   P.O. Box 126
   H-1808 Budapest, Hungary

India:
4. Themis Pharmaceuticals
   38 Suren Road
   Bombay 400093, India
5. Bombay Paxwell

Italy:

6. Instituto Chemioterapico Italiano S.p.A.
   Casella postale 1052
   20100, Milanc, Italy-

7. Italsintex S.r.l.
   4 Galleria P Contarini
   35100 Padova, Italy

8. Laboratorio Chimico Farmaceutico Giorgio Zoja
   20 Viale Lombardia
   20131 Milano, Italy

9. Farchemia di Martino Finnotto and Co. S.a.S.
   32A Via Bergamo
   24047 Treviglio
   Italy

10. Co. Farmaceutica Milanese S.r.l.
    37 via Gallarate
    20151 Milano, Italy.

Japan:

11. Lederle (Japan) Ltd.
    P.O. Box 957
    Tokyo Central, Japan

U.S.A.:

12. American Cyanamid Co.
    859, Berdan Avenue, Wayne NJ 07470 U.S.A.

Venezuela:

13. Cyanamid de Venezuela CA
    Apartado Carmelitas 11391
    Caracas, Venezuela

Manufacturers of 2-Aminobutanol

France:

1. Societe chemique de la Grande Paroisse S.A.
   Boite postale 158-07
   75326 Paris Cedex 07, France

F.R.G.:

2. E. Merck
3. Dr. Theodor Schuchardt and Co.

Italy:

4. Farchemia di Martino Finotto and Co. S.a.S.
   32A via Bergamo
   24047 Treviglio, Italy.

Switzerland:

5. Fluka AG
   9476 Buchs, Switzerland

U.S.A.:

6. IMC chemical Goup Inc.
   P.O. Box 207
   Terre Haute, IN 47808, USA

F.R.G.:

7. Chemische Werke Lahr GmbH
   Lahr, FRG.

Manufacturers of Isoniazid

Argentina:

1. Lepetit, Av. Coronel Roca 6254
   Buenos Aires, Argentina.

2. C.I.A.

3. Gierrado Ramon

China:

4. China National Chemicals Import Export
   Corporation
   Erh-Li-Kou
   Hsichio, Peking, China.

France:

5. Rhone-Poulenc Industries S.A.
   21 Rue Jean Goujon
   75360 Paris Cedex 08, France

F.R.G.:

6. Bayer AG
   5090 Leverkusen, Bayerwerk, F.R.G.

7. Dr. Theodor Schuchardt and Co.
   Postfach 801 549
   8000 Munich 80, FRG

8. E. Merck, Darmstadt, FRG

India:

9. Biological Evans Ltd.
   18/1 and 18/3 Azamabad
   Hyderabad - 20, India

10. Chemo Pharma Labs.
    Plot No. CS-215
    Sewri, Bombay 4000015, India

11. Suneeta Labs Ltd.
    502 Arun Chambers
    J. Dadajee Road
    Bombay 400034, India.

12. Pfizer Ltd., P.O. Box 667
    Bombay 400001, India

13. Chemical Industrial and
    Pharmaceutical Labs Ltd.
    289 Ballasis Road
    Byculla, Bombay, India

Italy:

14. Carlo Erba S.p.A.
    Casella postale 3996
    20100 Milano, Italy.

15. Farmitalia - Societe Farmaceutici Italiani S.p.A.
Casella postale 3075
20100 Milano, Italy

16. Istituto Sieroterapico Milanese
Serafino Belfanti
20 Via Darwin
20 143, Milano, Italy

Japan:

17. Iwaki and Co. Ltd.
4-1 Nihonbashi Honcho
Chuo-ku, Tokyo 103, Japan

18. Takeda Chemical Industries
2-27 Doshomachi, Higashi-ku, Osaka 541, Japan.

19. Yuki Gosei Kogyu Co. Ltd.
Kanemasa Building, 2-11 Takara-cho
Chuo-ku, Tokyo 104, Japan

20. Hamasi Pharmaceuticals Industries
Yamaguchi Bldg., 2-19 Doshomachi
Higashiku, Osaka 541, Japan

Rumania:

21. Chimimport Export

Sweden:

22. A.B. Bofors
P.O. Box 800
S-69020 Bofors, Sweden

Switzerland:

23. F. Hoffmann-La Roche and Co.
CH 4000, Basle, Switzerland

U.S.A.:

24. Reilly Tar and Chemical Corp.
151 North Delaware St.
Indianapolis, IN 46204, USA

25. Pfizer International Inc.
235 East 42nd Street
New York 10017, U.S.A.

26. E.R. Squibb and Sons
P.O. Box 4000, Princetown
New Jersey, U.S.A.

27. Park Davis and Co.
P.O. Box 118, G.P.O. Detroit
MI 48232, U.S.A.

Manufacturers of Gamapicoline:

F.R.G.:

1. F. Merck, Darmstadt, FRG

2. Rasching GmbH
   100 Mundenheimerstrasse
   6700 Ludwigshafen, Rhein, FRG

3. Dr. Theodor Schuchardt and Co.

Italy:

4. Carlo Erba S.p.A., Milano

Japan:

5. Yuki Gosei Kogyo Co. Ltd.
   Kanemasa building
   2-11 Takara-cho
   Chuo-ku, Tokyo 104, Japan

6. Koei chemical Co. Ltd.
   2-40 Dosho-machi
   Higashi-ku, Osaka 541, Japan

U.K.:

7. Croda Synthetic Chemicals Ltd.
   Oldbury, Warley
   Worcs. B69 4HF, U.K.

U.S.A.:

8. Reilly Tar and Chemical Corp.

9. Union Carbide Corporation
   270 Park Avenue
   New York, NY 10017, USA

10. Nepera chemical Co. Inc.
    Route 17, Harriman
    N.Y.-10926, USA

11. Crowley Tar Products Co. Inc.
    261 Madison Avenue
    New York, N. Y. 10016, USA

Manufactueres of Hydrazine Hydrate

France:

1. Products chimiques Ugine-Kuhlmann
   B.P. 175-16
   75782 Paris Cedex 16, France

F.R.G.:

2. Bayer AG, Bayerwerk, FRG

Japan:

3. Japan Hydrazine Co. Ltd.
   Lino Bldg, 2-1-1 Uchisaimai-cho
   Chiyoda-ku, Tokyo-100, Japan

4. Mitsubishi Gas Chemical Co. Ltd.
   Mitsubishi Bldg.
   2-5-2 Marunouchi
   Chiyoda ku, Tokyo 100, Japan

5. Otsuka chemical Co. Ltd.
   10 Bungo-machi
   Higashi-ku, Osaka 540, Japan

6. Daiho Kagaku K.K.
   10 Minoue-cho
   Kita-ku, Osaka 530, Japan

7. Hikari kako Co. Ltd.
   1-134 Kitabukuro-cho
   Ohmiya City
   Saitama Pref. 330, Japan

8. Koei Kasei Kogyu K.K.
   141 Oaze Shinkai
   Urama city, Saitama Pref. 338, Japan

9. Nissin Denka Co. Ltd.
   Ichibashi Bldg.
   4-14-2, Nihonbashi Honcho
   Chuo-ku, Tokyo 103, Japan

10. Toyo Hydrazine Industry Co. Ltd.
    Sankyo Bldg.
    4-10-5 Ginza, Chuo-ku
    Tokyo 104, Japan

11. Albright and Wilson Ltd.
    Industrial Chemicals Div.
    P.O. Box 3, Oldbury
    Warley Worcs. B694NL, U.K.

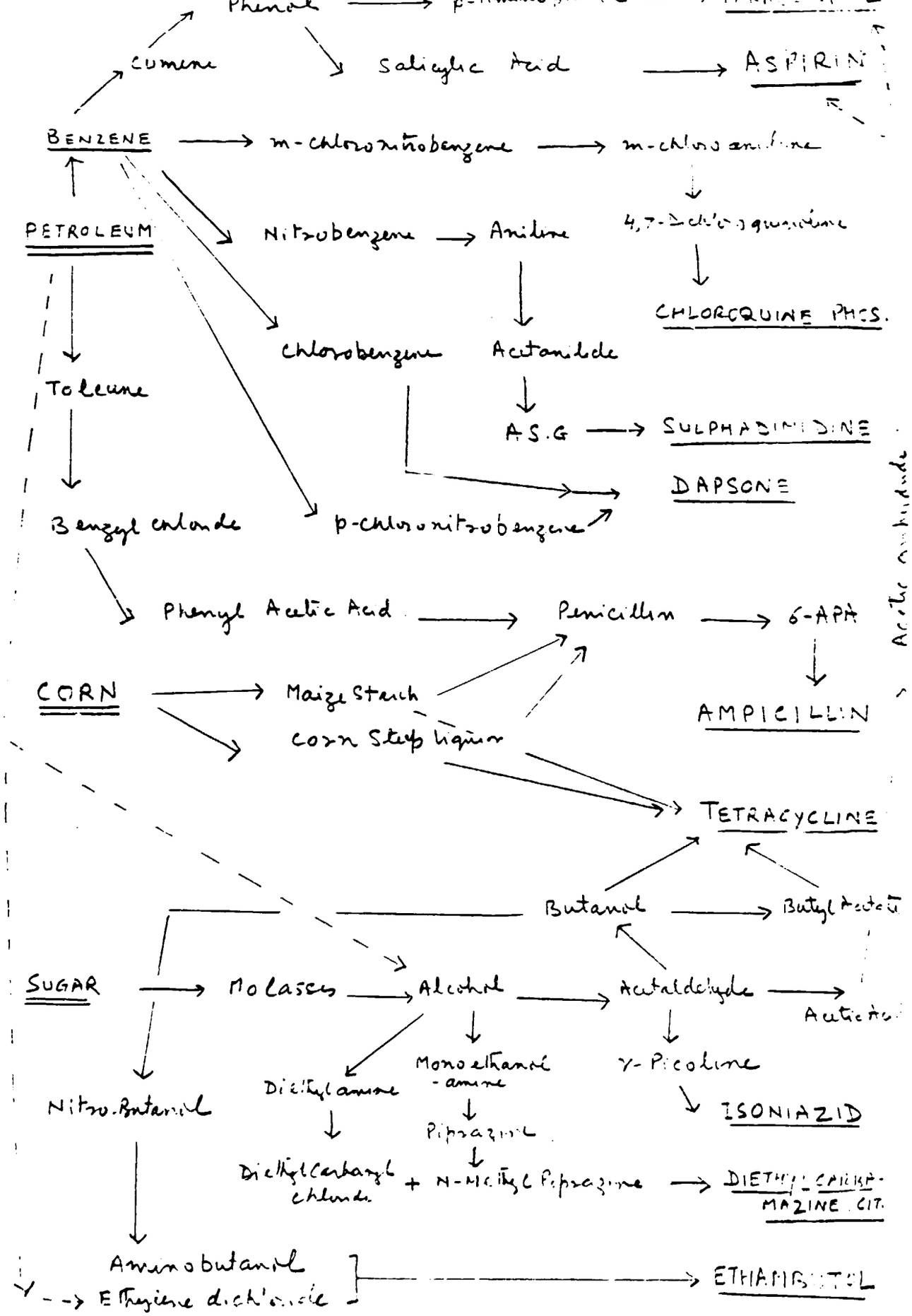
12. Fisons Limited
    Agrochemical Division
    Hauxton, Cambridge CB2 5HU
    U.K.

13. Imperial Chemical Industries
    Millbank, London SW1P 3JF, UK

14. May and Baker
    Dagenham, Essex RM10 7X5, UK

U.S.A.: 15. Olin Chemicals
    120 Long Ridge Road
    Stamford, CT 06904, U.S.A.

16. Hummel Chemical Co.
    P.O. Box 250
    South Plainfield, NJ 07080, U.S.A.


Phenol
p-Aminophenol
PARACETAMOL
Cumene
Salicylic Acid
ASPIRIN
BENZENE
m-Chloronitrobenzene
m-Chloroaniline
PETROLEUM
Nitrobenzene
Aniline
4,7-Dichloroquinoline
CHLOROQUINE PHOS.
Chlorobenzene
Acetanilide
Toluene
A.S.G
SULPHADIMIDINE
DAPSONE
Benzyl chloride
p-Chloronitrobenzene
Phenyl Acetic Acid
Penicillin
6-APA
CORN
Maize Starch
Corn Steep liquor
AMPICILLIN
TETRACYCLINE
Butanol
Butyl Acetate
SUGAR
Molasses
Alcohol
Acetaldehyde
Acetic Acid
Nitro-Butanol
Diethylamine
Monoethanol-amine
γ-Picoline
ISONIAZID
Piperazine
Diethyl Carbamyl chloride
+ N-Methyl Piperazine
DIETHYLCARBAMAZINE CIT.
Aminobutanol
--> Ethylene dichloride
ETHAMBUTOL
Acetic anhydride

Technical and economic analysis of the manufacture of 7 essential drugs.

1. Acetyl salicylic acid.

Acetyl salicylic is manufactured by acylation of salicylic acid with acetic anhydride at 50-60°C, followed by recrystallisation from aquous alcohol. The mother liquors are worked up for recovery of residual acetyl salicylic acid, acetic acid and salicylic acid. The consumption coefficients are given in Table I. It may be seen from this table that salicylic acid and acetic anhydride are the key intermediate/chemical for the production of acetyl salicylic acid. The cost of these two chemicals constitutes 74 to 75% portion of the cost of production of acetyl salicylic acid. The consumption of these two chemicals and their cost will play a vital role in the economics of the production. It may be seen from the Table that difference in the consumption of salicylic acid between the two manufactures is 0.11 per kg of anetyl salicylic acid. This will affect the production cost by 5 to 6%, depending on the cost of other inputs. For low value drugs like this, the cost of production is very sensitive to other factors like capacity of the plant, freight if the chemicals are imported, taxes levied on the imported goods and overheads. Salicylic acid, the key intermediate, is produced from phenol by reaction with sodium hydroxide which first gives sodium phenate. This under pressure at temperature of 170° to 190° C is cyclised in presence of carbon diaxide to give sodium salicylate. This is converted to salicylic acid and obtained by sublimation. Phenol is a common chemical, commercially produced from cumene which is produced from benzene.

2. It is recommended that production of acetyl salicylic acid should be taken using phenol as a starting material and minimum capacity of 1200 tonns per annum is considered economical size of the plant. However, acetylation of salicylic acid can be done at lower scales also, i.e. 15 to 20 tonns per annum.

3. Ampicillin

. Ampicillin Trihydrate, ampicillin anhydrons, sodium ampicillin and many other semi-synthetic penicillins are produced from 6-APA (Amino penicillic acid) which is obtained from Pot. Penicillin G, an antibiotic

produced by fermentation. Potassium benzyl penicillin is converted to Potassium benzyl penicillin dimethyl silyl ester with dimethyl dichloro silane, which is treated with phosphorous pentachloride to give imido chloride derivative. This on treatment with butanol and diethyl aniline gives dimethyl silyl imino ether derivative which on hydrolysis results into 6-APA. The method involves low temperature reactions and strict anhydrous conditions. 6-APA thus produced is isolated, purified and dried. The produce is used for the manufacture of number of semi-synthetic penicillins like ammoxacillin, cloxacillin, dicloxacillin, etc.

4. 6-APA is reacted first with triethyl amine to protect its free carboxylic acid group and then acylated with phenylglycine chloride hydrochloride. Ampicillin hydrochloride thus formed is isolated as napthyl sulphonic acid salt and then converted to ampicillin trihydrate. In one alternate process, Dane's salt of phenylglycine chloride is used for introduction of side chain.

5. 6-Amino penicillanic acid (6-APA) can also be produced by enzymatic conversion of Potassium benzyl penicillin. The technology is available with limited number of manufactures and involves methodology and equipment completely different from what is required for synthetic method.

6. The analysis of the process of manufacture and consumption of raw materials (Table II) indicates that the key raw materials are Potassium Benzyl penicillin, phenyl glycine chloride hydrochloride, dimethyl dichloro silane, dimethyl aniline and phosphorous penta chloride. The process requires low temperatures of -40° to -60° C which is generally achieved by the use of liquid nitrogen. The raw material cost input in the production of Ampicillin trihydrate is about 56% and the major share is of Potassium benzyl penicillin and phenyl glycine chloride hydrochloride. If the production is carried out from late stage of 6-APA then the raw material contribution to the cost of production is 70% mainly by 6APA and phenylglycine chloride hydro-chloride.

7. Potassium benzyl penicillin is produced by fermentation process using a selected penicillin producing strain. Spore inoculum is produced in the laboratory and checked carefully for freedom of contamination and then inoculated in seed tanks. The growth from the

seed tanks is inoculated in the main production fermentors containing sterilized nutrient medium. The production phase of penicillin is regulated by addition of selected feeds including the precursor phenyl acetic acid. The broth is harvested and filtered. The extraction of penicillin is carried out with the help of counter current extractor at a low temperature. Penicillin G is salted and dried. The important raw materials for production of penicillin are corn steep liquor, phenyl acetic acid, protein meal, ground nut oil and solvents like butyl acetate and butanol. Like all other antibiotics produced by fermentation, input cost of raw materials is around 45 to 50%. The consumption of utilities (steam, oxygen, compressed air, etc.) in production of antibiotics is quite high and input cost is around 20%.

8. It is recommended that the production of ampicillin should be carried out starting from Potassium benzyl penicillin and a plant of annual capacity of 30 to 40 tonns is considered economically viable. Semi-synthetic penicillins other than ampicillin can also be manufactured in the same plant. The production of ampicillin from 6-APA is more susceptible to the variation of cost on which 6-APA which is available from limited manufacturers.

9. Sulphadimidine. Acetyl acetone on condesnation with sulphaguanidine yields suphadimidine, which is isolated from unreated suphagnamidine. Sulphadimidine is converted to its sodium salt and treated with activated charcoal and further precipitated with hydrochloric acid to yield pharmaceutical grade product.

10. Sulphaguanidine is manufactured from acetanilide as starting material. (Table III). Acetanilide is reacted with chlorosulphonic acid to produce p-acetyl amino benzene sulphonyl chloride, which on treatment results into thamide. P-amino benzene sulphonamide is obtained by hydrosis of the amide and then condensed with guanyl urea to result in sulphaguanidine. Guanyl urea is produced from dicyandiamide.

11. The alternate technology for the production of sulphadimidine involves the use of acetanilide and chloro sulphonic acid. P-Acetyl amino benzene sulphonyl chloride thus produced is directly reacted with guanidine nitrate to give acetyl sulphaguanidine. This on condensation with acetyl acetone gives acetyl sulphadimidine which on subsequent hydro-

lysis gives sulphadimidine.

12. The two alternate technologies indicate that the key raw materials are acetanilide, acetyl acetone, guanidine nitrate, dicyandiamide, methyl isobutyl ketone and chlorosulphoric acid. The requirement would depend on the process being followed. P-Acetyl amino benzene sulphonyl chloride is also available commercially and can be used in place of acetanilide and chlorosulphonic acid thus avoiding one step which causes a lot of corrosion to the machinery and equipment.

13. The choice of process should depend on the requirement of sulphadimidine. For small requirements, a process starting from sulphaguanidine or p-Aminobenzene sulphonyl chloride is recommended. Annula plant capacity could be 20 to 25 tonns. For countries where the requirement is substantial, 100 T annual capacity plant is recommended utilizing the alternate technology making use of acetanilide, chlorosulphonic acid, acetyl acetone and methyl isobutyl ketone. This plant would require facilities for recovery of hydrochloric acid, recovery of solvents and neutralisation and effulent treatment. Again efficiency of the process will depend on the consumption of key raw materials and their cost. The raw material cost input is about 81.0% in the total cost of production.

14. Tetracycline. Tetracycline is produced by fermentation using a mutent of streptomyces aurofacines. The culture is transferred from flask to the seed tank having sterilized media. The time for seed cultivation in seed tank is 32-34 hours. The nutrient media for fermentor is prepared and sterilised and inoculated with the culture from the seed tank. The content of tetracycline by the end of fermentation is in the range of 15000 - 20,000 u/ml (depending on the type of strain). The fermented broth is transferred to the vessel where it is treated with oxalic acid and is cooled down. The treated broth is filtered and filtrate collected. It is precipitated with ammonia water and filtered. The cake is dried and then treated with butanol, oxalic acid, activated carbon and hydrochloric acid. It is filtered, crystallised and then centrifuged. This is then washed with butanol. The product is dried in vacuum rotary driers. It is understood that these are alternative processes for isolation from antibiotic to the filtered broth.

15. As may be seen from Table IV that the key raw materials are corn steep liquor, maize starch, dextrose, ground nut oil, benzyl thiocyanate and number of inorganic salts. It is important that these raw materials

are available in the country of production. Corn steep liquor gets deteriorated due to heat during transport and this plays an important role in the efficiency of production. This is followed by the cost of utilities which are around 20% of the cost of production. 100 T per annum plant is considered economically viable. The infrastructure required for antibiotic plant involves heavy capital investment.

16. Diethylcarbamazine. Diethyl carbamazine citrate is produced from piprazine hexahydrate. The first step involves the acylation of piprazine hexahydrate by diethyl carbamoyl chloride. Then N4-position is methylated by treatment with formaldehyde and formic acid to give diethyl carbamazine base. Treatment of purified base with an equimolar portion of citric acid yields the citrate. Diethyl carbanoyl chloride is produced from diethylamine and phosgene (Table V). The cost of raw material input is about 70% of the cost of production.

17. In an alternate process N-methyl piprazine is condensed with diethyl carbomyl chloride resulting 1-methyl-4-diethyl carbamoyl piprazine which on reaction with citric acid gives diethyl carbamazine citrate. The cost of raw material input is about 80% of the cost of production.

18. There is no difficulty in the availability of key raw materials for the production of this drug. Piprazine hexahydrate is manufactured on large scale either from monoethanol amine or ethylene diamine. Diethylamine is manufactured from ethanol and ammonia. Phosgene is available in cylinders. A 30 tonns per annum plant from piprazine hexahydrate and 10 tonns per annum plant from n-methul piprazine is recommended as an economic size unit. Diethyl carbamyl chloride is required in both the technologies and is produced using phosgene and diethylamine.

19. Dapsone. Dapsone (4,4-diamino-diphenyl sulphone) is either produced from p-chloro nitrobenzene or chlorobenzene. P-chloronitrobenzene is condensed with potassium xanthate to give dinitro diphenyl sulphide, which is oxidised to dinitro diphenyl sulphone. This product on subsequent catalytic reduction with Raney nickel and hydrogen gives dapsone (Table VI).

20. In the alternate process chlorosulphonation of chlorobenzene is followed by Friedel Crafts' reaction with another mole of chlorobenzene. This yields dichloro diphenyl sulphone which on ammonolysis gives dapsone.

21. The key raw materials are given in Table VII.

22. Chloroquine. The production of chloroquine phosphate involves a multiple step synthesis starting from basic chemicals like m-chloroaniline, ethoxy methylene malonic ester etc. (Table VII). M-Chloroaniline is reacted with ethoxy methylene malonic ester to yield m-chloro aniline-methylene, malonate. This on cyclisation, hydrolysis and decarboxylation followed by chlorination yields 4.7 - dichloroquinoline. The chloroquine base is prepared by condensation of 4,7 - dichloro quinoline with novaldiamine. This on treatment with phosphoric acid gives chloroquine diphosphate.

23. As may be seen from the Table VII, the key intermediates for this product are 4,7 dichloroquinoline or 4-hydroxy-7-chloroquinoline and novaldiamine. The manufacturers of dichloro and hydrochloroquinoline are the same who manufacture chloroquine phosphate/sulphate and for this reason there is difficulty in the availability of these intermediates at reasonable prices. These manufacturers prefer to sell chloroquine salts rather than the intermediates.

24. Novaldiamine is produced only by two companies. It is reported that one company in a developing country is likely to go into production of this item by end of 1982. The production of novaldiamine itself involves a lengthy chemical synthesis. Acetobutyxalactone is produced from ethylene oxide and aceto acetic ester. This on treatment with HCl gives acetopropylchloridehydrochloride which on condensation with diethylamine results into novalketone. This product on reductive aminolysis gives novaldiamine.

25. An analysis of consumption coefficients of raw materials (Table indicates that the key chemicals/raw materials are in-chloro aniline, ethoxy methylene malonic ester (alternately triethyl orthoformate and diethyl malonate which is produced from monochloro acetic acid) and novaldiamine. In two different processes the consumption coefficient of m-chloro aniline varies from 0.40 to 0.60 per unit of chloroquine phosphate produced. Similarly consumption coefficient of novaldiamine varies from 0.41 to 0.67 per

unit of finished drug. In case of consumption of ethoxy methylene malonate, the variation is 0.75 to 1.09. The high consumption of these 3 raw materials will upset the production cost. This is illustrated below.

Intermediate	Indicative Price per Kg of intermediate	Difference of consumption	Value US$
m-chloroaniline	12.00	0.20	2.40
Novaldiamine	20.88	0.26	5.43
E.M. Malonate	13.00	0.34	4.42

The high consumption of these 3 raw materials due to poor technology contributes to almost 25.7 percent of the total cost of production.

26. It is recommended to manufacture this product from the basic stage of m-chloro aniline. A plant with annual capacity of 80 to 100 tonns is considered economically viable.

27. Ethambutol. D-2 aminobutanol is reacted with ehtylene dichloride in presence of a base to get ethambutol, which is subsequently converted into its hydrochloride. Ethylene dichloride is a common chemical and is easily available. However D-2-aminobutanol is available from limited sources. The raw material cost input in the total cost of production is about 80%. Starting from D-2 aminobutanol plant of annual capacity of 8 to 10 tonns is economically viable.

28. Isoniazid. The production of Isoniazid (I.N.H.) involves oxidation of gamma picoline to isonicotinic acid, estrification of sionicotinic acid and conversion of ester to isoniazid by reacting with hydrazine hydrate. Different methods of oxidation are used at the first stage using different oxidising agent. In one of the methods potassium permanganate is used as oxidising agent and manganese dioxide is recovered. The recovery of manganese dioxide plays an important factor for cost of production in this method. In another method nitric acid is used as an oxidizing agent.

29. An alternative process for the production of isoniazid makes use of 4-cyanopyridine as a starting material, which on hydrolysis gives isonicotinic acid, followed by estrification with reaction with hydrazine hydrate.

30. The key raw materials (Table IX) for isoniazid are gamma picoline or 4-cyanopyridine, potassium permanganate, nitric acid and hydrazine hydrate depending on the process followed. The raw material cost input to the total cost of production is 63.5%. Plants with annual capacity of 10 to 30 tonns are considered economically viable.

Tables I to IX - Appendix III

Major raw materials required for manufacture of 9 essential drugs from illustrative list of UNIDO

I. Acetyl Salicylic Acid

S No.	Raw material	cons. coeff. company A	cons. coeff. company B
1	Salicylic Acid	0.88	0.77
2	Acetic anhydride	0.78	1.16
3	Caustic soda	0.50	0.60

II. Ampicilline Trihydrate

S No.	Raw material	cons. coeff. company A	cons. coeff. company B	cons. coeff company C
1.	6-APA	0.80	0.74	0.68
2.	Phenyl Glycine Chloride Hcl	-	-	0.66
3.	Phenyl glycine Dane's Salt	1.10	1.08	-
4.	Dimethyl dichloro-silane	N.A.	N.A.	0.53
5.	Methylene chloride	7.90	7.77	4.19
6.	Ehtyl chloroformate	0.51	0.43	N.A.
7.	Triethylamine	0.50	0.36	N.A.
8.	Liquid Nitrogen	N.A.	22.00	N.A.

III.a. Sulphadimidine via guanidine nitrate route

SNo.	Raw material	cons. coefficient of company A	cons. coefficient of company B
1.	Acetanilide	1.24	1.29
2.	Chlorosulphoric acid	4.50	4.97
3.	Guanidine Nitrate	0.96	0.88
4.	Acetyl acetone	0.80	0.56
5.	Methyl isobutyl ketone	1.60	1.00

IIIb. Sulphadimidine via Dicyandiamide route

SNo.	Raw material	cons. coefficient
1.	Acetanilide	1.81
2.	Chlorosulphonic acid	6.84
3.	Dicyandiamide	1.03
4.	Acetyl acetone	0.48

IIIc. Sulphaguanidine via dicyandiamide route

SNo.	Raw material	cons. coefficient
1.	Acetanilide	1.89
2.	Chlorosulphonic acid	7.13
3.	Dicyandiamide	1.08

IV. Tetracycline

SNo.	Raw material	cons. coefficient
1.	Corn steep liqour	3.07
2.	Maize starch	16.80
3.	Ground nut oil	4.20
4.	Calcium carbonate	2.03
5.	Butanol	3.55
6.	Oxalic acid	4.41
7.	Ammonium Nitrate	0.12
8.	Ammonium sulphate	2.26
9.	Benzyl thiocyanate	0.0003
10.	Mangenese sulphate	0.19
11.	Pot. Dihydrogenphasphate	0.013
12.	Sodium Hydroxide	0.10
13.	Ammonia	2.0
14.	Amylase	0.02

15.	Charcoal	0.194
16.	Hydrochloric Acid	0.41
17.	Acetone	1.69
18.	Magnesium sulphate	0.19

V.a. Diethyl carbamazine citrate

S.No.	Raw material	cons coeff.
1.	N-Methyl piprazine	0.30
2.	Diethylamine	0.51
3.	Citric acid	0.64
4.	Phosgene	0.85

V.b. Diethyl Carbamazine citrate starting from Piprazine hexahydrate

S.No.	Raw material	cons. coeff.
1.	Piprazine hexahydrate	1.41
2.	Acetone	9.20
3.	Benzoyl chloride	1.31
4.	Diethyl carbamyl chloride	0.67
5.	Citric acid	0.71
6.	Formalin (40%)	0.68
7.	Formic acid	0.61
8.	Hydrochloric acid	1.60
9.	Toluene	2.94
10.	Sodium Hydroxide	2.03

V.c. Diethyl Carbamyl chloride

S.No.	Raw material	cons. coeff.
1.	Diethyl amine	1.28
2.	Dichloro ethane	2.33
3.	Calcium chloride (anhydrons)	0.05
4.	Phosgene	1.15
5.	Caustic soda lye	0.45
6.	Ammonia	0.04

VIa Dapsone starting from p-Nitrochlorobenzene

S No.	Raw material	cons. coefficient
1.	p-Nitrochlorobenzene	2.50
2.	Carbon disulphide	1.50
3.	Pot. Hydroxide	1.40
4.	Ethyl alcohol	1.00
5.	Acetic acid	1.66
6.	Raney Nickel	0.07
7.	Chlorine	1.50
8.	Hydrogen	0.25

VIb Dapsone starting from chlorobenzene

S No.	Raw material	cons. coefficient
1.	Chlorobenzene	2.60
2.	Chlorosulphonic acid	2.20
3.	Aluminium chloride	2.00
4.	Hydrochloric Acid	1.00
5.	Ammonium Hydroxide	1.04
6.	Copper sulphate	0.175
7.	Activated Carbon	0.45

VII. Chloroquine Phosphate

S No.	Raw material	cons. coeff. of company A	cons.coeff. of company B	cons.coeff of comp.C
1.	m-chloroaniline	0.60	0.54	0.42
2.	Novaldiamine	0.67	0.48	0.44
3.	Ethoxy methylene malonic ester	1.09		0.78
4.	Triethyl orthoformate	-	0.67	-
5.	Monochloro acetic acid	-	0.66	-
6.	Sodium cyanide	-	0.25	-
7.	Ab. Ethyl alcohol	-	1.65	-
8.	Phosphoric acid	0.66	0.66	0.58
9.	Methanol	1.52	1.27	1.00
10.	Toluene	-	0.80	0.85
11.	Kerosene	0.56	-	-

VIII. Ethambutal

S.No.	Raw material	cons.coeff. of comp. A	cons coeff. of comp. B	cons. coeff. of comp. C
1.	D-2-Aminobutanol	1.10	0.90	0.85
2.	Isoprapanol	4.48	6.75	3.0
3.	Ethylene dichloride	0.45	0.45	0.45
4.	Sulphuric acid	2.69	2.10	N.A.
5.	Caustic soda flakes	0.38	0.38	0.2
6.	Hydrochloric Acid gas	-	-	-

IX.a. Isoniazide from Gamma-Picaline

S.No.	Raw material	cons. coeff. of comp. A	cons. coeff. of comp. B	cons.coeff. of comp. C
1.	Gamma-Picoline	1.00	0.89	1.08
2.	Pot. Permanganate	4.00	N.A.	N.A.
3.	Hydrazine Hydrate (80%)	0.43	2.26	0.53
4.	Methyl alcohol	1.25	N.A.	1.82
5.	Ammonia 25%	0.99	N.A.	0.70

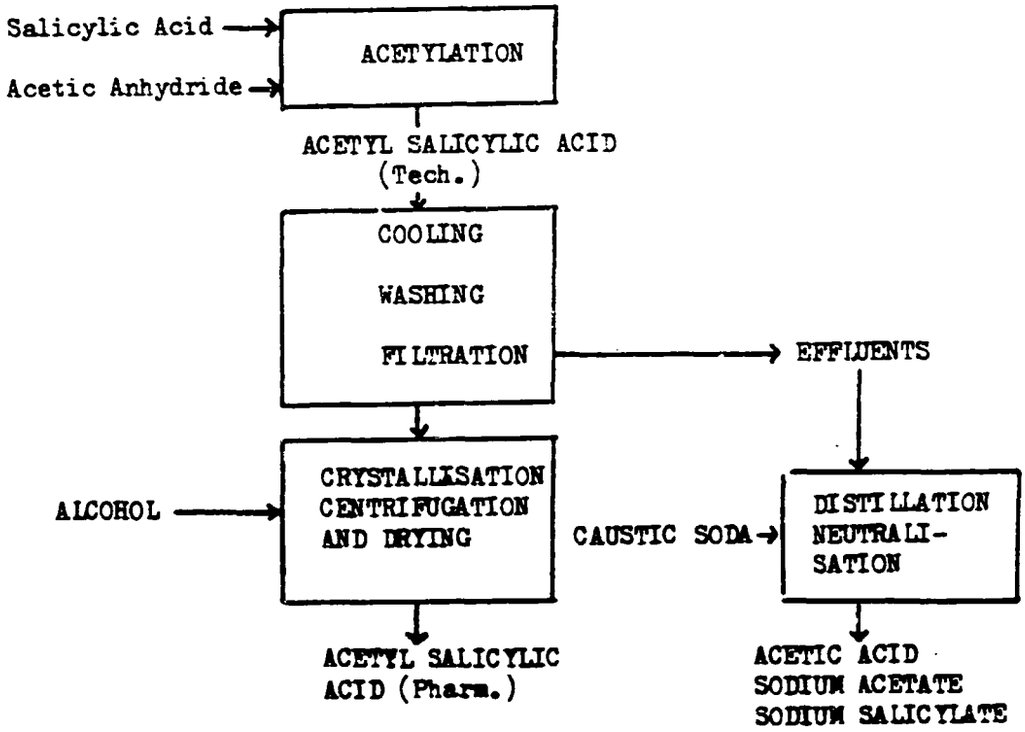
IX.b. Isoniazide from 4-cyano-pyridine

S.No.	Raw material	cons.coeff.
1.	4-cyanopyridine	1.20
2.	Resin IRA-402	0.20
3.	Ethanol	1.60
4.	Hydrazine Hydrate (80%)	0.55

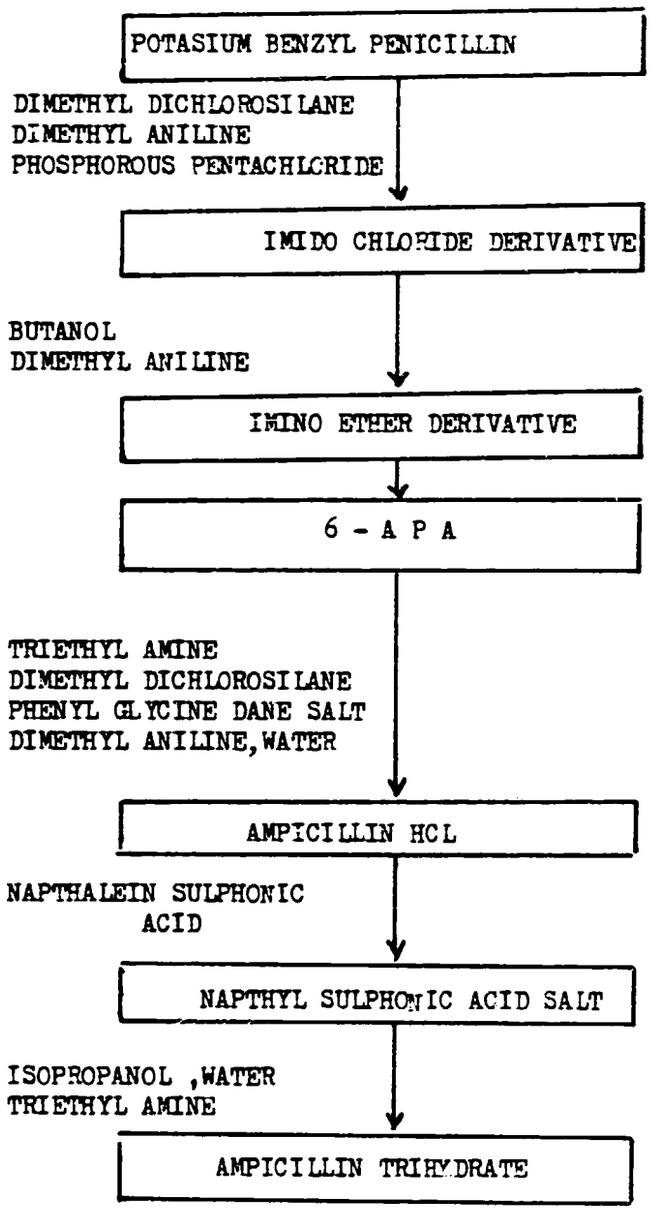
Flow sheets 1 to 9 - Appendix III

Process/Chemical Flow sheets for 9 essential drugs from illustrative list of UNIDO

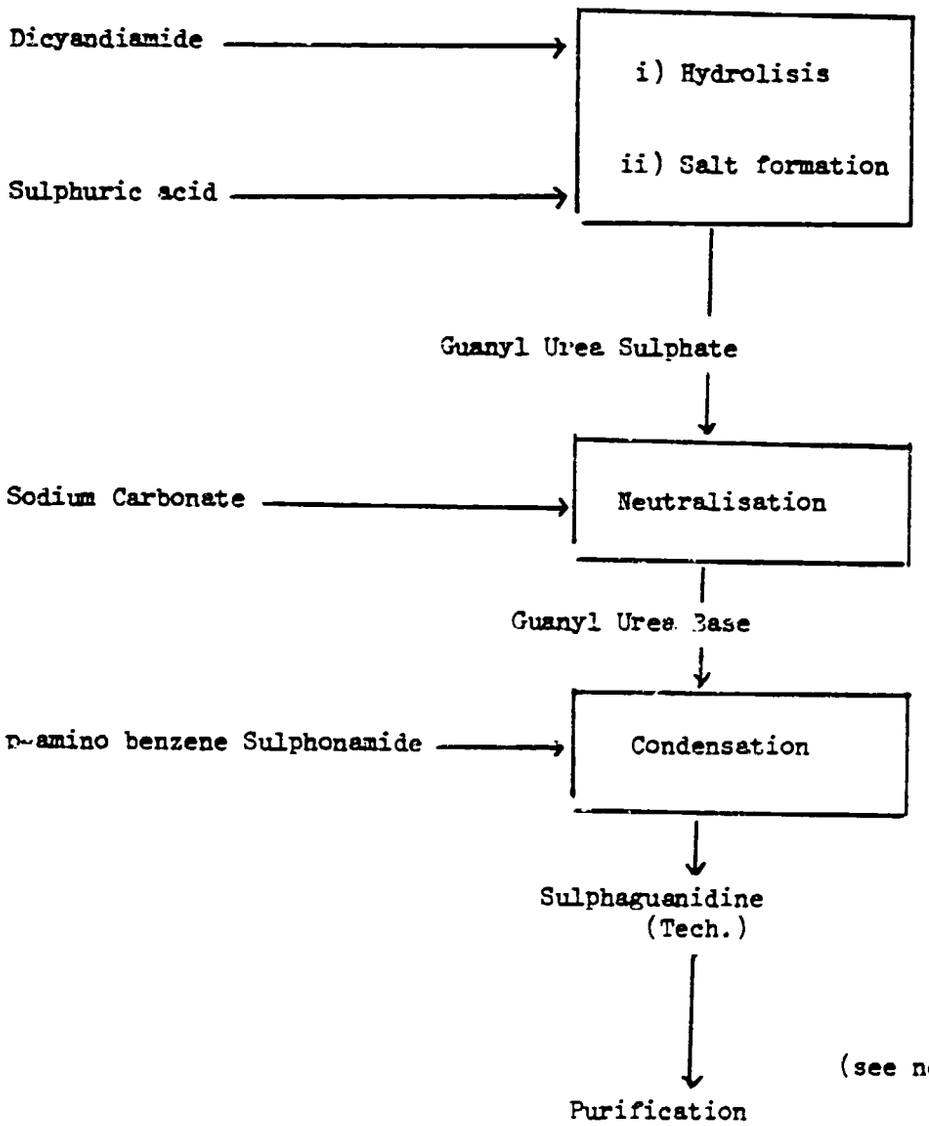
1. Acetyl Salicylic Acid



2. Ampicillin Tryhydrate

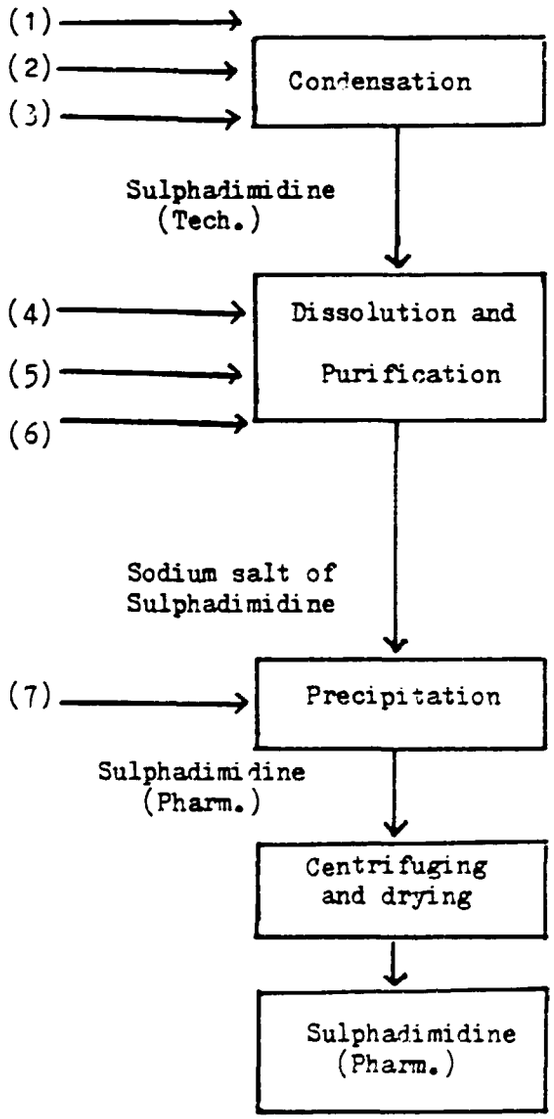


3. Sulphadimidine



(see next page)

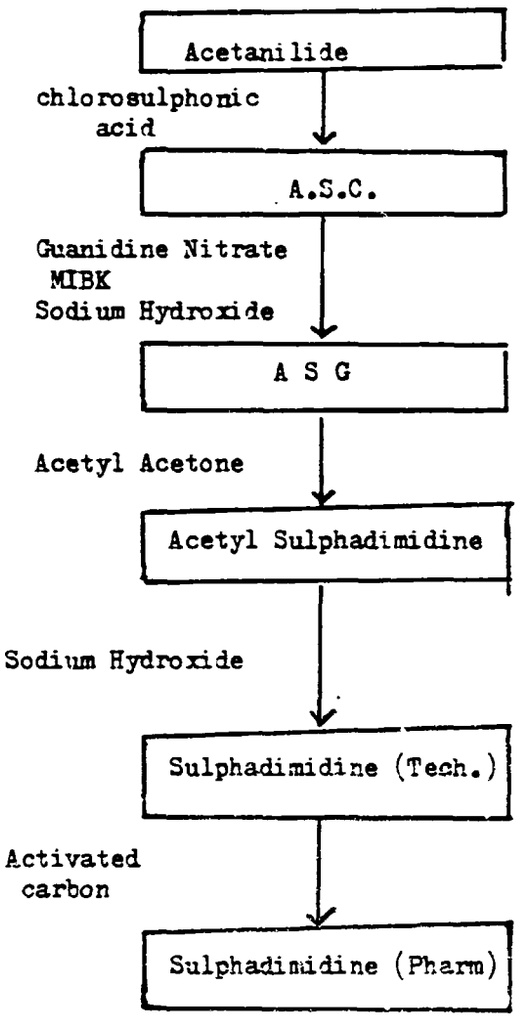
Sulphadimidine (contd from pre. page)



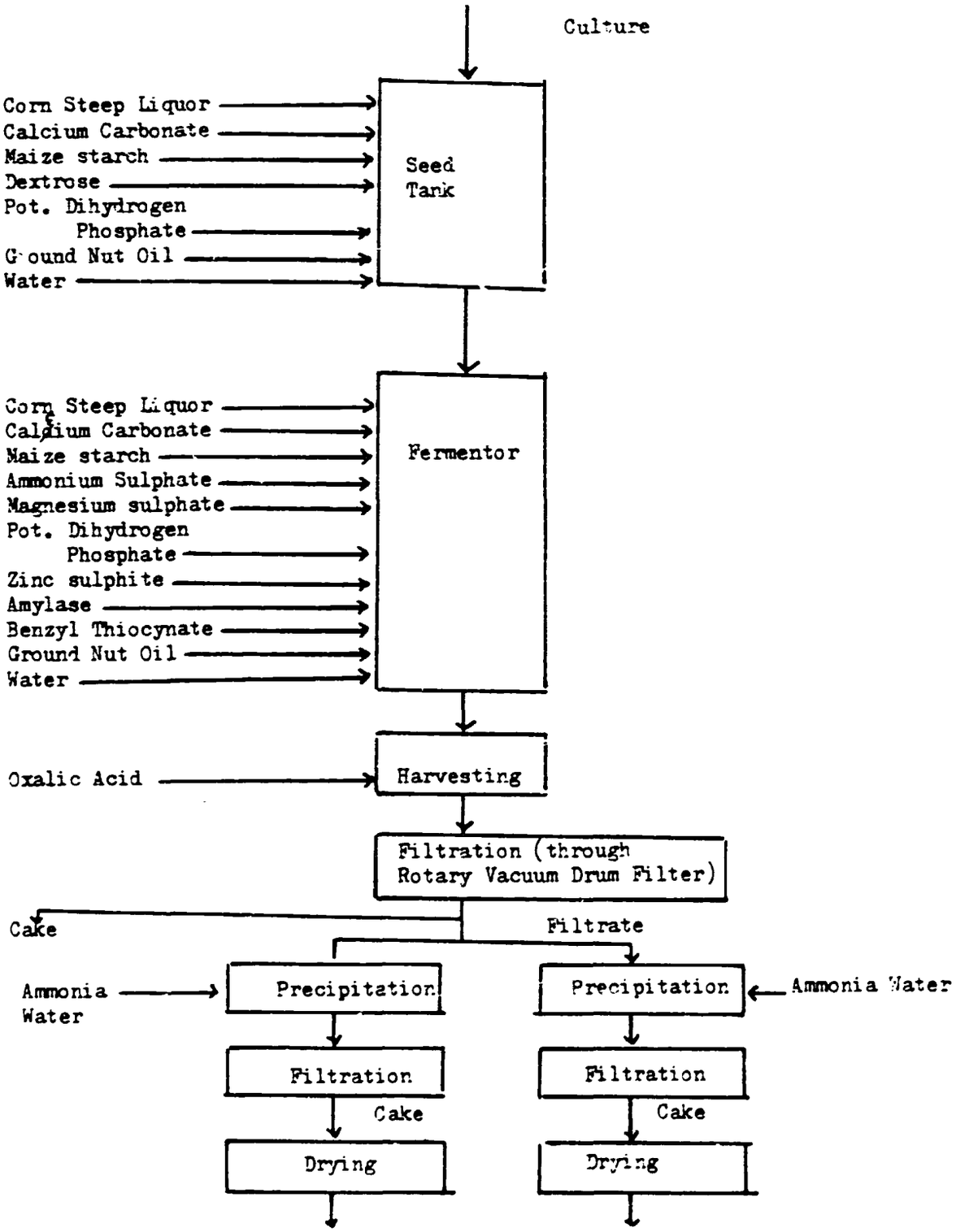
Raw-materials

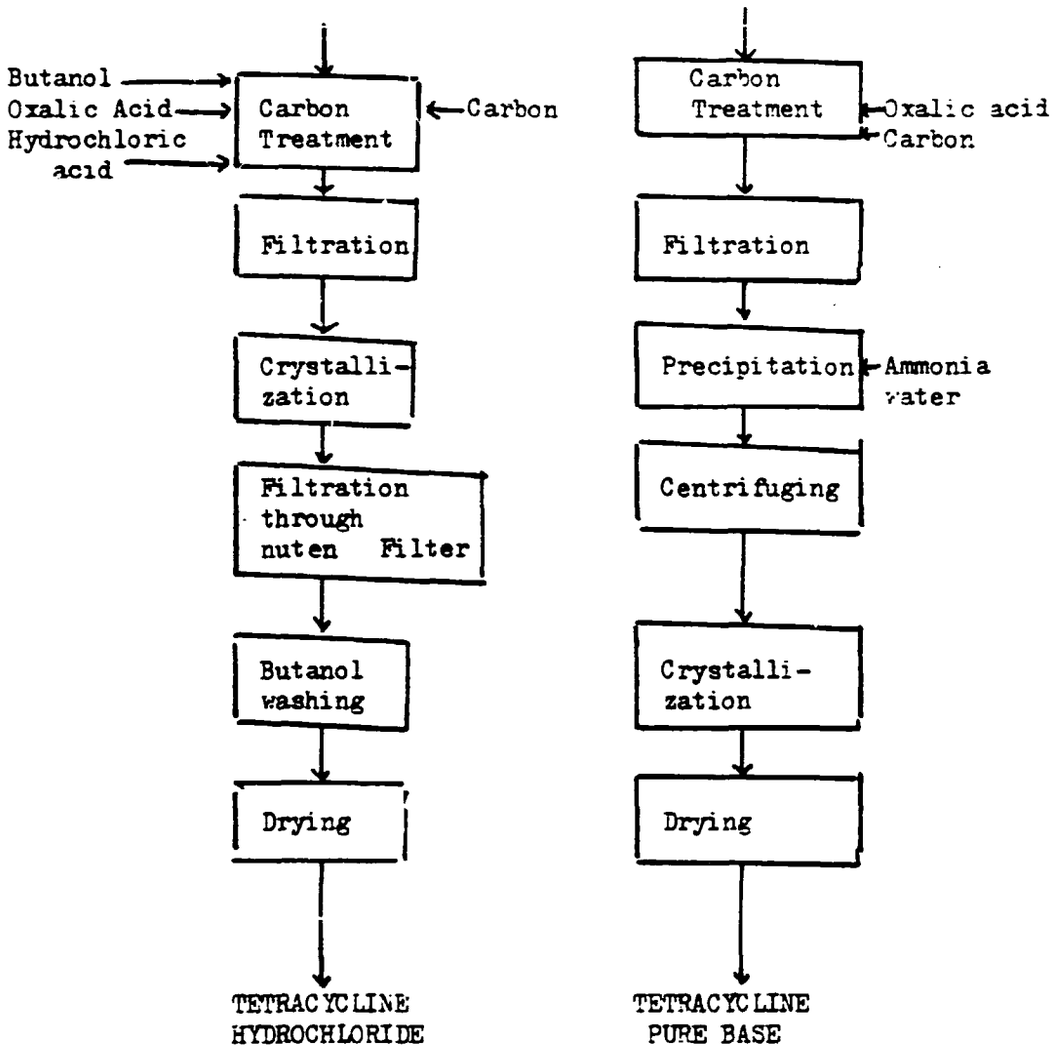
1. Sulphaguanidine
2. Acetyl Acetone
3. Acetic Acid
4. Sodium hydroxide
5. Hydrochloric acid
6. Activated carbon
7. Sodium hydrosulfite

Sulphadimidine (alternate process)

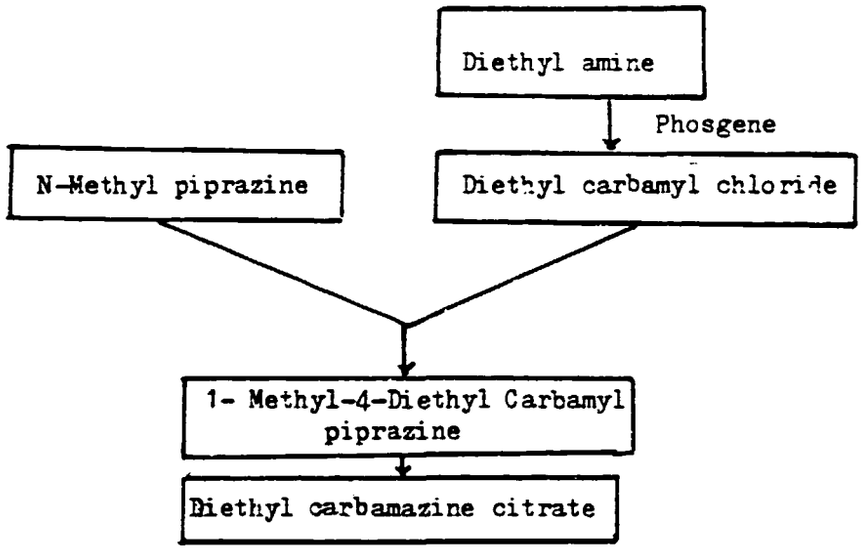


4. Tetracycline

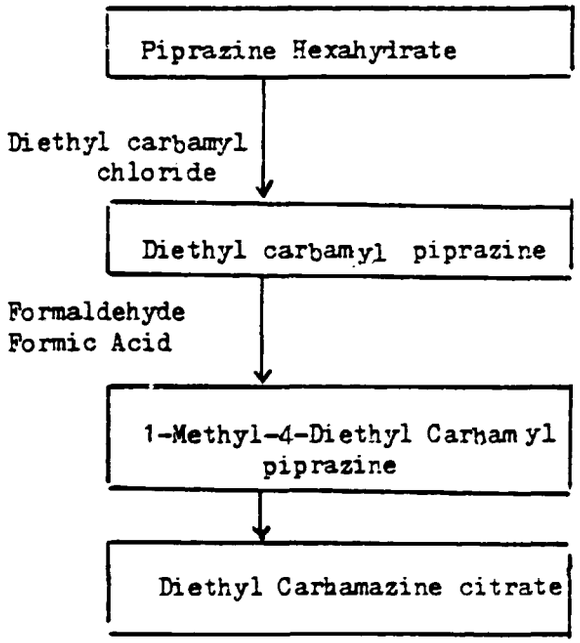



Butanol
Oxalic Acid
Hydrochloric acid
Carbon Treatment
Carbon
Filtration
Crystalli-zation
Filtration through nuten Filter
Butanol washing
Drying
TETRACYCLINE HYDROCHLORIDE
Carbon Treatment
Oxalic acid
Carbon
Filtration
Precipitation
Ammonia water
Centrifuging
Crystalli-zation
Drying
TETRACYCLINE PURE BASE

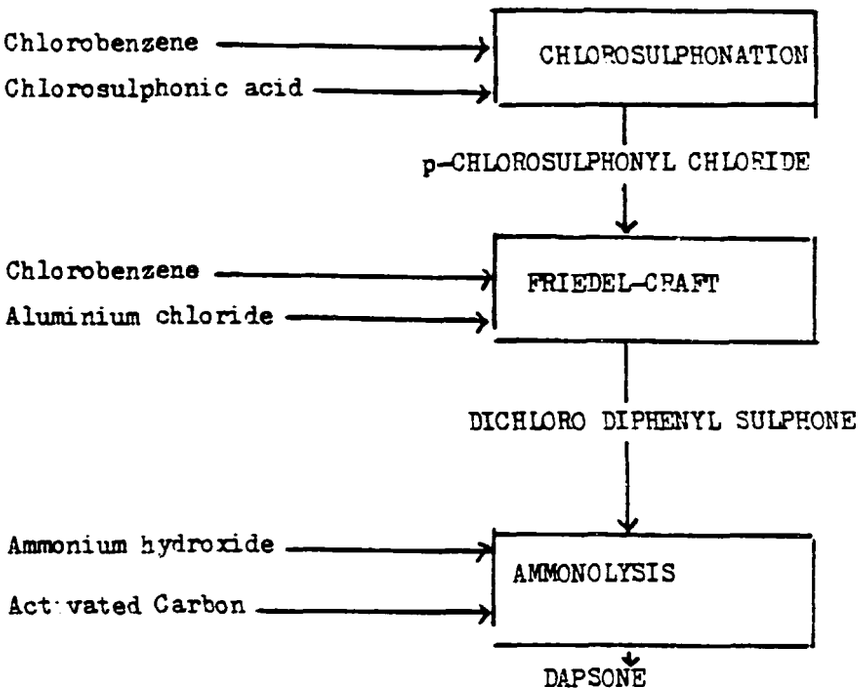
5. Diethyl carbamazine citrate



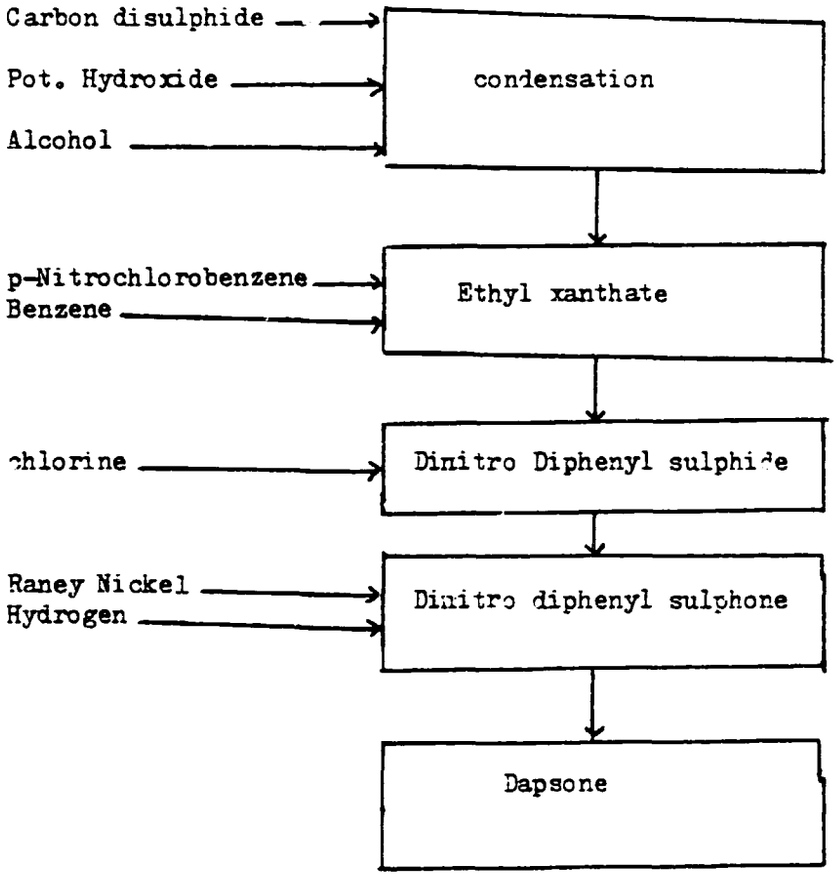
Alternate process



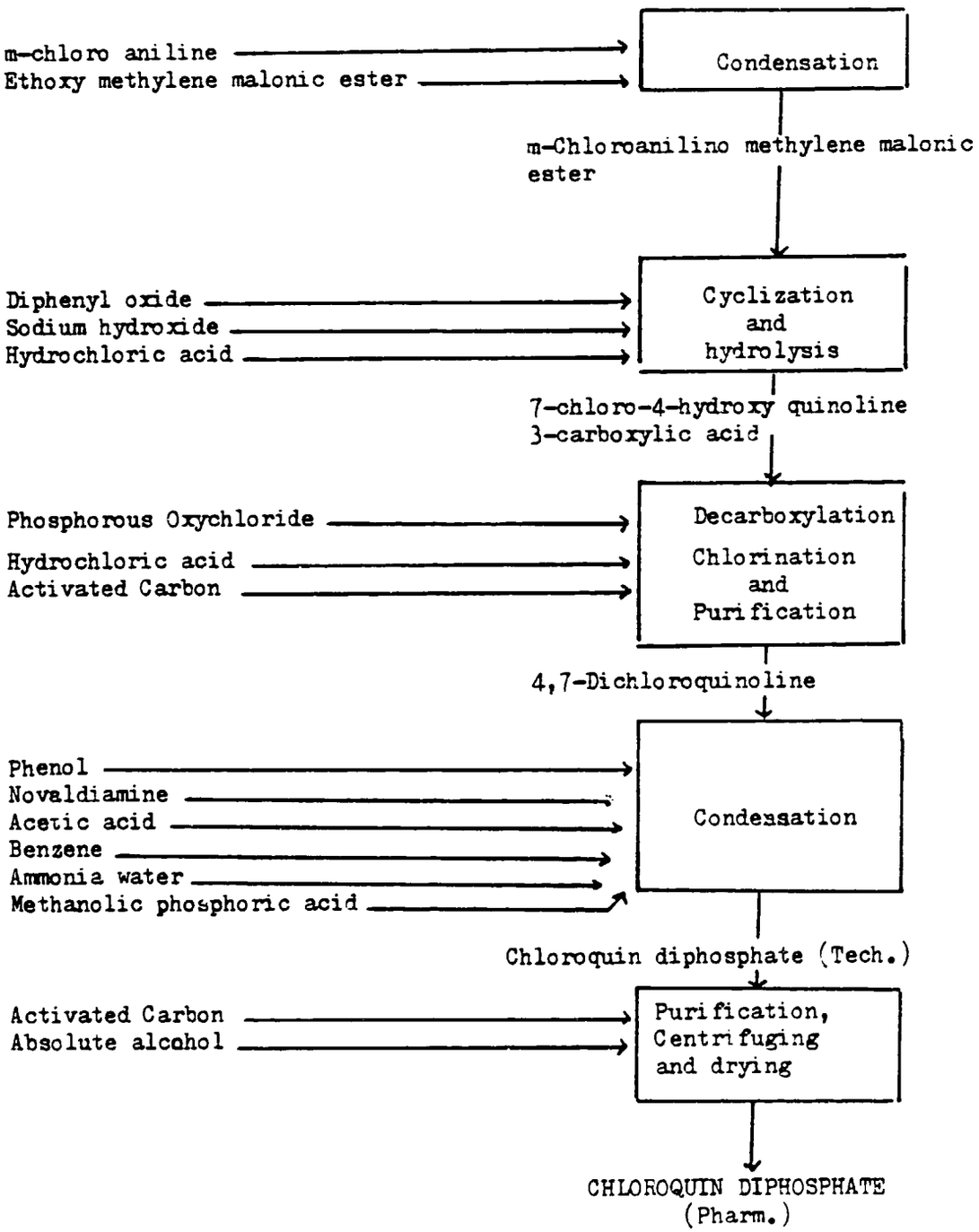
6. Dapsone


Chlorobenzene
Chlorosulphonic acid
CHLOROSULPHONATION
p-CHLOROSULPHONYL CHLORIDE
Chlorobenzene
Aluminium chloride
FRIEDEL-CRAFT
DICHLORO DIPHENYL SULPHONE
Ammonium hydroxide
Activated Carbon
AMMONOLYSIS
DAPSONE

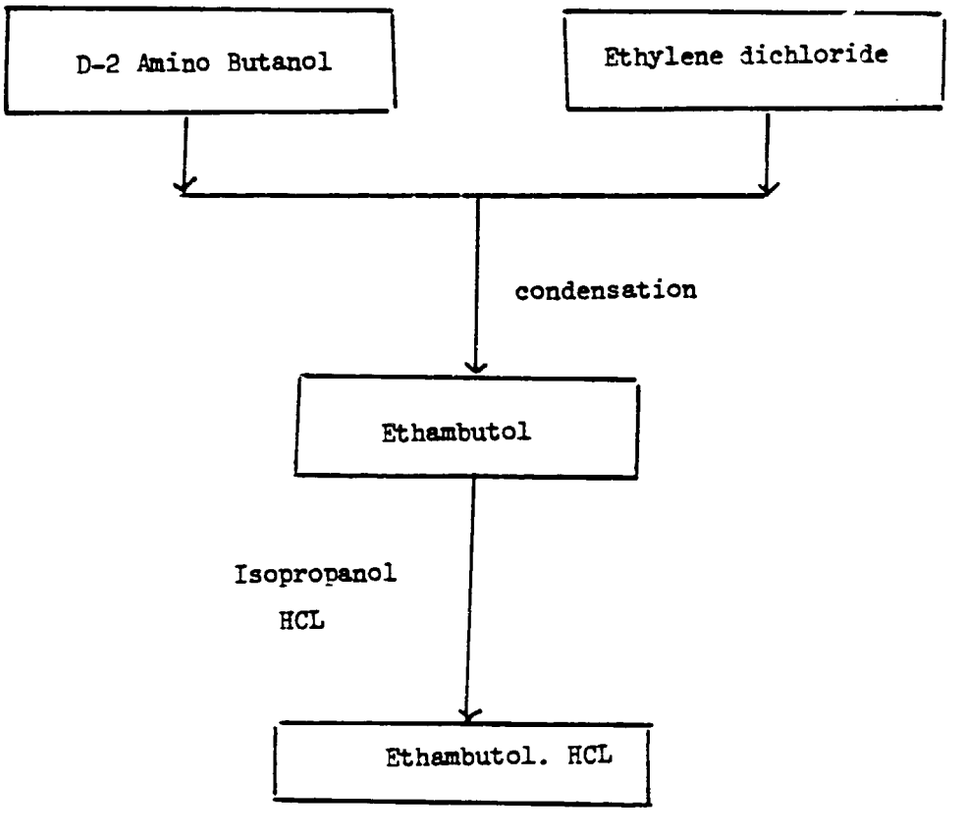
Dapsone (alternate process)



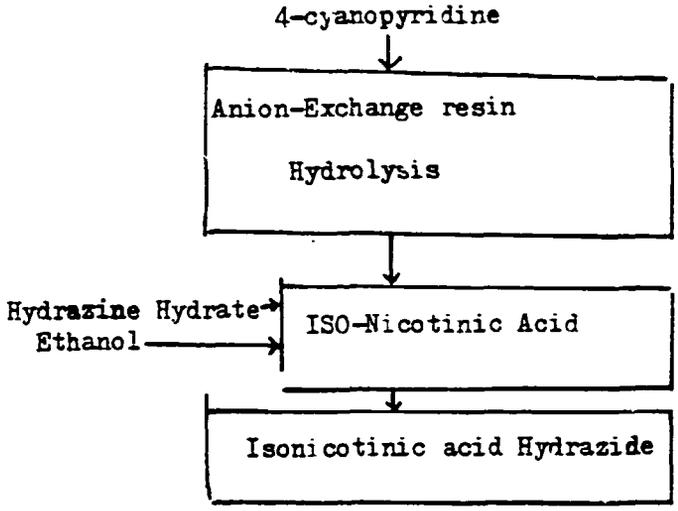
7. Chloroquine Phosphate



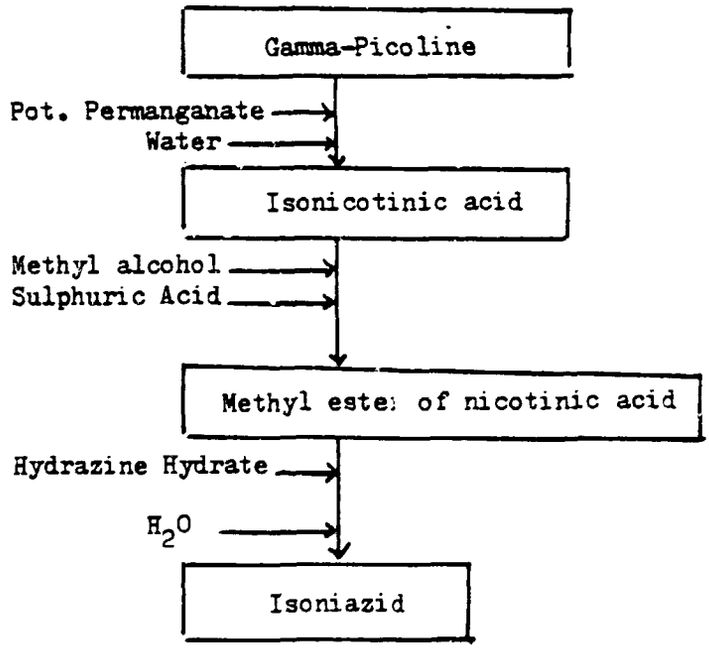
8. Ethambutol



9. Isoniazid



Isoniazide (alternate process)



Note: In another alternative process, first step oxidation of Gamma-Picoline is carried out by mixture of Nitric acid and sulphuric acid.

Elements of cost of manufacture of bulk drugs

The production cost of a drug depends on various inputs and these cost elements are given below.

i) Raw materials	a) Indigenous
	b) Imported
ii) Wages	a) Direct
	b) Supervisory
	c) Laboratory
iii) Services/utilities	a) Steam
	b) Power
	c) Water-normal temp
	d) Water - cooled to $5^{o}/10^{o}C$
	e) Brine (-) $5^{o}C$
	f) Compressed air
	g) Inert gas
	h) Liquid nitrogen
	i) Any other
iv) Repairs and Maintenance	a) Wages
	b) Stores
	c) Workshop expenses
v) Overheads	a) Administrative
	b) Quality control
	c) R and D (Process Development only)
	d) Stores and Purchase
	e) Effulent treatment,etc
	f) Safety, first aid and fire fighting
	g) Social - canteen, creche, etc.
	h) Royalties
vi) Depreciation	a) Equipment and machinery
	b) Building
vii) Interest	a) Fixed capital
	b) Working capital

Appendix V

Analysis of cost of production of bulk drugs involving chemical synthesis

Cost element / Product code								
Drug type	AS	DC	DC	ET	ET	IN	IN	SD
Raw materials	76.32	79.95	67.85	74.32	81.00	69.40	66.35	80.69
Wages	3.11	a	a	a	2.70	6.23	6.77	1.71
Utilities	1.24	1.68	2.74	1.94	1.86	7.70	5.41	5.24
Rep. and Main.	3.11	a	a	a	1.31	2.25	2.98	0.92
Overheads	10.22	16.68	26.84	23.72	9.35	12.02	12.97	5.12
Depreciation	2.80	1.50	1.10	a	1.13	2.40	5.48	2.36
Interest	3.17	0.17	1.46	a	2.06	a	a	3.95
	99.97	99.98	99.99	99.98	99.96	100.00	99.96	99.99

Note: a separate data not available, cost element included in overheads

Average cost input of raw materials 74.48%

Production status of 9 essential bulk drugs in developing countries and countries with centrally planned economies

Drugs	Countries
1. Acetyl salicylic Acid	Argentina, Brazil, China, Colombia Czechoslovakia, G.D.R., India, Mexico, Turkey, Yugoslavia.
2. Ampicillin:	Argentina, Brazil, India, Israel, Mexico, South Korea, Portugal, Peru, Singapore, Spain, Turkey.
3. Sulphadimidin:	Bulgaria, China, Egypt, Hungary, India, Israel, Mexico, Poland, U.S.S.R.
4. Tetracycline:	Argentina, Brazil, China, India, South Korea, Mexico, Spain, U.S.S.R.
5. Diethyl Carbamazine:	India, U.S.S.R.
6. Dapsone:	China, India, U.S.S.R.
7. Chloroquine:	Bangladesh, China, Hungary, India
8. Ethambutal:	Brazil, Hungary, India, Venezuela
9. Isoniazid:	Argentina, China, India, U.S.S.R.

Technologies available for transfer for the manufacture of 9 priority drugs.

Drug	Country from which technology is available
1. Acetyl Salicylic Acid.	Egypt, Poland, Romania*
2. Ampicillin	India, Portugal, South Korea, Turkey Romania.*
3. Sulphadimidine	Egypt, China*, India, Poland, U.S.S.R.*
4. Tetracycline	India, Portugal, France.
5. Diethyl Carbamazine	India, U.S.S.R.*, France, Sweden
6. Dapsone	U.S.S.R.*
7. Chloroquine	
8. Ethambutol	India
9. Isoniazid	India, Switzerland, U.S.A., U.S.S.R.*, Romania*, China*.

*Information provided during the First Consultation Meeting.