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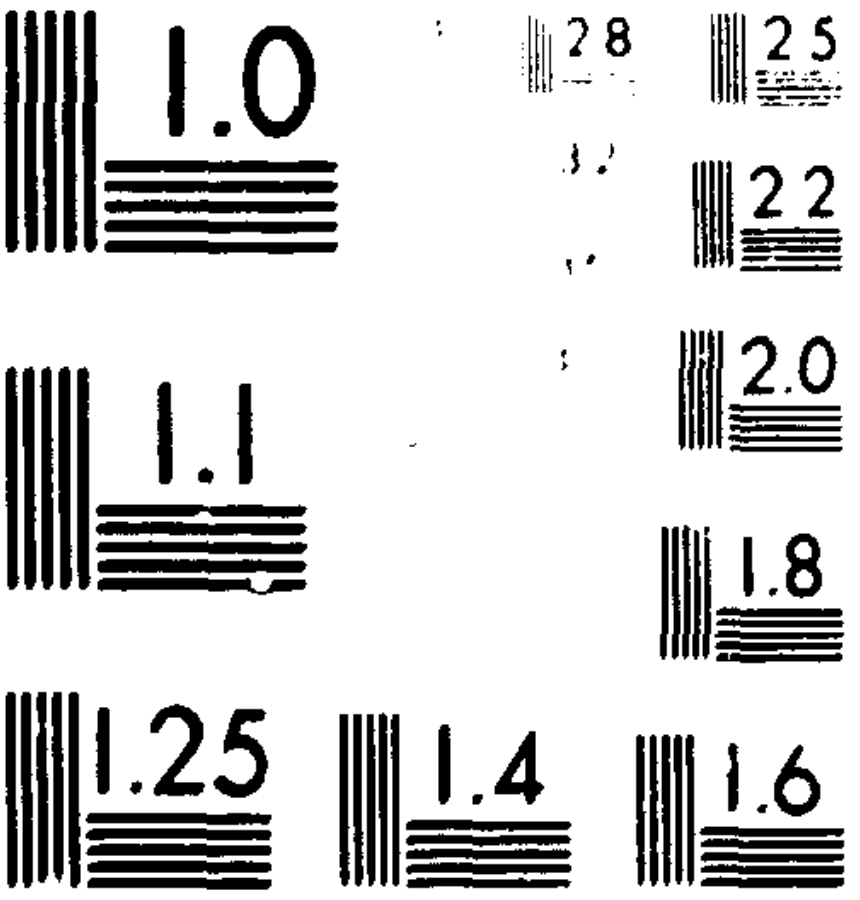

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Meeting of the Committee of
Experts on Pharmaceuticals
Paris, 11-13 October 1982

AVAILABILITY, PRICING AND TECHNOLOGY OF ESSENTIAL DRUGS AND THEIR INTERMEDIATES *

prepared by
the UNIDO secretariat

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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 aim of raising the former's share in the world industrial output through increased international co-operation.[1/] The General Assembly endorsed the above recommendations at its Seventh Special Session in September 1975 and decided that the System of Consultations should be established at global, regional, interregional and sectoral levels,[2/] and that UNIDO, at the request of the countries concerned, should provide a forum for the negotiation of agreements in the field of industry between developed and developing countries and among developing countries themselves.

2. The System of Consultations has been established under the guidance of the Industrial Development Board. The Board at its fourteenth session in 1980 decided to establish the System of Consultations 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;[3/]

b) Consultations would also permit negotiations among interested parties at their request, at the same time as or after consultations;[4/]

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;[5/]

1/ Report of the Second General Conference of the United Nations Industrial Development Organization (ID/CONF.3/31), Chapter IV, "The Lima Declaration and Plan of Action on Industrial Development and Co-operation", para. 66.

2/ Official Records of the General Assembly, Seventh Special Session, Supplement No. 1, para. 3.

3/ Ibid, Thirty-fifth Session, Supplement No. 16, para. 151(a).

4/ Ibid, para. 151(b).

5/ Ibid. para. 152.

d) Final reports of the consultations should include such conclusions and recommendations as agreed upon by consensus by the participants as well as others significant views expressed during the discussions.6/

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. Through these meetings UNIDO Secretariat identified the issues that might be suitable for consultations on this industry. The Global Preparatory Meeting, held in April 1980, recommended that the First Consultation Meeting on the Pharmaceutical Industry should consider the following three issues:

- The Pricing and availability of intermediates and bulk drugs;
- Contractual arrangements for the production of drugs;
- The availability, terms and conditions for the transfer of technology for the manufacture of essential drugs included in the illustrative list prepared by UNIDO in consultation with WHO.

4. The First Consultation on the Pharmaceutical Industry was convened in December 1980.7/ The conclusions and recommendations of the First Consultation on the three issues were as follows:

Issue I The pricing and availability of intermediates and drugs

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.

6/ Ibid, Thirty-second Session, Supplement No. 16, para. 163.

7/ See Report of the Meeting (ID/254).

(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 Contractual arrangements for the production of drugs

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 availability, terms and conditions for the transfer of technology for the manufacture of essential drugs

(a) The 26 essential drugs identified by UNIDO and essential and well-defined products based on medicinal plants constitute an illustrative 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.

There was a consensus on entrusting UNIDO with the preparation of a directory of sources of supply of essential drugs from both developing and developed countries.

5. As a follow-up of the First Consultation, UNIDO convened a Round Table Meeting on the Pharmaceutical Industry in Mohammedia, Morocco in December 1981[8/] and the following are amongst the recommendations of that meeting:

(a) The committee of experts to be set up in line with the recommendation of the First Consultation should pay particular attention to intermediates for which there are only limited sources of supply with a view to improve their economic availability at mutually acceptable terms and conditions, so as to assist the developing countries in the successful production of bulk drugs.

(b) In addition, the committee should pay special attention to those bulk drugs for which there are only limited sources of supply.

(c) The UNIDO should invite representatives for participation in the committees most of those manufacturers of intermediates and bulk drugs for which there are only limited sources of supply.

(d) UNIDO should prepare a directory with names of manufacturers and suppliers of the 26 essential drugs and their intermediates with details and specifications. Whenever requested by a developing country to provide information on indicative prices for those essential drugs, UNIDO will use its best endeavours to do so. The directory may also include similar information on additional essential drugs needed by developing countries. The directory should be updated periodically.

8/ See Report of the meeting UNIDO/PC.33, 1982

(e) The panel of experts to be convened by UNIDO should pay particular attention to the preparation of terms and conditions, variations thereof and background notes relating to agreements for the manufacture of intermediates and bulk drugs. This should be without prejudice to considering the other types of arrangements as described in UNIDO document PC/19. The already large experience of developing countries in agreements for the formulation of dosage forms should be adequately considered when dealing with arrangements for the transfer of technology for that purpose.

6. This meeting of the Committee of Experts on Pharmaceuticals has been convened in deference to the recommendations of the First Consultation on the Pharmaceutical Industry. Based also on the recommendations of the Round Table Meeting on the Development of the Pharmaceutical Industry held in 1981, UNIDO invited representatives of those manufacturers of intermediates and bulk drugs for which there are only limited sources of supply.

7. A directory of the sources of supply of essential bulk drugs, their intermediates and some raw materials compiled by UNIDO pursuant to the recommendations of the First Consultation on the Pharmaceutical Industry is also circulated for the review of the Committee and their comments.

8. The relevance of issues such as economy of scale, infrastructure, and technology to the Pharmaceutical Industry has been examined in depth during the First Consultation on the Pharmaceutical Industry.

IMPACT OF COST OF INTERMEDIATES AND RAW MATERIALS ON BULK DRUG COST

9. The production cost of a drug depends on various inputs such as raw materials, wages, utilities, overheads, depreciation etc. Out of these the most important element is the cost of imported raw materials and intermediate chemicals. The previous studies carried out by UNIDO revealed that the high prices of intermediates rendered the manufacture of bulk drugs uneconomic and this has been a major constraint to the growth and development of the Pharmaceutical industry in the developing countries. 9/

9/ The pricing and availability of intermediates and bulk drugs, UNIDO, ID/WG.331/4. Background paper for discussion on availability, pricing and technology of essential drugs, UNIDO/PC.14.

For the purpose of the study UNIDO selected nine essential drugs and these are indicated in Annexure 1. These drugs have been in existence for several years. In most cases patents have expired. These drugs are needed by the developing countries to cure diseases most prevalent in these countries. The developing countries also constitute large markets for many of these drugs.

10. In view of above UNIDO formulated a pricing scheme for the intermediates and presented to the First Consultation on the Pharmaceutical Industry[10/]. The main principle on which the scheme is based is as follows: The elements going into the cost of production of a drug include the cost of imported intermediates, domestic raw materials, utilities, wages, overheads, depreciation etc. Out of these two major components have been taken as the basis for the pricing scheme and these are:

(a) cost of imported intermediates and

(b) conversion cost which includes utilities, wages, overheads, depreciation etc.

The residual value obtained by deducting the conversion cost from the imported CIF price of the drug is apportioned to the imported intermediates. When there are two or more imported intermediates, the residual value is apportioned between the intermediates in the ratio in which these are utilized in the process. The resulting figure gives an indication of the prices at which these intermediates should be available in the international market (Annex 13).

The above scheme has been expressed as a mathematical formula and is appended to the Directory referred to above.

It should be noted that the above pricing scheme is meant to give some indication of the price range for the intermediates but does not in any way claim to quantify the prices in a precise manner to be used on a global basis.

10/ Ibid, ID/WG.331/4

11. With a view to find out if there have been any significant changes in the prices of intermediates, raw materials, bulk drugs, conversion cost, manufacturing cost and technology, UNIDO has chosen a developing country for the collection of data pertaining to the eight essential drugs on the above elements. Based on the data collected, UNIDO consultants have carried out studies on the following aspects:

(a) manufacturing costs
(b) intermediate prices
(c) conversion costs
(d) technolgoy.

ORIGIN OF PRICE DATA USED IN THE ECONOMIC STUDIES

12. Manufacturing costs have been determined on the basis of commercial scale manufacture in an advanced developing country.

The local infrastructure provides source of manufacture of the most simple, basic chemical raw materials, together with some less complex drug intermediates. The more elaborate intermediates are imported

In most instances process technologies and chemical yields are assumed to be competitive with those applying in developed countries. But where there is a short fall in process technology the fact is highlighted in the report.

The International CIF prices for bulk drugs and key intermediates have been derived from internationally published price data together with (where available) the CIF prices of actual importations into the advanced developing country. Prices refer primarily to those prevailing during the first half of 1982. Locally purchased raw materials, locally availble intermediates are priced without inclusion of local sale taxes etc.

Dapsone is omitted from this study because of the non-availability of process technology for the manufacture of this drug in developing countries.

PRESENTATION OF DATA

13. The data developed in this cost study is summarized in Tables I to VI and Annexes 2 to 12.

ANALYSIS OF DATA AND COMPARISON OF 1980-1982 DATA

14. (a) Manufacturing costs

With the exception of Acetyl Salicylic Acid (increase +12%) all manufacturing costs have shown decreases as follows:

Ampicillin	-34%
Sulphadimidine	-30%
Tetracycline	-29%
Diethylcarbamazine	-43%
Chloroquine	-20%
Ethambutol	-33%
Isoniazid	-52%

(b) Intermediate Prices

The following key intermediates have shown price increases over the period 1980 to 1982:

Acetic Anhydride	+42%
Salicylic Acid	+52%
Methylisobutylketone	+34%
Acetanilide	+8%

International prices for the above are closely linked to the prices of basic petrochemicals.

All other key intermediates have shown significant decreases in International CIF prices:

Phenyl Glycine Chloride Hydrochloride	-52%
6APA	-30%
Ethoxy Methylene, Malonic	-24%
Methyl Piperazine	-56%
2 Aminabutanol	- 8%
Gamma Picoline	-54%
Guanidine Nitrate	-40%

(c) Conversion costs

With exception of Acetyl Salicylic Acid (increase in conversion cost of an insignificant +1%) the remaining seven bulk drugs showed the following decreases in conversion costs:

Ampicillin	- 1%
Sulphadimidine	-35%
Tetracycline	-38%
Diethylcarbamazine	-66%
Chloroquine	-28%
Ethambutol	-38%
Isoniazid	-63%

The reasons for those substantial decreases in bulk durg conversion costs are various including improvements in process efficiency and chemical yields, and increases in annual plant loadings.

(d) Technology

There appears to be an improvement in the process efficiency in the case of Ethambutol while the technology used for the manufacture of tetracycline continues to be inadequate. It is a well known fact that high yielding microbial strains in the case of antibiotic manufacture contribute towards rendering the local manufacture viable.

REASONS FOR GENERAL DECREASE IN MANUFACTURING COSTS

15. (a) In summary the principal reasons for the general decrease in manufacturing costs 1980 to 1982 are:

(i) Decrease in the imported price of certain key intermediates.

(ii) Improvement in some instances of process efficiency and chemical yields.

(iii) A lowering of conversion costs.

(iv) An increase (CA+20%) in the dollar exchange rate which has the effect of decreasing the conversion cost and the cost of locally produced raw materials, when converted from local currency into dollars.

(b) Relationship between current Bulk Drug International Prices and current local Manufacturing Costs

(i) In spite of the substantial narrowing of differences between local manufacturing costs and International drug prices, significant differences still remain.

(ii) In only two cases is the cost of local manufacture lower than the International CIF price of the bulk drug:

Diethylcarbamazine	-8%
Ethambutol	-7%

However, one intermediate (d 2 aminobutanol) constitutes 78% of the total cost of manufacture of Ethambutol. Prevailing international prices for both the bulk drug and the intermediate could still be unreasonably high and yet show local manufacture to be economically viable.

(iii) The remaining essential drugs show local manufacturing costs exceeding International CIF prices for the bulk drug as follows:

Acetyl Salicylic Acid	+23%
Ampicillin	+31%
Sulphadimidine	+75%
Tetracycline	+57%
Chloroquine	+29%
Isoniazid	+10%

Impact of the cost of intermediates on the cost of bulk drugs

16. (a) Where there is a general decrease in the cost of intermediates

Out of the eight bulk drugs studied, the local manufacture in the cases of two drugs, that is, diethylcarbamazine citrate and isoniazid now appears competitive due to a marked decrease in the cost of imported intermediates -N-Methylpiperazine and Gammapicoline respectively.

(b) Where there has not been a decrease in the cost of intermediates

Out of the balance six drugs studied, the cost of local production of four drugs, that is, Acetyl Salicylic Acid, Ampicillin, Sulpha dimidine and Chloroquine phosphate continues to be uneconomic since there has not been a significant decrease in the prices of key intermediates - Acetic anhydride and Salicylic Acid and Methyl isobutyl Ketone. Since the cost of intermediates constitutes on an average 75 percent of the total manufacturing costs, it has considerable impact on the cost of the bulk drug.

Clearly there remains a considerable scope for further reductions in the International CIF prices of key intermediates specifically those mentioned above and possibly the one in the case of Ethambutol.

(c) Impact of Technology

The process efficiency and chemical yields clearly have a substantial impact on material usages and, therefore, on the cost of bulk drug manufacture. Of the eight drugs revieved in the study, the cost of local manufacture of one drug, that is, Tetracycline is excessively high because of the known short fall of process technology in fermentation.

With the remaining seven essential drugs, we have assumed that the current technology may be competitive, but we have no means of knowing for certain. There may well be scope for further reductions in manufacturing costs with the transfer of improved process technology possibly through the establishment of joint ventures for the production of bulk drugs and key intermediates in the developing countries.

CONCLUSIONS

17. (a) The economic viability of manufacture of two out of the eight essential drugs has improved over the period 1980-1982 for a variety of reasons. Out of these, one of the important factors has been a reduction in the import prices of some intermediates. This lends support to the view put forward by UNIDO in 1980 that a reduction in the then prevailing prices of intermediates to a reasonable and fair level would render the local manufacture of the concerned bulk drugs more viable.

(b) However, in a number of cases, local manufacturing costs are still in excess of the international bulk drug prices. A major factor responsible for this situation is that the intermediate import prices are still excessive in the case of certain drugs. With other drugs some scope exists for a reduction in the cost of the locally produced raw materials and in other cases a reduction in the conversion costs.

(c) In the case of one essential drug, the cost of local manufacture is excessive because of the known inadequacy of the present process technology. There may also be scope for the transfer of improved process technology for certain other drugs.

(d) The above conclusions have been based strictly upon the current international price levels of bulk drugs as well as imported intermediates. However, there is no guarantee that this price trend will continue. In case it continues, local manufacture will become more viable.

(e) Since local manufacture becomes viable when the prices of intermediates are reasonable there is a great potential for the establishment of new production units for bulk drugs as well as intermediates. In case the latter are produced in the developing countries, the local manufacture turns out to be even more viable.

(f) The First Consultation on the Pharmaceutical Industry revealed willingness on the part of 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. This study has shown that such a co-operation to promote manufacturing activities in the developing countries will be in their mutual interest.

(g) The developing countries currently base their production programmes on the availability through imports of intermediates. In case certain drugs become economically obsolete, the developed countries may no longer produce such drugs and the intermediates required for the same. The new drugs, as often is the case, could be beyond the reach of the developing countries. In such cases, developed countries could extend their co-operation in transferring technology to the developing countries for the manufacture of the bulk drugs and intermediates 3-5 years ahead of putting the new drugs in the market in place of existing ones.

TABLE I

BULK DRUGS COMPARISON 1980 AND 1982

Drug	CIF Price $/kg	1980 Manufacturing cost $/kg	Manufacturing cost percent of CIF Price	CIF Price $/kg	1982 Manufacturing cost $/kg	Manufacturing cost percent of CIF Price
Acetyl Salicy, Acid	2.1	3.3	159%	3	3.7	123%
Ampicillin	87	142	164%	78	97	131%
Sulphadimidine	10	20	200%	8	14	175%
Tetracycline	38	62	163%	28	44	157%
Diethylcarbamazine	21	23	110%	12	11	92%
Chloroquine	36	45	125%	28	36	129%
Ethambutol	43	82	190%	58	54	93%
Isoniazid	6	23	383%	10	11	110%

TABLE II

COMPARISON OF CIF PRICES BULK DRUGS 1980/1982

	CIF Price 1980 $/kg	CIF Price 1982 $/kg	Change
Acetyl Salicylic Acid	2.1	3.0	+43%
Ampicillin	87	78	-10%
Sulphadimidine	10	8	-20%
Tetracycline	38	28	-26%
Diethylcarbamazine	21	12	-43%
Chloroquine	36	28	-22%
Ethambutol	43	58	+34%
Isoniazid	6	10	+67%

TABLE III

COMPARISON OF MANUFACTURING COST 1980/1982

	Cost 1980 $/kg	Cost 1982 $/kg	Change
Acetyl Salicylic Acid	3.3	3.7	+12%
Ampicillin	142	97	-31%
Sulphadimidine	20	14	-30%
Tetracycline	62	44	-29%
Diethylcarbamazine	23	11	-43%
Chloroquine	45	36	-20%
Ethambutol	82	54	-33%
Isoniazid	23	11	-52%

TABLE IV

COMPARISON OF INTERMEDIATE PRICES 1980/1982

	Cost 1980 $/kg	Cost 1982 $/kg	Change
Acetic Anhydride	1.30	1.85	+42%
Salicylic Acid	1.68	2.56	+52%
Phenyl Glycine Chloride Hydrochloride	37.5	18	-52%
6APA	105	74	-30%
Ethoxy Methylene Malonic	13	10	-24%
Methyl Piperzine	27	12	-56%
2 Aminabutanol	54	50	- 8%
Gamma Picoline	5.4	2.5	-54%
Guanadine Nitrate	2.3	1.4	-40%
Methylisobutylketone	1.4	1.8	+34%
Acetanilide	2.0	2.2	+ 8%

TABLE V

COMPARISON OF CONVERSION COSTS

	Cost 1980 $/kg	Cost 1982 $/kg	Change
Acetyl Salicylic Acid	0.75	0.76	+ 1%
Ampicillin	17.30	17.16	- 1%
Sulphadinidine	3.70	2.40	-35%
Tetracycline	32.08	19.82	-38%
Diethylcarbamazine	8.67	2.92	-66%
Chloroquine	16.28	11.67	-28%
Ethambutol	10.30	6.42	-38%
Isoniazid	8.95	3.30	-63%

TABLE VI

BREAKDOWN OF MANUFACTURING COSTS 1982

	Percent cost Imported Intermediate %	Percent cost other materials %	Percent cost conversion %
Acetyl Salicylic Acid	0	80	20
Ampicillin	50	32	18
Sulphadimidine	38	45	17
Tetracycline	0	55	45
Diethylcarbamazine	33	42	25
Chloroquine	39	29	32
Ethambutol	79	10	12
Isoniazid	25	43	32

Annex 1

ILLUSTRATIVE LIST OF 9 ESSENTIAL DRUGS FOR WHICH FACILITIES FOR THE LOCAL MANUFACTURE OF ACTIVE INGREDIENTS SHOULD BE ESTABLISHED IN DEVELOPING COUNTRIES AND WHICH SHOULD BE GIVEN TOP PRIORITY.

ANAGELSICS

1. Acetylsalicylic Acid

ANTI-INFECTIVE DRUGS

Antibacterial drugs

2. Ampicillin
3. Sulphadimidine
4. Tetracycline

Antifilarial drugs

5. Diethylcarbamazine

Antileprosy drugs

6. Dapsone

Antimalarial drugs

7. Chloroquin

Antituberculosis drugs

8. Ethambutol
9. Isoniazid

Annex 2

ACETYL SALICYLIC ACID EX SALICYLIC ACID

A. Price

International CIF price of Bulk Drug $ 3.00 per Kg (1981-1982).

B. Process

Salicylic Acid is acetylated with Acetic Anhydride and the Acetyl Salicylic Acid so formed purified by recrystallisation from Alcohol.

C. Technology and Plant Capacity

Process technology and process yields used in these cost calculations are believed to be competitive.

Costs are calculated for a plant capacity of 1.200 tons per annum.

D. Manufacturing Cost of Bulk Drug ex-Salicylic Acid

Materials

	Usage Per Kg Bulk Drug	Price Per Kg	Cost Per Kg Bulk Drug	Percentage Total Material Cost
	Kg	US$	US$	%
Acetic Anhydride	0.7828	2.09	1.45	36
Salicylic Acid	0.8536	2.56	2.18	54
Caustic Soda)			0.42	10
Other Materials)			----	----
Total Materials			4.05	[illegible]

Conversion Costs

	US$
1. Utilities	0.16
2. Salaries and Wages	0.09
3. Depreciation	0.05
4. Repairs and Maintenance	0.03
5. Overheads	0.13
Total Conversion Cost	0.46
Total Bulk Drug Cost	4.51

E. Data Basis

Salicylic Acid Price based on International CIP prices (1981-1982).

All other materials are indigenous and based on local prices less local taxes (1981-1982).

F. Conclusions

CIF Price of imported drug:	US$ 3.00 per Kg
Local manufacturing cost:	US$ 4.51 per Kg

The cost study suggests that the International CIF price for the imported intermediate is uncompetitively high.

However, further manufacturing cost studies show that manufacture from Phenol produces a more competitive cost for Acetyl Salicylic Acid.

Annex 3

ACETYL SALICYLIC ACID EX. PHENOL

A. Price:

International CIF price of Bulk Drug (1982): $3.00/Kg

B. Process:

Phenol is reacted with Caustic Soda to produce Sodium Phenate, which is then combined with Carbon Dioxide under pressure to form Sodium Salicylate.

Salicylic Acid is acetylated with Acetic Anhydride and the Acetyl Salicylic Acid so formed is purified by recrystallization from Alcohol.

C. Technology and Plant Capacity:

Process technology and chemical yields are competitive. Cost calculated on plant capacity of 1,200 tons per annum.

D. Manufacturing Cost Bulk Drug:

All materials readily available. Phenol, Salicylic Acid and Acetic Anhydride are produced in some of the more advanced developing countries.

Raw Materials

	Usage Per Kg Bulk Drug	Price Per Kg	Cost Per Kg Bulk Drug	Percentage Total Materials Cost
	Kg	$	$	%
Phenol	0.7105	1.63	1.16	39
Acetic Anhydride	0.7828	1.85	1.45	48
Other Materials	—	—	0.37	13
Total Materials			2.98	100

Conversion Costs

1.	Utilities	0.25
2.	Salaries and Wages	0.14
3.	Depreciation	0.05
4.	Maintenance	0.10
5.	Overhead	0.22
	Total Conversion Cost	0.76
	Total Bulk Drug	3.74

.../...

E. Data Basis:

All indigenous raw materials Prices of 1981-82.

F. Conclusion:

Comparative costs are:

International CIF price (1982):	US$ 3.00/Kg
Manufacturing Cost:	US$ 3.74/Kg

The manufacturing cost is some 25% higher than the international CIF price, primarily because of the higher cost of indigenous materials.

Annex 4

AMPICILLIN TRIHYDRATE EX 6-APA

A. Price

International CIF price of Bulk Drug (1981-82): US$78.00/kg

B. Process

6-APA is acylised to produce Ampicillin.

C. Technology

Process and chemical yields in these cost calculations are believed to be competitive. Plant capacity for economic viability considered to be minimum 25 tons per annum.

D. Manufacturing Cost of Bulk Drug

The cost studies set out in this report are based upon importation of 6-APA and Phenyl Glycine Chloride Hydrochloride.

All other other materials are of indigenous origin. Imported intermediates are freely available.

Materials

	Requirements Per Kg FP	Price Per Kg	Cost Per Kg FP	Percentage of Total Material Cost
	Kgs	US$	US$	%
6-APA	0.66	74	48.84	61
Phenyl Glycine Chloride Hcl	0.64	18	11.52	14
Dimethyl Dichlorosilane	0.51	8	4.08	5
Methyl Chloride	4.1	1.40	5.74	7
Isopropanol	6.7	1.2	8.04	10
Dimethylaniline	0.4	3.1	1.24	2
Other Materials			0.10	1
Total Material Costs			79.56	100

Conversion Costs

	US$
Utilities	1.05
Salaries and Wages	1.98
Maintenance and Repairs	1.29
Overheads	4.45
Depreciation	4.98
Total Conversion Cost	13.75
Total cost of 6-APA	84.42

E. Data Basis

Imported raw materials: Average CIF prices 1981-82 (duty excluded)

Indigenous raw materials: Average prices 1981-82, local taxes excluded.

F. Conclusion

Comparative costs are:-

CIF price of imported 6-APA: US$74.00/kg
Manufacturing Cost: US$84.42/kg

Cost studies suggest that there is scope for a reduction in the international CIF price for Pencillin G.

Annex 5

6 Amino Penicillinic Acid Ex. Penicillin G

A. Price

CIF prices of 6-APA US$ 74/kg; based on imports made by major users in 1981-82.

B. Process

Pencillion G is reacted with Dimethyl Dichlorosilane to from Pencillin G Dimethyl Silyl Ester which is treated with Phosphorus Pentachloride to form Dimethyl Silylimino Ether. This derivative is hydrolysed to 6-APA.

C. Technology and Plant Capacity

Process technology is believed to be competitive.

D. Manufacturing Cost of 6-APA

This cost study assumes importation of Penicillin G. Potassium Ist Crystals which are said to be freely aavailable.

All other materials are from indigenous sources.

Materials

	Usage per kg of bulk drug	Rate per kg	Cost per kg of bulk drug	Percentage of total materials cost
	kg	US$	US$	%
Potassium Penicillin G. (1st Crystals)	2.40 BU	22.00	52.80	74
Butyl Alcohol	2.272 kg	1.39	3.79	5.50
Ammonium Hydroxide	2.226 kg	0.11	0.24	0.30
Chloroform	3.208 kg	1.16	3.72	5.50
Dimethylaniline	1.613 kg	2.59	4.18	5.7
Dimethylchlorosiline	0.802 kg	2.99	2.40	3.50
Phosphorous Penta-chloride	1.235 kg	2.86	3.54	5.50
Total materials			70.67	100.00

(Ampicillin Trihydrate ex 6-APA)

Conversion Costs

	US$
Utilities	2.20
Salaries and Wages	1.68
Depreciation	2.31
Maintenance	0.97
Overheads	10.00
Total Conversion Cost	17.16
Total Bulk Drug Cost	96.72

E. Data Basis

Imported Intermediates: Average CIF price (import duty excluded) of actual importations 1981-82.

Indigenous Materials: Average prices 1981-82 less local taxes.

F. Conclusion

Comparative costs are:

CIF price of imported bulk drug: US$78.00/Kg
Local Manufacturing Cost: US$96.72/Kg

Reduction in CIF price of intermediates would render local manufacture more competitive.

Annex 6

SULPHADIMIDINE

A. Price

International CIF price Bulk Drug 1982: US$8.00/kg.

B. Process

Acetanilide is reacted with Chlorosulphonic Acid to produce Acetylsulphanilylchloride; which is reacted with Guanidine Nitrate to yield Acetylsulphaguanidine. This product is refluxed with Acetyl Acetone to Actylsulphadimidine, which is subsequently hydrolysed with Alkali to Sulphadimidine.

C. Technology

Process technology and chemical yields are believed to be competitive. Plant capacity 500 tons per annum.

D. Manufacturing Cost Bulk Drug

Process involves importation of:

Acetyl Acetone
Methyl Isobutyl Ketone
Guandine Nitrate

All other raw materials are of indigenous origin and easily available.

Materials

	Usage Per Kg	Price	Cost Per Kg	Percentage Total Material
	Kg	US$	US$	
	Bulk Drug	Per Kg	Bulk Drug	
Methyl Isobutyl Ketone	1.046	1.82	1.91	16.00
Acetyl Acetone	0.327	6.07	2.02	17.00
Guanidine Nitrate	0.973	1.38	1.42	12.00
Acetanilide	1.482	2.17	3.17	27.00
Methyl Isobutyl Ketone	0.303	2.12	0.64	5.00
Acetic Acid	1.461	0.59	0.86	7.00
Caustic Soda	3.656	0.21	0.76	6.00
Chlorosulphonic Acid	5.676	0.15	0.87	7.00
Others	---	--	0.09	3.00
Total Material Costs			11.74	100.00

(Sulphadimidine cont)

Conversion Costs

	US$
Utilities	0.35
Salaries and Wages	0.40
Depreciation	0.40
Maintenance and Repairs	0.48
Overheads	0.67
	2.40
Total Bulk Drug Cost	14.14

E. Data Base

Imported Intermediates - average CIF prices (duty excluded); using actual importation 1981-82.

Indigenous Materials - average 1981-82 price, less local taxes.

F. Conclusion

Comparative costs are:

CIF price imported bulk drug: US$8.00
Local Manufacturing Cost: US$14.14

Manufacturing cost is high on account of high cost of Acetanilide and imported raw materials.

Annex 7

TETRACYCLINE HCL

A. Price

The International CIF price (import duty excluded) is US$27.6 per kg 1981-82. This price is based on actual imports.

B. Process

Tetracycline is manufactured by fermentation of a carefully optimised nutrient medium with a selected strain of S. Viridifacines.

Tetracycline Hydrochloride is recovered from the fermented medium by extraction and purification.

C. Technology

Technology is concerned with optimisation of the fermented medium and selection of strains of the micro-organism, both of which can contribute to increase antibiotic yields.

Cost of the finished Bulk Drug is also sensitive to fermenter volume and total plant capacity.

D. Manufacturing Cost Bulk Drugs

Raw materials are indigenously available.

	Cost PER Kg of FP US$
Total materials	24.36
Utilities	12.17
Salaries and Wages	1.50
Depreciation	0.80
Maintenance	2.50
Overheads	2.85
Total Conversion Cost	19.82
Total Bulk Drug	44.18

F. Conclusion

International CIF price imported Bulk Drugs US$27.60/kg
Local manufacturing cost: US$44.18/kg

The higher cost of local manufacture is due to:

(i) use of inferior technology
(ii) higher cost of local materials

Annex 8

DIETHYL CARBAMAZINE CITRATE:

A. Price:

International CIF price of bulk drug $ 12 per Kg; import duty omitted. Price based on quotations.

B. Process:

Methyl Piperazine is reacted with Diethyl Carbamoyl Chloride in the presence of a base to form Diethyl Carbamazine base; subsequently converted into the Citrate salt.

C. Technology:

Believed to be competitive.

D. Manufacturing Cost Bulk Drug:

Materials

All except N-Methyl Piperazine are local. This intermediate appears to be freely available.

		Requirements per Kg FP	Price per Kg	Cost per Kg FP.	Percent Total Materials Cost
		Kg	US$	US$	%
1.	N-Methyl Piperazine	0.32	12.37	3.96	44
2.	Other Materials			5.05	56
	Total Materials			9.01	100

Conversion Costs

		US$
1.	Utilities	0.26
2.	Salaries and Wages	0.32
3.	Depreciation	0.23
4.	Maintenance	0.45
5.	Overhead	1.06
	Total Conversion Cost	2.92
	Total Bulk Drug	11.93

(Diethyl Carbamazine Citrate)

E. Data Basis:

For N-Methyl Piperazine average imported cost 1981-82, excluding import duty. All other materials are indigenous and are included at average 1981-82 prices less local taxes.

F. Conclusion:

International CIF price Bulk Drug: US$ 12.00/kg.

Local manufacturing cost: US$ 11.33/kg.

The local manufacture now appears competitive due to the following reasons:-

(i) 43% decrease in bulk drug price since 1980

(ii) 54% decrease in the price of Methyl Piperazine since 1980

Annex 9

CHLOROQUINE PHOSPHATE

A. Price

CIF price of Bulk Drug based on average cost of importations 1981-82. US$28/kg

B. Process

Metachloroaniline is reacted with Diethyl Ethoxy Methylene Malonate and further reacted with Phosphorous Oxychloride to produce 4.7 Dichloro quinoline. The latter is condensed with Novaldiamine in the prescence of molten Phenol. Further reaction with Phosphoric Acid produces Chloroquine Phosphate.

C. Technology and Plant Capacity

Technology believed to be competitive. Cost calculations based on commercial scale production.

D. Manufacturing Cost of Bulk Drug

This cost study assumes importation of Diethyl Ethoxy Methylene Malonate and Novaldiamine; both of which are freely available. All other raw materials are from indigenous sources.

Materials

	Usage per kg Bulk Drug	Price per kg	Cost per kg Bulk Drug	Percentage of total materials
	kg	US$	US$	%
Diethyl Ethoxy Methylene Malonate	0.74	10.33	7.64	31
Novaldiamine	0.42	15.78	6.63	27
Metachloraniline	0.59	8.79	5.29	21
Other materials			5.18	21
Total Material Costs			24.74	100

Conversion Costs

Utilities	3.26
Salaries and Wages	1.45
Depreciation	0.85
Maintenance	0.98
Overheads	5.13
Total Conversion Cost	11.67
Total Bulk Drug	36.41

E. Data Basis

Imported Raw Materials	Average CIF price (duty excluded) actual importation 1981-82
Indigenous Materials	Average prices 1981-82 local taxes excluded.

F. Conclusion

Comparative costs are:

CIF price imported Bulk Drug	US$28/kg
Local manufacturing cost	US$36.41/kg

The cost of imported intermediates which account for 58% of the total raw material is high. Suitable reduction in price of imported intermediates can make local manufacture more viable. There is a further suggestion that local conversion costs per kilo could be improved.

Annex 10

ETHAMBUTOL — ex-d2 Aminobutanol

A. Price

International CIF price of bulk drug US$55 to US$58/kg. 1981/82; import duty excluded. Based on importation data.

B. Process

d-2 Aminobutanol is reacted with Ethylene Dichloride in the presence of Caustic Soda, then converted to Hydrochloride salt.

C. Technology

Process technology and clinical yields are believed to be competitive. Scale of production 30 MT/per year.

D. Manufacturing Cost Bulk Drug

Intermediate d-2 Aminobutanol is imported. All other raw materials are of indigenous origin. Sources of d-2 Aminobutanol are restricted.

Materials

	Requirements per kg. F.P.	Price per kg.	Cost per kg.F.P	Present total material
	kg.	US$	US$	%
d-2 Aminobutanol	0.86	50	43.00	89
Isopropanol	2.4	1.56	3.75	87
Other materials	—	—	1.78	4
Total Materials			48.53	100

Conversion Costs

Utilities	1.66
Salaries and Wages	0.66
Depreciation	0.50
Repairs and Maintenance	0.78
Overheads	2.82
Total Conversion Cost	6.42
Total Bulk Drug	54.95

E. Data Basis

Imported intermediate	Average CIF price (duty excluded) actual importation 1981/82
Indigenous materials	Average prices, local taxes excluded. (1981-1982)

F. Conclusion

Comparative costs are:

CIF price imported bulk drug	..	US$55 to US$58
Manufacturing cost	..	US$54.23

Local manufacturing is competitive even when intermediate is imported.

This is due to the following reasons:

(i) 35% increas in the cost of bulk drug 1980 to 1982;
(ii) 8% decrease in the cost of d-2 Aminobutanol;
(iii) 40% improvement in conversion efficiency.

In the light of the steep increase in the bulk drug price, there may still be scope for reduction in the bulk drug and intermediate prices.

Annex 11

ISONIAZID (INH) (ex-Gamma Picoline)

A. Price

International CIF price of bulk drug US$10.0 per kg 1981-82; based on quotations.

B. Process

Gamma Picoline is oxidised to Nicotinic Acid, from which Isoniazid is produced by reaction with Hydrazine Hydrate.

C. Technology

Technology on which these cost calculations are based is believed to be competitive.

D. Manufacturing Cost Bulk Drug

Materials

Gamma Picoline and Hydrazine Hydrate are freely available internationally.

	Usage per kg of FP	Price per kg	Cost per kg of FP	Percentage of materials
	kg	US$	US$	%
Gamma Picoline	1.08	2.50	2.70	37
Other materials	-	-	4.60	63
Total materials			7.30	100

Conversion Costs

	$/kg
Utilities	1.14
Salaries and Wages	0.49
Maintenance	0.26
Depreciation	0.31
Overheads	1.10
Total Conversion Cost	3.30
Total Bulk Drug	10.60

E. Data Basis

Gamma Picoline CIF price based on imports (duty excluded) 1981-82.

Other materials (indegenous) average prices 1981-82; local taxes excluded.

F. Conclusion

International CIF price of Bulk Drug:	US$10.00/kg
Cost of local manufacture:	US$10.60/kg

The local manufacture appears competitive becuase the price of Gamma Picoline dropped by 54 percent since 1980.

Annex 12

SULPHAGUANIDINE:

.....

A. Price:

International CIF price of Bulk Drug $ 4.50/kg, 1982

B. Process:

Acetanilide is reacted with Chlorosulphonic Acid to obtain Acetyl Sulphachloride which, on amidation and hydrolysis gives Sulphanilamide; which is hydrolysed with Dicyanadimide to obtain Sulphaguanidine.

C. Technology:

Process technology and chemical yields fairly good. Scale of production 300 MT/per year.

D. Manufacturing Cost Bulk Drug:

Intermediate Dicyanadinide is imported. All other raw materials are of indigenous origin. All raw materials are easily available.

Materials

	Requirements per kg of Bulk Drug	Price per kg	Cost per kg F.P.	Percentage total material
	kg	US$	US$	%
Dicyanadimide	1.12	0.80	0.90	11
Acetanilide	2.04	2.17	4.42	56
Others			2.54	33
Total raw materials			7.87	100
				$/kg
Utilities				0.77
Salaries and Wages				0.35
Depreciation				0.15
Maintenance and Repairs				0.31
Overheads				1.14
Total Conversion Cost				2.72
Total Bulk Drug Cost				10.59

E. Data Basis:

Imported intermediate:	Average CIF price (duty excluded) actual importation 1981/82
Indigenous materials:	Average prices 1981-82 excluding local taxes

F. Conclusion:

Comparative costs are:-

CIF price of imported bulk drug:	$ 4.50/kg
Local manufacturing cost:	$10.59/kg

There is scope for a reduction in the prices of major intermediates and in the conversion cost.

Annex 13

Illustration of Pricing Scheme

Chloroquine Phosphate

Ex-diethyl ethoxy Methylene Malonate and Novaldiamine

Calculation of desirable prices of EMME and Novaldiamine

		$/kg
1.	CIF price of Chloroquine Phosphate	28.00
2.	Conversion cost incurred per kg of production	11.67
3.	Residual value of materials (1 minus 2)	16.33
4.	Diethyl Ethoxy Methylene Malonate (EMME)	
	(a) Value assigned (31% of $16.33)	5.06
	(b) Usage kg per kg of Bulk Drug	0.74
	(c) Desirable CIF price (a÷b)	6.83
	(d) Actual CIF price	10.33
5.	Novaldiamine	
	(a) Value assigned (27% of $16.33)	4.41
	(b) Usage kg per kg of Bulk Drug	0.42
	(c) Desirable CIF price (a÷b)	10.50
	(d) Actual CIF price	15.78