OCCASION

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

DISCLAIMER

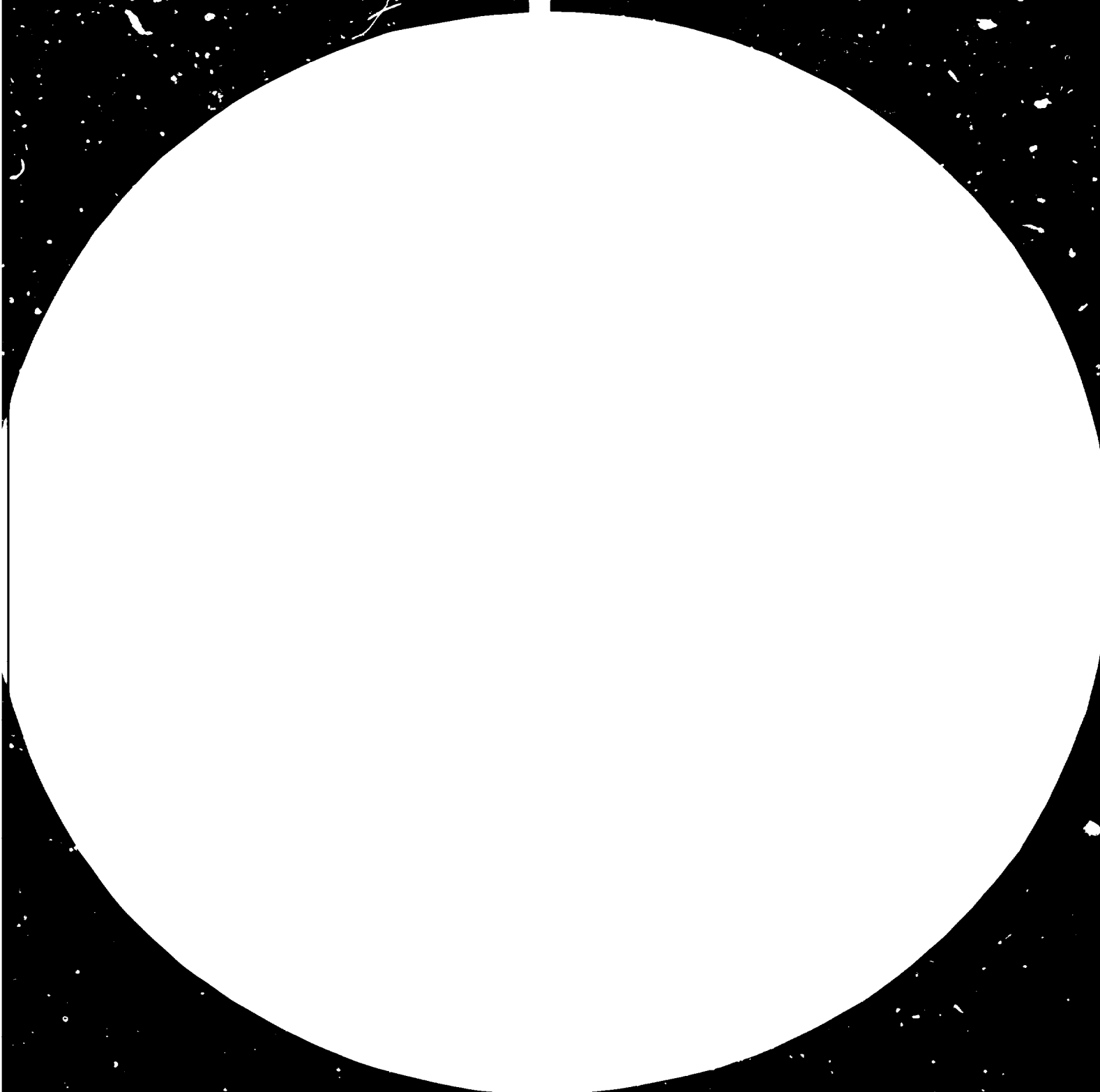
FAIR USE POLICY

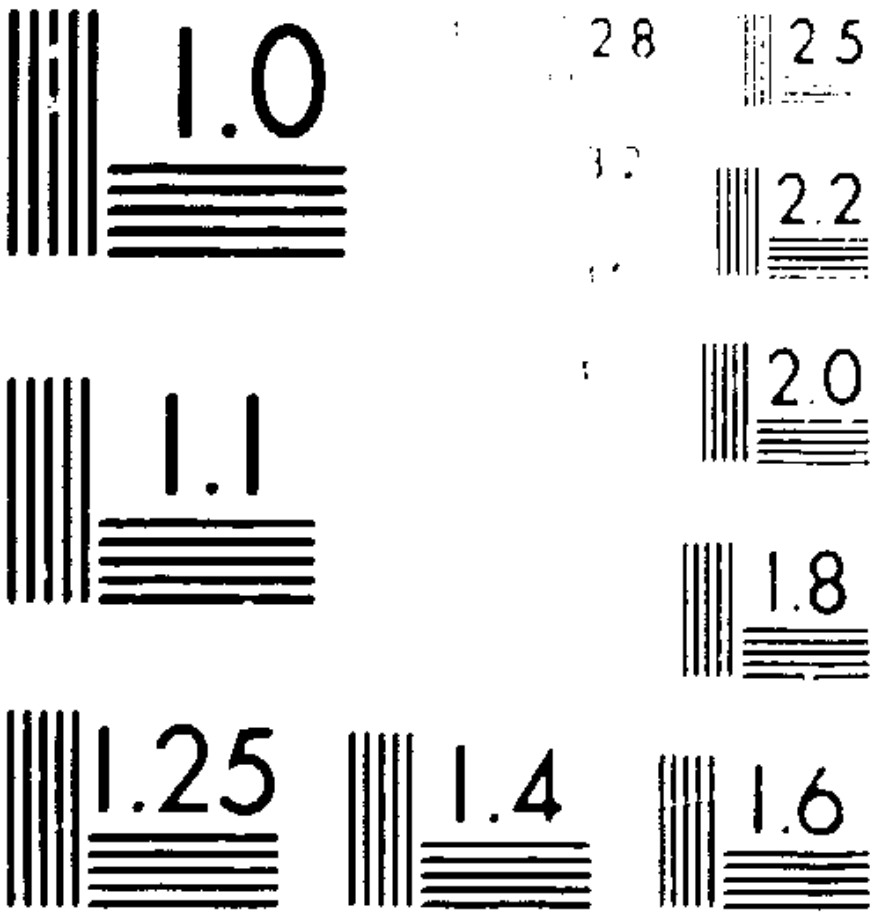
CONTACT

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

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

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




1.0
2.8
2.5
2.2
1.1
2.0
1.8
1.25
1.4
1.6

9221

09567

Distr.
LIMITED

UNIDO/IOD.299/Add.1
14 August 1978

English

UNITED NATIONS INDUSTRIAL
DEVELOPMENT ORGANIZATION

PRODUCTION PLAN FOR THE ARAB PHARMACEUTICAL INDUSTRY IN SELECTED ARAB COUNTRIES*

TF/INT/77/017
TF/INT/76/030
VC/INT/76/077

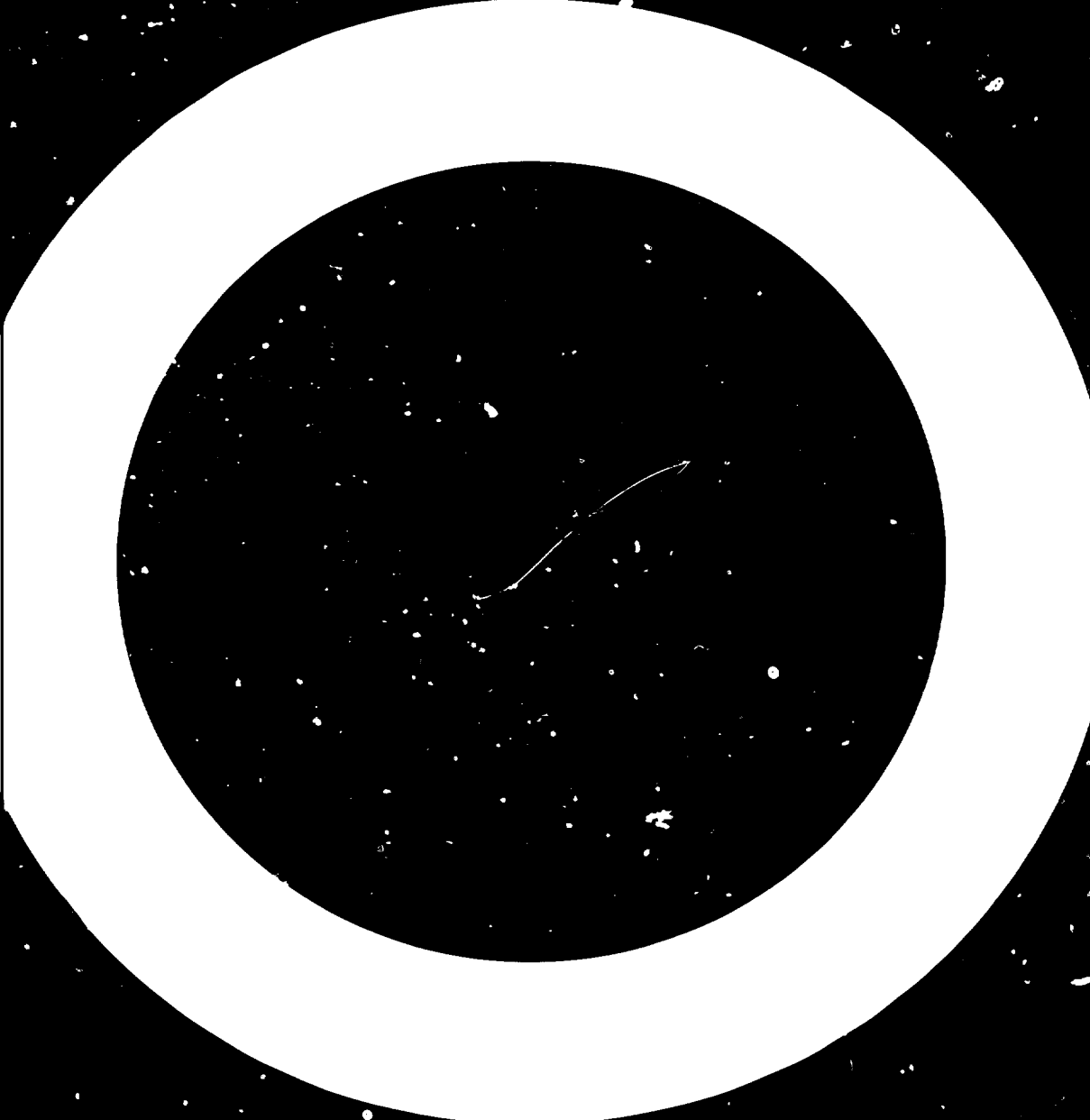
Volume two: Drugs and pharmaceuticals

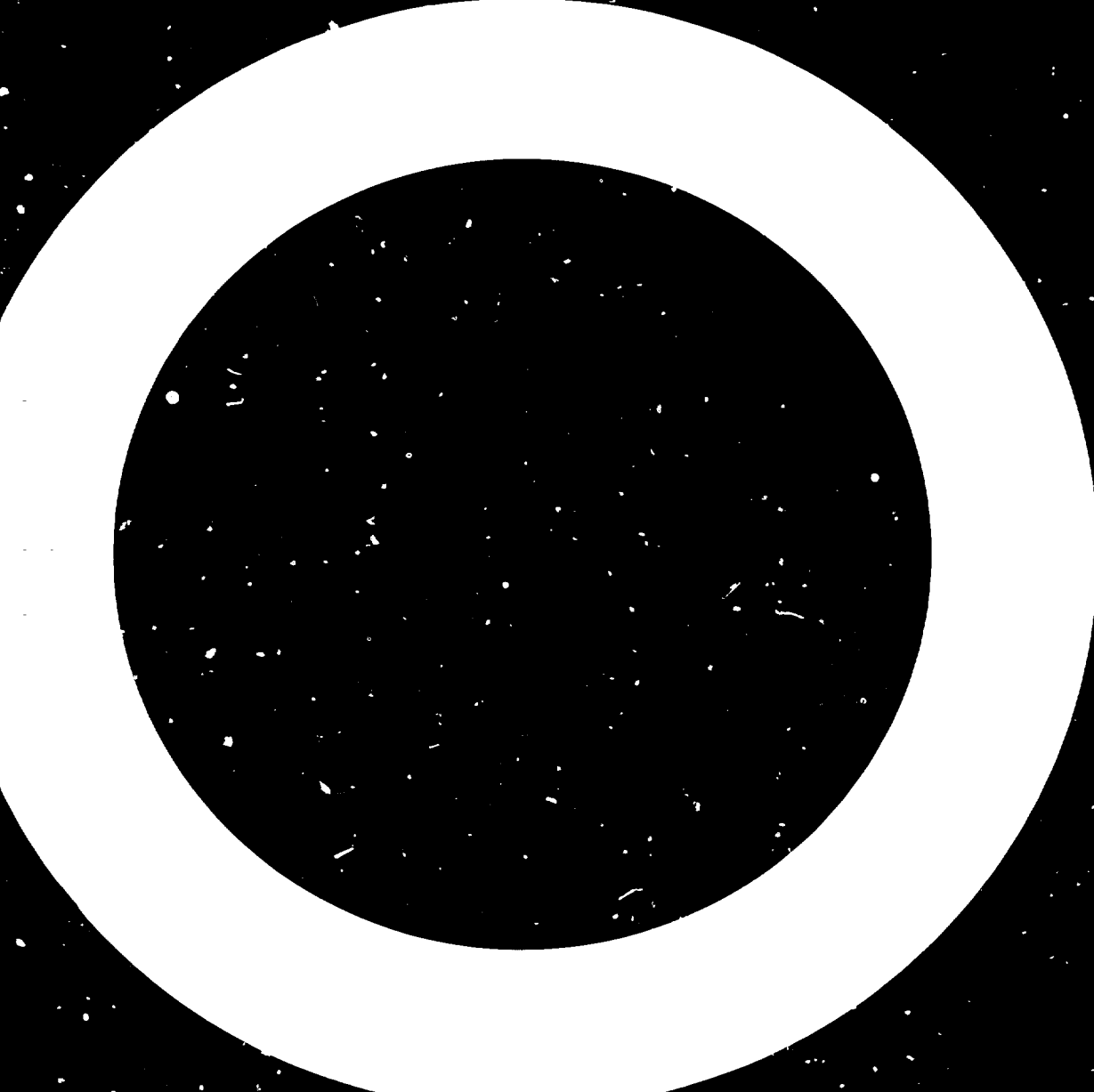
Prepared for the Arab Company for
Drug Industries and Medical Appliances (ACDIMA)
by the United Nations Industrial Development Organization

*This document has been reproduced without formal editing.

The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of the Secretariat of the United Nations concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries.

Mention of firm names and commercial products does not imply endorsement by the United Nations Industrial Development Organization (UNIDO).





CONTENTS

Tables

Tables

VIII. ANTIBIOTICS

A. Summary

I: Present

Strategy to fully utilize existing capacities

(a) Take up production of tetracycline at El-Nasr plant in Egypt on the basis of strain and technology available at S.D.I., Samarra, Iraq.

(b) Both S.D.I. and El Nasr plants should switch over to chemical precipitation method of recovery of tetracycline to fully utilize the available fermentation capacities.

(c) ACDIMA may procure a high yielding strain and technology for tetracycline for use in El Nasr and S.D.I. plants (a strain which gives about 22,000 U/ml. in place of one giving 9,500 U/ml. at S.D.I.)

(d) The output of tetracycline at El-Nasr and S.D.I. plants will come to about 85 tons per year. This can be achieved within 1 - 2 years.

(e) S.D.I. can in the course of time, replace existing 14 fermentors of $10M^3$ capacity by two fermentors of $80M^3$ capacity. El Nasr plant can similarly replace existing six fermentors of $10M^3$ capacity by one fermentor of $80M^3$ capacity.

(f) The cost of production of S.D.I. and El Nasr plants will then compare favourably with international price of tetracycline.

(g) This will provide necessary experience for technicians at S.D.I. and El Nasr plants to man the proposed ACDIMA antibiotic plant.

II: Future:

(a) Review requirements of antibiotics in the Arab Countries and make reliable forecast up to 1982 by which time the proposed plant is expected to materialize.

(b) Form a Project Group at ACDIMA to carry out prefeasibility and feasibility studies.

(c) Establish an antibiotics plant to manufacture penicillins, semi-synthetic penicillins and erythromycin.

(d) Select a firm to construct the plant based on criteria laid down.

III: Industrial Profile:

The proposed antibiotics plant should be designed to manufacture the following antibiotics:-

(1) Penicillins 200 M.T./annum

(Benzyl Penicillins - 75 M.T.
phenoxymethyl Penicillins - 25 M.T.
100 M.T. Will be processed into Ampicillin)

(2) Ampicillin 66 M.T./annum
and other semi-synthetic penicillins such as carbenicillin and cloxacillin.

(3) Erythromycin 20 M.T./annum
(stearate and estolate)

(4) Pharmaceutical preparation plant to process about 50% of the above bulk antibiotics into dosage forms ready for use viz:

Benzyl penicillins	37.5 M.T.
Phenoxymethyl Penicillins	12.5 M.T.
Ampicillin	33 M.T.
Erythromycin	10 M.T.

B. Present status

Existing facilities for the manufacture of antibiotics

In Egypt, El Nasr Company for pharmaceutical chemicals, a public sector unit was established in 1960 and production started in 1963. The plant is located in Abu-Zaabal, 45 Km. from Cairo. The project was implemented according to the co-operation agreement with the Soviet Union. The plant consists of different units for the production of synthetic pharmaceutical chemicals and antibiotics and industrial enzymes by fermentation. Since the commencement of production in 1964, the plant made commendable progress particularly in the field of synthetic drugs, intravenous solutions and industrial enzymes. The company co-operated with I.C.I. using their technology for production of sulpha drugs. A technical collaboration agreement in the field of synthetic drugs and dextrose with China is under implementation. The company supplies bulk raw materials to local companies for manufacturing finished pharmaceutical preparations. The company also established its own facilities for manufacturing pharmaceutical preparations to improve the economy. The Company also exports some of its products.

In the field of fermentation, El Nasr manufactures the industrial enzymes - L anylase for textiles and protease for leather. There is no basic production of antibiotics via, fermentation. However, Tetracycline Hydrochloride is manufactured from imported tetracycline base. Procaine penicillin and benzathine penicillin are manufactured from imported potassium penicillin. Mixtures of penicillins and streptomycin are prepared from imported antibiotics in bulk.

In Iraq, the State Company for Drug Industries owned by the Ministry of Health is located in Samarra, about 128 km from Baghdad. The project was also implemented with the technical assistance of the Soviet Union.

The plant comprises different units for fermentation and chemical purification and pharmaceutical preparations. The Company started to market its products in 1970. Since then the Company made remarkable progress particularly in the field of pharmaceutical preparations and entered into technical collaboration agreements with six International companies and some Arab companies.

The plant manufactures about 13 tons of Tetracycline Hydrochloride annually via fermentation to meet the requirements of Iraq.

S.D.I. imports most of the raw materials required in fermentation except few chemicals such as hydrochloric and sulphuric acids, ammonia and ammonium sulphate.

Thus in the Arab countries, facilities for the manufacture of antibiotics via fermentation are available in Egypt and Iraq. The plant in Egypt was set up to manufacture penicillin and streptomycin. However, this did not materialize and part of the fermentation capacity and the infrastructure are currently being utilized for the manufacture of industrial enzymes. The plant in Iraq was built to produce penicillin, streptomycin and tetracyclin. However, penicillin was stopped not long after its production was commenced. Streptomycin was never produced. Part of the fermentation capacity and the related infrastructure are at present being used to manufacture tetracycline to meet the local needs. One comes across similar factors at both the plants for not accomplishing the underlying objectives in establishing facilities for basic manufacture of antibiotics - production problems and uneconomical production due to obsolete technology and undersized fermentors.

Strategy to fully utilize existing capacities

It is, therefore, vital to find ways and means to utilize the existing

fermentation capacity and the related infrastructure for the manufacture of antibiotics required in the Arab countries, to reduce the burden of these overheads on other products currently being manufactured in these plants and to train personnel to man the ACDIMA antibiotic plant. There are adequate facilities in both the plant in the concerned areas such as microbiology, utilities, laboratories for in process and quality control, engineering and other infrastructure and required expertise and skills to undertake the basic manufacture through fermentation. Fortunately, most of the equipments and facilities for fermentation at both the plants are similar if not identical, since both have been supplied by the same organization. As a short term measure, therefore, a strategy has been worked out to activate both the plants in Egypt and Iraq, utilize the existing capacities and render the operations more economical and this is described in Appendices I and II. Broadly, the plan is to commence the production of tetracycline at El Nasr P.C. Company on the basis of the strain and technology in use at S.D.I. Samarra. Both these plants should then switch over to the chemical precipitation method of recovery of tetracycline according to the procedure given. The ion exchange method currently in use at S.D.I. is proving to be a bottleneck for utilizing the full fermentation capacity. Only 7 out of 14 available fermentors can be used on the basis of chemical recovery facilities existing on the basis of ion exchange process. Necessary equipments to affect the change over are available at the plants as indicated in Volume I under "Surplus facilities available". In the meantime, ACDIMA can arrange for the purchase of a high yielding strain for tetracycline to be used by both the plants. On the basis of 140 M^3 and 60 M^3 fermentation capacities available at S.D.I. and El Nasr respectively along with the required utilities and infrastructure, both these plants put together can manufacture about 85 tons of tetracycline base annually within 1 - 2 years according to the strategy outlined above. The culture strain for the

production of tetracycline currently in use at S.D.I. Samarra yields an average activity of about 9,500 u/ml in 140 hours. It is understood that culture strains for the manufacture of tetracycline with an average yield of 22,000 u/ml are available for about US$100,000. The requirements of five Arab countries - Egypt, Iraq, Libyan Arab Jamahiriya, Sudan and Syrian Arab Republic is currently put at about 79 tons per year as indicated in Volume I under "Requirements of Drugs and Pharmaceuticals". Thus the above recommendations apart from meeting the requirements of tetracycline, will result in the full utilization of existing manufacturing facilities at El Nasr and S.D.I., will provide the trained persons for manning ACDIMA antibiotic plant and will serve as nuclei for developing bigger ACDIMA plants. This is also in line with the declared objective of ACDIMA viz. 'to increase the quantity and upgrade the quality of the local industry, in a bid to meet the needs'. Above all, this will serve as a moral booster to the competent experts available at both El Nasr and S.D.I. and instil in them confidence which is vital for manning the proposed 250 ton ACDIMA antibiotic plant and pave a smooth way for the technological transformation. It is also likely that the experts in these plants may install 80 - 120 M^3 capacity fermentors in the course of time. Antibiotic plants in the developed countries over the years worked with fermentors ranging up to 300 M^3 capacity each. However, the optimum size preferred at present is about 120 M^3 capacity. Considering the capacities of utilities and other infrastructure available at El Nasr and S.D.I. plants, it is recommended that El Nasr may in course of time install one fermentor of 80 M^3 capacity and S.D.I. may install two fermentors of 80 M^3 capacity. A typical working drawing of one 80 M^3 capacity fermentor is given in the Annexure V. These fermentors could be installed within the fermentation buildings by making suitable alterations or outside the buildings by erecting a simple structure to provide shelter to the fermentors.

The fermentor should be provided with agitator, gearbox and motor of 400 H.P. suitable for the high yielding strains and technology. The layout drawings of different floors of the fermentation blocks in El Nasr and S.D.I. plants show that installation of new fermentors and accessories is feasible. The replacement of fermentors with 10 M^3 capacity by those of 80 M^3 capacity will result in reduction in the cost of production, will provide experience to the technical personnel in both El Nasr and S.D.I. plants of working with optimum sized fermentors. This experience will facilitate early commissioning and smooth functioning of the proposed antibiotics plants of ACDIMA.

The recommendation regarding taking up production of tetracycline was discussed with top executives of ACDIMA, El Nasr P.C.Co. Egypt and Head of Antibiotics Production S.D.I., Iraq and it was agreed that it would be technically feasible to take up the production of tetracycline at El Nasr plant on the basis of the strain and technology available at S.D.I. plant after making some arrangements in the equipments and providing some additional equipments, which could be easily organized at El Nasr and these could be classified as minor modifications. It was also felt that to start with El Nasr could adopt the ionexchange method for chemical recovery making use of the resin columns provided for Streptomycin manufacture. Both can then switch over to the chemical purification method for the recovery of tetracycline base. Both can also simultaneously introduce the new high yielding strain and technology when it is acquired at a future date. As regards cost of production of tetracycline at El Nasr plant, the cost is expected to be lower at El Nasr compared to S.D.I., since the cost of labour and utilities at El Nasr is lower than the corresponding figure obtaining at S.D.I.

C. Future development

Long term plan:

Establishment of an antibiotic unit by ACDIMA

ACDIMA desires to erect an antibiotics plant in Iraq for the production in bulk of the following antibiotics:-

(1) Penicillin as Sodium Pen G. injectable
Procaine Pen G. injectable
Benzathine Pen G. injectable
50 MT/annum

(2) Ampicillin trihydrate (including the required Pot. Pen G. to produce Ampicillin)
50 MT/annum

(3) Streptomycin Sulphate (as base) 50 MT/annum

(4) Tetracycline base and the production from it of hydrochloride, phosphate as well as oxytetracycline.

During discussions, it transpired that the above quantities were decided upon based on the deliberation of Technical committees, Medical opinion concerning drug consumption patterns, ability of ACDIMA to market etc. It was also stated that oxytetracycline was proposed to be manufactured via fermentation and not from tetracycline base as indicated above.

Tenders were invited for the preparation of prefeasibility and feasibility studies of the antibiotics plant to manufacture antibiotics referred to above and the tenderers were asked to submit their offers by 30 June 1977. The detailed feasibility study was proposed to be taken up only if conclusions of the prefeasibility were positive. ACDIMA also preferred to execute the project as a joint venture provided results of the feasibility study were positive.

It is relevant to discuss certain issues in this connection as follows:-

(1) Completion period of the project:

Based on the present programme, the prefeasibility and the feasibility studies will take about one year. The process of evaluation of these, negotiations and inviting offers to build the plant will take about one year. It will take about three years to build the plant. The plant will normally take three years to obtain the rated capacity. This will mean that the proposed quantities of different antibiotics will be produced after eight years from now. This is indeed a tight schedule and any delay at any stage may prolong this period. This will also lend support to the need to implement recommendations made earlier as a short term measure viz. Production of tetracycline at El Nasr and S.D.I. plants.

(2) Quantities of antibiotics proposed to be manufactured vis a vis the forecast of consumption:

Based on the present requirements of antibiotics for five Arab countries (Egypt, Iraq, Libyan Arab Jamahiriya, Sudan and Syrian Arab Republic) as indicated in Volume I, the current demands far outstrip the projected production, which will materialize within the next 5-8 years as indicated above. For example, the present requirement of tetracycline is about 79 tons, penicillins 64 tons and streptomycin 73 tons as against 50 tons planned in each case in the proposed plant. This shows that there is immediate need to review the consumption figures and make a realistic forecast for the period 1977-1982 by which time the proposed plant is expected to be commissioned.

(3) Location of the plant:

It is understood that the site for the plant near Baghdad has been decided upon.

(4) Relevance of the proposed Mix:

The quantum of antibiotics to be produced will primarily depend on the projected demand as well as the economy of scale. Based on the present trends in the construction of antibiotic plants in other countries, the pattern of drug consumption particularly in the Arab countries and the economy of scale, a plant for the production of penicillins, ampicillin and other semi-synthetic penicillins and erythromycin appears to be an economical proposition. Similar plants are under construction in Italy, Mexico and Poland. It is recommended that 50% of the basic drugs produced should be processed into pharmaceutical preparations or dosage forms by ACDIMA.in the above plant or in units located elsewhere mainly for two reasons. Formulation of bulk drugs into dosage forms will improve the profitability of the concern. Secondly, there is need to establish one or more formulation plants on the basis of the latest technological developments, good manufacturing practice and recognized quality standards to serve as models to the pharmaceutical preparation units in the Arab Countries with a view to upgrade their own standards.

(5) Recommended product Mix:

In the light of above, it is recommended that ACDIMA may construct a plant to manufacture the following antibiotics:

(1) Penicillins 200 M.T./annum

(Benzyl Penicillins - 75 M.T.
Phenoxymethyl Penicillins - 25 M.T.
100 M.T. will be processed into Ampicillin)

(2) Ampicillin 66 M.T./annum
(Trihydrate or anhydrous or both depending on demand forecast) and other semi-synthetic penicillins such as carbenicillin, cloxacillin.

(3) Erythromycin 20 M.T./annum
(stearate and estolate)

(4) Pharmaceutical preparation plant to process about 50% of the above bulk drugs into dosage forms ready for use. Tetracycline is not included as it is recommended for production at El Nasr and S.D.I. plants. Streptomycin is not included for reasons of economy and its doubtful future.

(6) Prefeasibility and Feasibility Studes:

It is suggested that a project group be formed at ACDLMA under the guidance of an outside expert and drawing experts from El Nasr and S.D.I. companies. This group will prepare the prefeasibility and feasibility studies based on different viable alternatives and according to the standard procedures

adopted for such studies. If necessary one financial expert and one experienced engineer from outside for short periods can be added to the group. It is expected that both these studies will be completed within six months. During this period negotiations can be carried out to secure the best available technology in each case. At the end of this period a project group would be functioning at ACDIMA. This group will then be able to undertake similar feasibility studies for other ACDIMA projects such as pharmaceutical chemicals and biological products. This project group will liaise with the firms constructing ACDIMA plants and will hasten the execution of the projects. This will also result in considerable savings in expenditure and time and is in the larger interests of ACDIMA. It is understood that El Nasr Co. recently prepared feasibility reports on Sulpha drugs and glucose and I.V. solutions of glucose for ACDIMA.

(7) Selection of a firm for carrying out prefeasibility and feasibility studies:

In case ACDIMA decides to entrust the work of preparing prefeasibility and feasibility studies to an outside party, it is recommended that the following factors be taken into account before selecting the party.

(a) Willingness of the firm to enter into a joint venture. This is a good safeguard to ensure that the execution of project will proceed in a business like manner.

(b) Representatives of ACDIMA should visit the projects recently completed or those under execution by the firm.

(c) Representatives of ACDIMA should verify the firm's claims regarding technology by actually visiting the manufacturing units, where such technology is in operation.

(d) ACDIMA should satisfy itself that the technology offered is the best or nearly the best available in the world in the respective fields.

(e) ACDIMA should satisfy itself that the project will be designed on the basis of the latest engineering design practices.

(f) It is desirable that the firm carrying out the prefeasibility and feasibility studies is entrusted with the responsibility of constructing the plant.

(g) Penalty clauses should be inserted wherever feasible to avoid slippages.

(h) Time is the essence in the field of drugs where obsolescence is rather high. ACDIMA should execute the project in the shortest period possible and realize the benefit before the drugs in question becomes obsolete.

(i) Certain amount of flexibility should be built into the plant to enable change in the spectrum or increase in the quantities with minor modifications to cope with the demand pattern.

D. Industrial profile

The Industrial profile is presented for an antibiotic plant with the recommended product mix and formulations.

The cost structure of an antibiotics plant based on fermentation is highly sensitive to the technology adopted particularly the culture strain of the micro-organism used in the fermentation process. Certain assumptions are made in this regard as outlined below:

a) Technology

i) Penicillin: Potency of the culture strain 30,000 Units / ml in 216 - 240 hours

ii) Erythromycin: Potency of the culture strain 3,500 Units / ml in 120 hours.

iii) Ampicillin: 1.5 kg of Potassium Benzyl Penicillin gives 1 kg of Ampicillin trihydrate.

b) Raw Materials

As indicated earlier, except few inorganic chemicals, the rest of the raw materials are currently imported by Egypt and Iraq. So prevailing international prices for raw materials used in the process are taken.

c) Land:

The value of land of the proposed site near Baghdad was assumed as also the construction costs in Iraq.

d) Man power

The prevailing wage structure in Iraq where the proposed plant will be located is taken.

e) Equipments

These are standard equipments according to present engineering practice. Most of these will be imported. The capacity of each fermentor is assumed to be 120 M^3.

f) Selling price of bulk and formulations

As regards bulk, the current prices in the international market are taken. As far as formulations are concerned, the prices prevailing in Egypt and Iraq are taken.

g) General

It is likely that the quantum of investment may undergo changes depending on various factors such as technology, prevailing construction and equipment costs, rebate on import duty and the extent of automation used.

A royalty of 5% on capital has been assumed. In case of lump-sum payment or joint venture this may vary.

The prevailing international prices of bulk drugs are taken as the selling prices of drugs produced.

Similarly, the selling prices of formulations are subject to price controls applicable in any of the Arab countries at any given time.

h) Sources of Technology

(1) Penicillin

(i) Toyo Jozo and Co., Tokyo, Japan
(ii) Meiji and Co., Tokyo, Japan
(iii) Kabi, Stockholm, Sweden
(iv) Pharmafin, Milan, Italy
(v) Pan Labs., New York, U.S.A.
(vi) Wyeth Lab. Radnor, Philadelphia, U.S.A.
(vii) Biochemie, Kundl/Tirol, Austria

(2) Ampicillin

(i) Beecham, London, U.K.
(ii) Wyeth Lab. Radnor, Philadelphia, U.S.A.
(iii) Pharmafin, Milan, Italy
(iv) Gist-Brocades, Delft, Holland
(v) Biochemie, Kundl/Tirol, Austria (6APA)

(3) Tetracycline

(i) Pharmafin, Milan, Italy
(ii) Pfizer, New York, U.S.A.
(iii) Squibb, New York, U.S.A.
(iv) American Cyanamid, New York, U.S.A.
(v) Arco, Switzerland

(4) Erythromycin

(i) Pierrel, Milan, Italy
(ii) Archifar, Milan, Italy
(iii) Pharmafin, Milan, Italy
(iv) Abbotts, Chicago, U.S.A.

i) Requirements of major raw materials

S.No.	Material	Annual requirement (in tons)
1.	Acetone	362
2.	Ammonia, liquor	44
3.	Ammonium Sulphate	102
4.	Butyl acetate	347
5.	N-Butyl alcohol	508
6.	Calcium carbonate	1,410
7.	Carbon Dioxide (gas)	346
8.	Corn Steep liquor	133
9.	D.B.E. Diacetate	6
10.	Dimethyl aniline	34
11.	Dimethyl dichlorosilane	31
12.	D-phenyl glycyl chloride hydrochloride	53
13.	Ether, diethyl	62
14.	Ethyl acetate	649
15.	Ethyl alcohol	72
16.	Isopropyl alcohol	71
17.	Lactose	8
18.	Lard oil	133
19.	Methylene chloride	772
20.	B-Napthalene sulphuric acid	173
21.	Peanut oil	130
22.	Phenyl acetic acid	129
23.	Phosphoric acid	40
24.	Poly vinyl pyrrolidine	2

S.No.	Material	Annual Requirement (in tons)
25.	Potassium acetate	143
26.	Potassium hydroxide	55
27.	Procaine hydrochloride	23
28.	Sodium carbonate	42
29.	Sodium chloride	27
30.	Sodium hydroxide	71
31.	Sodium sulphate	23
32.	Sucrose	2,096
33.	Sulphuric acid	235
34.	Triethyl amine	72
35.	Urea	72

j) Requirements of personnel

S.No.	Category	Number	Educational Qualifications
1.	Unskilled and semi-skilled (workers)	437	completed high school
2.	skilled (Technicians + Tradesmen)	198	After high school, with technical trade certificate
3.	Technical Supervisors	43	University graduates in chemistry, microbiology, pharmacy and engineering.
4.	Managerial cadre	39	University graduates in chemistry, microbiology, pharmacy, engineering and business administration with specialization and post graduates.

I. PENICILLINS — in 000 US $

A. Investment

i)	Proportional for production of 200 T in bulk	9,020
ii)	Proportional for formulation of 50 T of Penicillin	4,360
	Total	13,380

B. Sales Revenue

i)	Sale of 50 Tons of Penicillin in bulk at US $ 23 / kg	1,150
ii)	Sale of 50 Tons of Penicillin in formulations (Sale value of formulation at 202% of bulk)	2,323
	Total Sales	3,473

C. Cost of Production of bulk

Raw materials	730
Chemicals and auxiliary materials	300
Royalties at 5 % of annual sales	230
Manpower	933
Utilities	670
Maintenance at 5% of capital	451
Depreciation - 10% of capital	902
Taxes - 5% of capital	451
Total	4,667
Cost of sales 10% of sale in bulk	115
Total cost	4,782
Cost per kg (US$)	23.91
Sales revenue from 50 T of bulk	1,150
Cost of Production of 50 T of bulk	1,196
Net deficit	40

D) Operating results of formulations	in 000 US$
Sale value of 50 T in formulations	2,323
Operating costs including overheads, depreciation, interest and selling and distribution expenses	1,996
Net Margin	327
E) Profitability on sale in bulk and formulations	281

II . AMPICILLIN

A. Investment	in 000 US$
i) Proportional for production of 66 T in bulk	7,940
ii) Proportional for formulation of 33 T of ampicillin	2,875
Total	10,815

B. Sales Revenue	
i) Sale of 33 tons of Ampicillin in bulk at US $ 75 / kg	2,475
ii) Sale of 33 Tons of Ampicillin in formulations (sale value of formulation at 170% of bulk)	4,209
Total Sales	6,684

C. Cost of Production of bulk	
Raw materials	1,762
Chemicals and auxiliary materials	462
Royalties at 5% of annual sales	248
Man power	264
Utilities	66
Maintenance at 5% of capital	397
Depriciation at 10% of capital	794
Taxes at 5% of capital	397
Total	4,390
Cost of Sales 10% of sale in bulk	247.5
Total cost	4,637.5
Cost per kg (US$)	70.27
sales revenue from 33 T of bulk	2,475
Cost of Production of 33 T of bulk	2,318.8
Net margin	1,56.2

D. Operating results of Formulations		in 000 US$
Sale value of 33 T in formulations		4,209
Operating costs including overheads, depreciation, interest and selling and distribution expenses		3,617
	Net margin	592
e) Profitability on sale in bulk and formulations		748.2

III. ERYTHROMYCIN — in 000 US $

A. Investment

i) Proportional for production of 20 T of bulk	2,885
ii) Proportional for formulation of 10 T of Erythromycin	870
Total	3,755

B. Sales Revenue

i) Sale of 10 Tons of Erythromycin in bulk at US $ 100 / kg	1,000
ii) Sale of 10 Tons of Erythromycin in formulations (Sale value of formulations at 184.5% of bulk)	1,845
	2,845

C. Cost of Production of bulk

Raw materials	420
Chemicals and auxiliary materials	150
Royalties at 5% of annual sales	100
Man power	300
Utilities	30
Maintenance at 5% of capital	144
Depreciation at 10%of capital	289
Taxes at 5% of capital	144
Total cost of operation	1,577
Cost of sales 10% of sale in bulk	100
Total cost	1,677
Cost per kg (US$)	83.85
Sales revenue from 10 T of bulk	1,000
Cost of Production of 10 T of bulk	838.5
Net Margin	161.5

d) Operating results of Formulations — in 000 US $

Sale value of 10 T in Formulations		1,845
Operatings costs including overheads, depreciation, interest and selling and distribution expense.		1,586
	Net margin	259

e) Profitability on sale in bulk and formulations 420.5

IV. SUMMARY

		in 000 US $
A. Investment		
i) Penicillin		13,380
ii) Ampicillin		10,815
iii) Erythromycin		3,755
	Total	27,950
B. Sales Revenue		
i) Penicillin Bulk		1,150
Formulations		2,323
ii) Ampicillin, Bulk		2,475
Formulations		4,209
iii) Erythromycin Bulk		1,000
Formulations		1,845
		13,002
C. Net Margin		
i) Penicillin		281.0
ii) Ampicillin		748.2
iii) Erythromycin		420.5
	Total	1,449.7
Return on sales		11.15 %
Return on investment		5.19%

Appendix I

STRATEGY TO FULLY UTILIZE EXISTING CAPACITIES

1. El Nasr plant has 6 fermentors of 10 cubic meters capacity. El Nasr can adopt the technology of S.D.I. plant, Samarra, Iraq and produce 13 tons of tetracycline base per year. May take 3-6 months.

2. El Nasr plant and S.D.I. plant at Samarra can switch over to chemical precipitation method of recovery of tetracycline according to procedure given in Annexure IV. This will double output of S.D.I., Samarra. May take 6 months.

3. ACDIMA can purchase a high yielding strain to be used by both El Nasr and S.D.I. Samarra. Then both El Nasr and S.D.I. plants will be producing 85 tons of tetracycline base annually. May take 6 months.

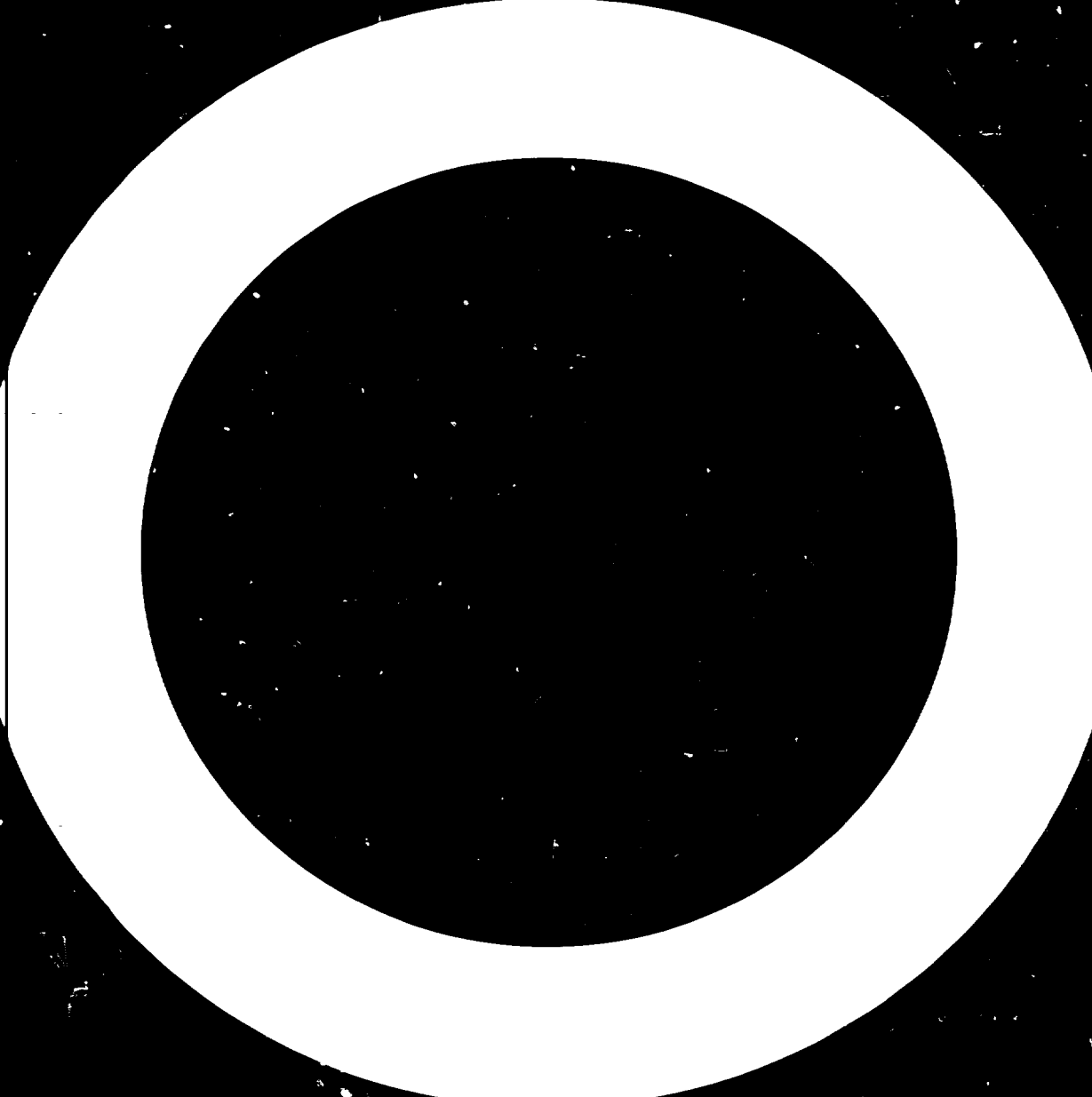
4. Thus Arab countries will be self sufficient with regard to tetracycline.

5. El Nasr and S.D.I. plants will have trained persons for manning ACDIMA antibiotic plants. These plants will be nuclei for developing bigger ACDIMA plants.

Appendix II

RECOVERY OF TETRACYCLINE BY PRECIPITATION METHOD

1. Add sulphuric acid to fermentation broth to PH 3. Then add oxalic acid till the PH comes down to pH 1.7.
2. Depending on condition of broth, add 1-2% of filter aid (diatomaceous earth) and filter (rotary vacuum filter, if available).
3. Maintain the temperature of broth at 10°C.
4. Add caustic soda solution of pH 9.0.
5. Filter the slurry and discard filtrate.
6. Make the cake into a slurry in deionized water. Add sulphuric acid to pH 3.0 and oxalic acid to pH 1.7.
7. To decolorize and remove impurities, add 2.5 kg. of activated carbon and a detergent e.g. arquad (LS) 1% v/v.
8. Filter under vacuum, wash the solids and discard the solids.
9. Add sodium Hydro-sulphide, plus a small excess of versene (EDTA) and 25% sodium hydroxide solution to pH 4.3. Maintain the temperature of slurry at 10°C and agitate for about 8 hours.
10. Filter and wash the cake with deionized water.
11. Dry in a suitable dryer (preferably a fluidised bed dryer) till it has a moisture content of about 13%. Base trihydrate of tetracycline is thus obtained.



IX. SYNTHETIC DRUGS

A. Summary

0.1. Short term basis:

a) Continue cooperation with other companies and aquisition of reaction know-how for quick start of production of new products in idle equipment.

b) Organize work groups for process development and provide suitable equipment to participate in the implementation of laboratory scale processes to technical scale in order to make practical experience available to own staff.

c) Initiate first construction stage of multipurpose plant and start production there with procedures already developped by said work groups.

d) Refrain from committing immediately to a large multipurpose plant without prior experience. For urgently needed drugs prefer dedicated production units during short term period. Organize personnel training in management and maintenance.

0.2. Long term measures:

a) Carry out enlargements of existing multipurpose plant and eventually erect other full size plants in other locations.

b) Consider cooperation with producers of organic intermediates to assure low-cost supply of important base materials.

B. Present supply of synthetic drugs in the Arab countries

1.1. Producers and production facilities:

Of all Arab countries, only Egypt is producing synthetic drugs in bulk, mostly from imported raw materials. All synthetic operations are concentrated at El Nasr Pharmaceutical Company in Abu Zaabal, 45 km to the North East of Cairo. El Nasr Pharmaceutical Company has been established in 1960 under the terms of an agreement with the Soviet Union and production started in 1963. The company belongs to the public sector of industry and encompasses production facilities for chemical synthesis, fermentation and formulation, which are well integrated with centralized utility services and supply lines.

In the course of time, extensive changes and improvements in machinery and procedures have been carried out and capacities and experience have been created for a considerable line of products.

The principle of unit production is implemented throughout and all installed equipment is dedicated to specific products.

Appendix I gives the manufacturing programme of synthetic drugs with actual production targets of 1977, as communicated by El Nasr Pharmaceutical Company.

For some products, actual output is only a fraction of installed capacity. Also, some equipment is currently not in use. Three reasons can be seen for this:

a) insufficient demand or, in principle, disadvantages against competing products;

b) inflexibility of installed equipment which prevents switching to another product;

c) discontinuation for economic reasons of production of some precursors or intermediates in favor of purchasing. With labor costs at a comparatively low level, one source of excessive product cost must be an inefficient synthesis procedure.

1. 2. Expansion and improvement of production:

An increase of the number of synthetic drugs and the purchase of new know-how is under active consideration at El Nasr Pharmaceutical Company and a role is envisaged for ACDIMA in supporting some of the necessary investment. A list of products to be manufactured newly or with improved technology is given in appendix II. Capacities are adjusted for the needs of the total Arab market and the quantities

required together with the necessity to minimize production cost to the low level of the world market for certain bulk drugs like e.g. salicylic acid or sulfas make it mandatory to optimize the design of production units dedicated to single products. The cooperation of firms with special experience has therefore been invited and offers have been received. A production unit for acetaminobenzene sulfonylchloride is under construction presently and units for salicylic acid, PAS, niacinamide/ INH, paracetamol and dextrose are planned.

Many drugs on the Arab market are consumed in quantities not big enough to render economical the erection of a separate production unit. On the other hand, existing capacities are only partly used and excess equipment is available at El Nasr plant. Beside lower cost, adaption of existing equipment will also result in the start-up of new productions in much shorter time.
In line with this thinking, assessments and bids for cooperation have been invited from other firms and the know-how for 13 chemicals to be manufactured by

adapting existing apparatus

1. 3. Development of production know-how:

A more general way of tackling new productions should be discussed at this point. The cost of aquisition of know-how for a product of small volume will, in general, influence unfavorably product economy. Given the low cost of labor in Arab countries, it will be cheaper to invest in laboratories and man-power and to carry out the development and optimization of some reaction procedures with a minimum of outside intervention. Skilled personnel in El Nasr plant has proven its professional ability to cope with similar problems and may be the nucleus of a group assigned to development tasks.

The following measures have to be taken to provide capacities for working out manufacturing procedures:

a) assign personnel with university training and qualified laboratory technicians to development duties only.

b) provide laboratory space and equipment for preparative work on batches of 0.1 - 5 kg. It is felt, that existing facilities and apparatus is not well suited for this scale. Also, outfit

for modelling plant conditions (columns, extractors, centrifuges) has to be available.

c) provide additions to the already existing valuable pilot plant for scaling up batches, e.g. reaction vessels of 50, 100, 300, 500 l. This can be done by using available idle equipment.

d) provide additions to the already existing technical library, e.g. all reference works of organic synthetic chemistry and technology.

Information on the course, mechanism and yields of the synthesis of known drugs can always be gained from the technical literature, but details and precise procedures are generally not revealed. It may be realistically assumed that on the basis of this information, a laboratory group of 1 university-trained chemist and 3 qualified lab-technicians will be able to work out the detailed procedure, ready to be transferred to production scale, of 2 reaction steps in one year.

A hypothetical example is given:

The evaluation of production procedures for a group of 13 chemicals

would involve the optimization of approx. 35 reaction steps and can be accomplished in 5 years by 4 work-groups.

Necessary investment and cost will be (2o% depreciation assumed):

1. Laboratory: installation, preparative apparatus, centrifuges, rotary and film evaporator etc. for 4 groups	US$	15o ooo
2. Pilotscale reaction vessels (5o l, 1oo l, 3oo l, 5oo l, partly available)	US$	3o ooo
3. Manpower, 16 men à 75o,-LE/yr., 5 years, 3o % overhead added	US$	5o ooo
4. Chemicals, utilities	US$	1o ooo
Total cost in 5 years	US$	24o ooo

It goes without saying, that the possibility to issue licenses, better adaptability to changing raw materials and general flexibility in the production programme will be further benefits from this investment. It is suggested, that the organisation of process developing groups, if decided upon, should be made soon

1.4. Investment in synthetic pharmaceutical production:

1.4.1. Short term measures:

It has already been said under 1.2., that work is under way to utilize existing surplus equipment. A list of chemicals next in line for production has to consider technical feasibility and the demands of the market. A selection of drugs satisfying both criteria is compiled in section E and industrial profiles for these chemicals have been worked out.

More new apparatus will be needed for these productions, because all useful surplus material will then be back in use. It is suggested, that investment in the first stage of a multipurpose plant should be considered here rather than assembling small new units independent of each other.

Main advantages of a multipurpose plant are:

a) flexibility of production program
b) economy for small productions
c) simultaneous coordinated production of several products or intermediates for best utilization
d) stepwise enlargement possible.

On the other hand, certain points have to be scored against the idea of a multipurpose installation:

a) specification of equipment has to be very high for the sake of versatility and often reactions are made in apparatus more expensive than necessary.

b) Very good coordination of parallel operations is needed to avoid inefficient use of the plant.

c) A certain time is lost when products are changed because of cleaning and adaptions.

It is felt that the small demand for most drugs at the present time makes a strong case for a multi-purpose plant with, at first, small capacities. Buildings as well as utility supply should be planned to allow for several further additions, which will become necessary with growing demand of the Egyptian and all-Arab market. A short technical profile of the plant in the first two stages is given in section D. Experience gained in the management and operation of the small plant will prepare management personnel and a staff of operators for larger plants to follow.

1.4.2. Long term measures:

With increasing quantities of drugs synthesized, three options will be considered:

a) taking some drugs e.g. vitamins from the multi-purpose plant to new dedicated units,

b) adding units with big reactor capacities and, eventually, new independent multipurpose plants at the same or at other locations.

c) Starting the productions of products in special units which are economical only in big volume, or with cheap starting materials e.g. vitamin C, nicotinic acid.

The availability of at least one multipurpose plant will still give the flexibility to adapt production to changing demands, to smaller but important products and eventually to products demanding high skills and versatility in manufacturing, e.g. steroids.

Also, suitable raw materials will become available in the second half of the next decade from Arab petrochemical plants. It may be ACDIMA's wish to participate in ventures which will provide intermediates common to pharmaceutical and other industries (e.g. food processing, dyes, herbicides, rubber) in order to encourage and speed up the decision to start their manufacture in Arab countries. This applies to the following product groups:

a) Acetaldehyde, acetic anhydride, ethylacetate, methylethyl pyridine, ethyl acetoacetate, chloroaceticacid, malonic acid,

b) acrolein, methylpyridines, ß-cyano pyridine, nicotinic acid

c) nitrobenzene, aniline, chloroanilines, phenyl hydrazine

d) benzoic acid, benzoyl chloride, benzyl cyanide

These plants will necessarily have to be incorporated in petrochemical complexes and ACDIMA's contribution has to be in the field of financing.

C. Availability of raw materials from other industries

Special attention has been dedicated to the present and future production of raw materials for synthesis by petrochemical plant going on stream or beeing in the planning or construction stage in many Arab countries.

The following conclusions are drawn:

a) aromatic solvents (benzene, toluene, xylenes, ligroin, naphtha) are available in export quantities from current operations

b) other organic solvents (methanol, ethanol, butanol) are produced in quantities sufficient for local consumption in the countries of origin.

c) ethylene dichloride and ethylenglycol will be produced in large scale in 5 years

d) basic inorganic chemicals and urea are in plentiful supply

e) no direct starting materials for pharmaceutical synthesis are produced or planned for production in the next years, but will eventually be considered under the necessity for diversification.

An overview of chemicals from petrochemical and other sources for the bulk synthesis of pharmaceuticals is given. The present production and the expected availability within the next 5 years is studied and given for each of the Arab Countries.

2.1. The vast resources of oil and gas in some Arab countries - 60% resp. 25% of world's proven reserves - so far have only been used marginally for the production of refinery products and chemicals by their respective producer countries. To illustrate this point, it may be noted, that the total Arab oil refining capacity in 1975 was only 13% of Arab oil production. This situation will be totally different by 1980, when many of the large scale refinery and petrochemical projects launched since 1975 have come on stream in every one of the oil and gas producing Arab countries.

It is common to almost all projects, that they confine themselves to the production of ethylene, propylene, and C_4-hydrocarbons and their immediate derivatives as HDPE, LDPE, PP, PVC, ethylene oxide, ethylene glycol and amino-ethanol on the one hand and to aromatics as benzene, toluene, xylene, styrene, dimethyl terephthalate, caprolactam and the polymers made from these on the other hand. In addition, methanol is or will be produced from natural gas by some countries. Not unexpectedly, plans for the diversification of those primary products into a broader line of chemicals have been postponed until the projects of 1975-1980 have come on stream. The second generation of chemicals actually provides most of the starting materials and solvents for the bulk synthesis of pharmaceutical chemicals. A selected list of some of these products of major importance is given below.

Organic chemicals from petrochemical sources as solvents and raw materials of pharmaceuticals:

Chemical	Example for use
dichloro ethane	solvent
ethanol	solvent
acetic acid	acetanilide, ASC
acetic anhydride	acetylsalicylic acid
butanol	solvent

Chemical	Example for use
ethyl acetate	solvent
subst. malonic esters	barbiturates
ethanolamine	piperazine
cyclohexane	solvent
acetone	solvent
i-propanol	solvent
phenol	salicylic acid
m-aminophenol	p-aminosalicylic acid
p-aminophenol	paracetamol
chloro-benzene	solvent
p-nitrochloro-benzene	dapsone
aniline	sulphas
dimethylaniline	base, solvent
m-chloroaniline	chloroquine diazepam chlordiazepoxide
benzylchloride	pethidine
benzaldehyde	chloramphenicol
guanidine	sulphas

Inorganic chemicals available from petrochemical operations (including fertilizer production, sulfur recovery and chlorine production form sea water):

chlorine

bromine

sodium hypochlorite
soda
potassium salts
sulfuric acid
oleum
hydrochloric acid
nitric acid
ammonia
urea
guanidine
ammonium sulfate

It should be noted, that fermentation is another source of chemicals already used in large scale in Arab Countries. Ethyl alcohol, butanol and acetic acid are produced in several countries by this method.

2. 2. Availability of pharmaceutical raw materials from Arab productions

As the capacities of petrochemical projects are presently largely exceeding the demands of the Arab markets, considerable quantities of their production will have to be accommodated on the world market in competition with countries having a highly integrated production program. With due consideration of the high

investment in infrastructure, increased competitiveness cannot be expected from cheaper production costs. Therefore, despite the lack of projects for the immediate future, integration into a diversified line of down-stream chemicals will inevitably have to occur and may be expected for the period 1984-1990 in the Arab countries. This will at a later time make available some of the chemicals of list 1 and all of list 2 within the Arab economic community.

2.3. Production of chemicals in various Arab countries

Data on already existing or projected production of various inorganic and organic chemicals selected with consideration of their usefulness in pharmaceutical synthesis is presented below separately for each country. It is understood, that a part or all the amount produced may be taken up by the local market or another down-stream production (e.g. ammonia - urea). Still the quantities used in pharmaceutical synthesis are comparatively small and can always be diverted.

The information presented was collected on visits in Iraq, Kuwait and Libyan Arab Jamahiriya in September 1977. Some data are from a 1977 literature source (1) and from (7).

2.3.1. Iraq: Ref.: (1), (2), (3), (4), (7)

Petrochemical Projects

Petrochemical Project Basra 1: using natural gas, on stream in 1980 to produce:

130,000 mt/yr of ethylene
60,000 mt/yr PVC
60,000 mt/yr LDPE
30,000 mt/yr HDPE
40,000 mt/yr caustic soda chem. grade

Enough polypropylene will be produced for the production of

50 Mio bags

(for agricultural products), present production being 20 Mio/yr.

Petrochemical Project Basra 2: in the planning stage and not yet approved is laid out for the input of

200,000 - 300,000 mt/yr of naphtha

to give in 1985: benzene for the production of styrene and polystyrene
toluene
xylenes for the production of dimethyl-terephthalate and fibres
butadiene for the production of rubber
acrylonitrile for the production of fibres
ethanolamine

The capacity of this complex will eventually be doubled.

Fertilizer projects:

Basra fertilizer plant is in operation using natural gas to give

84,000 mt/yr (200 mt/day) of ammonia
52,000 mt/yr of urea
138,000 mt/yr of ammonium sulfate
325 mt/yr of sulfuric acid

A first extension is now being commissioned to add

800 mt/day of ammonia
1,300 mt/day of urea from the ammonia

A second extension under construction will produce in 2 lines

2,000 mt/day of ammonia
1,620 mt/day of urea from ammonia

No nitric acid will be produced.

Sulfuric Acid

Sulfuric acid is produced from recovered sulfur in Kirkuk and Meshrakoil fields.

Methanol: not produced, but a study for the production from natural gas is being carried out.

Ethylalcohol: from fermentation

Recent production in 2 plants

4,000,000 l/yr

Planned production is for

6,500,000 l/yr

Butanol: will be produced from petrochemicals at a later time. A study revealed a fermentative process to be uneconomical.

Glucose: from dates

40,000 mt/yr. of the annual production of 350,000 mt. of dates will be processed to give a mixture of glucose and fructose as 68 % aqu. solution at an amount of 30,000 mt/yr. In pilot studies the crystallisation of pure glucose was achieved. This crystalline product is likely to be suitable for pharmaceutical purposes, its quantity could be 5,000 - 8,000 t/yr.

Tartaric Acid

From 10,000 mt/yr of grapes, which will be processed for 1,500 mt/yr of grape juice concentrate, 50 mt/yr of crude tartaric acid will be produced by deep cooling. No decision has so far been made about its further processing.

2.3.2. Kuwait: Ref.: (1), (5), (7)

Petrochemical projects

A LPG plant to produce 5,000,000 mt/yr of propane, butane and natural gasoline will be the source of copious quantities of ethane to produce

325,000 mt/yr of ethylene, which is further processed to
130,000 mt/yr of LDPE
320,000 mt/yr of styrene
130,000 mt/yr of ethylenglycol

The study for this project will be ready by end of 1977 and actual production may be expected in 1982 considering 1 year for the engineering and 4 years for construction. An Aromatics project to use naphtha as a feedstock is already approved, but engineering has not yet started; possible start-up time is 1982; production will be

283,000 mt/yr of benzene
60,000 mt/yr of o-xylene
86,000 mt/yr of p-xylene

This production is intended for export.

Fertilizer Projects

Ammonia: Extensive fertilizer facilities already exist at Shuaiba using natural gas. Capacities exist for

660,000 mt/yr of ammonia
664,000 mt/yr of urea
130,000 mt/yr of sulfuric acid

Source of sulfur is Kuwait National Petroleum Company, which recovers it from sour streams.
In 4 additional plants, liquid ammonia and 550 mt/day of urea, shortly to be increased to 950/day are produced.

Projects still away from implementation are concerned with producing butadiene, methanol and petroprotein.

2.3.3. Libyan Arab Jamahiriya: Ref.: (1), (6), (7).

Petrochemical Projects

A steam cracker is under design in Tobruk, which will produce

300,000 mt/yr	(1,000 mt/day) of ethylene
170,000 mt/yr	of propylene
270,000 mt/yr	of pyrolysed gasoline
60,000 mt/yr	of C_4-hydrocarbons

Only 150,000 mt/yr of total ethylene production is already committed for the production of

50,000 mt/yr	of LDPE
50,000 mt/yr	of HDPE
50,000 mt/yr	of ethylene glycol

The remainder of 150,000 mt/yr will be available for export and other productions. Studies are under way to decide between the production of acrylonitrile, cumene, phenol and acetone or polypropylene as the best use for propylene.

Aromatics will be extracted from the pyrolized gasoline fraction to give benzene, toluene and xylenes, which will go into the production of 20,000 mt/yr of polyester-fibres. Butadiene will be the product from the C_4 - cuts. There may be a production of

18,000 mt/yr of caprolactam

pending a decision between the latter and acrylonitrile as basic material for fibres. Phenol and acetone or cyclohexane are alternative intermediates of 2 processes to produce caprolactam and would be vital for pharmaceutical synthesis.

Fertilizer Projects

Breda- plant will produce from natural gas already in 1977 in quantities of

1,000 mt/day of ammonia to go into

1,000 mt/day of urea

An extension of this capacity to add

1,725 mt/day of ammonia

is under design.

Methanol:

For Breda, the production of

1,000 mt/day of methanol

will start in 1977. For the moment, Algeria and Libya are therefore the only Arab producers of solvent methanol.

Inorganic Chemicals:

Abu Kammash is the location of an electrolysis plant already under construction to put out

50,000 mt/yr of hydrogen chloride

50,000 mt/yr of 99 % caustic soda

60,000 mt/yr of chlorine

for the production of PVC and

8,000 mt/yr of sodium hypochlorite

The feasibility study for a similar plant in Mrada is under way.

Production will be

100,000 mt/yr of chlorine, bromine and magnesium oxide.

2.3.4. Saudi Arabia: Ref.: (1), (7)

Petrochemical Projects

Yanbu: as joint venture with Shell Int., due on stream in 1982

450,000 mt/yr of ethylene

45,000 mt/yr of ethylen dichloride

300,000 mt/yr of styrene

300,000 mt/yr of caustic soda

Yanbu: as joint venture with Mobil, due on stream in 1982

450,000 mt/yr of ethylene

160,000 mt/yr of ethylene glycol

400,000 mt/yr of styrene

200,000 mt/yr of polyethylene

Jubail: 2 projects of similar size are under consideration.

Methanol:

Jubail: a venture for the production of

600,000 mt/yr (2,000 mt/day) of methanol

is presently being negotiated.

Ammonia/Urea:

Damman: Present production is

200,000 mt/yr of ammonia

350,000 mt/yr of urea

Additional production under planning in Jubail amounts to

450,000 mt/yr of urea

Sulfuric Acid:

In Damman, a production of

18,000 mt/yr of sulfuric acid

is operative.

2.3.5. Tunisia: Ref.: (7)

Capacities for 300,000 mt/yr of ethylene are considered in Tunisia for the next decade.

2.3.6. Algeria: Ref.: (1)

Petrochemical Projects:

Arzew: based on natural gas, a petrochemical production

is due on stream in 1977 to deliver

120,000 mt/yr of ethylene
48,000 mt/yr of LDPE
36,000 mt/yr of chlorine
41,000 mt/yr of caustic soda
40,000 mt/yr of vinylchloride
35,000 mt/yr of PVC
280,000 mt/yr of aromatic extraction products.

Fertilizer Projects

Arzew: there is an existing production of

330,000 mt/yr of ammonia
140,000 mt/yr of nitric acid
140,000 mt/yr of urea
175,000 mt/yr of ammonium nitrate

Expansion to double capacity is under way for all these products.

2.3.7. Morocco: Ref.: (1)

Most of Morocco's chemical industry centers on phosphates and fertilizers; towards 1990 , capacities for

600,000 mt/yr of urea

may become operative. A complex to produce soda, chlorine and PVC is under construction. Sulfuric acid and ammonia are produced as intermediates for phosphoric acid and ammonium phosphate production.

2.3.8. Dubai and Abu Dhabi: Ref.: (1)

Production from natural gas of

2,000,000 mt/yr of ammonia

1,000,000 mt/yr of urea

is due on stream in 1979 with 2 more ammonia plants under consideration.

A plant for

230,000 mt/yr of sulfur is due for operation

in 1977 and plans for the production of

5,000 mt/yr of sulfuric acid

are under study.

2.3.9. Quatar: Ref.: (1)

Petrochemical Projects:

A project based on natural gas is in advanced planning for the production of

300,000 mt/yr of ethylene

140,000 mt/yr of polyethylene

Fertilizer Projects:

Natural gas is also the feedstock for an operative production of

270,000 mt/yr of ammonia

300,000 mt/yr of urea

2.3.10. Egypt: Ref.: (1), (7)

The production of chemicals is reported in some detail in (7). Therefore, only a list of quantities and/or capacities together with an indication of present or future availability is given here.

Petrochemicals

Ethylene, LDPE, HDPE and PVC are in consideration for production in a joint venture with Montedison and production of DMT, inorganic chemicals and polyester fibres is intended.

260,000 mt/yr of ammonia in 2 plants: on stream
280,000 mt/yr of urea: on stream
550,000 mt/yr of urea: due on stream 1978
500,000 mt/yr of urea: projected
35,000 mt/yr of caustic soda: available
32,000 mt/yr of soda (capacity 100,000 mt/yr available)
50,000 mt/yr of chlorine: available
2,500 mt/yr of hydrochloric acid: available
15,000 mt/yr of hypochlorite: available
63,000 mt/yr of ferric chloride: available
1,000 mt/yr of hydrogen peroxide: available
280,000 mt/yr of nitric acid in 2 plants : on stream
385,000 mt/yr of ammonium nitrate: on stream

As a byproduct of coke production are available

3,500 mt/yr of benzene
500 mt/yr of toluene
250 mt/yr of xylene
50 mt/yr of crude phenol
350 mt/yr of refined phenol
1,200 mt/yr of naphthalene

Sulfuric acid is produced as intermediate in fertilizer production.

Solvents

Ethyl alcohol, produced from molasses is available in quantities to satisfy local needs.
Butanol from fermentation of molasses is produced in amounts still insufficient for local consumption.
Glacial acetic acid is available from fermenting ethyl acetate and butyl acetate are also produced in Egypt.

2.3.11. Syrian Arab Republic: Ref.: (1).

Small capacities for ammonia are operative and a major petrochemical project, timed to start in 1985 will produce

57,000 mt/yr of polyethylene
62,000 mt/yr of propylene
64,000 mt/yr of polyvinyl chloride

The production of aromatics will be considered in a second stage. A plant for production of 300,000 mt/yr of ammonia is in design and urea capacity is under construction.

2.3.12. Jordan: Ref.: (1)

Sulfuric acid will be produced by 1979 from imported sulfur; from the Dead Sea, 1,000,000 mt/yr of potassium chloride will be available in mid- 1980.

2.3.13. Sudan and Somalia:

No petrochemical production is on record.

Conclusions

From an inspection of the data presented, it can be concluded, that aromatic solvents, mineral acids, ammonia, ammonium sulfate, methanol and ethanol are already available in large or sufficient quantities.

A wider range of solvents, chlorine and alkali will be amply available within 5 years. On the other hand, projects for fine chemicals (e.g. aniline, chloraniline) are nowhere on record for the immediate future.

As processes for these chemicals are optimized for comparatively large throughput integrated into large chemical operations in Europe, Japan and North America, the production of minor quantities needed for pharmaceutical use is not likely to be economical in the next decade.

References

1. A.H. Kislin, Chem. Week March 23, 1977
2. Dr. A. Al-ani, Head of Planning, Ministry of Industry, Baghdad
3. H. Al Saffar, Ministry of Industry, Baghdad
4. Dr. F. Al-Saadi, Food expert, Ministry of Industry, Baghdad
5. Mousa F. Ma'rafi, Planning and Development Dept., Petrochemical Industries Company K.S.C. Kuwait City
6. Dr. Ali Sahli, Director of Refineries, National Petroleum Organization, Tripoli, Libya.
7. Dr. Zacharia Khafaga, Dr. Abdel Fattah Shawki; Brief Report 1975

D. Multipurpose plant

3.1. General outline

The following description gives a general idea of one of many possible solutions of a multiprupose plant. The possibility of stepwise enlargement is stressed. Initial capacity will encourage the synthesis of chemicals with few reaction steps and in lesser quantities; one further step of expansion is described, which allows the production of multistep products.

It is the mainpurpose of this proposal to provide an opportunity for gradual build-up of expertise in the fields of

process development from laboratory stage
integrated plant management
integrated plant operating skills
skills in maintenance of apparatus
skills in maintenance of pneumatic and electronic controls.

All of these skills are vital for successful and undelayed operation and cannot be expected to be aquired within short time. The point is stressed, that initial plant size and number of reactors should not be very large, but space and capacity of utility installations should allow later extensions. It is

suggested, that the plant in its primary stage is located adjacent to El Nasr Pharmaceutical Co. and will be supplied with utilities and manpower from there. Initial investment can be kept down in this way. Despite the availability of plant personnel from El Nasr main factory, provisions should be made with the contracting company or others for special training of the work force, especially in maintenance of sophisticated equipment.

Time schedule:

Tendering, engineering proposal	1 year
Construction: 1st stage	2 years
Operation of 1st stage	2 years
Expansion to 2nd stage	1 year

3.2. Description of plant:

3.2.1. Buildings:

Mainproduction building: 5-storied steel-concrete building, constructionally subdivided in 6 units 12 x 2o m; 4 units occupied in 1. stage. 1 Unit can be separated by brick wall for hazardous or toxic operations, other units form large nave, horizontally divided by concrete floors into 5 levels:

Function of levels:

Top level (20 m): short term storage, charging bins

4th level (15 m): reactors, condensors

3rd level (10 m): centrifuges, filters

2nd level (5 m): driers, mills

Ground level (0 m): packing, holding tanks, floor

Each level has enough floor space for movement of fork-lifters.

3.2.2. Ancillary buildings: storage, refrigeration units (brine), maintenance shops, in-process control and analytical laboratories, lavatories, social rooms. 2 Buildings.

3.2.3. Solvent storage: underground facility

3.2.4. Gas storage: open roofed structure

3.2.5. Rail access

3.2.6. Sewage treatment tanks

3.2.2. through 3.2.6. may be unnecessary in 1.stage

3.3. Equipment:

Explosion proof constructions throughout.

3.3.1. Reactors: all equipped with agitator, stainless steel or glas condensors (1o m^2), heating/cooling jacket, permanent pipe connections to adjacent vessels and to several holding tanks (on ground floor), rubber hose connections should be avoided.
Pressure resistant vessels equipped with pressure proof condensors.
Reactors with high temperature oil heating in separated unit.
Traffic way for fork-lifter access to every reactor.

1	4 ooo l	enamelled	
4	2 ooo l	- " - /	
1	2 ooo l	- " - / oil heating	
1	2 ooo l	- " - / 1o ato	
1	1 ooo l	- " -	
4	6 ooo l	- " -	2.stage
1	4 ooo l	stainless steel	
1	2 ooo l	- " -	
1	2 ooo l	- " -	
1	1 ooo l	- " - / 1o ato	
1	1o ooo l	- " -	2.stage
2	6 ooo l	- " -	2.stage
1	2 ooo l	- " - / 1o ato	2. stage

3.3.2. Measuring tanks:

15	1oo - 75o l	glass, enamelled, stainless steel mild steel polypropylene	
12	5oo - 1 ooo l	- " -	2. stage

3.3.3. Holding tanks:

25	2 ooo - 2o ooo	mild steel stainless steel	
15	'6 ooo - 2o ooo	- " -	2. stage

3.3.4. Solvent storage tanks:

8	5o ooo	mild steel,	2. stage

3.3.5. Pumps for liquids:

8	1o - 75 m^3/hr	enamelled	
4	75 m^3/hr	- " - ,	2. stage
12	1o - 75 m^3/hr	stainl.steel	
6	75 m^3/nr	- " - ,	2. stage
1o	special purpose		

3.3.6. Product stills: oil heated

2	250 l	stainl. steel - glass	
1	500 l	stainl. steel	
1	1 000 l	- " - ,	2. stage
4	oil pumps, 0,1 Torr		

3.3.7. Solvent stills; evaporators:

1	film evaporator, 600 l/hr, stainl. steel	
1	- " - , - " -	2. stage
2	stripping columns, stainl. steel	
1	- " - , glass	

all distilling vessels with 6 000 l capacity;

1	fractionating unit, 1 000 l

3.3.8. Centrifuges: stepless, peeler-type and other

4	750 mm	stainless steel	
3	1 200 mm	- " - ,	2. stage
2	750 mm	rubberized	
1	1 200 mm	- " -	2. stage

3.3.9. Filters:

12	(2o 2. stage)	enamelled and stainl. steel

3.3.1o. Dryers:

1 traydryer, 6 chambers. 25 m^2 each tray area
1 tumble dryer, 3m^3
2 tumble dryers, 3m^3 2. stage
2 fluidized bed dryers, 1oo kg batches
3 - " - , 2oo kg batches, 2. stage

3.3.11. Vacuum pumps: water ring pumps to be avoided in a recycled water system
central vacuum system not recommended

12 (+ 8, 2. stage) self priming type (refrigerated)
4 (+ 2, 2. stage) steam pumps, ceramic

3.3.12. Ancillary equipment:

4 (+ 2, 2. stage) mills and sieves
3 fork lifters, charging bins: stainless steel and polypropylene

3.3.13. Gas absorbers for each reactor, sewage dilution tanks, neutralisation tank, oil separator

3.3.14. Refrigeration, brine (-8°)

1 unit 4oo ooo kcal/hr (2.stage)
1 ice generator
1 ice mill

3.3.15. Utilities:

	1. stage	2. stage
steam 7 ato, t/yr	2o ooo	35 ooo
water, total, m^3	1 Mio	1,5 Mio
electricity, 38o V, 5o cps	1,5 Mio	2,5 Mio
refrigeration, brine kcal/yr	2 Bio	3 Bio
nitrogen, m^3/yr	1oo ooo	15o ooo

3.3.16. Spare part reserve:

2 reactor bodies, centrifuge, 1o pumps etc.

3.3.17. Manpower: 4 shift-operation

2 managers
4 production engineers
1o technicians (maintenance, laboratory)
6o workers

5o % increase for 2. stage

3.3.18. Total investment:

5,7 Mio US$ 1. stage
9,3 Mio US$ 2. stage (total)

3.3.19. Annual cost: 2o % deprec. on apparatus
1o % deprec. on buildings
manpower
utilities

1. stage: 1,1 Mio US$
2. stage: 1,9 Mio US$ (total)

E. Industrial profile of some synthetic drugs suggested for production

4. 1. Short term proposals:

Some synthetic drugs and intermediates are proposed which are considered suitable for production in idle equipment at El Nasr Pharmaceutical Company. A detailed list of all surplus apparatus was not available for checking against the requirements in individual productions; The group of chemicals suggested for production in Table 1 is therefore to be understood as list of options according to the possibilities of the remainimg pool of equipment.

The criteria for chosing or rejecting a chemical for short-term-production were:

a) products should be easy to synthesize

b) available equipment uncommitted

c) products should represent therapeutic groups not produced so far in Arab countries

d) products should be taken from requirements of drugs or should be intermediates (also for antibiotics, e.g. procain, potassium, phenylacetate)

e) products marked for separate production units are not considered (exception: niacinamide, isoniacid during the time untill start-up of special plant)

f) products recently withdrawn or restricted on some markets because of side effects (hydroxyquinolines, metformin) or of limited use (nalidixic acid)

g) drugs produced in optimized very large scale operations abroad and clearly uneconomical (e.g. ascorbic acid)

Table 1: Chemicals and drugs for short term production

benzyl nicotinate	
calcium glycerophosphate	
chloroquine	
dapsone	
ethambutol	
ethyl nicotinate	(intermediate)
guaiacol glyceryl ether	
methylphenyl malonate	(intermediate)
methyl phenyl acetate	(intermediate)
metronidazole	
niacinamide	
nikethamid	
niridazole	
nitrofurantoin	
nitrofurazone	
phenobarbitone	
phenytoin	
phthalyl sulfathiazole [1]	
potassium phenylacetate	
thiacetazone	

1) Phthalylsulfathiazole can partly substitute halogenated hydroxyquinolines, which may be withdrawn from the market.

4. 2. Long term proposals:

The proposals assume the existence of a least one multipurpose plant and of special units for optimized large scale production. Special units permitting hydrogenation under pressure should be included in planning. (Table 2)

Some profiles for drugs in Table 1 and 2 are given in the following pages. Data from the literature on production procedures are notoriously sketchy and profiles therefore are estimates with a large margin of error. Cost estimates are subject to the same uncertainity and have not been detailed.

Table 2: Chemicals for long term production

ascorbic acid	(economy questionable)
thiamine	
pyridoxal	
axerophthol	(economy questionable)
propyphenazone	(substitute for aminopyrazolones)
theophyllin	
piperazine base	
nitrofurfuraldehyde diacetate	(intermediate)
novoldiamine	(intermediate)
4,7 - dichloroquinoline	(intermediate)

BENZYL NICOTINATE

Ref: -

Materials: for 2 t

benzylalcohol	1,84 t
nicotinic acid	2,o t
dichloroethane (recov.loss)	1,5 t
sodium hydroxide 5o%	1,5 t
hydrochloric acid	2,o t

Equipment:

1 reactor 5oo l, steel, water separator, solvent still, product still, filter for recovered nicotinic acid

CHLOROQUINE

Method of preparation: substitution of 4,7-dihalo-quinoline

Ref.: Ger.pat. 683692 (1939)

US pat. 2233970 (1941)

A.R. Surrey, H.F. Hammer, JACS 68, 113 (1946)

R.L. Kenyon, J.A. Wiesner, C.E. Kwartler, Ind. Eng. Chem. 41, 654 (1949)

Materials: for 6o t

4,7-dichloro quinoline	38,5 t
novoldiamine	3o,7 t
phenol	12,3 t
phosphoric acid 7o %	54,4 t
methanol	35 kltr

Equipment:

1 reactor, 1ooo, agitator

1 vessel, 2ooo, agitator, enamelled

1 reactor, 1ooo, agitator

1 crystallizer, steel

1 measuring tank

solvent still, centrifuge, drier

Time: 4o days

DAPSONE

Method of preparation: oxydation of 4,4'-dinitro diphenyl sulfide, followed by reduction of nitrogroups.

Ref.: US pat. 2385899 (1945)

Materials: for 5 t

p-nitrochlorobenzene	8,3 t
sodium sulfide	4,1 t
acetic acid	18,o t
sodium hypochlorite 3o%	16,2 kltr.
stannous chloride	54,4 t
hydrochloric acid	41,o kltr.
sodium hydroxide	1oo,o t
ethanol (after recov.)	7,o kltr.

Equipment:

1 reactor, 1ooo l, stainl. steel

1 reactor, 2ooo l, stainl. steel

1 reactor, 4ooo l, enamelled

1 vessel, 6000 l, stainl. steel

1 vessel, 2000 l, steel

3 measuring tanks, 500 l

rubberized centrifuge

centrifuge, stainl. steel

drier

solvent distillation, glass

Time: 60 days

DIETHYL PHENYL MALONATE

Method of preparation: ester condensation with diethyl oxalate followed by decarbonylation.

Ref.: BIOS 766, 46

Materials: for 30 t

ethyl phenylacetate	22,4 t
diethyl oxalate	22,4 t
sodium ethylate	22,8 t
hydrochloric acid	56,1 t
benzene (recovery loss)	3,2 t

Equipment:

2 vessels 1000 l, stainless steel with agitator

1 vat

1 separation vessel with agitator, wide opening

2 measuring tanks, 500 l

1 reactor, enamelled, to attain 170°

product still, 600 l

Time: 100 days

ETHAMBUTOL

Literature data insufficient for evaluation of industrial profile.

ETHYL NICOTINATE

Intermediate for niacinamide

Method of preparation: ethanolysis of acid chloride

Ref.: G. Lock, Pharm. Ind. 14, 366 (1952)

Materials: for 25 t

nicotinic acid	25,5 t
thionyl chloride	41,6 kltr.
ethanol	21,8 kltr.
benzene	6,2 kltr.

Equipment:

1 reactor, 1000 l, agitator, condensor, enamelled

1 vessel, 2000 l, enamelled (separator)

1 vessel, 2000 l, steel

product still 300 l, vacuum pump

Time: 120 days

ETHYL PHENYLACETATE

Method of preparation: ethanolysis of nitrile

Ref.: BIOS 766, 45

Materials: for 3o t

benzyl cyanide	5o,3 t
conc. sulfuric acid	54,5 t
ethanol	43,1 t
benzene (recov.loss)	7,o t
sodium carbonate	3,4 t
hydrochloric acid	1,o t

Equipment:

1 reactor, 1ooo l, agitator, condensor

1 vessel, 4ooo l, with agitator

1 measuring tank, 5oo l

product still, 1ooo l, or parallel stills

filter for phenyl acetic acid

Time: 75 days

FURAZOLIDONE

Ref.: US pat. 2759931 (1956)

H.J. Sanders, R.T. Edmunds W.B. Stillman, Ind. Eng. Chem. 47, 358 (1955)

Materials: for 1o t

5-nitro-furfural-diacetate	9,9 t
hydroxyethylhydrazine	3,9 t
sodium methylate	o,3 t
diethyl carbonate	6,1 t
methanol	6 kltr.
isopropanol	1,5 kltr.

Equipment:

1 reactor, 500 l, agitator, condenser, stainl. steel

1 reactor, 1000 l, agitator, condenser

2 measuring tanks

centrifuge

dryer

Time: 40 days

GUAIACOL GLYCERYL ETHER

Ref.: Span. pat. 212920

Materials: for 10 t

guaiacol	7,65 t
dihydroxychloro-propan	6,79 t
sodium hydroxide	2,24 t
benzene (rec.loss)	6,2 kltr.

Equipment:

1 reactor, 1000 l, agitator, condenser, stainless steel, steam injector, film evaporator, pressure filter, centrifuge

Time: 15 days

ISONIACIDE

Method of preparation: hydrazinolysis of ester

Ref.: Lock, Pharm.Ind. 14, 366 (1952)

Materials: for 2o t

isonicotinic acid	24,1 t
thionylchloride	27,7 t
hydrazine hydrate	1o,5 t
ethanol (recov.loss)	5,o t
benzene (recov.loss)	3,o t

Equipment:

1 reactor, 1ooo l, agitator, condenser, enamelled

2 reactors, 2ooo l, agitator, condenser, stainl. steel

1 measuring vessel, 5oo l

1 vessel, 2ooo l, steel

1 product distillation, 25o l

Time: 45 days

METRONIDAZOLE

Ref.: US pat. 2944061

Cossar, Arzneim.-Forsch. 16, 23 (1966)

Method of preparation: reaction of 2-methyl-5-nitro-imidazole with ethylenchlorohydrin

Materials: for 5 t

2-methyl-5-nitro-imidazole	16,5 t
ethylenchlorohydrin (recov.loss)	41,4 t
chloroform (recov.loss)	1o,o t
ethyl acetate	5,o t

Equipment:

3 reactors, 2000 l, stainless steel

1 crystallizer, 2000 l, stainless steel

3 storage tanks, 4000 l

continous extractor

pressure filter

centrifuge

Time: 50 days

NIKETHAMIDE

Method of preparation: reaction of nicotinoyl chloride with diethylamine

Ref.: Swiss pat. 90807

Materials: for t

nicotinic acid	10,6 t
thionylchloride	15,0 t
diethylamine	6,3 t
benzene (recov.loss)	5,0 kltr.

Equipment:

2 reactors, 500, 1000 l, enamelled, condenser, absorber

2 measuring tanks, 200 l, product still 250 l

solvent still

Time: 65 days

NIRIDAZOLE

Ref.: M. Wilhelm et al. Helv.Chem. Acta, 49, 2449 (1966)

Materials: for 2 t

2-amino-thiazole-HCl	4,93 t
conc. nitric acid	1,3 t
conc. sulfuric acid	4,3 t
sulfamic acid	o,1 t
act. carbon	o,2 t
ammonia	
chlorethyl isocyanate	7,5 t
tetrahydrofuran (rec.loss)	4,o t
chloroform (rec.loss)	2,o t
light benzine (rec.loss)	2,o t
dimethyl formamide (rec.loss)	3,o t
methanol (rec.loss)	2,o t

Equipment:

5 reactors, 1ooo l, agitator, stainless steel

1 vessel, 4ooo l, stainl. steel

1 reactor, pressure proof (4 ato)

2 measuring tanks

1 reactor, 6ooo l, mild steel

nutsche filter, pressure filter

film evaporator, centrifuge

Time: 2o days

NITROFURAZONE

Ref.: US pat. 2416234 (1947)

H.J. Sanders, R.T. Edmunds, W.B. Stillman

Ind. Eng. Chem. 47, 358 (1955)

Materials: for 5 t

5-nitro-furaldiacetate	5,9 t
urea	2,4 t
hydrazine hydrate	2,o t
isopropanol	1,o kltr.
sulfuric acid	1,3 kltr.

Equipment:

1 5oo l reactor, condenser, agitator, stainless steel

1 1ooo l reactor, enamelled

2 measuring tanks

1 crystallizer 5oo l steel

1 pressure filter

centrifuge

drier

Time: 3o days

PHENOBARBITONE

Method of preparation: ethylation of dimethyl phenylmalonate, condensation with dicyandiamide, saponification

Ref.: Kirk-Othmer III, 68

Materials: for 2o t

dimethyl phenylmalonate	27,2 t
ethyl bromide	16,7 t
dicyandiamide	9,7 t
sodium methylate	28,2 t
hydrochloric acid	27,2 t
sulfuric acid	64,4 t
5o% sodium hydroxide	4,1 t
charcoal	o,6 t
methanol (recov.loss)	27,o t
benzene (recov.loss)	1,2 t
trichloroethylen (loss,1o%)	5,8 t

Equipment:

5 reactors, 2ooo l

5 vessels, 5oo - 4ooo l

product still

solvent still

film evaporator

Time: 6o days

PHENYTOIN

Method of preparation: reaction of benzil with urea

Ref: US pat. 265392o

I. Klosa, Chem. Tech. 4, 371-2 (1953)

Materials: for 5 t

benzaldehyde	6,5 t
acetic acid (rec.loss 2o%)	3,2 kltr.
sodium cyanide	o,o5 t
ammonium nitrate	2,74 t
copper sulfate	o,o5 t
sodium nitrite	o,o25t
potassium hydroxide	1,6 t
urea	4,o5 t
hydrochloric acid	2,4 kltr.

Equipment:

1 reactor 2ooo l, agitator, condenser

2 measuring vessels, 5oo l, pressure filter

3 centrifuges, solvent still, 2ooo l

Time: 3o days

PHENYLBUTAZONE

Available literature information insufficient for evaluation of industrial profile

PHTHALYL SULFATHIAZOLE

Ref.: Fr. pat. 57652 (1953)
Fr. pat. 972920
US pat. 2324013-15 (1943)

Materials: for 25 t

bromoacetaldehyd diethyl acetal	18,0 t
thiourea	13,3 t
ACS	21,7 t
pyridine (recov. loss)	5,0 t
phthalic anhydride	10,5 t
conc. hydrochlorid acid	
sodium hydroxide	

Equipment:

2 reators, 2000 l, 4000 l, agitator, condensor, enamelled
pressure filter
2 crystallizers
centrifuge
4 measuring tanks
solvent still

Time: 35 days

POTASSIUM PHENYLACETATE

to be taken up after start of penicillin production

Method of preparation: hydrolysis of nitrile

Ref.: Kirk-Othmer, 15, 213

Materials: for 15 t

benzylcyanide	15,2 t
potassium hydroxide	14,5 t

Equipment:

1 reactor, 4000 l, agitator, steam injector, condenser, pressure filter

product used as aqueous solution

Time: 15 days

THIACETAZONE

Ref.: Das, JACS, 75, 1241 (1953)

Materials: for 20 t

p-amino-benzaldehyde	28,1 t
acetic anhydride	23,7 t
hydrazine 75 %	25,0 t
ammonium thiocyanate	54,6 t
chloroform (recov.loss)	7,0 t
ethanol	5,0 t

Equipment:

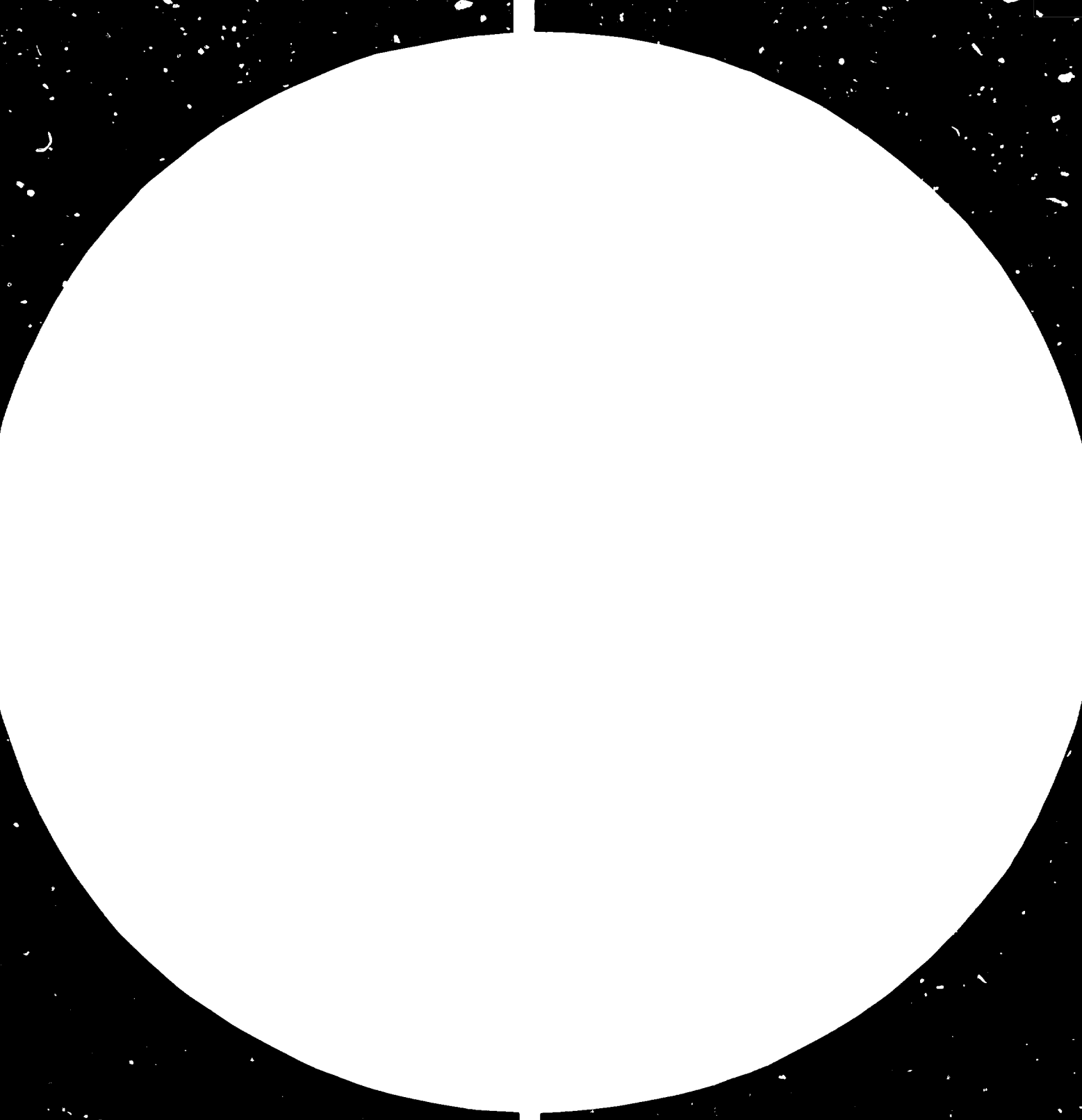
2 reactors, 1000 l, agitator, condenser

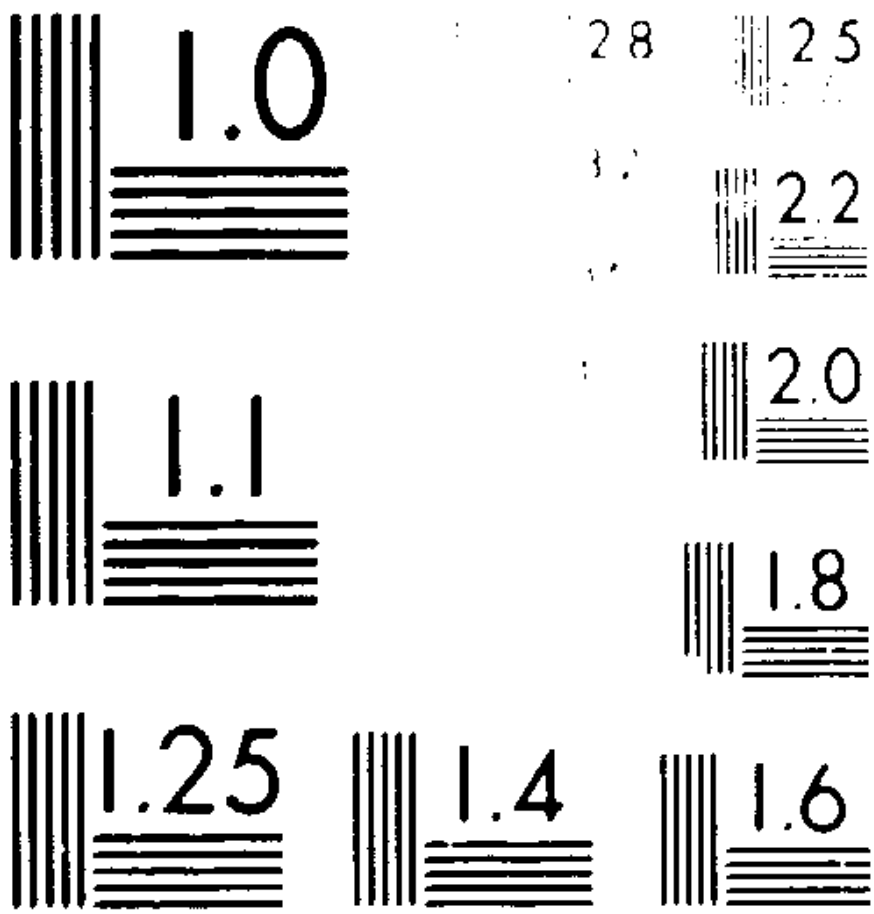
2 crystallizer, pressure filter, solvent still

2 measuring tanks

Time: 75 days


80.11.24




1.0
2.8
2.5
2.2
1.1
2.0
1.8
1.25
1.4
1.6

F. Production plan for drugs recommended for synthesis in a multi-purpose plant

Comments and economic analyses

The list of drugs as recommended for short term production in Table 1 has been compiled with reference to the following criteria

a) usefulness in Arab countries
b) feasibility of synthesis
c) products already under active planning or implementation have been excluded as they are not likely to be the subject of a parallel second effort.

Thus important drugs may appear missing, which have in fact already been dealt with.

A list of drugs which can be produced within the capacity of the proposed multipurpose plant is identical with the contents of Table 3. Ample remaining capacity permits the synthesis of several more bulk drugs which should be seen as examples. An economical analysis for a production programme as given in Table 4 was carried out.

The value of analysis is limited by severe restrictions, which have to be clearly pointed out:

a) detailed chemical information on the conditions, time requirement and yields of individual reactions can be obtained only by either i) purchase of knowhow from a producer or ii) experimental process evaluation. The technical literature practically never yields technological details. Any estimates as given hereunder were arrived at by exercising professional expertise, but may be subject to gross errors.

b) intelligent planning of parallel or subsequent productions in a multipurpose plant is possible only in conditions as described under a)

c) product and raw material prices generally are available only from queries to commercial dealers unless the information from running productions can be tapped. For commercial reasons, information on a larger number of chemicals is not easily revealed in the absence of plausible evidence of forthcoming purchases. Some of the data used therefore are estimates arrived at by making economically and chemically reasonable assumptions. These data have been put in parentheses. Prices taken from daily operations of an Austrian producer include taxes and freight and may be higher than offers to ACDIMA.

Mode of calculation

Although the profitability of individual productions has been indicated, it should be understood that a clean separation between several productions running simultaneously in a multipurpose plant is difficult to make. The annual cost of plant operation, excluding chemicals, but including manpower, utilities and depreciation has been added in estimated aliquots to individual productions. Uncommitted aliquots from idle time of the plant (maintenance) have been added to the total sum of all costs. Although individual profitabilities can be calculated, it is more practical to consider the economic result of all productions of a year taken together. For this reason, individual productions have been accepted even when they turned out to moderately uneconomical, but a few highly uneconomical products have been eliminated. These latter calculations are given separately.

The treatment of working capital was done in the same line of thinking. At first, the total working capital was added to the cost of individual productions of the first year

rather than spreading it over a 10-year span of time, as would be unlogical with a fast changing production programme. The excess amount of working capital thus charged to individual products was refunded by adding to the total profit of the whole plant. Profitability is not changed deeply by this procedure and uneconomical processes still show up clearly. Taxes and interest have been disregarded.

As result, a multipurpose plant of the size proposed did indeed show a profit, thus permitting to carry on productions even of some few individually uneconomical items which may be desirable from the point of view of selfsufficiency of the Arab market.

The following detailed calculation sheets also contain indications of the therapeutic use and of producers, which may be willing to transfer know-how. The cost of aquisition of know-how should be seen in relation to the production value as found on the same page (5 - 20 %).

Table 3. Investment for multi-purpose plant
(million US dollars)

Type of investment	1st stage (12 reactors)	2nd stage (20 reactors)
construction		
buildings	1,5	2,2
reactors incl. spare parts	0,75	1,2
condensors, heat exchangers	0,075	0,1
measuring vessels	0,065	0,1
holding tanks incl. solvent storage	0,3	0,5
pumps	0,04	0,06
distillation equipment	0,16	0,25
solvent recovery units	0,25	0,40
vacuum pumps	0,05	0,08
centrifuges	0,27	0,6
filters	0,04	0,06
dryers	0,3	0,8
ancillary equipment	0,15	0,2
refrigeration	0,75	1,75
sewage treatment	1,0	1,0
Total investment	5,7	9,3
depredation/yr:		
buildings	0,15	0,22
apparatus	0,84	1,42
manpower incl. overhead	0,04	0,06
utilities	0,14	0,24
Annual cost:	1,17	1,94

Piping, electrical wiring and electronic control equipment included.

Table 4. Economical analysis for production programme, first stage of MMP

Product	Prodn. cost	Sales value
acetylsalicylic acid	1 692 512,-	1 841 000,-
benzyl nicotinate	17 363,-	14 037,-
Ca-benzoyl-PAS	526 671,-	548 000,-
chloroquine	628 654,-	660 000,-
diethyl-phenyl-malonate	208 159,-	240 000,-
ethyl nicotinate	194 462,-	443 250,-
furazolidone	50 [illegible]5,-	78 400,-
guaicol glyceryl ether	76 901,-	79 500,-
isoniacide	122 340,-	96 000,-
metronidazole	130 292,-	99 550,-
niacinamide	537 562,-	554 000,-
nikethamide	75 393,-	113 200,-
nitrofurazone	27 753,-	33 638,-
paracetamol	405 991,-	315 000,-
potassium phenyl acetate	54 509,-	67 500,-
phenytoin sodium	20 963,-	55 150,-
phthalyl-sulpha-thiazole	152 993,-	140 000,-
thiacetazone	283 652,-	314 600,-
	5 383 295,-	6 122 038,-
plant operation cost during maintenance, product switching etc.	385 726,-	
bonus for working capital (90 %)		1 050 529,-
Total	5 769 021,-	7 172 567,-
Profit		1 403 546,-
Return on investment: 4 yrs.		

Acetyl salicylic acid: 700 t

Raw materials	$/kg	quantity(mt)	$/total
salicylic acid	1,52	550,0	836 000,-
acetic anhydride	0,746	625,0	466 250,-
ethanol (recov.loss)	0,468	160,0	74 880,-
Total raw material			1 377 130,-
product credit	0,450	290,0	130 500,-
operation cost			101 582,-
working capital			344 000,-
Total production cost			1 692 512,-
Calculated price	2,42		
Market price	2,63	700,0	1 841 000,-
Return			148 488,-

Use:
mild analgesic

Producer:
Bayer, Merck-Darmstadt, Bofors/Sw, Rhone-Progil/France, etc.

Remark: The market price for acetyl salicylic acid was quoted $ 0,73/kg in Arab countries; a price of $ 2,63 is quoted in Austria for pharmaceutical grade product.

Benzyl Nicotinate: 2 t

Raw materials:	$/kg	quantity	$ total
benzyl alcohol	1,892	1,84	3 482,-
nicotinic acid	2,70	2,0	6 919,-
dichlorethane	0,41	1,5	615,-
lye	0,086	1,5	129,-
hydrochloric acid	0,072	2,0	144,-
Total			9 770,-
Aliquot of annual plant operation cost:			5 093,-
working capital			2 500,-
Total cost of production:			17 363,-
calculated price:	8,68	2,0	
market price:	(15,7)		31 400,-
Return			14 037,-

Use:
rubitaciant agent in ointments

Producers:
Merck-Darmstadt, Nordmark/Gy., Givandan-Lavirotte/France, Siegfried AG/Switzerland

Calcium-Benzoyl-PAS: 100 t

Raw materials:	$/kg	quantity(mt)	$ total
PAS	4,05	61,6	249 480,-
Benzoyl chloride	1,42	59,7	84 774,-
lye	0,086	41,0	3 560,-
Calcium hydroxide	0,070	29,8	2 086,-
ethanol (recov.loss.)	0,468	20,0	9 360,-
Total raw material			349 260,-
aliquot of annual plant operation cost			90 411,-
working capital			87 000,-
Total production cost			526 671,-
Calculated price	5,27		
Market price	5,48		548 000,-
Return			21 329,-

Use:
Tuberculostatic

Producer: -

Chloroquine diphosphate: 60 t

Raw materials:	$/kg	quantity (mt	$ total
4,7-dichloroquinoline	(5,70)	38,5	219 450,--
novoldiamine	(7,10)	30,7	217 970,--
phenol	0,412	12,3	5 064,--
phosphoric acid	(0,25)	54,4	13 600,--
methanol	0,148	35,0	5 190,--
Total raw material			461 274,--
Aliquot of annual plant operation cost:			52 380,--
working capital			115 000,--
Total cost of production			628 654,--
Caluclated price	10,48		
Market price	11,00	60,--	660 000,--
Return:			31 346,--

Use:
Antimalariae, "ARALEN", "RESOCHIN"

Producers:
Bayer, Hilton-Davis Chemicals Ltd./Great Britain,
ICI, Rhone-Poulenc

Diethyl phenyl malonate: 30 t

Raw materials	$/kg	quantity(mt)	$ total
ethyl phenyl acetate	(4,0)	22,4	89 600,-
diethyl oxalate	(1,2)	22,4	26 880,-
sodium ethylate	0,641	22,8	14 620,-
hydrochloric acid	0,072	56,1	4 040,-
benzene	0,258	3,2	825,-
Total raw material			135 965,-
Aliquot of plant operation cost			38 194,-
working capital			34 000,-
Total production cost			208 159,-
Calculated price	6,94		
Market price	(8,00)	30,0	240 000,-
Return			31 841,-

Use:
intermediate
Producer:
Dynamit Nobel / Gy

Ethyl nicotinate: 25 t

Raw materials:	$/kg	quantity (mt)	$/total
nicotinic acid	2,70	25,5	68 850,-
thionyl chloride	0,70	41,6	29 120,-
ethanol	0,468	21,8	10 202,-
benzene	0,258		1 600,-
Total raw material			109 772,-
Aliquot of plant operation cost			57 290,-
working capital			27 400,-
Total production cost			194 462,-
Calculated price	7,78		
Market price	17,73	25,0	443 250,-
Return			248 788,-

Use:
rubifaciant, intermediate

Producer:
Givandan-Lavirotte / France, Societé de Laire / France

Furazolidone: 10 t

Raw materials:	$/kg	quantity(mt)	$/total
5-nitro-furfural diacetate	(2,2)	9,9	21 780,-
hydroxyethyl hydrazine	(0,9)	3,9	3 510,-
sodium methylate	0,641	0,3	192,-
diethyl carbonate	(0,80)	6,0	4 880,-
methanol	0,159	6,0	954,-
isopropanol	0,350	1,5	525,-
Total raw material			31 841,-
Aliquot of annual plant operation cost			10 185,-
working capital			8 000,-
Total production cost			50 026,-
Calculated proce:	5,00		
Market price:	7,84	10,0	78 400,-
Return			28 374,-

Use:
topical antimicrobial, "FUROXAN", "TOPAZONE"

Producer:
Norwich Pharmaceutical/USA, Farmitalia/I, Orphahell/NL

Guaiacol glyceryl ether: 10 t

Raw material:	$/kg	quantity(mt)	$/total
guaiacol	(4,60)	7,65	35 190,-
dihydroxychloro-propan	3,123	6,79	21 205,-
sodium hydroxide	0,217	2,24	486,-
benzene	0,258	6,2	1 600,-
Total raw material			58 481,-
Aliquot of annual plant operation cost			3 820,-
working capital			14 600,-
Total production cost			76 901,-
Calculated price	7,69		
Market price	7,95	10,0	79 500,-
Return			2 599,-

Use:
Cough remedy constituent, "GUAIPHENESIN",

Producer:
Haarmann-Reimer/Cy., Merck-Darmstadt
Peboc Ltd./GB, Rhone-Poulenc, Orgamol/Switzerland

Isoniacide: 20 t

Raw materials:	$/kg	quantity(mt)	$/total
isonicotinic acid	(2,5)	24,1	60 250,-
thionylchloride	0,639	27,7	17 700,-
hydrazine hydrate	0,912	10,5	9 576,-
ethanol	0,468	5,0	2 340,-
benzene	0,258	3,0	774,-
Total raw material			90 640,-
Aliquot of annual plant operation cost			30 556,-
working capital			22 600,-
Total production cost			143 796,-
Calculated price	7,19		
market price	4,80	20	96 000,-
Return			- 47 796,-

Alternative preparation: from isonicotinic acid

via isonicotinamide;

requires: 1 pressure vessel
3 reactors / crystallizers, evaporator, centrifuge

Time: 20 days

Raw materials:	$/kg	quantity(mt)	$/total
isonicotinic acid	(2,5)	26,0	65 000,-
ammonia (gas)	(0,30)	16,3	4 900,-
hydrazinhydrate	0,912	11,0	10 032,-
ethanol (recov.loss)	0,468	3,5	1 638,-
Total raw material			81 570,-
Aliquot of annual plant operation cost			20 370,-
working capital			20 400,-
Total production cost			122 340,-

Total production cost			122 340, -
Calculated price	6,12		
Market price	4,80	20	96 000,-
Return			- 26 340,-

Use:
tuberculostatic, INH
Producer:
Bayer, Merck-Darmstadt, Rhone-Poulenc, Carlo Erba/I, Farmitalia/I, AB Bofors/Sw

Metronidazole: 5 t

Raw material	$/kg	quantity(mt)	$/total
2-methyl-5-nitro-imidazole	(3,5)	16,5	57 750,-
ethylene chlorohydrine	(0,26)	41,4	10 764,-
Chloroform (recov,loss)	0,458	10,0	4 580,-
ethyl acetate	0,51	5,0	2 550,-
Total raw materials			75 644,-
Aliquot of annual plant operation cost			35 648,-
working capital			19 000,-
Total production cost			130 292,-
Calculated price	26,06		
Market price	19,91	5,0	99 550,-
Return			- 30 472,-

Use:
trichomonacidal, "METRONIDAZOLE"

Producer:
Gerot/Austria, May-Baker/GB, Fabbrica Italiana Sintetici-Vicenza/I

Niacinamide: 100 t

Raw materials:	$/kg	quantity (mt)	$ total
nicotinic acid	2,70	130,0	351 000,-
ammonia agn.	0,08	70,0	5 600,-
ethanol (losses)	0,468	15,0	7 020,-
carbon	0,69	10,0	6 900,-
catalyst	1,0	1,7	1 700,-
Total raw material			372 220,-
aliquot of annual plant operation cost			75 342,-
working capital			90 000,-
Total production cost			537 562,-
Calculated price	5,37		
Market price	5,54		554 000,-
			16 438,-

Use:
Vitamin, "NICOTAMIDE", VITAMIN PP"

Producer:
Loba-Chemie/Austria, Hoffmann-La Roche-Grenzach/Gy, Merck-Darmstadt, Givandan-Lavirotte/F, Rhone-Poulenc, Carlo Erba/I, AB Bofors/Sweden, Lonza/Switzerland

Nikethamide: 10 t

Raw materials:	$/kg	quantity(mt)	$/total
nicotinic acid	2,70	10,6	28 620,-
thionyl chloride	0,70	15,0	10 500,-
diethylamine	1,04	6,3	6 552,-
benzene (recov.loss)		5,7	1 470,-
Total raw material:			47 142,-
aliquot of annual			
plant operation cost			16 551,-
working capital			11 700,-
Total production cost			75 393,-
Calculated price	7,54		
Market price	11,32	10,0	113 200,-
Return			37 807,-

Use:
respiratory stimulant "CORAMINE"

Producer:

Merck-Darmstadt, Givandan-Lavirotte/France,
Societéde Laire/France, Carlo Erba/I, Siegfried/Switzerland

Nitrofurazone: 5 t

Raw materials	$/kg	quantity(mt)	$/total
5-nitro-furfuraldi-acetate	(2,20)	5,9	12 980,-
urea	0,125	2,4	300,-
hydrazine hydrate	0,912	2,0	1 824,-
isopropanol	0,351	0,79	277,-
sulfuric acid	0,305	2,4	732,-
Total raw material			16 113,-
aliquot of annual plant operation cost			7 640,-
working capital			4 000,-
Total production cost:			27 753,-
Calculated price	5,55		
Market price	6,72	5,0	33 638,-
			5 885,-

Use:

topical antibacterial, "NITROFURAL", "FURAZIN",

Producer:
Boehringer-Mannheim, Dott.Formenti-Milan/I,
Profarmaco-Milan/I, Zambon-Milan/I,
Lab. Espinos-Bofill/Spain, Lisac/Spain,
Norvich-USA

Paracetamol: 100 t

Raw materials:	$/kg	quantity (mt)	$ total
p-Nitrophenol	0,950	122,0	115 900,-
iron	0,561	116,0	65 076,-
acetic anhydride	0,746	79,0	58 934,-
hydrochloric acid	0,072	17,0	1 224,-
rectif. spirit	0,468	50,0	23 400,-
Total raw material			264 534,-
aliquot of annual plant operation cost			100 457,-
working capital			66 000,-
product credit: acetic acid		75,0	- 25 000,-
Total production cost			405 991,-
Calculated price	4,06		
Market price	3,15	100,0	315 000,-
			- 90 991,0

Use:
mild analgesic

Producer:
Bayer, Hoechst, Merck-Darmstadt, Rhone-Poulenc Roussel-Uclaf etc.

Potassium phenylacetate: 15 t

Raw materials:	$/kg	quantity (mt)	$/total
benzyl cyanide	2,209	15,2	33 571,-
potassium hydroxide	0,578	14,5	8 388,-
Total raw material			41 959,-
aliquot of plant			
operation cost			2 550,-
working capital			10 000,-
Total production cost			54 509,-
Calculated price	3,63		
Market price	(4,5)	15,0	67 500,-
Return			12 991,-

Use:
Precursor for Penicillin G

Producer:
Haarmann-Reimer/Cy, Albright-Wilson Ltd./GB
Societé de Laire/France, ICMESA, Milan/I

Phenytion - Sodium: 5 t

Raw materials	$/kg	quantity(mt)	$/total
benzaldehyde	1,02	6,5	6 630,-
acetic acid	0,461	3,2	1 475,-
ammonium nitrate	0,370	2,74	1 014,-
urea	0,125	4,05	506,-
potassium hydroxide	0,578	1,6	925,-
hydrochloric acid	0,072	2,4	173,-
Total raw material			10 723,-
aliquot of annual plant operation cost			7 640,-
working capital			2 600,-
Total production cost			20 963,-
Calculated price	4,19		
Market price	11,03	5,0	55 150,-
Return:			34 187,-

Use:
anticonvulsant, antiepileptic, antiarrhythmic
5,5-DIPHENYL HYDANTOIN-Na

Producer:
Nordmark/Cy, Societé de Laire/France, Recordati/I

Phthalylsulphathiazole: 25 t

Raw material:	$/kg	quantity(mt)	$/total
bromoacetaldehyde diethyl acetal	(3,2)	18,0	57 600,-
thiourea	0,793	13,0	10 309,-
ACS	(1,2)	21,7	26 040,-
pyridine	1,29	5,0	6 450,-
phthalic anhydride	(0,74)	10,5	7 770,-
Total raw material			108 169,-
Aliquot of annual plant operation cost			17 824,-
working capital			27 000,-
Total production cost			152 993,-
Calculated price	6,12		
Market price	5,60	25,0	140 000,-
Return			- 12 993,-

Use:
intestinal antimicrobial, non-resorbable sulfa

Producer:
A/S Synthetic Aarhus/Denmark, May-Baker/GB,
Rhone-Poulenc, Istituto chemioterpico Italiano/I,
Gruppo Lepetit/I

Thiacetazone: 20 t

Raw materials	$/kg	quantity(mt)	$/total
p-amino-benzaldehyde	(4,0)	28,1	112 400,-
acetic anhydride	0,746	23,7	17 680,-
hydrazine	0,912	25,0	22 800,-
ammoniumthiocyanate	0,973	54,6	53 126,-
chloroform	0,458	7,0	3 206,-
ethanol	0,468	5,0	2 340,-
Total raw material			211 552,-
aliquotof annual			
plant operation cost			19 100,-
working capital			53 000,-
Total production cost			283 652,-
Calculated price	14,18		
Market price	15,73	20,0	314 600,-
Return			30 948,-

Use:

tuberculostatic "CONTEBEN"

Producer:
Bayer, Serva International/Cy., Smith-Nephew/GB
Fermion OY/Finland, Fluka/Switzerland

Clearly uneconomical products by process chosen

Dapsone: 5 t

Raw materials:	$/kg	quantity (mt)	$ total
p-nitrochlorobenzene	1,122	8,3	9 313,—
sodium sulfide	0,273	4,1	1 118,—
acetic acid	0,461	18,0	8 308,—
sodium hypochlorite 30%	(0,20)	16,2	3 240,—
stannous chloride	(0,8)	54,4	43 520,—
hydrochloric acid	0,072	41,0	2 952,—
sodium hydroxide (lye)	0,086	100,0	8 615,—
ethanol	0,468	7,0	3 274,—
Total raw material			80 340,—
Aliquot of annual plant operation cost			98 214,—
working capital			20 000,—
product credit			
stannic hydroxide	(0,3)	25,0	- 7 620,—
Total production cost			190 934,—
Calculated price	38,19		
Market price	(15,0)		75 000,—
			- 115 934,—

Ethyl phenylacetate: 30 t

Raw materials	$/kg	quantity(mt)	$/total
benzyl cyanide	1,75	50,3	111 127,-
conc. sulfuric acid	0,305	54,5	16 600,-
ethanol	0,468	43,1	20 170,-
benzene	0,258	7,0	1 806,-
sodium carbonate	0,098	3,4	335,-
hydrochloric acid	0,072	1,0	72,-
Total raw material			150 110,-
Aliquot of plant operation cost			25 463,-
working capital			37 500,-
Total production cost			213 073,-
Calculated price	7,10		
Market price	(4,00)	30,0	120 000, -
Return:			- 93 073,-

Use:
intermediate of PHENOBARBITONE

Producer:
Haarmann-Reimer /Cy, Societé de Laire / France,
ICMESA-Milan / I

Niridazole: 2 t

Raw materials:	$/kg	quantity(Mt)	$/total
2-amino-thiazole hydrochloride	(5,2)	4,93	25 636,-
conc.nitric acid	0,154	1,3	200,-
conc. sulfuric acid	0,305	4,3	1 311,-
sulfamic acid	(0,80)	0,1	80,-
Chloroethyl isocyanate	(1,5)	7,5	11 250,-
tetrahydrofuran (loss)	(1,2)	4,0	4,800,-
chloroform (rec.loss)	0,455	2,0	910,-
light benzene (loss)	0,357	2,0	714,-
dimethyl formamide (loss)	1,00	3,0	3 000,-
methanol (recov.loss)	0,159	2,0	318,-
Total raw material			48 219,-
Aliquot of annual plant operation cost			20 370,-
working capital			12 000,-
Total production cost			80 589,-
Calculated price:	40,29		
Market price:	not available		

Use:
amebicidal, schistosomicidal, "AMBILHAR"

Producer: -

Phenobarbitone: 20 t

Raw material:	$/kg	quantita (mt)	$/total
dimethyl (or ethyl) phenyl malonate	6,94	27,2	188 768,-
ethyl bromide	3,167	16,7	52 890,-
dicyandiamide	(1,3)	9,7	12 610,-
sodium methylate	0,641	28,2	18 076,-
hydrochloric acid	0,072	27,2	1 958,-
sulfuric acid	0,305	64,4	19 642,-
50 % lye	0,086	4,1	353,-
charcoal	0,507	0,6	304,-
methanol (recov.loss)	0,159	27,0	4 303,-
benzene (recov.loss)	0,258	1,2	310,-
trichloroethylene (loss)	(0,35)		2 030,-
Total raw material			301 244,-
aliquot of annual plant operation cost			76 390,-
working capital			75 300,-
Total production cost			452 934,-
Calculated price	22,65		
Market price	6,15	20,0	123,000,-
			- 329 934,-

Use:

sedative, hypnotic, "LUMINAL", "PHENOBARBITAL"

Producer:

Bayer, Merck-Darmstadt, May-Baker/GB, Rhone-Poulenc, Farmitalia

G. Comments on a proposal made by the Indian Drug and Pharmaceuticals Ltd (IDPL) to ACDIMA

The economy of proposal by IDPL for the production of 8 drugs with idle equipment available at El Nasr Pharmacuetical Company was studied. Restrictions as pointed out before also apply here, but the precise quantities of chemicals used as offered by the tenderer could be used.
Calculations as shown there under show an economic loss. The reason for this result may again be a higher level of prices for chemicals due to freight and taxes. As ACDIMA will not have to pay import tax, a production still may be feasible and the study should be repeated with prices as applicable as the Arab market.

Mode of calculation:

In contrast to the calculations quoted on preceding pages, working capital was added to production costs in aliquots of a 10-year span, because all productions are independent of each other and will be run permanently in dedicated apparatus.

Total balance: IDPL - project

Product:	Prodn. cost	Sales price:
Analgin	1 184 310.-	1 059710.-
Paracetamol	286 159.-	315000.-
Piperazine citrate	42 362.-	43250.-
Piperazine phosphate	36 400.-	40000.-
Piperazine adipate	41 477.-	41268.-
Diazepam	47 336.-	38600.-
Sulphamethoxazole	107 958.-	100800.-
Trimethoprim	52 527.-	38950.-
	1 798 529.-	1 677578.-
Balance:		- 120951.-

ANALGIN: 200 t

Raw materials:	$/kg	quantity(mt)	$/total
pyrazolone	(2,20)	244	536 000,-
dimethylsulfate	0,758	274	207 692,-
sodium hydrox. (solu.)	0,074	668	49 432,-
sodium hydroxide (flakes)	0,225	62	13 950,-
sodium nitrite	(0,3)	92	27 600,-
sodium bisulfite	(0,185)	404	74 584,-
sulfuric acid	0,305	80	24 400,-
formaldehyde	0,196	64	12 544,-
act. carbon	0,690	8	5 520,-
benzene (losses)	0,258	136	35 088,-
rect. spirit (losses)	0,468	250	117 000,-
Total raw materials			1 103 810,-
Utilities			24 000,-
Labor: 15 + 1			14 000,-
Overhead: 25 %			3 500,-
Depreciation (10 %)			39 000,-
Total cost of production:		200,0	1 184 310,-
Calculated price:	5,92		
Market price	5,30		1 059 710,-
Return			- 124 600,-

Capital cost: additional equipment

2 reactors	65 000,-
2 centrifuges	65 000,-
various	10 000,-
working capital	250 000,-
Total Fixed and Working	390 000,-

Paracetamol: 100 t

Raw materials:	$/kg	quantity (mt)	$ total
p-nitrophenol	0,950	122	115 900,-
iron	0,561	116	65 076,-
acetic anhydride	0,746	79	58 934,-
hydrochloric aced	0,072	17	1 224,-
rectif. spirit	0,468	50	23 400,-
Total raw material			264 534,-
Utilities			15 000,-
Labor: 12 + 1			11 300,-
Overhead: 25 %			2 825,-
Depreciation: (10 %)			17 500,-
Total cost of production:			311 159,-
Byproduct credit: acetic acid		75	25 000,-
		100	286 159,-
Caluclated price:	2,86		
Market price:	3,15		315 000,-
Return:			28 841,-

Capital cost: additional equipment

2 reactors	65 000,-
1 centrifuge	35 000,-
various	10 000,-
working capital	65 000,-
	175 000,-

Piperazine citrate:	25 t		
Raw materials:	$/kg	quantity (mt)	$ total
piperazine hexahydrate	(0,85)	23,5	19 975,-
citric acid	0,648	17,3	11 207,-
carbon	0,690	0,65	448,-
hydrosulphite	0,750	0,073	55,-
rectified spirit (losses)	0,468	10,0	4 677,-
Total raw materials:			36 362,-
Operating costs: 33 % of total (see below)			6 000,-
Total cost of production:		25,0	42 362,-
calculated price:	1,694		
market price	1,730		43 250,-
Return			888,-

Piperazine phosphate:	25 t		
Raw materials:	$/kg	quantity	$ total
piperazine hexahydrate	(0,85)	29,6	25 160,-
phosphoric acid	(0,25)	19,8	4 950,-
carbon	0,690	0,34	235,-
hydrosulphite	0,750	0,053	55,-
Total raw materials			30 400,-
Operating costs: 33 % of total			6 000,-
Total production costs:		25,0	36 400,-
Calculated price:	1,456		
Market price:	(1,60)		40 000,-
Return			3 600,-

Piperazine adipate:	25 t		
Raw materials	$/t	quantity (mt)	$ total
piperazine hexahydrate	(0,85)	25,0	21 250,-
adipic acid	(0,75)	19,2	14 000,-
carbon	0,690	0,25	172,-
hydrosulphite	0,750	0,053	55,-
Total raw materials			35 477,-
Operating costs: 33 % of total (see below)			6 000,-
Total production costs		25,0	41 477,-
calculated price:	1,659		
Market price:	1,651		41 268,-
Return			- 209,-

Operating costs: all piperazine salts

Utilities	4 500,-
Labor: 8 + 1	8 000,-
Overhead: 25 %	2 000,-
Depreciation: (10 %)	3 500,-
Total operating costs	18 000,-

Capital cost: additional investment	
Filter, mill, dryer	10 000,-
working capital	25 000,-
Total Fixed and working	45 000,-

Diazepam: 2 t

Raw materials:	$/kg	quantity	$ total
p-Nitrochlorobenzene	1,122	2,45	2 750,-
benzyl cyanide (d=.99)	2,210	1,99	4 400,-
chloracetyl chloride (d=1.42)	2,130	3,71	7 910,-
hexamine	(0,15)	1,72	265,-
carbon	0,690	0,42	290,-
iron (sponge qual.)	0,561	1,62	910,-
sodium hypochlorite	(0,20)	1,43	290,-
p-toluene sulfonyl chloride	(1,30)	2,8	3 640,-
dimethyl sulfate (d=1,33)	0,758	1,73	3 820,-
pyridine (losses)	1,290	0,94	1 220,-
sulphuric acid (d=1,8)	0,305	5,04	1 535,-
hydrochloric acid	0,072	0,32	23,-
sodium hydroxide (lye)	0,077	3,70	285,-
soda	0,098	0,02	72,-
methanol (losses)	0,159	19,3	3 084,-
benzene (losses)	0,258	2,89	745,-
toluene (losses)	0,240	6,72	1 613,-
dichloro ethane (losses)	0,410	3,80	1 558,-
rectified spirit (losses)		6,21	2 906,-
methyl isobutyl ketone	(0,50)	0,86	460,-
ether (losses)	0,60	2,60	1 560,-
Total raw materials			39 336,-
Utilities			1 000,-
Labor: 10 + 1 20 %			2 000,-
Overhead: 25 %			500,-

Diazepam cont'd

Depreciation			4 500,-
Total cost of production:		2,0	47 336,-
Calculated price:	23,67		
Market price:	19,30		38 600,-
Return:			- 8 736,-

Capital cost: additional equipment

1 Centrifuge	30 000,-
1 dryer	5 000,-
working capital	10 000,-
Total Fixed and Working	45 000,-

Sulphamethoxazole: 5 t

Raw materials	$/kg	quantity (mt)	$ total
diethyl oxalate (d=1,078)	(1,2)	10,9	13 400,-
sodium	1,60	1,2	1 790,-
ACS	(1,20)	6,4	7 680,-
sulphuric acid (d=1,8)	0,305	5,2	1 590,-
hydrochloric acid (d=1,19)	0,072	4,5	324,-
hydroxylamine.HCl	5,67	4,25	24 100,-
sodium hypochlorite	(0,20)	2,0	400,—
lye	0,077	7,6	590,-
ammonia water	0,05	11,7	580,-
carbon	0,690	0,76	524,-
recti fied spirit (losses)	0,468	35,0	16 380,-
dichloroethane (losses)	0,410	10,0	4 100,-
pyridine (losses)	1,290	7,0	9 030,-
acetone	0,300	5,5	1 500,-
benzene	0,260	11,5	2 970,-
Total raw materials:			84 958,-
Utilities:			5 000,-
Labor: 15 + 1, 50 % of year			7 000,-
Overhead: 25 %			3 500,-
Depreciation (10 %)			7 500,-
Total cost of production:		5,0	107 958,-
calculated price:	22,00		
Market price:	20,16		10 080,-
Return			- 7 158,-

Sulfamethoxazole cont'd.

Capital cost: additional equipment

1 reactor	15 000,-
1 centrifuge	30 000,-
various	10 000,-
working capital	20 000,-
Total Fixed and working	75 000,-

Trimethoprim: 1 t

Raw materials:	$/kg	quantity (mt)	$ total
ethoxy propionitrile			
3,4,5-trimethoxy-	(1,5)	1,3	1 950,-
benzaldehyde	(19,5)	2,2	42 900,-
guanidine . HCl	0,37	3,1	1 150,-
sodium	1,60	0,87	1 393,-
methanol	0,159	4,48	714,-
carbon	0,690	0,18	124,-
acetic acid	0,462	1,4	646,-
ammonia liqu.	0,4	2,0	800,-
Total raw materials			49 677,-
Utilities			500,—
Labor: 4 + 1 20 %			900,-
Overhead: 28 %			250,-
Depreciation: 10 %			1 200,-
Total production cost:			52 527,-
Calculated price:	52,53		
Market price:	38,95		38 950,-
Return			-13 577,-
Working capital			12 000,-
No additional investment assumed			
Total Fixed and Working			12 000,-

H. Economic feasibility study for the production of thiamin hydrochloride

Quantity produced: 65 t

Main intermediates of synthesis:

ethoxypropionitrile
acetamidin hydrochloride
sodium 1-hydroxymethylene-2-ethoxy-propionitrile
1-dimethoxymethyl-2-ethoxy-propionitrile
α-chloro- -acetyl-butyro-lactone
3-acetyl-3-chloro-propanol
2-methyl-4-amino-5-acetaminomethyl-pyrimidine
2-methyl-4-amino-5-aminomethyl-pyrimidine
(2-methyl-4-amino-5-pyrimidyl -methyl-4-amino-pyrimidyl-5)-
-methyl-dithiocarbaminate
thiamin hydrochloride

Main starting materials:

acrylonitrile
acetonitrile
α-acetyl-butyrolacton
carbondisulfide
formic acid

Capital Investment:

Building and equipment:	Mio $
production building laboratory, storage	900 000,-
32 reactors 2 m3	800 000,-
measuring tanks	20 000,-
storage tanks	50 000,-
condensors, heat exchangers	200 000,-
extractors	30 000,-
filters	10 000,-
10 centrifuges	300 000,-
dryers	120 000,-
pumps	20 000,-
3 solvent recovery units	120 000,-
nitrogen supply	20 000,-
compressor	50 000,-
refrigeration	80 000,-
auxiliary equipment	20 000,-
piping	200 000,-
control devices	50 000,-
Total	2 990 000,-
Working capital	250 000,-
Total capital costs	**3 240 000,-**

Raw material costs:	$/kg	quantity(mt)	$
sodium	1,6	110,0	176 000,-
formic acid (incl.losses)	0,45	90,0	40 500,-
acrylonitrile	0,88	63,0	55 400,-
acetonitrile	(0,4)	73,0	29 200,-
α-acetyl-butyrolacton	2,40	50,0	120 000,-
chlorine	0,388	39,8	15 400,-
dimethylsulfate	0,760	146,0	111 000,-
calcium chloride	0,66	80,0	52 800,-
aqu. ammonia	0,08	130,0	10 400,-
hydrogen peroxide 30 %	0,587	26,0	15 300,-
hydrochloric acid	0,072	180,0	13 000,-
soda ash	0,098	65,0	6 400,-
acetic anhydride	0,746	60,0	44 800,-
lye	0,086	100,0	8 600,-
carbon disulfide	(0,80)	45,5	36 400,-
decolorizing carbon	0,690	4,0	2 800,-
sulfuric acid 50 %	0,150	25,0	3 700,-
barium chloride	(0,8)	100,0	80 000,-
methanol	0,15	65,0	9 700,-
ethanol	0,468	65,0	30 400,-
acetone	0,29	65,0	18 800,-
dichloroethane (loss)	0,19	30,0	5 700,-
carbontetrachloride	0,338	30,0	10 100,-
Total raw materials			896 400,-

		$
Total capital costs		3 240 000,-
Raw material costs		896 400,-
Utilities		120 000,-
Manpower 50 persons		20 000,-
Overhead		5 000,-
Depreciation: 10 %		324 000,-
Total cost of production		1 365 000,-
Calculated product price	21,06	
Market price	10,39	675 350,-
Profit		- 689 650,-

Producers:

A/S Synthetic/Denmark, Bayer, Hoffmann-La Roche, Merck-Darmstadt, May-Baker/GB, Rhone-Poulenc, Richardson-Merrill, Naples/I

Comment:

The result of the economical calculation shows that the production of thiamin-hydrochloride can be achieved in an economical way only in larger volume by highly optimized plant layout. It will be noticed, that in this calculation raw material costs exeed the sales value of the product; only large productions will be able to assure low raw material prices and accomodate the cost of depreciation of fixed and working capital.

Appendix I

SYNTHETIC BULK PRODUCTS OF EL NASR PHARMACEUTICAL COMPANY (EXCLUDING INTERMEDIATES) WHICH HAVE BEEN MANUFACTURED IN PAST YEARS OR ARE PRESENTLY MANUFACTURED

Product	Prodn. target 1977 (metric tons per annum)
Sulfanilamide	15
Sulfacetamide	75
Sulfacetamide-Na	2o
Sulfaguanidine	75
Sulfadimidine	65
Sulfadimidine-Na	3o
Chloramphenicol	12
Chloramphenicol palmitate	2
Chloramphenicol stearate	-
Tolbutamide	4o
PAS	-
Salicylic acid	1o 1)
Na-salicylate	15
Methylsalicylate	-
Salicylamide	5o
Acetylsalicylic acid	4oo
Ca-benzamidosalicylate	6o
Ferric ammonium citrate	-
Diiodohydroxyquinoline	-

1) sublimed

Appendix II

PROJECTS UNDER STUDY OR UNDER EXECUTION FOR NEW OR IMPROVED SYNTHETIC PRODUCTION UNITS

	Production targets (mt/a)
Acetanilide	500
Acetylaminobenzene-sulfonylchloride	800 [1]
Sulfanilamide	500 [1]
Sulfacetamide	100
Sulfaguanidine	100
Sulfadiazine	250
Sulfamerazine	40
Sulfadimidine	100
Salicylic acid	700 [1]
Acetylsalicylic acid	700
PAS	-
Niacinamide	100
INH	50
Paracetamol	100
Dextrose	500

1) implemented figure

Analgin	200
Piperazine salts	75
Sulfamethoxazole	5
Trimethoprim	1
Diazepam	2

Drugs intended to be developed from laboratory to production scale in cooperation with outside assistance and with the use of existing surplus equipment:

Riboflavin-phosphate
Glibenclamide
Allopurinol
Xylocaine
Furosemide

Appendix III

LIST OF SOME REPRESENTATIVE CONSULTING FIRMS AND SUPPLIERS OF EQUIPMENT FOR PHARMACEUTICAL FACTORIES INCLUDING MULTI-PURPOSE SYNTHESIS PLANTS

General planning, integrated units:

Austroplan, Österreichische Gesellschaft für Planung, A-1102 Vienna, Triesterstrasse 33, Austria

The Badger Company Inc., Cambride, Mass. 02142, USA

The A.P.V. Company Ltd., Crawley, West Sussex, RH 102 QB, Great Britain

Buehler-MIAG GmbH, Braunschweig, 33 Braunschweig, Ernst-Amme-Strasse 19, FRG

Chemical Plant and Machinery Assoc. of India, Mackinnen Mackenzie Building, Ballard Estate, Bombay 400 038, India

Chemocomplex, 1062 Budapest, Nepköztarsasag utja 60, Hungary

R.L. Dalal and Cy/Dalal Consultants and Engineers Private Ltd., 86, Dr.Annie Besant Rd., Worli Naka, Bombay-4000 18, India

INGECO SpA, Via M. Gonzaga 7, I-20123 Milan, Italy

Pharmaconsult, D-6900 Heidelberg, Kußmaulstrasse 10, FRG

SPEICHIM, 106 Rue d'Amsterdam, Paris 9^{ieme}, France

Zimmer Aktiengesellschaft, D-6000 Frankfurt 60, Borsigallee 1-7, FRG

Representing several Japanese consulting firms:

NISSHO-IWAI CO. LTD.

Lugeck 1-2/7/40
1010 Vienna

Reactors; heat exchangers

Henry Balfour Co. Ltd., Leven, Fife, Scotland, Great Britain

Gebr. Boehler Co., AG, D-4000 Duesseldorf 11, Hansa-Allee 321 FRG

De Dietrich Cie, 7-67110 Niederbronn-les-Bains, France

Lampart, H-1475 Budapest, Box 41, Hungary

Pfaudler-Werke AG, D-6830 Schwetzingen, Scheffelstrasse 55, FRG

Schwelmer Eisenwerk Mueller Co., GmbH, D-583 Schwelm, Loherstrasse 1, FRG

Vereinigte Edelstahlwerke AG (VEW), A-1010 Vienna, Elisabethstrasse 1, Austria

Centrifuges:

Alfa-Laval AB Celleco, Box 94, S-14700 Tumba, Sweden

Ellerwerk, Otto Ellerbrock Maschinenfabrik, D-2000 Hamburg 60, Steilhooperstrasse 102-116, FRG

Ferrum AG, Maschinenfabrik, CH-5102 Rupperswil, Switzerland

Rousselet S.A., Rue Montalivet B.P. 129, F-07104 Annonay, France

Extractors:

Baker Perkins Chemical Machinery Ltd., Westfield Road, Peterborough PE 3 6TA, Great Britain

Dryer:

Titus, D-6148 Heppenheim

Pumps:

Chemiepumpenbau AG, CH-4800, Zofingen, Sitzerland

W.Dickow Pumpenfabrik, D-8264 Waldkraiburg, Siemensstrasse 22, FRG

Friedrichsfeld GmbH., D-6800 Mannheim 71, Steinzeugstrasse 50, FRG

W. Hedrich Vakuumanalgen, D-6331 Katzenfurt, FRG

Ochser Sohn GmbH Co, A-4020 Linz, Austria

Waste water treatment:

BAMAG Verfahrenstechnik GmbH, D-6308 Butzbach, Wetzlarer-straße 136, FRG

Appendix IV

ECONOMICS OF THE OFFER OF AB BOFORS CHEMATUR

Two production plans for the production of:

700 mt acetyl salicylic acid
100 mt niacinamide
60 mt isonicotinic acid hydrazide (INH)

Value of materials delivered:

acetyl salicylic acid plant:	$
10 reactors/crystallizers (2-4 m^3 assumed)	300 000,-
12 tanks	80 000,-
1 evaporator (assumed: falling film type)	50 000,-
4 measuring/dissolving vessels	20 000,-
15 centrifugal pumps	30 000,-
2 centrifuges 1000 mm	120 000,-
4 heat exchangers/condensors	20 000,-
1 filter	2 000,-
1 dryer (stream type assumed)	100 000,-
1 refrigeration unit	50 000,-
piping, fitting, wiring	250 000,-
monitoring and controls	80 000,-
var. auxiliary equipment	100 000,-
	1 202 000,-

Niacinamide - INH - plant:	
4 reactors/crystallizers (2-4 m^3 assumed)	120 000,-
11 tanks	75 000,-
1 evaporator (assumed: falling filmtype)	50 000,-
10 centrifugal pumps	20 000,-
2 centrifuges	120 000,-
4 heat exchangers/condensors	20 000,-
3 filters	6 000,-
1 dryer (stream dryer assumed)	100 000,-
piping, fitting, wiring	160 000,-
monitoring and controls	50 000,-
auxiliary equipment	100 000,-
Total	821 000,-

	$
Total value of materials delivered	2 023 000,-
Price of AC BOFORS CHEMATUR (1 Skr = 0,209 $)	4 123 000,-
Estimated charge for engineering, knowhow	2 100 000,-

Economic feasiblity of a production of acetyl salicylic acid, niacinamid and INH according to AB Bofors CHEMATUR offer

Raw materials:	$/kg	quantity (mt)	$ total
Acetyl Salicylic acid 700 t			
Salicylic acid	1,52	560	581 200,-
Acetic anhydride	0,746	665	496 090,-
pyridine	2,84	3,5	9 940,-
decolorizing carbon	0,69	3,5	2 415,-
byproduct credit acetic acid dil.	0,152	210	- 31 920,-
Total			1 057 725,-
Niacinamide: 100 t			
Niacin	2,70	130	351 000,-
ammonia fl.	0,116	70	8 120,-
decolorizing carbon	0,69	10	6 900,-
boric acid	(0,4)	1,3	520,-
ammonium molybdate	(2,0)	0,4	80,-
Nitric acid, sodium hydroxide		...	100,-
Total			366 720,-

Isoniacid: 60 t	$/kg	quantity(mt)	$ total
Isonicotinic acid	(2,5)	87,0	217 500,-
ammonia	0,116	47,0	5 450,-
hydrazine hydrate	0,912	30,0	27 360,-
decolorizing carbon	0,69	6,7	4 620,-
Boric acid	(0,4)	0,9	360,-
ammonium molybdate	(2,0)	0,3	60,-
Nitric acid, sodium hydroxide		...	100,-
ethanol	0,468	34,8	16 290,-
Total			271 740,-
utilities: total			100 000,-
manpower: total 30			30 000,-
overhead			7 000,-
depreciation of plant assembly cost (10 yrs)			5 000,-
depreciation of working capital (10 yrs)			49 000,-
Total			191 000,-

Total balance:

Total raw materials:	1 696 185,-
utilities manpower, overhead , depreciation of assembly cost and working capital	191 000,-
depreciation of Bofors price	412 300,-
Total cost of production	2 299 485,-

sales values:	$/kg	t	
acetyl salicylic acid	2,63	700	1 841 000,-
niacinamide	5,54	100	554 000,-
INH	4,80	60	288 000,-
Total value of production			2 683 000,-
Profit			383 515,-

	$
calculation of return of investment:	
Capital to BOFORS	4 123 000,-
Working capital	490 000,-
assembly cost	50 000,-
Total Fixed and Working Capital	4 663 000,-
Total cost of production (raw materials, utilities, labor, overhead, without depreciations	1 833 185,-
Total sales value of products	2 683 000,-
	849 815,-

Return of investment: 5.5years

Appendix V

OFFER FOR MULTI-PURPOSE PLANT

1. The manufacturing cost of a drug in a multipurpose plant is likely to be higher than a plant designed for the manufacture of only one item. In the latter case, the plant is usually designed for higher production capacity. It operates continuously for a production of only one item resulting in better efficiencies of production, and it is possible to select a type and size of equipment to minimise the initial investment and the cost of operation. Single product plants, however, are feasible only when the requirement of a particular drug is large enough to put up a special plant for the same. In many developing countries the need is for the manufacture of small quantities of variety of drugs with the lowest possible investment. The multipurpose plant is, therefore, more suited to meet the requirements of a small developing country.

2. In a multipurpose plant, for synthetic drugs, the minimum capacity is about $\frac{1}{2}$ ton per day to maximum of about 2 tons per day. The cost of such a plant would vary according to the range of drugs selected and the source of supply of the equipment.

3. The grouping of products in a multipurpose plant could best be done according to the kind of equipment to be utilised. The basic conversion step is carried out in reactors and the material of construction used for these reactors could be the best consideration for grouping of the products. We give below the type of products which could be manufactured in different types of reactors:

Glasslined Reactor	Methyl Salicylate
	Aspirin
	N-acetyl-paraminophenol
	Phenacetin
	Lidocaine
Stainless Steel Reactor	Nicotinamide
	Isoniazid
Cast Iron Reactor	Phenylbutazone

The grouping suggested by you is not very feasible and we would, therefore, suggest the above mentioned groupings.

5. The concept of multipurpose plant and its advantages are as follows:

A modern plant for pharmaceutical products must provide for the manufacture of an extensive line of basic pharmaceutical chemicals. In designing a plant for a developing country this problem is even more significant because

- the needs of a developing country are for a number of small volume products.
- sophisticated automation is generally not required.
- average life of a plant is higher and the plant must take care of new products, technology for which is still under development.

In most of these situations a multipurpose plant in which a number of products in relatively small quantities can be manufactured is IDEAL. Multipurpose plants generally are not automated and are used to manufacture a number of products either sequentially or to some extent simultaneously using a single/double series of equipment.

The Sarabhai team of technical experts has specifically developed a multi-purpose design for a "developing country", on the threshold of industrial development in pharmaceuticals. The product mix and capacity are optimally balanced to minimize initial investment and yet to cover a broad spectrum of pharmaceutical chemicals. Enough flexibility is provided in the design to take care of the varying and ever changing demands of the pharmaceutical market. In this design, provision has been made to increase the capacity substantially by marginal additional investment.

Product mix

The product mix selected for initial production is as follows:

1. Methyl salicylate
2. Aspirin
3. Paracetamol
4. Nicotinamide
5. Isoniazid
6. Phenacetin
7. Phenyl butazone
8. Lidocaine

The plant is designed to produce approximately 200 tons of pharmaceutical chemicals per year. A number of other pharmaceutical products can be manufactured from the same set of equipment (see list in annexure 3). The average batch size for each of the products chosen is uniform.

The uses of the product-mix suggested are as under:

(a) Methyl salicylate: It is used as a flavouring agent and also as a counter-irritant. As a flavouring agent it is equal to winter-green oil or sweet birch oil. As a counter-irritant, it is applied to the skin in the form of a liniment;

(b) Aspirin: It is employed as an antipyretic and analgesic in a variety of conditions;

(c) Paracetamol: It is an analgesic compound and is used to relieve the pain of headaches, nyalgias, arthralgic and other pains arising from muscles and joints and peripheral nerve affections;

(d) Nicotinamide: It has identical properties as Vitamins of the B group;

(e) Isoniazid: It is the most potent tuberculostatic antibacterial agent. It has also been employed as a prophylactic for use in persons constantly exposed to tubercular patients;

(f) Phenacetin: It is an analgesic and antipyretic having the same general field of usefulness as the salicylates;

(g) Phenyl butazone: It is a synthetic pyrazolone derivative having analgesic and antipyretic properties;

(h) Lidocaine: It is a potent local anesthetic with a potency twice that of an equal concentration of procaine. The drug may be combined with epinephrine to delay absorption, prolong its action and reduce its toxic effects.

Capital investment

The capital investment has been worked out for a multi-purpose plant to produce 200 tons of pharmaceutical chemicals per year.

Assumptions:

(a) The plant capacity is on the basis of 2-shift/300 day operation. Only dryers will be operating during the third shift;

(b) Electric power 440 V/50 c/s/3/ and raw water are assumed to be available;

(c) The prices of equipment are estimated as of April 1977 and are subject revision on actuals basis;

(d) Engineering workshop, office equipment, vehicles, warehousing racks are not included in the estimate;

(e) The cost of plant and machinery is considered on FOB Bombay basis.

Fixed capital investment

	Cost $US	Contingency $US
Land 10,000 m^2	*	*
Land development	*	*
Building 1,200 m^2 (annexure 2)	120,000	10,000
Process equipment (annexure 1)	200,000	9,000
Services equipment (annexure 1)	90,000	4,000
Laboratory equipment (annexure 1)	20,000	
Clearance and forwarding	5,000	2,000
Installation and erection including electricals 20% on equipment	50,000	5,000
Pre-operatives	22,000	2,000
Interest during construction	*	*
Know-how and engineering fees at 5%	22,500	-
	529,500	32,000

* not included

Working capital investment

The working capital, at 30% of the fixed investment, is assumed to be $US 150,000. This, however is dependent upon the price and availability of raw materials, packaging materials, credit policies and sources of supply.

Total investment

		$US
Fixed capital investment (excluding land and interest during construction		561,500
Working capital investment		150,000
	Total	711,500

Process description

A brief description of the process to be employed for each of the pharmaceutical chemicals is given in this section.

Methyl salicylate

Salicylic acid is estrified with methanol, by refluxing for about 3-4 hours, in the presence of sulphuric acid. Most of the methanol is distilled off, then it is diluted with ice water. The acqueous phase is discarded and the oily phase is washed with bicarbonate solution. It is then dried over sodium sulphate and vacuum distilled.

Aspirin

Acetylation of salicylic acid with acetic anhydride, at 50-60°C for about 1 hour. Dilute the mixture with cold water and allow it to cool, then filter the solids - recrystallize the crude product from aq. alcohol.

N-Acetyl paraaminophenol

Acetylation of p-aminophenol with acetic anhydride at 60-70°C for 2 hours. The product is isolated with ice water. It is recrystalized with hot water, after carbon and hydrosulphite treatment.

Nicotinamide

Hydrolysis of 3-cydnopyridine in presence of IRA 402 or an equivalent resin, for 3-4 hours. The resin will have to be converted into OH form from the chloride form with 5% sodium hydroxide solution. Nicotinamide solution is concentrated and washed with alcoholic ammonia, and then crystalized if necessary.

Isoniazid

Hydrolysis of 4-cyanopyridine at 70-80°C for 3-4 hours, in the presence of IRA 402 resin. The crude product is isolated by concentration. It is converted to hydrizide with alcohol and hydrazine hydrate.

Phenacetin

Acetylation of p-phenetidine* with acetic anhydride is carried out at 40-50°C. After 10 minutes cool and filter the solids. The product is recrystallized from methanol, centrifuged and dried.

Phenylbutazone

Ethylester of n-butylmalonic acid is condensed with diphenyl hydrazine in the presence of sodium methoxide at 80-100°C for 3-4 hours to give crude phenylbutazone. Xylene is used as solvent. The crude product is extracted in water and acidified with hydrochloric and acetic acid (pH 5.5). The product obtained is filtered and recrystallized from aq. acetone. It is dried in vacuum dryer. Solvents are recovered by distillation.

Lidocaine

Chloroacetyl chloride is added to the mixture of m-xylidine benzene and triethylamine at about 20°C with constant stirring. Triethylamine hydrochloride is dissolved in water and chloro-acetylxylidine is taken in ethanol. It is refluxed with diethylamine for 4-5 hours to obtain crude Lidocaine base. This base is hydrochlorinated in butanol and the solids are centrifuged and recrystallized from ethanol. It is then dried in steam heated dryers.

Manufacturing inputs

Raw materials

The quantities of raw materials required per kg of the product are given in annexure 4, A-H. Most of these materials are well known and are readily available in the international market.

Packaging materials

The nature of packaging for each of the chemicals and type of packaging material to be used are described in annexure 5. The minimum size of packing is also indicated.

Manpower

The technical and administrative manpower requirements for a capacity of 200 t per year have been estimated in annexure 6.

Services

The services available at the site are listed in annexure 7.

---

* p-phenetidine is prepared from p-nitrophenetole by reduction.

Annexure 1

ESTIMATED COST OF EQUIPMENT

A. Process equipment

Quantity	Item
2	Glasslined reactor 1,000 litres, jacketted with anchor agitator, condenser, receiver 500 litres
2	SS reactor jacketted with stirrer, 100 litres MS receiver 500 litres
3	MS distillation unit (1,000 litres) with receiver (5,000 litres)
1	Cast-iron reactor jacketted anchor-type stirrer, MS receiver 500 litres
2	SS 316 centrifuge, 1,000 mm diameter
1	MS rubber-lined centrifuge, 1,000 mm diameter
2	Steam-heated dryer, 72 aluminium trays (80x80x3)
2	Vacuum steam-heated tray dryer with trays as above
3	SS crystallizer with jacket and anchor-type stirrer, 5,000 litres
2	Pressure leaf filter SS
	Total cost FOB Bombay: $US 200,000

B. Services equipment

2	Water ring vacuum pump, 80 m^3/h
2	Air compressors with receiver, 30 cfm, 30 psi, with receiver
1	Steam generating plant 600 kg/h, with water softener and accessories
1	Refrigeration plant for chilled water 20 TR with cooling tower
6	Water circulation pumps
1	DM water plant
Set	Electrical distribution panel LT/HT circuit breaker
	Total cost FOB Bombay $US 90,000

C. Laboratory equipment

2	Balances
Set	Glassware
1	Vacuum pump
1	Muffle furnace
1	Electric oven
1	pH meter
Set	Misc. instruments, thermometers, melting point apparatus etc.
	Total cost FOB Bombay $US 20,000

Annexure 2

BUILDING AND LAND REQUIRED

	m^2
Production building	400
QC laboratory	50
Raw material and semi-finished goods storage	100
Services	300
Packing, warehouse and stores	200
Office area	100
	1,150
Open area for cooling tower and tanks	200
	1,350
Land required (with no major expansion planned)	10,000

Annexure 3

LIST OF OTHER PRODUCTS WHICH CAN ALSO BE MANUFACTURED IN THIS PLANT AND THEIR USES

Procaine hydrochloride	-	local anesthetic
Nitrofurantoin	-	antiseptic
Clofibrinic acid	-	antichollesteremic
Hydroxyurea	-	anti cancer agent
Chloropropomide	-	oral hypoglycemic
Tolbutamide	-	oral hypoglycemic
Ferrous fumarate	-	haematinic agent
Clonidine hydrochloride	-	anti hypertensic
Phthalyl sulphacetamide	-	anti bacterial agent

Annexure 4

BATCH SIZE AND RAW MATERIAL REQUIREMENT

A. Methyl salicylate

Batch size - 150 kg

Raw material	Kg of raw material per kg of final product
Salicylic acid, CP	1.0
Methanol	1.0
Con. sulphuric acid	0.1
Sodium bicarbonate	0.5
Sodium sulphate	0.5

B. Aspirin

Batch size - 80 kg

Salicylic acid, CP	0.775
Acetic anhydride, CP	1.16
Alcohol (ltrs)	1.25

C. N-acetyl paraminophenol

P-aminophenol, USP or BP	0.8333
Acetic anhydride, CP	1.00
Sodium hydrosulphite	0.02
Activated charcoal	0.10

D. Nicotinamide

Batch size - 80 kg

3-cyanopyridine, C	1.05
Resin IRA 402	0.02
Sodium hydroxide	0.10
Sodium chloride	0.10
Alcohol (ltrs)	0.10
Ammonia	0.00625
Activated charcoal	0.0625

E. Isoniazide

Batch size - 80 kg

4 cyanopyridine, C	1.2
IRA 402	0.02
Sodium chloride	0.10
Sodium hydroxide	0.10
Alcohol (ltrs)	0.10
Ammonia	0.00625
Activated carbon	0.0625
Hydrazine hydrate (ltrs)	0.5

F. Phenacetin

Batch size - 150 kg

p-nitrophenetole, CP	1.25
Iron powder	1.333
Formic acid	0.0267
Sodium hydroxide	0.034
Acetic anhydride	1.0
Methanol (ltrs)	1.0

G. Phenylbutazone

Batch size - 150 kg

Ethylester of b-butylmalonic acid	1.253
Diphenyl hydrazine	1.067
Sodium methoxide	0.307
Hydrochloric acid	0.200
Acetic acid	0.0347
Xylene (500-450) (ltrs)	0.333
Acetone (100-70) (ltrs)	0.200

H. Lidocaine

Batch size - 150 kg

m-xylidine	0.687
Chloroacetyl chloride	0.643
Triethylamine	0.673
Diethylamine	0.373
Hydrochloric acid	0.247
Ethanol (400-350) (ltrs)	0.333
Butanol (200-180) (ltrs)	0.133
Benzene (200-170) (ltrs)	0.200

Annexure 5

SPECIFICATION AND PACKAGING MATERIALS REQUIRED

Product	Grade	Packing
Methyl salicylate	USP	25 litres carboys
Aspirin	USP	Polyethylene bags fibre drums, 25 kg
N-acetyl paraminophenol	USP	Polyethylene bags fibre drums, 25 kg
Nicotinamide	USP	Polyethylene bags fibre drums, 2 kg
Isoniazid	USP	Polyethylene bags fibre drums, 2 kg
Phenacetin	USP	Polyethylene bags fibre drums, 25 kg
Phenylbutazone	USP	
Lidocaine	USP	

Annexure 6

MANPOWER REQUIREMENTS

A. Technical

	Shift 8-4 General	Shift 6-2 First	Shift 2-10 Second	Shift 10-2 Third	Total
Plant manager	1	-	-	-	1
Senior chemist	1	1	1	-	3
Maintenance engineer	1	-	-	-	1
Junior chemists	2	2	2	-	6
Skilled operators (process)	1	2	2	1	6
Unskilled operators (process)	2	5	5	1	13
Maintenance operators	2	2	2	1	7
Total	10	12	12	3	37

B. Administrative and other

General manager	1
Sales manager	1
Accountant	1
Accounts assistant	1
Purchase/sales assistant	2
Warehouse in charge	1
Warehouse assistant	1
Watchmen/security	2
Clerks/PA	5
Typist/steno	2
Workers	5
Total	22

Annexure 7

SERVICES AVAILABLE

Steam at 6 kg/cm^2 pressure

Chilled water at $8^{\circ}C$

Oil-free compressed air at 30 psi

Vacuum at 700 mm Hg below atmosphere

DM water

Soft water

Raw water

X. FERMENTATION PRODUCTS

A. Summary

Introduction

A list of products which could be made by fermentation in the Arab countries is given together with an indication of the technology involved. It is necessary to asses in each case the current requirements, the forecast for the next ten years and the economics of production. The latter becomes all the more important in view of the fact that some of these products are also made by Synthetic route.

Present

Ethanol, Acetic Acid and Enzymes are currently being manufactured in Egypt and possible other arab states. It is recommended that the possibility of augmenting these capacities be considered.

Future

a) Citric Acid

An industrial profile is given for citric acid on the basis of shallow tray fermentation process and using cane molasses as carbon source. The estimated cost of porduction compares very favourably with the current market price. The factors which have to be investigated before establishing a plant for the manufacture of citric acid have been highlighted.

b) Feed Yeast

A modified industrial profile is presented for yeast. Fodder yeast is presently being manufactured in Egypt for export using cane molasses in the fermentation medium. The desirability of establishing a model plant for the production of dried yeast for use as protein concentrate for both animals and humans has been emphasized. For animals, Yeast will be incorporated into the feed rations. For humans it is suggested that it be incorporated into a basic food such as flour. The different aspect to be considered before actually embarking upon such a project have been outlined.

B. Introduction

There are five categories of possible products based on fermentation as illustrated below:

1. Organic Solvents: ethanol, butannol, acetone glycerol
2. Organic acids : Acetic, lactic, citric, gluconic
3. Enzymes: Proteinases, ammylases, lactases
4. Nutritional supplements - vitamins, amino acids, protein concertrates, yeast.
5. Antibiotics - Penicillins, Streptomycin, Tetracycline Bacitracin

There are two basic requirements for the production of usable goods by fermentation processes: a source of fermentable carbon and an organism which produces the desired product or is itself the desired product. Usually, economic constraints dictate that the cheapest form of fermentable carbon be used, and in the case of much of the Arab countries this is the sugar in molasses. In those areas rich in oil the potential exists for the use of methane and other n-paraffins as the carbon source, but this potential is not likely to develop to any extent because these sources are also potentially more expensive than molasses.

The availability of molasses in the Arab countries has been reported as follows:

Egypt	300 000 tons	(cane)
Morocco	127 000 tons	(beet)
Tunisia	52 000 tons	(beet)
Sudan	30 000 tons	(cane)
Syrian Arab Republic	18 000 tons	(beet)
Iraq	16 000 tons	(date)
Lebanon	3 000 tons	(beet)

Algeria and Libyan Arab Jamahiriya, data not available

It is seen that there is an adequate supply of molasses for the establishment of fermentation industries, although it is not evenly distributed geographically. The largest supply, (Egypt) is not at present fully utilized at home, two-thirds being exported to Europe. While exports are a good and necessary source of "hard" currency, they are an increasingly better source, the more value is added to them before export.

1. Organic solvents

a) Ethanol:

The fermentation of molasses to ethanol and the recovery of the alcohol by distillation is well known art which is practiced in Egypt and probably elsewhere in the Arab countries.

b) Acetone - Butanol:

These two solvents can be produced by fermentation of molasses using a strain of clostridium acetobutylicum. In molasses medium the ratio of the solvents produced is: butanol 6.3, acetone 3 and ethanol 5. These are separated in a rectifying column. The acetone-butanol process is somewhat more difficult than the ethanol process. The residual broth after the removal of the solvents is rich in riboflavin and can be evaporated to dryness and used as an animal vitamin B2 concentrate.

c) Glycerol:

Glycerol may be produced micro-biologically by a modification of the ethanol fermentation. The modification consists of adding sodium sulphite or a mixture of normal sulphites and bisulphites to the fermenting mash. Yields of 22% glycerol, 30% ethanol and 50% acetaldelyde, based on sucrose used, cab be obtained.

2. Organic Acids

a) Acetic acid:

This is presently being manufactured in Egypt by both the bio-oxidation of ethanol and as a by - product from the production of acetyl salicylic acid. No information about its manufacture elsewhere in the Arab countries is available.

b) Lactic acid

Lactic acid is an easy fermentation to carry out to the crude acid stage. There are several strains of Lactobacillus which will ferment the sugar in molasses. A growth factor supplement such as corn steep liquor may be advantageous. Purification of the crude acid is difficult. The chemical sequence of precipitation as calcium lactate followed by double decomposition with sulphuric acid to recover the acid and precipitate the calcium sulphate must be done twice. It is difficult to remove the water from the final solution.

The preferred procedure is to esterify the crude acid with an alchohol - ethanol can be used - then recover the acid by saponification after fractional distillation. This is a complicated procedure but if the volume cab be made great enough so that the resultant pure lactic is cheap enough, there is potentially a very large market demand for the production of methalcrylate plastics.

c) Citric acid

This product is of particular interest to ACDIMA and an industrial profile has been worked out and is presented separately.

d) Gluconic acid

For this acid a glucose medium such as hydrolyzed starch, rather than molasses must be used. Also it is an aerobic process and requires good aeration . There is a choice of several genera of organisms Acetobacter Pseudomonas, penicillium, Aspergillus. The fermentation batch time is about forty hours. Continuous fermentation is a possibility.

3. Enzymes

Two enzymes are presently being manufacured in Egypt: Alpha amylase and a proteinase. The former is used in desizing cotton and the latter in the tanning industry. Alphaamylase and Beta anylase working together could be utilized in hydrolyzing corn starch to glucose. Glucose is needed for certain fermentations eg. antibiotics and riboflavin.

The list of enzymes which can be made from fermentation is long.

4. Nutritional supplements

a) Vitamins

i) Riboflavin (vitamin B^2)

A vitamin B2 concentrate can be obtained by drying the broth from the acetone- butanol fermentation after solvents have been stripped off. An alternative fermentation is available in which the riboflavin is the main product.

It must be noted that the organisms used in this more specific fermentation are pathogenic to the growing cotton plant. Therefore, whereever this fermentation is carried out, great care must be taken to ensure that the organisms do not get out of the factory to infect the vegetation, particularly cotton, in the surrounding country side. This involves filtering and sterilizing the air issuing from the fermentation tanks, serilizing the liquid wastes and locating the factory as far from vegetation as is feasible.

Two organisms are favourable - Eremothecium ashbyii and Ashbya gossypii . It should be noted that riboflavin can also be produced by chemical means, the method of choice by Hoffman La Roche.

ii) Vitamin B 12

Unlike other vitamins appearing in the human and animal diets , vitamin B 12 is exclusively a product of the biosynthetic activity of microorganisma. It is essential for the growth and well-being of many animals but must be obtained either by ingestion of food of animal origin or from commensal organisms within the animal's own digestive tract.

Vitamin B 12 is not a single substance but a group of cobamides closely related chemically. A similar group, B 12 analogs or pseudo B 12, promote the growth of certain microorganisms only, and have no value nutritionally for man or animals.

Vitamins B 12 are produced by wide range of bacteria and streptomyces but not by yeasts or molds.

Of particular interest to ACDIMA is the possibility of recovering the vitamin from the spent biomass of the tetracycline process in Iraq.

Alternatively the blomass can be dried and used as a crude Vitamin B 12 concentrate.

It is of course possible to make a special fermentation for Vitamin B 12 only. However the recovery process is the same as for the biomass of tetracycline and it is suggested that this be dealt with first.

iii) Vitamin C

As stated earlier the production process of Vitamin C is only partly microbiological. Very briefly, the process is : d- glucose is electrolytically reduced to d-sorbitol. D-sorbitol is dehydrogenated to l-sorbose by acetobacter suboxydans, the only microbiological step.

iv) Thiamin, Nicotinamide, Folic, Biotin and other members of the B complex

When desired as pure chemicals, these vitamins are produced sythentically. To extract them from natural sources is more expensive However they occur in relatively large quantities in Yeast and in this form can be used as a nutritional supplement.

v) Yeast (or single protein S.C.P.)

Yeast as a product of a fermentation process is of particular interest to ACDIMA. Therefore, a separate industrial profiel is presented.

vi) Amino Acids

These are three nutritionally essential amino acids which are produced by a microbioligical transformation of a specific precursor. These are:

a) L-threonine fron alpha-alpha diamino- pimelic acid by an auxotroph of E coli or

L-threonine from L-homoserine by a variety of bacterial cultures e.g. Bacillus, Xanthomonas, Pseudomonas etc. This process requires the preliminary production of L- homoserine by auxotrophs of Mc. glutamicus.

b) L-tryptophan from indole, indolepyruvic acid or anthranillic acid by Claveceps purpurea.

c) L- isoleucine from DL-alpha-aminobutyric acid by B subtills.

d) L-Lysine is an essential amino acid which is accumulated in the culture medium of various phototropic and auxotrophic bacteria e.g. Eserichia Coli and Aerobacter aerogenes. It is also accumulated by yeasts in a medium to which has been added a suitable precursor such as alpha-amino adipic acid, alpha-beta-adipic acid or 5-formy 1-2 oxovaleric acid.

vii) Flavouring agent

There is, however, one amino acid, L-glutamate, which as the monosodium salt, is a flavouring agent widely used in Europe and North America. This may become of interest to ACDIMA and therefore is mentioned here.

Although organisms which accumulate L-glutamic from sugar base are available, a cleaner fermentation results by using organisms which are able to utilize acetate, e.g. Corynebacterium acetoglutamicum. Since acetate is a chemical which is available in Egypt both as a by-product of the manufacture of acetyl salicylic acid (see under acetic acid) and from the bio-oxidation of ethanol, and since also there appears to be a

large possible market for momosodium glutamate (MSG), there is reason to believe that the matter should be looked into in a thorough manner. Two aspects are important: research on the technology and the market potential.

A list of products, which could be produced in Arab countries based on Fermentation is given above. However, it is necessary to assess in each case the current requirements, the forecast for the next ten years and the possibilities of export as also the economics of production. In the case of certain products such as Butanol, acetone, glycerol and riboflavin the economics of production by fermentation vis a vis by synthetic process has to be evaluated. As regards some of the nutritional supplements such as thiamin, folic acid and amino acids, the requirements are normally so small that large scale manufacture will be hardly economical.

C. Present status

a) Ethanol

As indicated earlier, ethanol is produced by fermentation of molasses in Egypt and probably in other Arab countries. The quantaties produced are probably adeuqate to supply the home market and there is no compelling reason to believe that a large increase is imminent. Competitive to fermentation alcohol is that which can be produced from petrochemicals. This is usually considered cheaper. However, petro-chemical alcohol requires a large production to serve a large market within a radius of easy transportation. This set of circumstances may not exist and therefore it is likely that fermentation alcohol will not become obsolete.

b) Acetic Acid:

As indicated earlier, this is currently being manufactures in Egypt. It is assumed that the health authorities in the Arab countries like their counterparts in the rest of the world will be reluctant to agree to the use of acetic acid as vinegar in the food industry, unless it is produced from alcohol which itself has been "naturally" produced. This means that fermentation alcohol and vinegar are symbiotic. On the other hand, chemically produced acetic acid can be concentrated to the glacial form and can find industrial uses wherever a mild neutralizer is needed, such as deliming hides in a tannery. The future market for acetic acid as vinegar will probably reflect the size of the urban population. If the latter rises slowly, so will

the demand for vinegar.

c) Enzymes

As mentioned earlier, alpha anylase and proteinase are manufactured in Egypt. It would seem that the course of wisdom would be to refrain from producing other enzymes until a home market of adquate size was demonstrated.

D. Future development

a) Industrial profile for Citric Acid

It has been estimated that the consumption of citric acid in the Arab countries would be 2000 tons per annum in 1980 as indicated in Volume I. It is noted that this, apparently, is the estimated consumption for drug use only. If non-drug use in considered, the figure of 2000 may be much too small.

The following comments apply to a plant conceived to produce 3000 tons per annum of anhydrous citric acid.

1.. Choice of process

Citric acid is produced by a strain of Aspergillus niger growing on a molasses solution. The mold first grows from spores, then secretes the citric acid into the solution. Air is required, and it may be supplied by arranging either that the mold be grown on the surface of a ventilated shallow tray of molasses medium, or in a deep stirred tank through which air is bubbled. Although it is often stated that the deep tank method is more economically attractive than the shallow tray method, this cannot be accepted unequivocally for all circumstances.

There is little doubt that the shallow tray method is the easier method to carry out. The skill to operate a shallow-tray process exists at present in Egypt and perhaps elsewhere in the Arab countries. Therefore a preliminary design for a shallow-tray plant was worked out and preliminary cost estimated made.

Preliminary cost estimate for a plant making 3000 T citric acid per annum

Assumption

Fermentation yield of citric acid will be 60% of sugar input. Losses in processing will be 30% of fermented yield.

Area required:

A- for fermentation	3500 M^2
B- for processing et al	3500 M^2
	7000 M^2

Capital costs

Building at 100 L.E. Per M^2	700000
Equipment (100% of building)	700000
	1,400,000

Interest

8 % per annum = 122,000 p.a.	37.3 per ton

Depreciation

a) Building (20 years) 35,000 p.a.	11.7 per ton
b) equipment (10 years) 70,000 p.a.	23.4 " "

Maintenance

At 5 % 70,000 p.a.	23.4 " "
	95.8

Materials

Material	Price/ton	Tons required for ton citric	Price per ton citric
H_2SO_4	45	0.70	31.50
Molasses	20	4,00	80.00
NH_4NO_3	114	0.02	2.28
Methanol	140	0.20	28.00
$Ca(OH)_2$	6	0.65	4.00
			145.78

Summary of costs

	L.E. per ton for citric
Capital	95.8
Materials	146.0
Labour (25 at 360 p.A)	3.0
Administration overhead (100% labour)	3.0
Steam 20 tons.At 0.1	2.0
Electricity (100 Kwat at 0.006)	6.6
Water ($46M^3$ at 0.35)	1.6
Market price 555.	258. 0

A note on cost analysis

Although the figures given on the preceeding page are thought to be derived from reliable sources, the very fabourable ratic of cost estimate to market price is cause for skepticism.

It is noted that no charge is included for land, due to ignorance of a fair price, but, it is considered most unlikely that inclusion of land values would destroy the favourable ratio.

It is further noted that any one of the items or all of them together could be raised 25 % and the favourable ratio would still not be destroyed.

Design of Proposed Plant:

Please refer to figures I and II

An orthodox process is recommended, viz:

1. Fermentation on shallow trays.
2. Separation of citric broth from myceleal mat.
3. Neutralization of citric acid with lime.
4. Separation of calcium citrate.
5. Acidification with H_2SO_4.
6. Separation of citric acid solution.
7. De colourization with activated carbon
8. Separation of de colourized citric acid solution.

9. Passage through cation exchange column.

10. Concentration of citric acid solution by evaporation.

11. Crystallization of citric acid.

12. Separation of citric Crystals.

13. Packaging crystals into drums.

14. Drying of crystals.

RECOMMENDATIONS

ACIMA should investigate the following factors before taking a decision to go in for the manufacture of citric acid.

a) A review of requirements of Citric Acid in Arab countries is warranted. As against an annual requirement of 2000 tons by 1980, the actual quantity of citric acid planned for import by Egypt in 1977 is only 304 tons.

b) The suitability of cane milasses as carbon source in the fermentation has to be investigated. A plant in India set up with Technical collaboration of a firm from the developed county suffered serious setback due to the non-suitability of cane molasses available in India. Infact, the foreign firm developed its process on the use of beet molasses. Cane molasses contain certain inhibitors -- such as trans-aconitic acid.

c) In the light of above, in case beet molasses is to be used, the anticipated availability and economics of production have to be evaluated.

d) Economics of fermentation using molasses vis a vis methane is to be investigated.

e) The traditional shallow process of fermentation is recommended as against deep tank method for certain reasons such as ease of operation. The relative economics has be worked out.

In case the shallow tray process is adopted in the proposed plant, it is necessary to carry out research on the following subjects connected with the manufacturing process.

i) Optimum liquid depth in the trays

ii) Seed spore medium

iii) Crystallization of citric acid

iv) Mutagenesis of the mould

v) Deep tank fermentation parameters.

f) Economics of recovery of citric acid by counter current solvent extraction vis a vis by the route of calcium citrate is to be assessed.

g) The most important prerequisite to take up the manufacture is the culture stain of micro-organizm fit for commercial production and the cost of this has to be included in the cost estimate given above.

In the light of above, it is obvious that ACDIMA after establishing the feasibility and necessity to take up manufacture of citric acid, may go in for technical collaboration for obtaining the micro-organism, technology and for constructing the plant.

Modified Industrial Profile for Feed Yeast

Introduction

In this report a number of products have been listed which can be made by fermentation. The list is by no means exhaustive but represents those products which could be of interest to ACDIMA within the reasonable future. Some of them may be of immediate interest, some of them may be of interest at a more distant time and some of them may never be of interest.

It may be said that it is unlikely that any one, or all of them together, will ever utilize fully the supply of fermentable carbohydrates available in the Arab countries.

What is needed is a commodity which can be made in all the molasses producing areas of the Arab countries, which has a sufficient value in utility that a market exists for all that can be produced.

Yeast as the Universal Product:

It is suggested that yeast is such a commodity. Although the proximal objective of ACDIMA is to expedite the production of drugs. the distal objective is to raise the health level of all the Arab people. Moreover this must be done at a period of history when population pressure will make a shortage of protein so necessary for good health for many people most probable.

Yeast has the capacity to some degree to alleviate both protein and vitamin deficiencies.

If the reasonable assumption is made that molasses is grown to yeast at a yield of 7.5 % then the following table can be constructed

Country	Population	Ton Molasses per annum	G protein per person per day
Egypt	37,232,000	300,000	1.66
Morocco	17,311,000	127,000	1.51
Tunisia	5,612,000	52,000	1.90
Sudan	17,759,000	30,000	0.35
Syria	7,346,000	18,000	0.50
Lebanon	3,244,000	3,000	0.19
Sub Total	88,504,000	530,000	1.02
All countries	145,558,000	530,000	0.75

It is seen from this table that on the average 0.75 g protein are available to each person per day if all molasses is grown to yeast.

Yeast moreover, is a useful source of some vitamins as may be seen from the following table

Vitamin	ug/100 g dried yeast
Thiamine	2,800
Riboflavin	6,200
Biotin	200
Folic Acid	700
Nicotinic acid	28,000
Pantothnic acid	9,500
B 6	3,400
B 12	0

RECOMMENDATION:

It is recommended that ACDIMA consider the desirability of establishing a model plant for the production of dried yeast, and this plant be used for training personnel from all over the Arab countries so that from time to time new plant can be built and staffed wherever there are molasses.

The yeast produced will be used in two ways: as a protein concentrate for both animals and humans. For animals, the yeast will be incorporated into feed rations, For humans it is suggested that it be incorporated into a basic food such as flour.

The process of Yeast Production

Yeast can be produced either batch-wise or continuously. In either case air must be supplied, otherwise the yeast will produce alcohol, but will grow very little.

Continuous Culture (figure IV)

In order to introduce more efficiency, continuous culture has been developed. The principle of this is to feed the yeast at such a rate that it overflows the tank when the yeast is at its maximum rate of growth. This nutrient medium will contain the sugar, nutrilites, a source of nitrogen (ammonium sulphate or urea) and a source of phosphate.

In order that the overflow from the growth tank be fully representative of the entire contents of the tank, the tank must be well stirred and fully baffled.

Since the rate of feeding and the concentration of the nutrient solution are both variable at will, it is the oxygen transfer rate which is the controlling factor in any particular installation.

The harvest tank will have a much diminished air supply compared to the growth tank - just sufficient to satisfy the demand of the small amount of nutrient carried over.

The growth tank can, of course, consist of a series of tanks rather than one single tank.

From the harvesting tank the yeast is concentrated into a thick cream by centrifuges.

The next step presents alternatives: the thick cream may be dried directly on a vacuum roller drier as shown in Figure IV or in a spray drier.

Or it may be compressed to a puty-like consistency in a filter press. This cake may be ground into small pieces and spread out on a wire mesh tray to be dried in a flow of air. This latter procedure requires less capital and steam but occupies a larger area.

Under a set of given conditions, in a yeast factory built around a growth tank of usable volume of $135M^3$ it can be shown that nearly 6 tons protein can be harvested daily using 80 tons molasses, 4.65 tons Ammonium sulphate and 2.19 tons Phosphoric Acid. Expressed differently, to produce 1 ton protein requires 13.3 tons molasses, 0.78 tons Ammonium Sulphate and 0.36 tons Phosphoric Acid.

Choice of Organism

Many organisms have been used: Saccharomuces cerevisiae and Torulopsis utilis being the most common. The organism chosen should have a bland taste and high rate of growth.

It is sometimes said that yeast contains too high a nucleotide content for human taste. This is a valid objection only when the intake is high.

On the other hand, research on removing nucleotides could well be in order, considering the probable future demand for protein.

Cost

It is not possible to estimate the cost with the available data. First the growth characteristics of the organism must be firmly established. Then pilot plant runs must be carried out to ascertain the minimum nutritional requirements for maximum yield of nitrogen and phosphate. At current prices molasses 20 LE, ammonium sulphage 300 LE and phosphoric acid 2745 LE per ton, the cost of raw materials per ton of protein is about 1500 LE. The total cost will be in the neighbourhood of twice that figure on 3,000 LE.

In addition, the method of drying must be established.

With this information available, a plant can be designed and costed. It may turn out that the cost of producing yeast for animal and human use will be said to be uneconomical by orthodox accountants. If this happens it will be because orthodox accounting only deals with things which have a value in exchange.

Good health has no value in exchange but has a high value in utility. Orthodox accounting consequently ignores the value in utility. ACDIMA may not be so selective in outlook.

RECOMMENDATIONS

a) As regards fodder yeast, Societe des Sucreries et de Distillerie D'Egypte currently makes fodder yeast and exports it to Europe. There is no competetive protein concentrate in Egypt. So this production can be expanded.

b) One of the objections to using yeast for humans is the damage due to salmonella infection. Sterilization of all ingredients used in fermentation, might overcome this problem, but this would make the process too expensive.

c) Before taking up the manufacture of food yeast for humans, the acceptability aspect should be thoroughly gone into. This is particularly so inview of the serious setback suffered by an experimental plant set up in West Indies for the manufacture of food yeast as the local population did not like its taste.

Type Culture Collections

Type culture collections in Egypt are not large. Rather they are working collections serving the interests of the particular organizations which own them: Ministry of Agriculture, University Soils Department (Aim_Shames) National Research Centre.

No attempt is made to function as a distributing centre for other laboratories on a large scale.

This is as it should be. There are already large cultures in United States, Canada and United Kingdom to mention only three which can serve the world including Egypt.

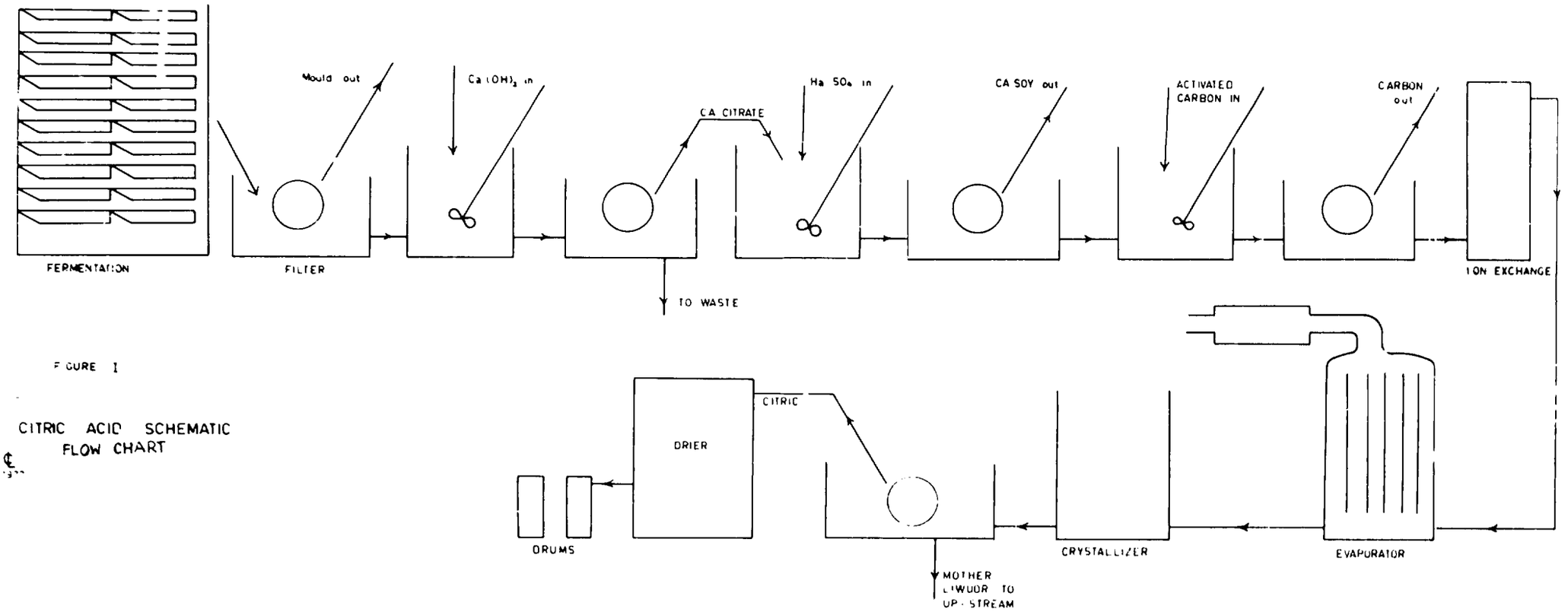
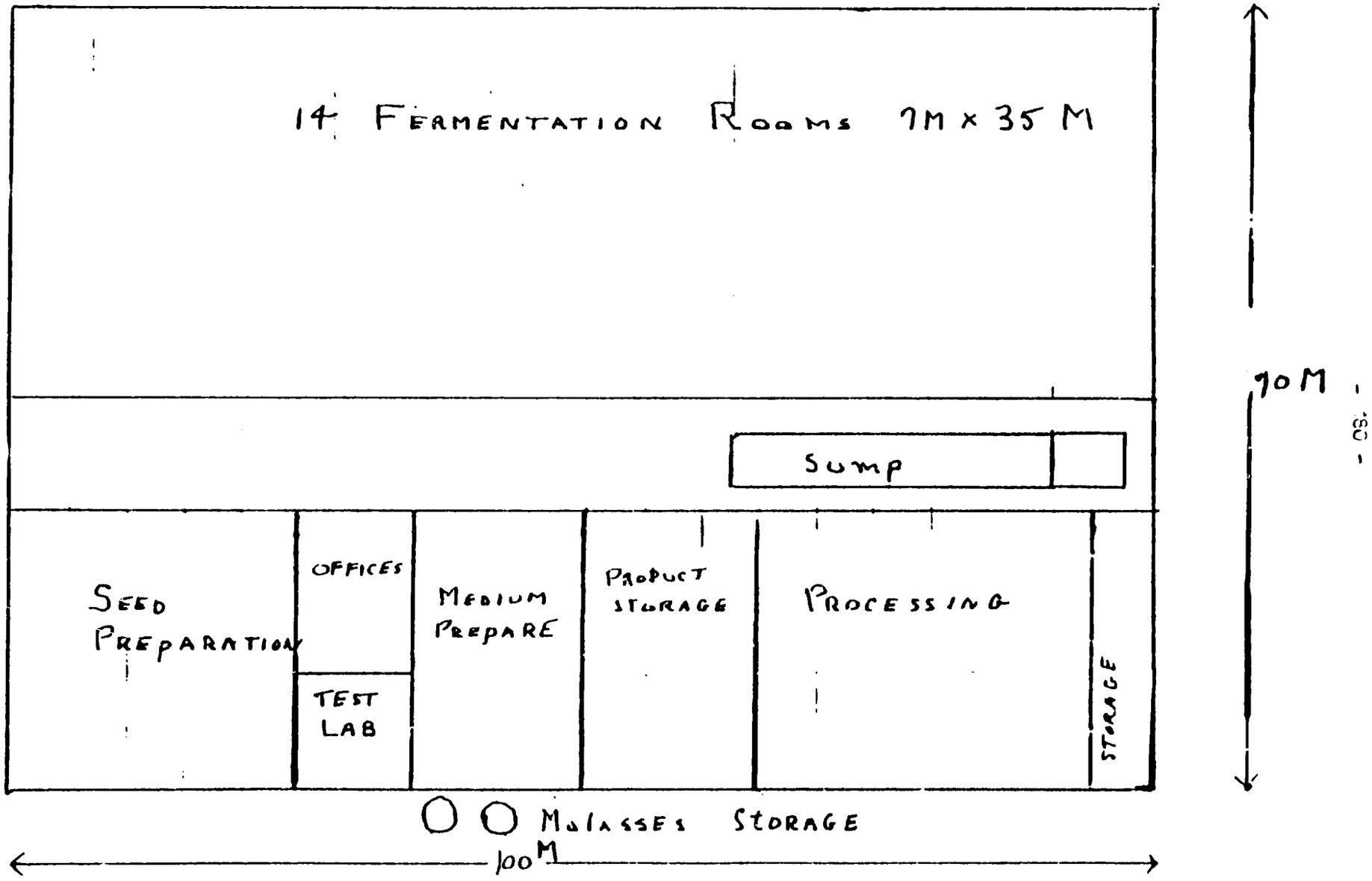


FIGURE 1

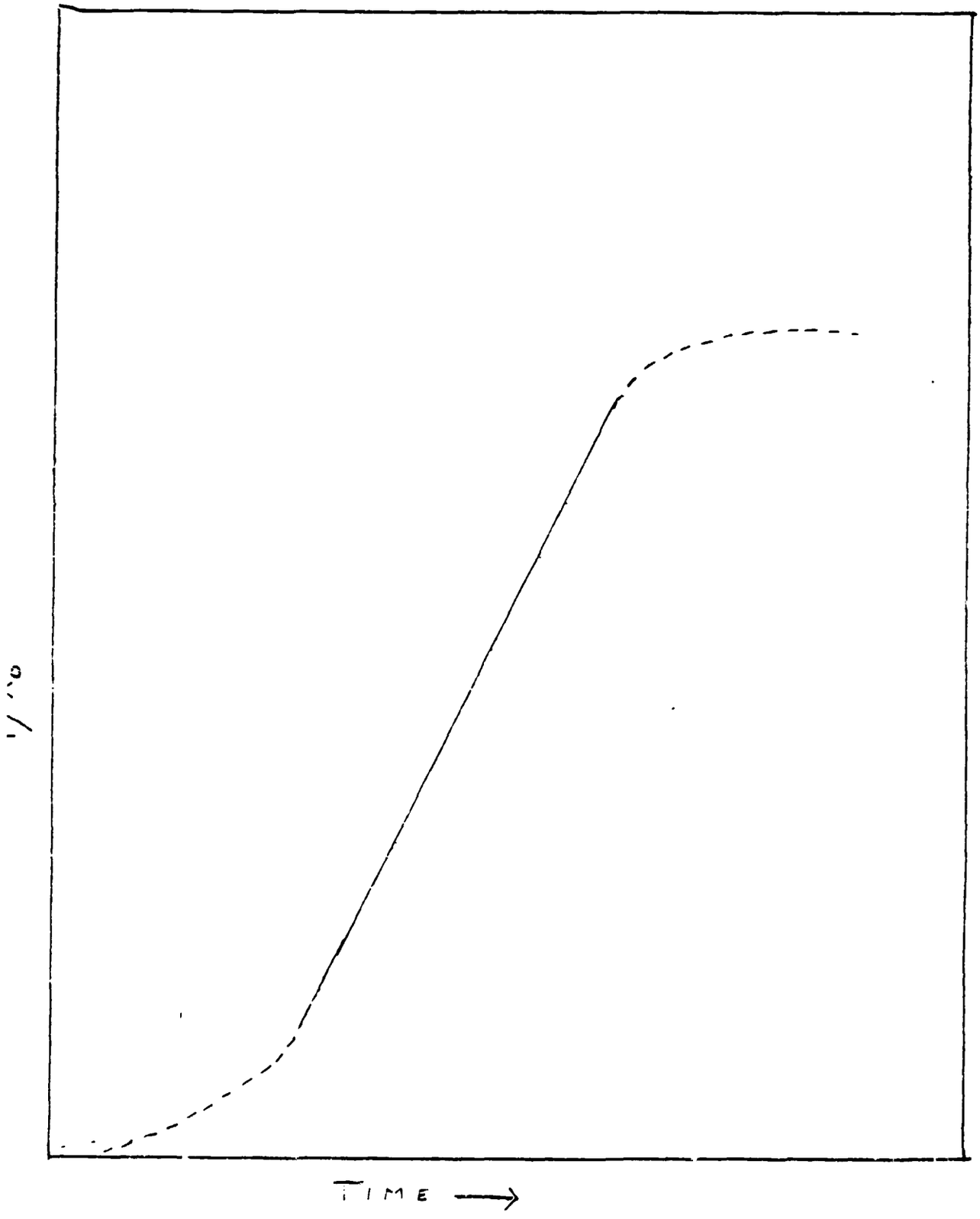
CITRIC ACID SCHEMATIC FLOW CHART

Figure II. Layout of citric acid plant



Scale: 1cm = 5m

Figure III. Idealized growth curve



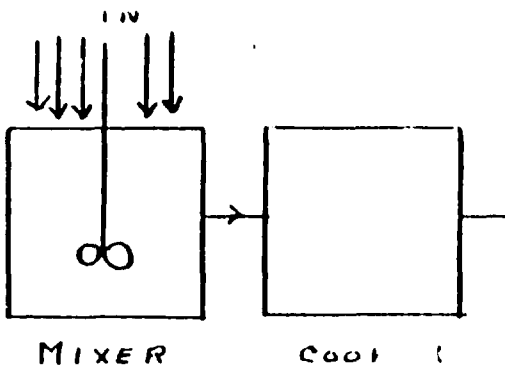
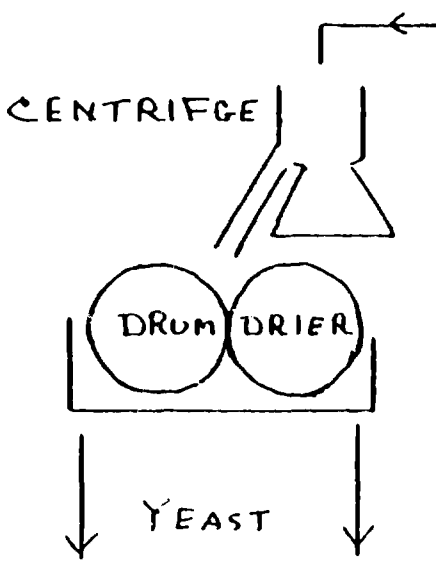
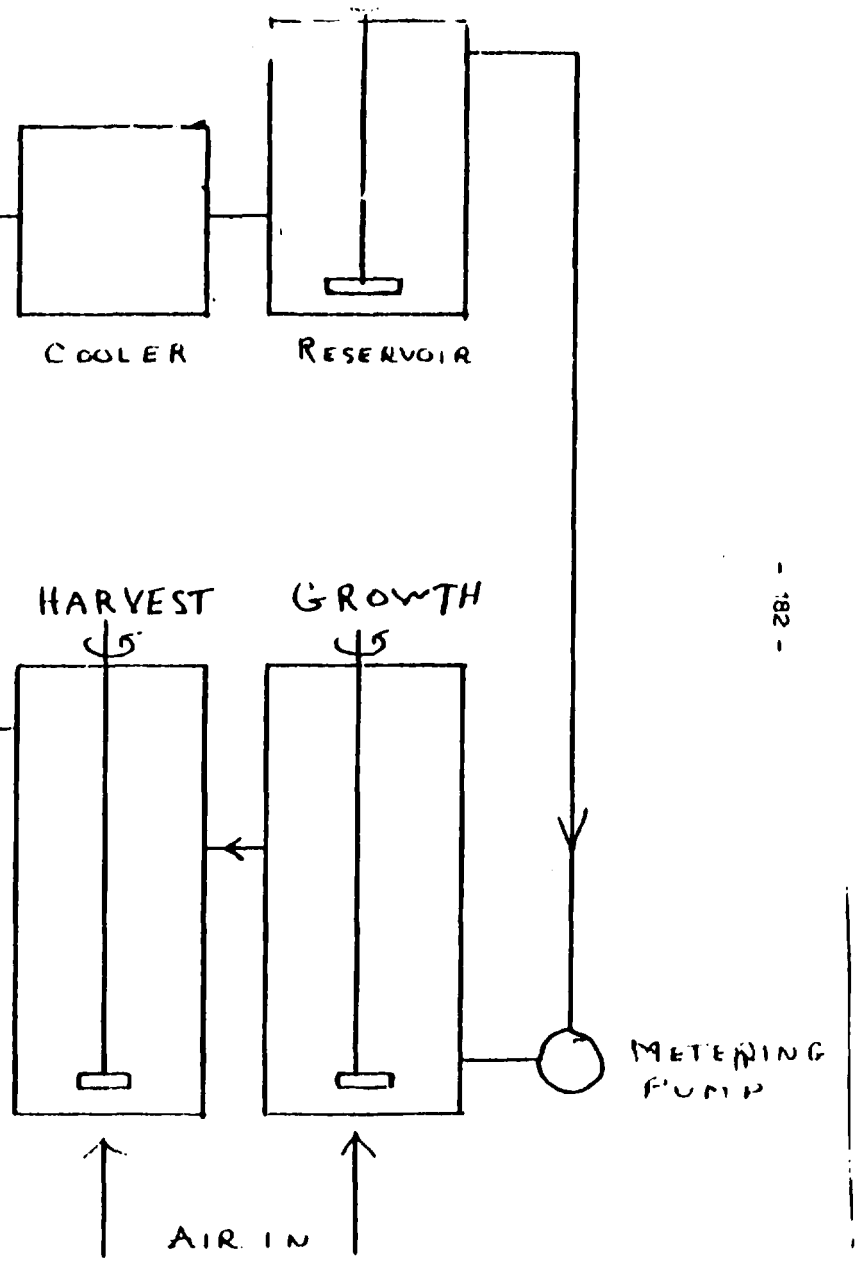


FIGURE IV
BLOCK DIAGRAM
FOR
YEAST CULTURE




COOLER
RESERVOIR
HARVEST
GROWTH
METERING PUMP
AIR IN

XI. VETERINARY FORMULATIONS AND PACKAGING

A. Summary

Present

Most forms of Veterinary Medicines could be carried out using the same facilities that are used in the production of human medicines. The construction of a separate entity for the processing and packaging of Veterinary products will, therefore, depend on what products are actually needed.

A survey of C.I.D. formulation plant in Assuit, Egypt has been conducted for carrying out dual operations to produce both pharmaceutical and Veterinary medicines in the same entity. This plant at the present time is only being utilized at about 30 % of its available floor space. The observations are as follows.:

a) Veterinary Medicines

These can be processed using the existing equipment after overhauling.

b) Processing of Animal Feed Products

i) The present facilities can be used by increasing the height of the ceiling in a section of the building. Alternatively, a new machine which will fit into the existing space can be procured;

ii) A third alternative is to build a pre-fabricated unit as a separate entity to accommodate the machine recommended.

c) Crop Chemicals

A separate pre-fabricated wall-roof unit has to be built for this unit.

d) Pharmaceutical Processing:

The internal construction of the existing building should be designed to G.M.P. standards and equipment to assure ample capacity for 5 - 10 years requirements may be acquired.

Future

A plan is given for the establishment of a pharmaceutical - veterinary fromulation plant having the following annual capacity (8 hour shift)

Products	Capacity
Tablets (compressed and coated)	250 - 300 M
Hard Gelatine capsules	100 - 150 M
Soft Gelatine capsules	50 - 60 M
Liquids (Syrups and Suspensions etc.)	300,000 L
Ointments - Creams	150,000 kg.
Suppositories	required for sale

A lay out is suggested, total estimated cost including building, services, processing equipment and office requirements is given. Guidelines have been laid down for plant construction. A separate entity may be constructed for Antibiotic processing and packaging and necessary equipment to operate this facility maybe provided.This recommendation is in line with G.M.P. guidelines.

The"estimated"capacity as indicated above can be doubled by working two 8 hour shifts with very few changes in the internal design. Industrial profile for the above is given.

Instead of building a multitude of complete formulating plants (small and large) in every area concerned, it is suggested that a "unit" of a pharmaceutical plant , one for each country may be built viz. one entity to produce tablets and pack where there is a high demand for tablets and very few liquids.

B. Present utilization of existing facilities for the production of pharmaceutical and veterinary medicine

The purpose of survey of C.I.D. plant in Assuit, Egypt was to establish its suitability to produce given line of veterinary medicine in all required forms and dosages; weed preventer products and a line of Animal Feed Additives, these in conjunction with a line of pharmaceutical Medicines (not including a Sterile Line of items)

The plant at present is approximately 4,500 Sq. M. and at the present time is only being utilized at about 30% of its available floor space.

The equipment on hand, in most instances is old, but, with some proper repairs and maintenance could give good service and capacity, sufficinet to fill the needs (in the following suggested area) for some time into the future.

The building and facilities appear to be in good condition and all services are on hand and also in working condition.

The following would be the suggestions to make the plant into an economical; dual operation to produce both Pharmaceutical and Veterinary medicines in the same entity.

It would cost "money" to put these ideas into operation, so would any development no matter how small or large, but these suggestions would at least use these facilities as they are at present with a much reduced total outlay in hard cash.

No. I Veterinary Medicines Take the equipment now on hand, have it all completely over-hauled by competent people to a good operating condition and then use primarily for the processing of Veterinary medicines, where possible, the area for operations would be the furthest area from the Entrance to the plant (appeared to be the south-west end).

This move would give sufficient operating equipment to, at least start into most lines of Veterinary medicines adn as the demand, to start, would ot be high, the capacity from these medicines would sufficiently fill the needs.

Either arrange a contract with a Company such as Manesty to repair these machines, (on C.I.D. premises) to a sound working condition, also at the same instance arrange to have some competent mechanically inclined employee receive some good training from the contract. (suggested).

Processing of Animal Feed Products

There are two routes to operate these facilities.

a) Use the facilities (building) on hand and modify.
b) Build a pre-fabricated unit of a sufficient design to give people comfort and product protection.

To use the present facilities and the machine for which the plans are submitted it is necessary to increase the height of the present ceiling to N.L.T. 30 M. in a section of the south west part of the building or procure an alternate design machine which would fit into the present space, - J.H. Day of the U.S.A. produce a machine that would fit. It is a "Nauta" style mixer and does a good job of mixing this kind of product.

Use the machine for which the plans are given and build a pre-fabricated unit as a divorced entity. This could be built very cheaply as weather would not be a problem, a wall-roof design is required to give product and people protection from the heat.

Crop Chemicals

This unit would require a separate entity of the same structural design as above (a pre-fabricated wall-roof) There is ample acreage on hand.

Pharmaceutical processing

In this instance there is an opportunity to start a plant with G.M.P. It is felt that here is ACDIMA's so called chance of a life-time by having a building already on hand, with most of the services and facilities incorporated to design the internal construction to G.M.P. standards and acquire good equipment to assure ample capacity for the 5 - 10 year requirements. As the plant is very close to (or part of) the University of Assuit, there would be an ample supply of Control People, also the fact of an Agricultural Experimental farm being on hand would certainly be an added fact to utilize this facility to its utmost.

The City of Assuit appears to be a central area for the production of all Veterinary products particularily for Upper Egypt. The same would apply for Pharmaceuticals, a plant of medium capacity would be ideal.

In conclusion, the use of these facilities is advocated for veterinary medicines and Pharmaceuticals as soon as possible. There is ample room in this set-up for some Person with an active imagination and also being well trained to build and operate a profitable Company.

C. Suggested pharmaceutical/veterinary formulation plant, and principle equipment required

LAND AREA - 30 Acres (12Hectares)
PLANT AREA (floor) - 90,000 Square Feet (8,400 Sq. M)
No of EMPLOYEES - 200 (plant)
- 90 (Office)
PLANT CAPACITY (ESTIMATED) - (12 months) 8 Hour shift

Tablets (Compressed and Coated)	250 - 300 M
Hard Gelatine Capsules	100 - 150 M
Soft Gelatin Capsules	50 - 60 M
Liquids (Syrup - Suspensions etc)	300,000 L
Ointments - Creams	150,000 Kg
Suppositories	required for sale

Services Required

Steam (horse Power)
Electricity (operational Process) 500 H.P.
Air Pressure (200 P.S.I.)
Vacuum Supply
Refrigeration
Air Conditioning
Conditioned (people Comfort) not humidity controlled
Sewers
Water (hot-cold-sterile-distilled and deionized)
Disposal of waste
Disposal of waste (Dangerous)
Serviced Land

Plant Construction (External)

Steel beam framework to required size

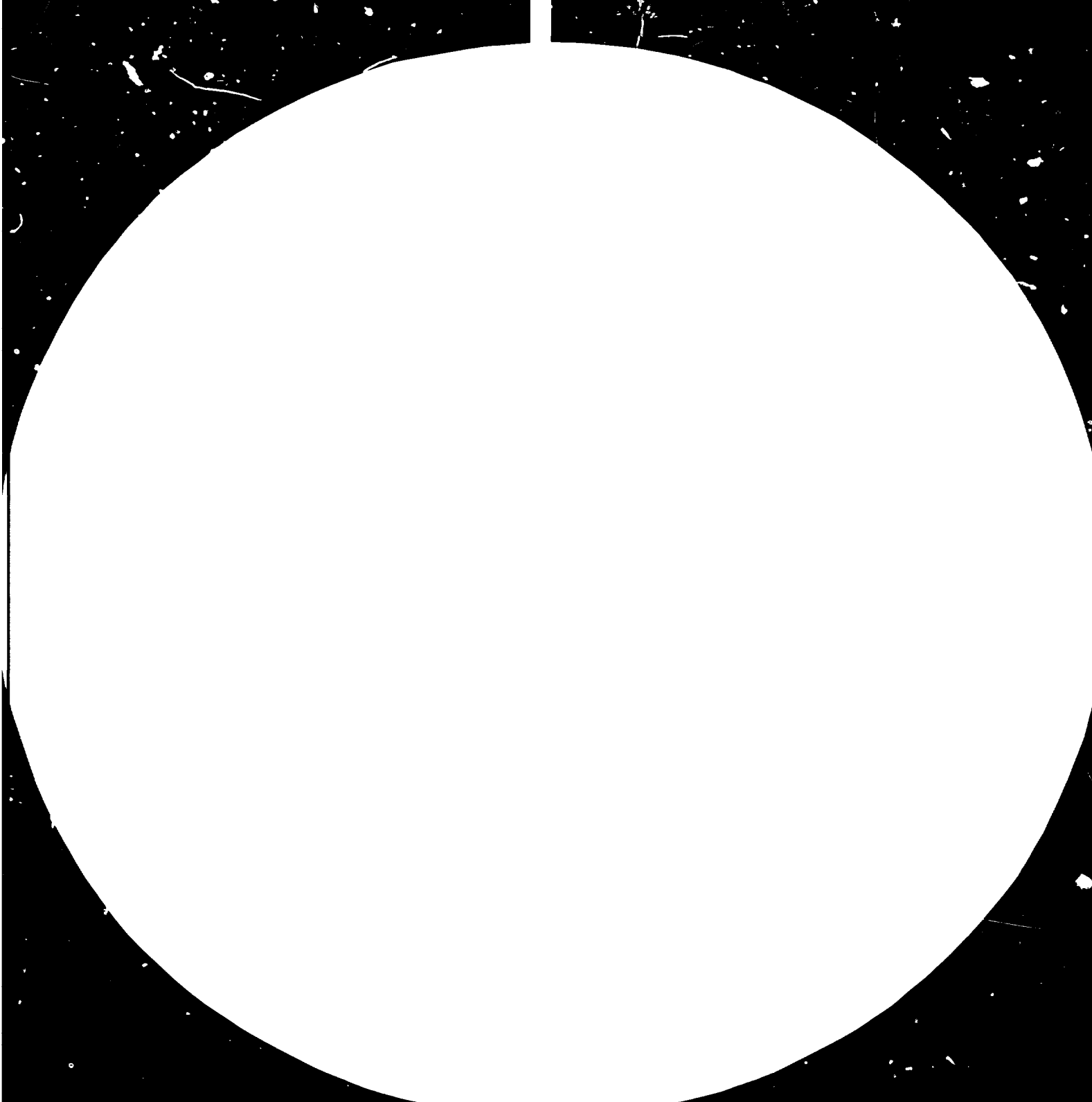
Outer walls to be of a pre-formed design either constructed of metal - preformed cement or other pre-stressed material suitably insulated for the area.

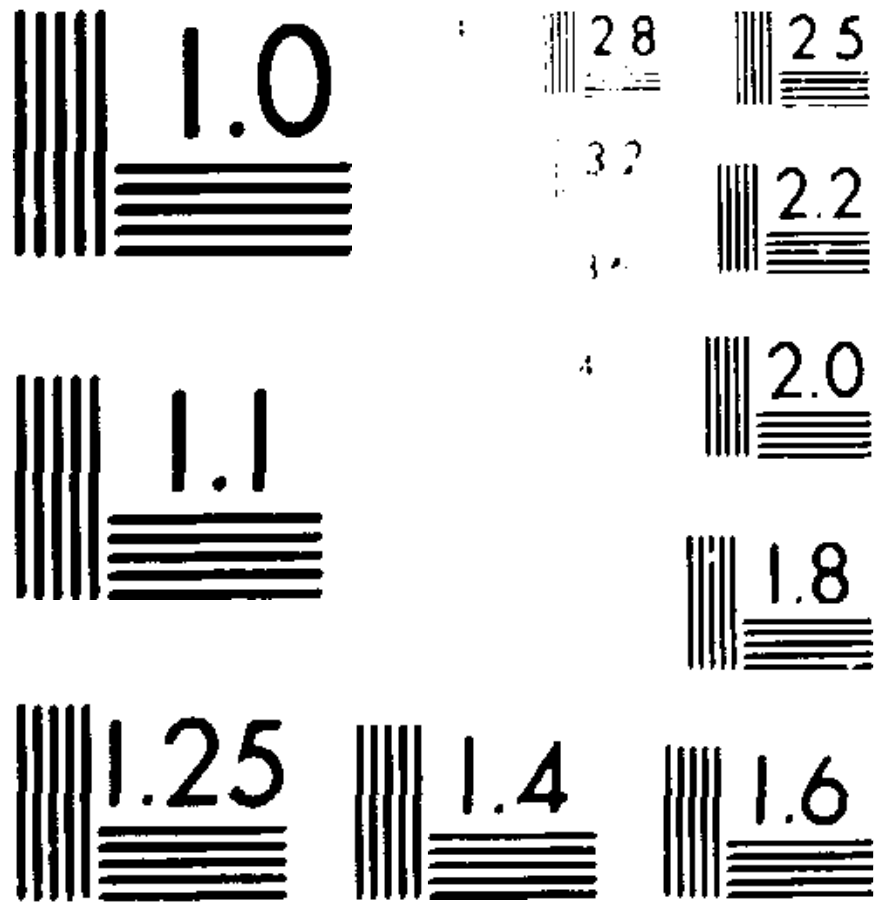
Roof and ceiling could be a pre stressed laminated truss of a suitable design and of other than wood construction.

Plant Construction (Internal)

All walls - ceilings - floors to be of a design and material to meet present G.M.P. regulations.

a) Walls ceilings and floors to be joined by a "Cove designed corner
b) Floors should not be constructed of Tile in any form, floors should be of non porous cement with a polished hardened surface, coated with a non porous material such as the Sprayed on Poly Vinyls that areimpervious to operating hazards, such as solvents-trucks etc.
c) Floor drains should be designed with ample capacity, with normal or legal "Traps" in the lines, also where possible, be fitted with some form of a "closing" dev .
d) All electrical lighting should be recessed and either of a dust-proof or Explosion proof design, depending on the area of operation.
e) Electrical switching (inter-Dept) should be recessed and capped where possible, also constructed under either dust-proof or explosion-proof standards.
f) Piping- Conduits- Electrical Wiring should be housed in a false ceiling - wall or imbedded in the floors (in some departments) damp areas to avoided.
g) Plumbing design and location - all piping should be housed in a false wall or suitable channel and flush fittings be used where possible.
h) All piping housed in Channels or false walls should be housed in an area so designed to give easy accessability for repairs etc.
i) Cement floors in all Liquid - Powder or any formulating area should be of a "bonded" or grounded design (to eliminate any chance of a spontaneous or flash explosion).
j) Internal divisional walls (non-supporting) should be of a portable design (G.M.P. approved) to facilitate expansion or change in internal plan, if and when required.





k) All windows to be hermetically sealed except "people comfort windows" (which would not be in the process areas). These would be suitably screened (if this did not interfere with the air conditioning facilities).

Plant Maintenance - Engineering

The drawing to house these facilities has not been allocated in any specific area in the final layout. It is suggested that when the required design is finalized, this department can be considered to be as centrally located as possible taking into consid ration the cost of piping steam - distilled water - deionized water - electricity etc. is very costly, also the repair and maintenance department should be as central as possible in case of emergency. The final plan (needless to say) will depend very much on the geography of the acreage(land) that is procured.

General Offices

This area has been located on the outside walls in all instances. This will facilitate exapansion if and when required also to be as centrally located as possible.

Executive Offices

(If internal standard rules require) could be placed on a second-floor immediately above the main or front entrance accessable from the Lobby. This would also assure that valuable floor space (main floor) is occupied by the production Department. This second floor could also house any conference rooms etc that would be deemed necessary.

Plant Design

Plant design has been planned to minimize expansion problems as much as possible(personal opinion).

If and when the plant requires an addition it is suggested that the area for expansion be designed approximately the same as the unit (area) presently in use. This would enable the movement and the use of the present equipment in a given square meter with little lost space.

It is also suggested that sufficient acreage be acquired in the first instance to accommodate at least 20 years of growth and expansion. This will be about 250,000 square feet (23,150 Sq. M.) of factroy space equal to 2.5 times the present floor space (suggested).

Note

Each unit has been drawn as a separate entity and could be located in a multiple of actual layouts, the control of the actual processing would not be affected in any way.

The common factor of "flow" has been utilized as much as what appears possible, as indicated in the suggested layout.

Antibiotic Processing and Packaging (Non Sterile)

There are not any facilities indicated for the production of antibiotics in the drawings.

According to the most recent "Directives" from the Health Protection Branch in Canada, this group of products (Antibiotics) cannot be sufficiently controlled during the processing or Packaging to completely ensure that "Cross-Contamination" of other pharmaceutical products manufactured in the same building could be a guaranteed fact. Therefore the production of these products must be performed in a building completely divorced from the main plant.

These restrictions, at the present time apply to all forms of Pencillin - Erythromycin and Streptomycin in all strengths (dosage).

In the light of above it is emphasized that the construction of a separate or divorced entity be seriously considered.

This separate entity would be all inclusive, in other words it would be designed to process - fill and package all medications that would be considered to be an Ahtibiotic.

The necessary equipment to operate this facility would be required and assigned to the production of these products only.

It is suggested that sufficient and competent personnel are trained to operate this plant and they not be used in other operations.

Veterinary Medicines (Most forms)

This particular phase of pharmaceutical processing could be carried out using the same facilities that are used in the production of human medicines .

The compatibility of the two branches of medicines in most forms will present no problems.

If capacity became a factor in the production of both, the addition of equipment and personnel would defeat this problem at least for the present time and according to the formulations now available, some time into the future.

Therefore it is suggested that the construction of a separate or divorced entity for the processing - packing of Veterinary products, at-least not until all of the Arab Countries have come to a final decision as to what products are needed to control the various predominant diseases how the 1.000's of farmers are going to be instructed in the use of these medicines also the general overall picture is clarified.

The Arab people realize that with the addition of people and machines most of the capacities could be greatly increased. The above is stated assuming that the personnel are "properly trained" in all aspects of pharmaceutical processing and in the most knoledgeable use of these additional machines.

Operating and Processing Equipment

All formulating equiment should be operated in an "isolated area" and stored under sanitary conditions when not in use.

All formulating equipment should (where possible) be made "portable" to facilitate more economic use of the equipment and to ensure the equipment is used in a divorced area. (areas should be available where portable machines can be used.)

These areas should be equipped with a suitable exhaust system and all other services required in the operation of this equipment.

All vehicles used in the transportation of all aspects of pharmaceutical production should be of Tubular construction, with all open ends sealed and all joints arc-welded, wheels to have a neoprene tire and sealed bearings.

Affiliated equipment such as scoops - trays - small containers, paddles etc. should be of Stainless steel No 304 - 312 construction or of acceptable P.V.C.

Glassware should be housed in a closed area that could be recessed into the wall.

All operating equipment (housed or portable) should be equipped with a "grounding" device or be of a "static"proof design.

The attached list of processing equipment is the estimated requirements to facilitate the operation of the Pharmaceutical Formulating plant, which design and drawings have been submitted to ACDIMA.

The indicated equipment has been suggested, in design and quantity, to be used as a "One Department Use Machine" , therefore there are duplications.

If the suggested plan is accepted, and the building is built to the submitted design, some of the suggested equipment could be eliminated (if a strict clean-up procedure is layed down and adhered to), as individual machines could be utilized in various departments for multiple processing.

Some of the machines are indicated by an (* asterick) that could be eliminated (depending on the products produced) for the present time and still have a G.M.P. operation.

The equipment indicated could in two 8 hour shifts double the "estimated" output of this suggested plant with very few changes in the internal design.

Dry Powder Mixing - Granulating - Grinding - Compression

	Machine	Size	1976 Approx. cost Canadian $
	Pony Style Mixer	200 - 300 L	25,000
	Granulator (Extruder)	10 Cu. Ft.	18,000
*	Granulater (Sigma)	10 Cu. Ft.	12,000
	Oscillating Granulater		6,500
	Fitzpatrick Mill		9,000
*	Fitzpatrick Mill (Force Fed)		12,000
	Homoloid Mill		8,000
	Fluid Bed Dryer	100 - 150 Kg.	9,000
	Ribbon Mixer(c/Liguid Inj.)	50 - 70 Cu. Ft	40,000
	Cone Blender (with liq Inj.)	40 Cu. Ft.	25,000
*	Cone Blender(with liq Inj.)	20 Cu. Ft.	18,000
*	Fitzpatrick Mill (Enclosed)		12,000
	Pot Mill	42"	8,000
	Ball Mill	60"(Depending on Products)	9,500
	Hoist (Travelling Electric)		5,000
	Dustless Powder Loading		10,000
	Drying Ovens (6 Sections)		30,000
	Trays and Racks for Drying Ovens(S.S)		60,000
	Hobart Mixer	50 Kg.	7,000
*	Herb Mill (if required)		4,500
*	"V" Shell Mixer (c/Liq. Inj.)	20 - 30 Cu.Ft.	15,000
	Ribbon Mixer	20 Cu. Ft.	15,000
	Tote containers		?
	Tablet Press Rotory	1 x 53 Head	45,000
	Tablet Press Rotary	2 x 43 Head	70,000
	Tablet Press Rotary	2 x 16 Head	20,000
	Tablet Press Rotary	1 x 12 - 16 Head (Heavy Duty)	12,000
	Tooling (Punches and Dies)		100,000
	Tablet Dedusters		5,000
		Total	610,500

In Process Tablet Testing

Machine	Size	Cost
Hardness Tester		2,000
3 - Size (Calibrating)		500
Friability		2,000
Disintegration		2,000
Punch and Die Control Charts - Polishing and Cleaning		3,000
Punch and Die Storage		2,000
Punch and Die Resurfacing		5,000
	Total	16,500

Transport Equipment - Service Equipment

2 - Lift Trucks	40,000
Steam Boilers	75,000
4 - Hand Trucks 2 wheel (pipe frame)	1,000
Air Pressure Compressor (200 p/S.I.)	25,000
6 - Flat Bed Trucks (Pipe constructed frame)	2,500
5 - Vacuum Cleaners	3,000
4 - Travelling Ladders	3,000
Vacuum equipment (if required)	25,000
500 - Skids (metal tube construction)	50,000
Electrical Test Meters	2,000
1 - Metal Lathe	15,000
Service Tools (saws, hammers, pliers etc.)	10,000
1 - Drill Press	5,000
1 - Band saw	5,000
3 - Electric Drills 1/3 H.P., 1 H.P., 2 H.P.	2,000
Total	263,500

Coating (Sugar and Spray) - Polishing

Machine	Size	1976 Approx. Cost Canadian $
2 - Coating Pans (stainless steel)	42"	20,000
4 - Coating Pans (stainless steel)	60"	48,000
2 - Vertical or Can Shape Polishing pans	42"	12,000
1 - Accella - Cota Spray Coating pan	602	25,000
2 - Compressed Air Spray Guns and Nozzles		3,000
1 - Tablet sorter (reversing belt type)		10,000
	Total	118,000

Filling - Finishing

Automatic Liquid Filler (Gravity or Vacuum)	20,000
Capping machine (automatic)	7,000
2 - Individual Dosage Packaging Machines	75,000
1 - Shrink - wrap (strech Wrap) or heat tunnel	15,000
2 - Semi - Automatic Labellers	20,000
Carton staplers, sealers skids, trucks	
Hand labelling equipment	15,000
Total	174,000

Liquid - Ointment - Cream - Suppository

Machine	Size	1976 Approx. cost Canadian $
Suppository Moulding equipment		?
Hobart mixer	60 kg.	8,000
2 - Mixers (portable - air driven) Var.	2. H.P.	3,000
2 - Gear Pumps (stainless steel)	20 G.M.P.	4.000
Homogenizer		12,000
Homoloid mill		9,000
Filter press 18" (stainless steel)		16,000
Coloid mill (premier)		12,000
Jacketed - Mixer pressure tank	100 - 150 L	15,000
2 - Var. speed electric mixers	5 H.P	7,000
2 - Tanks (stainless steel)	150 L	20,000
1 - Tank (stainless steel) dimple jacketed	1,000 L	15,000
3 - Tanks (stainless steel)	100 L	4,500
Pony type mixer (double blade)	150 kg,	20,000
Turbo Mixer - opposed directrion jacketed homogenizer	2 H.P.	5,000
Roller Mill	36"	25,000
Automatic Tube - Jar Filler		30,000
Cooling Room		10,000
Turbine mixer	10 H.P.	10,000
"Moyno" style pump		5,000
	Total	230,500

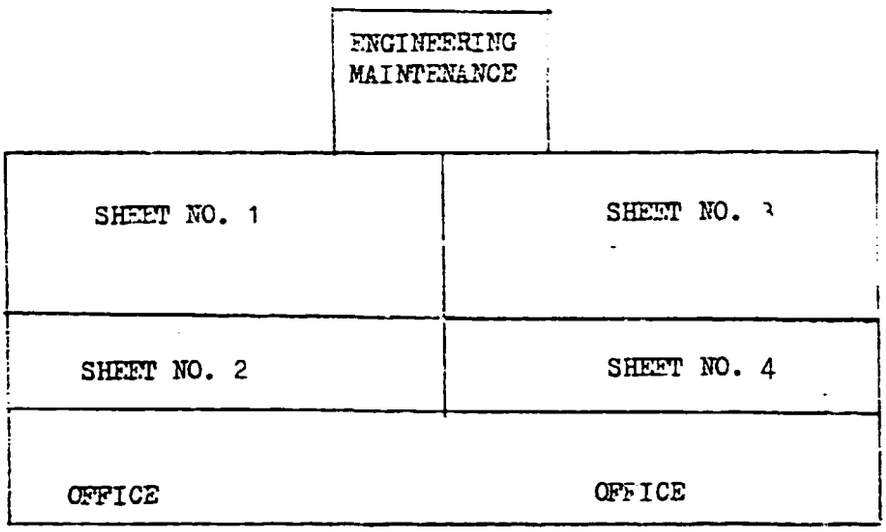
Soft - Gelatin Process - Fill - Sort - Package

Pressurized or Vacuum Gelatin Mixer		25,000
Aireating Equipment		10,000
Soft gelatin Unit Dosage		20,000
Curing room		10,000
Sorting table		5,000
Packaging		20,000
	Total	90,000

Hard Capsule Filling - Sort Polishing

Machine		Cost
7 - Eli Lilly - Parke-Davis Encapsulating		140,000
or		
4 - "K" Injection (encapsulating or Hofliger and Karg Model 288 (suggested)		200,000
4 - Cleaning - Sorting Tables (vacuum)		6,000
1 - Accilla - Cota pan (suggested only) (for cleaning)		25,000
	Total	231,000

The sheets (4) in the plan are numbered as 1 - 2 - 3 - 4 and were originally layed out in the following sequence:



This is only a suggested plan, this can be changed in a multiple of ways to suit the geography and products processed.

Total Estimated Cost - Building - Services - Processing Equipment - Office requirements

Building	250,000
Services	100,000
Equipment (Processing)	1,350,000
Office furniture etc.	100,000
Miscellaneous	150,000
Operating transport equipment, maintenance equipment, engineering euipment	263,500
Total	2,215,500

The following comments are purely suggestions, they may appear a little drastic at first reading but it is suggested that they be given some thought and consideration.

It may be advisable, instead of building a multitude of complete Pharmaceutical formulating plants (small or large) in every area concerned to go another route for instance a "Unit" of a Pharmaceutical plant, one for each country.

In other words, if Saudi Arabia had a high demand for tablets and very few liquids, build an entity to produce tablets only, plus the packaging, then if Iraq had a high sale of filled capsules build a powder mixing and encapsulating plant there, plus the packaging unit and if the climate in North Egypt was more suitable for the processing of Hard capsules, build it there. These instances are only stated to give an indication of what this suggestion could mean to the countries involved.

If this route was followed it would reduce the problems of allocation shipping and control. This concept would also save a considerable amount of money and greatly reduce the time span of the date of completion and give the ACDIMA group much more control (if control is the correct word to use at this stage in time) at the procurement and Q.C. levels.

If the original concept of producing in some countries and then shipping the bulk products to other areas for filling and packaging is followed, there would be other problems,(physical)to contend with. For example: when shipping tablets in bulk containers the lower $\frac{1}{4}$ of the tablets tend to crush and revert to powder, the problem is due to the bulk weight and handling during shipment. Part of the problem can be corrected by formulating to a harder tablet, but, if this route is followed, the disintegration of the tablet becomes a problem, also the tablets tend to chip or crack badly. This on the assumption that the problem of rough handling could not be corrected to an acceptable point.

The bulk of shipping of filled capsules is also adversely affected by weight-handling and humidity. The weight will force the capsules to separate, this can create numerous problems especially if the activity of the diluent is deliquescent to any extent.

Liquids, syrups or suspensions , these products can be seriously affected when shipped in bulk. Syrups can revert to sugar, this then either requires heating or filtering to rectify, thereby creating the chance of a non uniform product in respect to dosage and the cosmetic appearance. Suspensions would more than likely separate or "stratify", depending on the product this could create a medicine that could not be corrected in any way to be sure of a product meeting "Content uniformity" standards.

Creams and ointments - in bulk would be almost impossible to ship in this heat except by refrigeration controlled trucks or freight cars. If creams are shipped or housed in or under refrigeration they will also tend to layer out or stratify, thereby destroying the product in most instances.

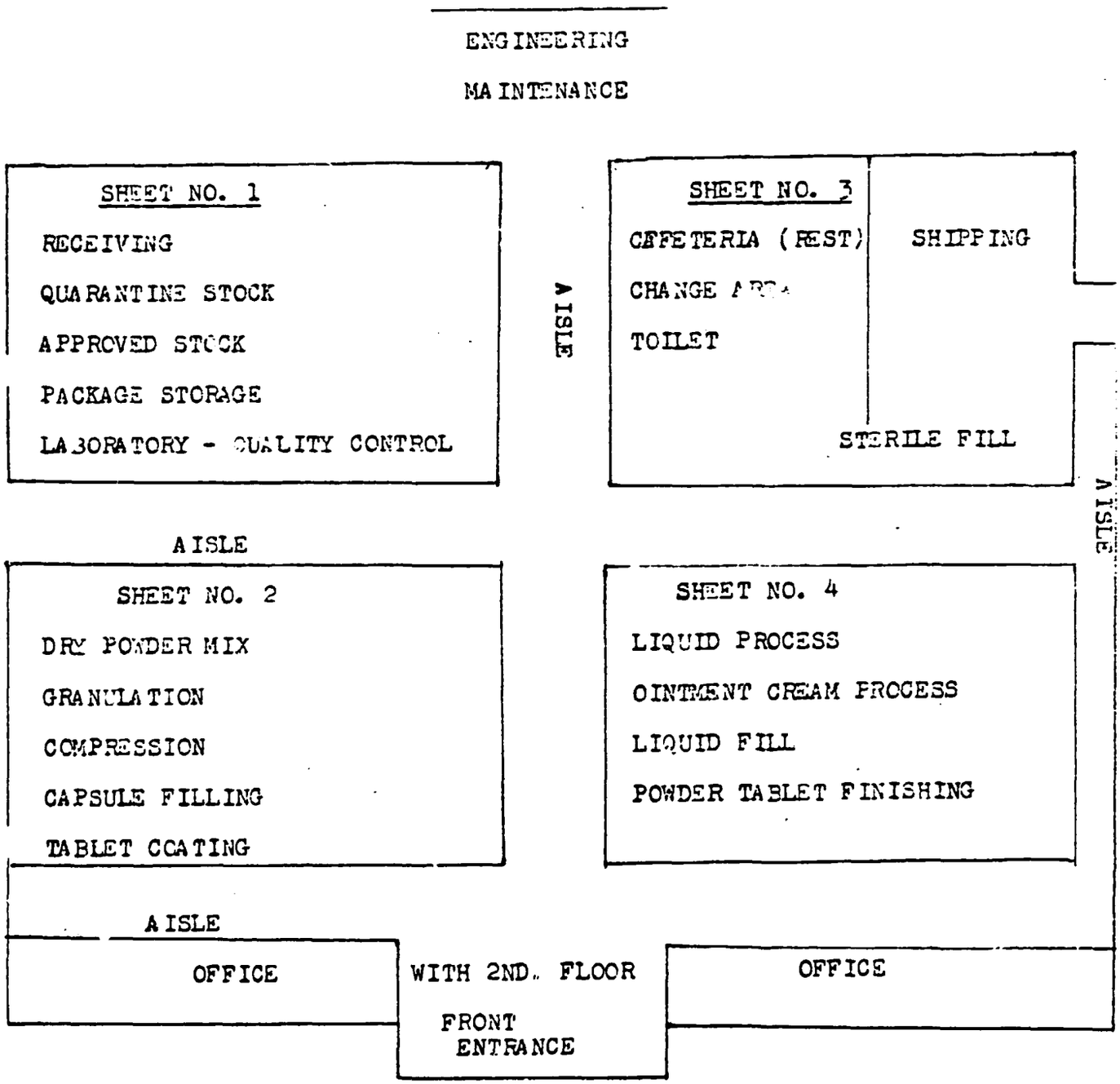
As stated previously, shipping in bulk can cause numerous problems that are difficult to correct. One has to contend with the Quality Control of the final product, this would not be G.M.P.

Please note:

The procurement of the required Chemicals for these smaller entities in the various countries would not be affected to a great extent, some extended shipping would be involved.

Requirements could still be requested through a central agency, in the same aspect as at present and distribution could be handled by "regional"shipping with little problems.

SUGGESTED LAY- OUT OF FORMULATING PLANT



Animal feed product

A suggested formulation of an "Animal feed product" would be as follows:

Carrier ----------Rice Bran meal or Hulls
----------Soybean meal or Hulls
----------Or a combination of both

Activity

a) Liquid or powder form. Note: if activity is a Multi-vitamin mineral - sulpha or antibiotic, a premix should be made with some form of edible or compatible diluent such as lactose - starch H.M.C, or any other= of choice.

b) Activity in Liquid form should be premixed with a diluent such as a light mineral oil or soybean of av.790 S.G. The oil has a multiple purpose assists greatly in distribution of the activity controls the dust and thereby assists in the packaging operation Oil content 1 - 1.5% by weight.

Therefore basic formulation would be:

------- Carrier
-------Diluent Oil (1-1.5% by weight.)
-------Activity

Please note:

The requirement for the "protein"content of a given meal is not known for Egypt. It is suggested that a standard is set in this respect, high content can adversely affect the absorption of the activity.

Animal feed product as

Multi vitamin powder
Multi mineral powder
Multi antibiotic powder
Single activity of above
Concentrate form
Dosage form

Suggested process using the submitted schemetic plans for Animal feed products

1) Sufficient meal or Bran is added to the mixer to fill the machine about ½ full (approx.900 Kg.) to be added with the machine in operation.

Note The meal or Bran would have been previously dried to the Moisture Content

Standards that have been applied. It is suggested that moisture content be set at N.L.T. 10% by weight.

Note

If the moisture is too low, absorption could be affected also packaging could be extremely difficult.

2) At this point the Activity should be added:

Note

If the activity is in liquid form a premix should be made of approximately 1 - 1.5% by weight of either a light mineral oil or soybean oil of appromimately .790 S.G. and the activity.

Note

If the activity is in Powder form - a premix of the Activity or Activities plus a compatible powder such as Lactose- Starch or any other of choice should be made.

Liquid to be sprayed at a rate so that the addition of the premix liquid and the Q.S. quantity of Meal is completed at the approximately same instant.

Powder form added as a diluted form in the same area as the meal is added. Alternate additions are suggested for instance "meal,powder, meal, powder" until the batch is completed. The oil (.5 - .7 %) would require addition "before" the addition of the Powdered Activity.

When the addition of the required ingredients is completed, it is suggested a further 1.5 - 2 hours mixing would be required.

The minimum lot size using the indicated machine would be N.L.T. 4.5 Tons especially if the liquid activity is used as the sugar blades will become exposed at a lower quantity.

The"oil" content using the Powdered Activity would be approximately .5 - .7% by weight. Oil is used once again to assist in distribution and the binding of the Vitamins etc, to the meal, this practically eliminates the chance of de-mixing (which does happen in Animal feed products) or separation.

Please note

The degree of heat and the humidity in Egypt may indicate that the Meal or bran used, may not require "drying". This would be a local decision.

It is suggested that if the expected volume is sufficient either manufacuture or procure two of these machines. This will speed the processing

also relieve one machine that can be used as a stand-by piece of equipment in case of mechanical problems. This may very rarely happen.

Please note:

One should be aware of one other critical point in the processing of most Animal feeds. The maximum mixing time would be 2 hours. It has been mentioned in this resume that 1.5 - 2 hours is required, this is normally correct, but with a new product it is suggested that the mixing time is started (after all additions are completed) at 1 hour and then gradually increased until the "content uniformity" is within limits (if required time is needed),...

The "Vibrator"on the "Bulk Storage" tank does not normally require to be in operation at all times, only when the meal becomes compacted from standing or is wet.

One little item that is very important is that the meal should be checked at least once a week, very carefully, in respect to Vermin and infestation of worms or weevils. In Canada, nitrogen gas (or some inert gas) forced through the meal from the bottom of the tank has been used for a period of 1 hour in every 24 hours.

Note

The machine must be kept in operation while bagging or transferring to Bulk containers.

Feed Additives Process Ecuipment - Design

Meal or Carrier Storage

The tank would be of a sufficient size to store at least 35 - 50 metric tons. It should be constructed of mild steel that has been coated with an inert rust inhibitor or of Stainless Steel. The tank should be housed under some form of heat deflector or roof that would at least protect the material from excessive heat. It is suggested that some form of air-pump be incorporated into the lower part of the tank to force nitrogen gas through the bran or meal at least for 1 hour inevery 24 hours. This procedure will at least reduce the problem of vermin and worms.

Drying Oven (for the meal)

This can be either natural gas or Electric fired to control the amount of heat applied. The auger can be speeded up or slowed and/or the heat may be adjusted, this gives double control that does facilitate speed and heat adjustment.

D. Production of a weed killer

PLANT DESIGN AND DESCRIPTION OF UNITS TO PRODUCE A WEED PREVENTER PRODUCT USING SOLVENT AS A BASE

Melting Ovens

They are approximately 48' in length and 8' wide internal measurements.

The walls are constructed of stressed galvanized metal approx. 2" thick with fiber glass insulation packed in the air space.

The ceiling is of the same design as the walls with a 6"-8" layer of loose insulation on the outside of the ceiling.

The floor is of reinforced cement with floor level rollers (for instance sections of a conveyer system) this is to facilitate the movement of the cold and hot containers of activity).

Pumps

They are of approx. 50 G.P.M. (V.S.) and of a gear design, required motor (Electric) is 5 H.P. usually mounted as a direct drive unit.

Make-up Tanks Numbers 1 and 2

They are of a mild steel construction - Arc. Welded. These two tanks are a "baffle design" with a top entry (at least) 25 H.P. turbine mixer. The bottom of the tanks are a "dish Pan" design.

Please Note: One should use the turbine design to facilitate assured dispersion of the activity.

Filter Press

This is of stainless steel construction of a total approx. capacity of 100 litres. The internal construction is of 3-4 vertical plates with "stretched 50 micron S.S. wire" filtering area. These plates are supported in a vertical position. When the Press is started an initial amount of inert filter-aid is added to approx. 50 l. of the material to be filtered. This mixture is recirculated through the press until clear or until the plates are covered. At this point the appropriate valves are opened and normal filtration is commenced. The press would normally operate at approx. 70-75 P.S.I.

Scale and Scale Tank:

The scales are of a "Commercial Load" design and of a capacity of 250,000 lbs. gross wt. the supports of the scale are bedded in a reinforced cement pad approx. 12" thick. The scale has a remote reading (indicator). The tank is of mild steel construction horizontally mounted, with a 25 H.P. Top-side entry mixer.

Storage Tanks

They are of a mild steel arc-welded construction, size would depend on the volume of the lot size. One would require at least two of these tanks.

Please Note:

The style or design of press that is suggested, may be used that is with the "S" steel wire mesh screen. This will enable one to purchase a press with a "reverse" flow facility incorporated. This then will allow one to "back-wash" to clean the press rather than pulling it down to clean for every lot. This facility will certainly pay for itself in a short period of time.

Note:

The normal assays and tests on this form or design of product are the following:-

Activity Content +	1%
Clarity	Water clear
Emulsion	should form a suitable emulsion when combined with water to facilitate spraying.

"WEED PREVENTER" PROCESS USING LIQUID (MELTING) ACTIVITY

Assuming that a solid form of Activity that requires either melting or breaking into small pieces is used.

The melting will normally require about 48 hours at a temperature of not more than 115°C.

The melted activity is then pumped into number 1 and number 2 tank (if the lot size requires the use of both tanks) which had previously been approximately ½ filled with Solvent or sufficient solvent to cover the mixer blades. The mixer should be in operation before the addition of the Activity is commenced.

When the pumping of the Activity is completed, mixing should continue for about 45 minutes to assure complete dispersion.

After dispersion is complete appropriate valves are opened to pump the solution of Activity and Solvent through the 50 micron filter press at about 70-75 P.S.I. (Note: material to be recycled through the filter press until completely clear, by opening recycling valve sufficient to retain pressure but allow material to return through press. Some form of inert "filter aid" will be required to cover the filter plates to ensure a clear product) into the tank mounted on the scales or (Make-up tank) which had previously been filled with Solvent sufficiently to cover the blades of the agitator. Once again as stated above, the agitator should be in operation before the addition of the filtered solution is commenced. When filtering is completed the following is started.

Add to Tank No.2 (or No.1) sufficient Solvent to cover the agitator blades, add the required amount of "Saponification Chemical" to the Solvent (with the agitator in operation). Dispersion should be attained in about 15 minutes. After addition is completed, when material is approved the appropriate valves are opened and the solution is pumped through an 80 mesh in-line screen to the Make-up (Scale) tank. When addition is complete all mixing is stopped and then the valves involved are opened and the batch is Q.S. to required weight with the Solvent.

After the lot is at the required weight, mixing is resumed and continued for about 2 hours.

Samples and required tests and assays are performed.

Note:

If Liquid Activity is used, one would not require the Ovens for melting (that is quite obvious), mixing could also be reduced. The ratio of weight per litre may require adjustment. Filtering may not require a 50 micron plate which would also reduce the cost.

Please note, paper or cloth filter pads are not a satisfactory unit to use when filtering a solvent based product, most of these pads (paper cloth) appear to disintegrate after a short time.

XII. PHARMACEUTICAL FORMULATIONS

A. Summary

An assessment has been made of the present status of pharmaceutical formulation plants and pharmaceutical storage facilities in Egypt, Iraq, Kuwait and the Sudan and recommendations are given for improved quality assurance and production capacity. The existing pharmaceutical formulation plants in the Arab countries produce only 50% of the Arab countries' pharmaceutical needs. The forecast based on current annual production dollar volume indicates that approximately 35 formulation plants capable of an annual production of US$35 million should be built to provide approximately 44% of the Arab countries' pharmaceutical needs by 1985. In view of this, it is recommended that ACDIMA may take the following measures:-

a) Create a master marketing plan and select the dosage form mix that would be produced under the ACDIMA label.
b) Create joint ventures with Arab and non-Arab countries.
c) Establish formulation plant profiles and construction projections.
d) Plan the location of formulation plants in the Arab countries.
e) Establish standards of good manufacturing practices for its manufacturing plants.
f) Advise on the feasibility of regional bulk buying where applicable.
g) Establish a comprehensive integrated training programme for its initial and future plant personnel. These are broadly classified for implementation on a short term and long term basis as follows:

Present

(i) ACDIMA should establish contact with existing pharmaceutical industry to initiate the formulation and production of a limited group of products under ACDIMA's label and according to ACDIMA's GMP.

This will result in increased and efficient utilization of existing plants and equipment, introduction of ACDIMA's name and products to the Arab market and setting an example for improved G.M.P. and other capabilities in these companies.

(ii) Include a high priority programmed co-operation with the existing pharmaceutical (private and public sectors) manufacturers to utilize to the maximum the capabilities and capacities of the existing plants.

(iii) ACDIMA should undertake a long term (five year and ten year) projections to establish market trends and the fulfilment of health needs of the Arab countries.

(iv) Introduce formal training programme in processing and packaging operations to maximize efficiency of labour personnel.

(v) All plants should study the feasibility of implementing two shifts in all formulation plants. This will result in an increase of approximately 30% over and above present production.

Future

(i) Set up a feasibility study for establishing one or more soft gelatin manufacturing plants.

(ii) Develop at once a formulation plant devoted solely to the manufacture LVP's, SVP's and other sterile products (with the exception of biologicals). It is strongly recommended that the formulation plants should not include a parenteral operation in conjunction with tablets, liquids, ointments, etc. Such a plant will entail an investment of US$6.4 million and have an annual turn over of US$15.0 million.

(iii) Set up a totally integrated hard gelatin and powdered capsule operation (i.e. the manufacture of both the empty shells and filled capsules).

This plant will involve an investment of US$7.0 million.

(iv) Establish model formulation plants which do not contain parenteral, capsule (Hard and soft), powders and granules operation. Tablets, liquids, ointments and creams and suppositories will be manufactured in this unit. A typical plant will entail an investment of US$4.8 million.

(v) Set up animal feed and veterinary premixes plants and veterinary pharmaceuticals formulation plants. The basic plant layouts and cost projections used in the human manufacturing (without parenterals) operations are applicable in these cases too.

(vi) Establish facilities for packaging and labelling from bulk finished product where it would not be feasible to construct a formulation plant due to small population, lack of technology, difficulty of accessibility, etc.

(vii) The location of new plants should be complementary to improving existing plants and recommendations are made on suitable locations.

B. Current assesment of the status of pharmaceutical formulation plants and pharmaceutical storage facilities in some Arab countries (Egypt, Iraq, Kuwait and Sudan), and recommendations for improved quality assurance and production capacity

To determine the assessment the following companies were visited:

The El-Nasr Pharmaceutical Chemicals Co.,
Abuzaabal, Cairo, Egypt.

The Chemical Industries Development (C.I.D.) Co.,
Main Plant: Talbia, Giza, Egypt.
Branch Plant: Assuit, Egypt.

The Nile Co.,
Cairo, Egypt.

The Alexandria Drug Co.,
Alexandria, Egypt.

The Kahira Co.,
Cairo, Egypt.

The State Company for Drug Industries,
Samarra, Iraq.

The Kuwait Pharmaceutical Plant of the Ministry of Health,
Kuwait City, Kuwait.

The Sudanese Chemical Industries,
Khartoum, the Sudan.

1 Assessment and Recommendations in Light of International Standards of Good Manufacturing Practices (GMP's)

For the purpose of a comprehensive review of current operations and consequent recommendations, comments will be made under the following headings:

1.1.1 Personnel.
1.1.2 Premises and Equipment.
1.1.3 Sanitation.
1.1.4 Raw Material and Packaging Material Tests.
1.1.5 In Process Manufacturing and Quality Checks.
1.1.6 Finished Product Tests.
1.1.7 Quality Control Department.
1.1.8 Stability Testing.
1.1.9 Recall System.
1.1.10 Product Information Records.
1.1.11 Self Inspection Programmes.
1.1.12 Records and Samples.
1.1.13 Parenteral Operations.
1.1.14 Importation of Finished Dosage Forms, Raw Materials and Pharmaceutical Machinery.
1.1.14 General.

1.1 Summary of Findings (F) and Recommendations (R) on Manufacturing Practices

1.1.1 Personnel

(F) There was lack of management skills and lack of staff in disciplines other than in pharmacy.

(R) Short and long term management training programmes at all levels of management and supervision should be instituted.

1.1.2 Premises and Equipment

(F) Equipment and premises were poorly maintained.

(R) All premises and equipment should be routinely cleaned after each operation. Physical premises and equipment should be improved to ensure controlled environments to permit maintenance of GMP.

1.1.3 Sanitation

(F) - Unsanitary habits of employees.
- Improper outer garments of employees.
- Unsatisfactory housekeeping.
- Lack of monitoring systems of employees' health.

(R) - Formal instruction for employees regarding personal sanitary habits.
- Formal instruction in good housekeeping practices.
- Initial check on employees' health on first employment and periodically during ongoing service with the organization.

1.1.4 Raw Material and Packaging Material Tests

(F) Tests were not of the latest compendial standards and were often incomplete.

(R) Test procedures should be periodically revised to update methodology and modus operandi.

1.1.5 In-Process Manufacturing and Quality Checks

(F) Processing information was incompletely written. Too many procedures were left to the discretion of the employee.

In-process quality control checks were insufficient.

(R) Recording of all processing procedures in writing.
The inclusion of all pertinent data as part of the master manufacturing, packaging and testing records.
The reproduction of the data listed above for each production work order so that they are available during the batch production as visible instructions to the employees.

1.1.6 Finished Product Tests

(F) Outdated test procedures.
No random sampling of finished products for testing.
No testing for identification of final packaged dosage forms.
Bench personnel in the laboratories could change tests without prior approval of management.

(R) Update test procedures.
Formalize testing procedures.

1.1.7 Quality Control Department

(F) Equipment not properly used.
No written record of complaints by the health professionals or record of investigation of complaints and the corrective action taken.
Personnel did not appear to understand the true function of the quality control department.

(R) Comprehensive, indepth course of instruction on utilization of equipment and demands required of quality control personnel.

1.1.8 Stability Testing

(F) Incomplete stability testing.
No renewed stability testing if one of the ingredients or type of packaging changed.
No identificaiton of degradation by-products attempted.

(R) A formal stability programme should be instituted in all companies.
Stability testing in high temperature, high humidity environments should be mandatory on every type of packaged pharmaceutical product.

1.1.9 Recall System

(F) No formalized system of recall.
No management committee to review problems or institute recalls existed in any of the companies visited.

(R) Establish the means to institute recalls.
Create a recall committee in each plant.

1.1.10 Product Information Records

(F) Very little information readily available in the companies relative to contraindications.
Some therapeutic claims made by some companies for their products highly improbable.

(R) Preparation of complete product monographs, for example see appendix I.

1.1.11 Self Inspection Programmes

(F) No self inspection programmes exist currently in the companies visited.

(R) Establishment of a self inspection team and programme in each company.
Institution of periodic intracorporate inspections.
Creation of a Pan-Arab inspection committee to create a common standard of inspection.

1.1.12 Records and Samples

(F) Not every company maintained samples of every lot of product for a significant period of time.
Samples were kept under unsatisfactory conditions (e.g. No environmental controls of air in sample rooms; samples of every final packaged dosage form were not maintained.)
Records did not contain all the information necessary for each lot of product, e.g. quantity of yield, number of labels used.
In view of the fact that many of the records were in Arabic a true assessment of the records was not possible.

(R) Samples should be maintained in a uniform environment so that a long term assessment of each lot of product can be made under standard conditions.
Uniform methodology for the maintenance of records for each type of dosage form should be established.
Assessment by an expert who is completely familiar with the Arabic language should be made.

1.1.13 Parenteral Operations

(F) Uniformly bad; for details see 2.1.1.2.

(R) The recommendations were so extensive that they have been incorporated as a "Guide for Parenteral Drugs Manufacturing and Personnel Training" in appendix II.

1.1.14 Importation of Finished Dosage Forms, Raw Materials and Pharmaceutical Machinery

(F) Storage in public sector facilities were in general very poor from the points of view of controlled environments, overcrowding, careless handling resulting in excessive damage to packaging and exposure to the elements.
Lack of expiration dates on pharmaceutical materials.
Uneconomical purchasing.

(R) Ensure that analytical documentation and correctly dated products are imported.
Proof of product stability should be supplied by all foreign principals.
Storage facilities should be expanded and modified to provide adequate environmentally controlled and spacious facilities.
More economical unit purchasing.
The packaging specifications required should be an important part of all purchase specifications supplied by Arab pharmaceutical companies to their suppliers.

1.1.15 General

(F) Of the utmost concern were the many unsatisfactory conditions present in parenteral manufacturing facilities in particular and other manufacturing facilities in general.

(R) Firstly the utmost priority should be given to upgrading facilities of this type. As a matter of fact this should be a separate Pan Arab project distinct from any ACDIMA or other pharmaceutical manufacturing activity.
Secondly every effort should be made to change the attitudes of management and labour towards improving operational quality and maintenance procedures before embarking on large scale capital expansion programmes.

1.2 Detailed Findings on Manufacturing Practices

1.2.1 Personnel

All of the experts were very impressed with the excellent academic qualifications at all levels of management and the professional staff. Technically, all the professionals exhibited considerable theoretical scientific knowledge. We appreciated the extraordinary effort that it must have taken to create, with the minimum of extra-territorial technical assistance, the health disciplines in Egypt and to establish and expand the pharmaceutical industry to its present state. It was assessed, however, that the professional expertise could be improved by increasing the number of professionals in other scientific disciplines. For example, in many of the large pharmaceutical companies in Egypt the ratio of engineers, biochemists, microbiologists and chemists to the total number of employees were unacceptable. There appeared to be a preponderance of pharmacists.

It appeared also that the professional managers and supervisors were given very little formal training in the science of management. Senior management seemed incapable of, or unwilling to to delegate responsibilities and decision making authority to lower echelons of management.

1.2.2 Premises and Equipment

The equipment observed in the pharmaceutical manufacturing, testing and packaging areas of the companies visited were of the highest standard. Very significant capital dollars had been expended on ultra modern tabletting, liquid filling, small volume parenteral (SVP), large volume parenteral (LVP), ointment processing and encapsulating machinery, and laboratories.

There is obviously a desire on the part of the pharmaceutical industry in the Arab states to invest in, procure and operate the most sophisticated pharmaceutical manufacturing and testing systems available. The problem appears to be, however, the utilization of the equipment for maximum productivity and the effective maintenance and management of this equipment. For example it was difficult to comprehend how highly sensitive electronic quality control laboratory testing equipment could operate at optimum efficiency in a totally uncontrolled environment where temperatures

exceeding 35° Centigrade and excessive levels of humidity are relatively common factors. Supporting materials for the use of these highly sophisticated equipment seemed to be unavailable: for example, international reference standards and periodically standardized reference test solutions.

In all of the public sector companies the quality of the physical plant and the maintenance of equipment were well below international standards.

Ceilings, floors and walls were not constructed, finished or maintained in such a way as to prevent the introduction of extraneous matter into the drug products manufactured.

Windows in various manufacturing areas were left open to the outside environment permitting the entry of sand, dust, flies, etc. into the processing areas; these unsatisfactory conditions could result in the contamination of the products manufactured therein.

Walls were crumbling in some manufacturing areas, resulting in the presence of fine particles of cement scattering throughout the area.

Doors and windows were left open between working areas in all of the plants, so that finely powdered material could migrate throughout the plant. This problem could lead to the potentially hazardous situation whereby the manufacturing of antibiotics (e.g. penicillin), steroids (oral contraceptives) in one part of the plant could cause contamination of other drug products manufactured in the same general area. Especially where penicillin is concerned there are well documented case histories of often fatal anaphylactoid reactions upon the administration of penicillin or penicillin contaminated products.

Spilled raw materials in working areas were not cleaned up immediately. As a result the material was "tracked" to other parts of the plant on the soles of the workers' shoes.

Machines (especially tabletting, encapsulating, coating, powder blending and filling, and liquid blending equipment) were not isolated from each other by enclosures in separate cubicles. As a result possible cross-contamination of drug products could take place.

Overhead pipes and other service equipment were not concealed. Dust and raw material residues collected on them and could easily fall into the hoppers of equipment operating below.

Toilet facilities were inadequate. In many instances toilet tissue, liquid soap dispensers and disposable paper towels were not available. These conditions do not promote acceptable personal hygiene habits among production workers.

Many plants had open drains in the processing areas. These drains had "dead spots", i.e. areas where the flow of water-borne material to the sewers had deposited refuse. These dead spots are ideal breeding places for vermin and bacteria.

Equipment did not seem to be completely dismantled and steam cleaned or washed with detergents after each lot of product was manufactured. This comment is evidenced by the observation of powders and granulations and residues of different colours on the same tablet or liquid filling machine.

On questioning management in most plants there appears to be no routine scheduling of periodic maintenance checks of equipment to observe "wear and tear" changes in tolerances, conditions of punches and dies, accuracy of measuring devices, etc.

There appeared to be no written procedures for the routine cleaning of working areas. As a matter of fact, routine periodic cleaning of operational areas were absent in many plants. The evidence of thick dust on windows, badly stained floors, accumulation of considerable debris under filling tanks, tabletting machines and packaging materials attest to this statement.

Environmental controls were lacking in many critical processing areas. For example, the area where effervescent granules were made in some plants had no humidity control. Similarly areas used in the manufacture of capsules, acetylsalicylic acid and salicylamide tablets had no temperature and humidity controlled environments.

Equipment used in some processes had no temperature indicating devices, (e.g. there were no temperature indicating devices in the manufacture of ointments and no operational temperature and pressure recording equipment in the autoclaving equipment in the parenteral drug manufacturing areas of a number of companies visited).

1.2.3 Sanitation

Sanitation in general was below accepted international standards. The many open windows and doors have been alluded to in the previous section.

Male workers in the manufacturing and maintenance areas wore generally soiled outer clothing which did not appear to be changed frequently. Excluded from this statement are personnel working at "dirty" stations, e.g. colour coating of tablets.

Head coverings were absent in many instances. In the plants where they were a part of the personnel's attire they were improperly used. For example, the head covers used did not cover all of the hair.

It was noted that employees in many plants handled tablets, suppositories and other pharmaceutical dosage forms with bare hands. The hands of many women employees had flaking nail polish on their finger nails.

Comments on the parenteral operations will be made under Section 1.2.13.

In a number of manufacturing operations personnel were noted sweeping the floors in work areas during production operations.

There was no clear indication that the health of personnel employed in the pharmaceutical sector was closely screened on initial employment or at regular intervals during their service with the company.

It was observed that a number of employees had bandaged fingers, hands, ankles, toes, etc. Nevertheless these employees were in intimate contact with dosage forms.

It was not evident that routine observations of physical malaise among employees were made and that these employees were encouraged to seek special medical attention.

There was little evidence of a detailed formal programme for training of employees in the high standards of personal hygiene required in the pharmaceutical formulation industry.

1.2.4 Raw Material and Packaging Material Tests

In every company visited raw materials were tested. However, it seemed that many tests were conducted against outdated standards (e.g. British Pharmacopeia 1968 when the 1973 edition is the official compendium).

Concomitantly it appeared that the bench scientist or technologist could change the testing methodology at will from one compendium standard to another depending on the difficulty of the test methodology and the availability of reagents.

The identification of quarantined raw materials was unclear. There appeared to be no clearly defined procedures for identifying quarantined materials in holding areas.

Packaging materials seemed to be subjected to a minimum of tests. For example numerous statements were made relative to the finishing of the necks of locally produced glass bottles and the resulting poor closures. Also many comments were heard from Arab countries pharmaceutical management relative to the poor quality of packaging materials produced locally. Yet these materials were still being used.

1.2.5 In Process Manufacturing and Quality Checks

Although all manufacturing instructions followed master formulations, apparently in only a few companies were these manufacturing instructions direct photocopies of the master.

The general rule appeared to be that the manufacturing instructions were copied by hand or by typewriter from the master formulation. There was no evidence that these transcriptions were reviewed and checked by scientifically qualified personnel who attested that they had performed these checks by adding their initials to the production order. In several instances overages in certain raw materials (e.g. antibiotics and vitamins) were added but there were no written statements on the master concerning the percentage overage.

There was no written indication on the batch sheets that suitably qualified persons weighed and checked all raw materials going into a batch of product.

Many important details were missing from master and production formulations. For example, agitation times and speeds for liquids; temperatures for heating ointments; compaction pressures for tablets;

coating instructions for the coating of tablets; in process checks; etc.

Procedures for quarantining in process materials were not defined. There were a number of indications that materials were released for use although quality assurance parameters were not met.

There were absolutely no indications that quality control limits of variability were established at appropriate stages in the processing. For example, there were no procedures to establish what steps should be taken by quality control if the yield of actual bulk product were outside the theoretical yield limits.

The initials of personnel performing each step in the process were not recorded on the production order to ensure that the worker had actually performed the operation.

It did not appear that measuring devices (weighing scales, liquid measuring containers, etc.) were periodically checked for accuracy.

It did not appear that packaging operations were performed following the issuing of individually numbered packaging orders.

All packaging operations did not appear to be performed according to comprehensive and detailed written operating procedures or specifications which should include the identification of the equipment used to package the drugs, the adequate separation of packaging lines packaging different drugs and disposal procedures for unused printed packaging materials.

The initials of personnel supervising the packaging operations and withdrawing the bulk drugs for packaging did not appear to be recorded on the packaging order.

1.2.6 Finished Product Tests

Although each finished product appeared to be tested against a specification, in many cases the specification was outdated. For example a number of companies were testing products against the U.S.P. XVIII and B.P. 68 monographs when the U.S.P. XIX and the B.P. 73 are the current pharmacopeial reference standards.

Furthermore, official compendia were not updated through receipt of official addenda and amendments.

There appeared to be no statistically random sampling of final dosage forms for test purposes.

It was not very clear that packaged final dosage forms were tested for identity to ensure that the product packaged was indeed the same as the label.

In a number of companies it was evident that the head of the quality control department did not affix his signature to the final release of final dosage forms or tested raw materials.

In a number of instances it appeared that the individual quality control technologists in the laboratories could change the tests required within the specifications of a product to another test if for example materials for the test stated in the specification was not available without management approval.

1.2.7 Quality Control Department

All the companies in the public sector of the pharmaceutical industry had well established quality control departments, staffed by highly qualified personnel. Within the quality control departments were excellent laboratories containing the most sophisticated of modern equipment. As a matter of fact some of the equipment seen in the laboratories of the Egyptian public sector companies are now being introduced to North American pharmaceutical companies.

However, in many instances the equipment did not appear to be in use or were under utilized. In some instances the support glassware for the equipment did not appear to be available.

Laboratory personnel were seen to be titrating volumetric solutions out of burettes which were hand held.

In some instances it did not appear that quality control personnel were responsible for reviewing all documentation including processing and packaging orders and ensuring that all specifications and limits had been met.

There appeared to be no formal written record of complaints received by companies concerning any faulty product that may have been detected on the market by physicians, hospital administrators, pharmacies, nurses, etc.

The quality control department did not appear to be responsible for the inspection and disposition of all returned drugs to ensure that no defective drugs were readmitted to warehouse stocks.

1.2.8 Stability Testing

All companies appeared to have some form of stability testing programmes. However products were not always tested for stability in the containers in which they will be marketed.

No stability testing appeared to be performed when a change in formulation took place, for example a change of excipient or filler. Similarly if the coating procedure of a tablet was changed no stability tests appeared to be conducted on the new dosage form. It was apparent that many pharmaceutical companies in the public sector were going to strip and aluminum foil packaging. There was no indication that products packaged in this way had been subjected to stability testing.

No attempt appeared to have been made to identify degradation by-products in current formulations.

1.2.9 Recall System

The manufacturers did not appear to have written procedures capable of immediate implementation for the complete and rapid recall of any lot of a drug from the market. These procedures should contain samples of form letters to be sent to the physicians, pharmacists, hospitals, etc.; samples of the type of envelope indicating the urgency of the recall; and the format of the committee of the company which would make the decision relative to the recall of that product.

1.2.10 Product Information Records

Although all companies had excellent information available on their premises and in their catalogues a significant quantity of vital information was lacking.

It appeared that most of the product information available was written to demonstrate the quality and efficacy of the various drug products. Very little information was available relative to contraindications, adverse reactions, precautions, treatment of toxic effects or overdosage.

Some of the claims made on labels and in catalogues and promotional literature could not be supported by internatonally acceptable published scientific research.

Product monographs were not available for all dosage forms.

1.2.11 Self Inspection Programmes

None of the companies which were visited seemed to have a self inspection programme to monitor their day to day operations or quality control programmes.

1.2.12 Records and Samples

Many companies did not appear to keep adequate numbers of samples to ensure that tests could be performed on these lots of products should a problem arise. In many instances the samples were retained in very poor environmental conditions which did not protect the quality of the samples. Those records that were maintained appeared to be in a very lucid form and were readily available for review.

1.2.13 Parenteral Operations

1.2.13.1 Terminally sterilized.
1.2.13.2 Aseptically filled.

It was noted that all the companies involved in the manufacutre of parenterals possessed the most modern equipment to produce the highest quality product.

However, of the most grave concern to the experts was the quality of the manufacturing and testing procedures.

1.2.13.1 Terminally sterilized products

In many instances the filling process and sealing or closure areas where this type of product was manufactured did not appear to be provided with a supply of sterile filtered air under positive pressure. The areas did not appear to be subjected to disinfectant sprays prior to operation or disinfectant wipe downs.

In general it was not evident that the sterilizing operations were routinely checked to ensure the effectiveness of the sterilizing process. Only one manufacturer indicated that they routinely ran normal filling operations using thioglycollate medium which was sterilized in the normal way and then incubated to test the efficacy of the sterilizing procedures.

Some companies did not commonly employ sterilizing indicators with each sterilizer load.

Many of the autoclaves and sterilizing equipment seen did not appear to have recording charts indicating temperature and pressure readings. Where recording equipment was part of the apparatus, this equipment was non-functional in some instances.

There were no records to indicate that the time elapsed between the preparation of the distilled water or other solvent and the terminal sterilization of the drug did not exceed 24 hours unless suitable precautions were taken to prevent bacterial growth.

Specific written instructions for the cleaning of the areas of terminal sterilization and equipment used therein; preparation of closures, containers; manufacturing procedures for bulk materials; instruction relative to the dress of personnel entering the parenteral area; environmental tests to be run during production; filling and packaging procedures; and special precautions did not appear to be available.

There appeared to be no fixed procedures for the routine performance of bacterial counts on the air in the area used to manufacture and process terminally sterilized drugs.

1.2.13.2 Aseptically filled drugs

In general the premises in which these products were manufactured were unsatisfactory. Ceilings, walls and floors were not completely sealed so that they could be washed efficiently and effectively after each use. There was no indication that antiseptic sprays and wipe downs were used in these areas before a processing operation took place. Light fixtures in several instances protruded from the ceilings and could collect dust or extraneous matter.

We were unable to inspect at close quarters the air filtration systems in the aseptical filling operations. However in a number of instances we were unable to detect the flow of positive pressure air away from these areas. We also noted floor drains and sinks in these areas where bacterial growth could take place thus contaminating a supposedly aseptic area.

In a number of plants ultraviolet light was used but there was no evidence that their emissions were checked routinely. These lamps are non-effective if the emission rate is below 70%.

It was noted that many companies had installed laminar flow equipment. However the periodic testing of the efficacy of the laminar flow units left much to be desired. Too much emphasis and credence was placed on the claims of the laminar flow manufacturer's literature.

Many of the personnel working in the aseptic filling areas were improperly dressed.

Head coverings were out of place permitting the exposure of much hair.

Although hands were gloved, sleeves were rolled up permitting the exposure of the forearms in many places.

Many employees were seen to be improperly clad around the feet.

A number of employees were found without face masks.

There was no evidence that employees working in the parenteral areas were subjected to periodic medical checks.

In some companies the aseptic processing area was not checked routinely for the quality of air by performing bacterial air counts. As a matter of fact these counts should be performed in the sterile area at least once during each day when processing or filling operations are carried out.

There appeared to be no routine monitoring of maintenance of sterility in the aseptic filling operation by carrying out normal sterile thioglycollate or other microbiological media fills with their subsequent incubation.

There was no routine calibration of the temperature recording equipment used on the animals involved in pyrogen testing.

1.2.14 Importation of Finished Dosage Forms, Raw Materials and Pharmaceutical Machinery

The control of these two classes of commodities are in the hands of two public sector agencies.

In general every attempt is made to acquire finished products and raw materials from reputable international sources. However, the storage and general handling of the merchandise after receipt on the premises were totally unacceptable.

1.2.14.1 Finished Dosage Forms

These were stored in buildings without environmental controls. Doors and windows were open and the bottles were covered by a thin layer of dust.

Where expiration dates were seen on labels, a number of products were observed with marginal expiration dates, i.e. the date of expiration on the label was within 2 to 3 months of the day of the visit. Many products with known stability problems: antibiotics, vitamins, products containing acetylsalicylic acid and salicylamide did not have expiration dates on the labels or dates of manufacture.

Many products were packaged in clear glass instead of light resistant amber glass.

Many tinctures, liquid extracts, disinfectants, surgical soaps, etc. were imported by the hundreds in uneconomically small bottles of 100 ml to 500 ml. Low cost items, e.g. Epsom salts, were imported in final packaged dosage forms in one half or one kilo tins, the most uneconomical forms of purchasing.

We were unable to ascertain if the manufacturer's certificates of analysis accompanied each lot of product.

1.2.14.2 Raw Materials

Raw materials imported to the Arab countries are not generally packaged for high temperature and high humidity areas.

They were left exposed to high temperatures and humidities in warehouses with uncontrolled environments.

Several bags of raw material were seen lying on platforms and trucks outside of the warehouse for what was obviously a long time evidenced by dust and holes in the containers made by vermin and careless handling.

1.2.14.3 Pharmaceutical Machinery

Machinery was seen lying around in the open in the most shocking state of neglect. Half broken crates exposed delicate equipment to the elements and the hostile environment of dust, sand and bird droppings. It was obvious that many pieces of equipment had been lying around in these conditions for a very long time. An outstanding example was the radioactive cobalt purchased from Atomic Energy of Canada which already has been lying at the site of the radiation sterilization plant for one year and will not be installed for perhaps another year. In view of the cost and half-life of this material a significant capital loss has already accrued to this project.

As a matter of fact many foreign and Egyptian companies were bitter in their comments relative to the processing and release of raw materials and machinery. After unloading at the port of entry and before arrival at the plant's destination, it was considered that too much time had elapsed for the processing and too much damage had been done to the material in the above mentioned interim.

1.2.15 General

In general the unsatisfactory state of the pharmaceutical manufacturing plants in the Arab countries may be attributed to the attitudes of personnel to management and maintenance.

It was quite clear to the experts in their visits that every product manufactured in the public sector plants was easily marketed because of the demands of the market place. Because of this factor the senior management did not appear to think it was necessary to implement changes that would upgrade their operations to bring them more in line with internationally accepted standards.

From the point of view of maintenance it seemed that funds were readily available for the purchase of capital equipment and therefore the maintenance of existing equipment did not seem to enjoy a high priority. In addition the workers did not seem to appreciate that the lack of maintenance decreases the efficiency of equipment use resulting in lower production volumes.

1.3 Short and Long Term Recommendations for Upgrading Current Manufacturing Practices

1.3.1 Personnel

Short Term Recommendations

Senior management should be encouraged to travel abroad as soon as possible to visit their multinational principals' plants which must perform according to international GMP. Furthermore they should be encouraged to spend significant periods of time working in several branches of their multinational principals to acquaint themselves with the latest developments in quality management.

Management should also be subscribing to various publications on good manufacturing practices such as the Gold and Green Sheets of the U.S. Food and Drug Administration (FDA), the Federal Register of the U.S., the many publications of the governments of Canada, the United Kingdom, Federal Republic of Germany and Sweden to acquaint themselves with the changes in quality assurance management procedures.

Senior management of all of the public sector companies should immediately organize local seminars for senior and middle management to exchange ideas as to how best GMP can be upgraded on a short term basis. Experts in quality assurance from industries and governments outside of the Arab countries should be invited to act as advisors and lecturers at these seminars.

Long Term Recommendations

Senior management in collaboration with senior officials from the Ministry of Health and the faculties of pharmacy and other pharmacological sciences should convene a committee to create a programme in quality assessment or quality control management and quality control principles which would be built into the curricula of the relevant university faculties.

Senior government and industrial quality assurance personnel should design inplant quality control and quality assurance programmes for the initial training of all personnel as well as the ongoing indoctrination and upgrading of the knowledge of good manufacturing practices.

In general one cannot over-emphasize the crucial necessity to change the attitudes of senior management in particular and the attitutdes of all other employees in general as they relate to establishing good pharmaceutical manufacturing practices in the Arab countries. On a short term basis because of the vast demand for medicines in the Middle East, the existing companies in the Arab countries have no difficulty marketing their products irrespective of quality. However from a long term point of view as the Arab consumer and health discipline practitioners become more and more sophisticated they will demand products that meet the higher standards of internationally acceptable good manufacturing practices. Unless the present companies start taking steps to upgrade their operations immediately they may find that within 5 to 10 years they no longer are respected in the market place and as a result may find themselves in serious economic difficulties because of unmarketable products.

1.3.2 Premises and Equipment

Short Term Recommendations

Implement at once an indepth comprehensive house-cleaning programme based on detailed written instructions.

Wherever possible and taking into consideration the intense heat, insist that all windows and doors to working areas be kept closed.

Manufacturing areas which can be effectively closed off from the rest of the plant should be so structurally modified so as to permit a complete environmental control system to be put in to regulate temperatures and humidities in those areas.

All processing equipment which may create problems of contamination of other drug products should be immediately enclosed in their own cubicles and the necessary environmental control equipment installed. Examples of these types of equipment are tabletting equipment, encapsulating equipment, powder filling equipment, granulating equipment, certain large liquid manufacturing equipment, etc.

Detailed maintenance programmes should be created at once which would permit the present equipment to be dismantled after every production run for thorough cleaning and maintenance check. These cleaning and maintenance instructions should be recorded in operational manuals which should always be available in the particular work areas or at specific work sites.

All work areas should be maintained in an orderly fashion. Raw and packaging materials should be neatly stacked; finished goods should be dusted periodically and a system of rotation be designed to ensure that the oldest lots of product go out to the market place before the newer batches of products.

Long Term Recommendations

Immediately cease the building of multi-storied structures in the heart of densely populated centres where environmental pollution is a serious impediment to GMP, and transportation of goods is extremely difficult.

Establish plant and safety engineering sections in all pharmaceutical plants to improve the quality of operations and to ensure the safety of the workers. It was remarkable to note that in many potentially hazardous processes that the employees wore neither safety helmets, shoes, goggles or gloves. It was also noted that many pieces of equipment were operated without necessary safety devices.

It is suggested that some of the earnings of companies in the public pharmaceutical sector be used to bring the present operating plants up to an acceptable standard of GMP rather than remitting these funds into the public treasury.

All future plants should be designed from the very beginning to meet the highest levels of good manufacturing practices. If the Arab countries wish to produce pharmeceutical products which conform with the highest internationally accepted standards of GMP, then the Arab pharmaceutical companies must implement in-plant conditions which will bear the scrutiny of the international market place and foreign regulatory agencies.

1.3.3 Sanitation

Short Term Recommendations -

Immediately start seminars to teach the employees the high standards of personal hygiene and plant sanitation necessary in a responsible pharmaceutical entity.

In all washrooms install liquid soap dispensers and disposable paper tissue containers. Institute an intensive programme to remove all insects, vermin and debris from the plant.

Create precise detailed clean-up procedures for work areas including walls, floors and sinks. These procedures should include the type of disinfectant to be used, the concentration and how often the disinfectants are to be applied.

All eating should be confined to a specific section of the plant. It was noted that several employees in many plants were eating on the job and scraps of food which were obviously the remains of past meals were strewn around the work areas.

In view of the environmental conditions in the Arab countries it should be company policy to clean outer working garments every day. Head covers should be mandatory in all manufacturing areas.

Workers with obvious signs of physical malaise such as bandaged hands, feet and other types of surgical dressings should be checked by their supervisors to see whether the illness of the workers could affect the quality of the product.

If a worker returns after a long illness management should review his medical history to ensure that he is clearly well and that his presence in the plant will not affect the quality of the products.

A pre-employment medical examination should be a prerequisite for hiring an employee.

Periodic health examinations of all employees especially those working in a sensitive operation such as parenteral durg manufacturing should be standard practice in pharmaceutical companies in the Arab countries.

Long Term Recommendations

The creation of audiovisual techniques such as slides, film shows in sanitary techniques should be created so that they can be used as teaching tools to all personnel levels in the pharmaceutical industry.

Multinationals which have licensed companies in the Arab countries to produce their products should be encouraged to advise and assist Arab counterparts in matters pertaining to sanitary practices.

All pharmaceutical companies should subscribe to journals on sanitation and sanitary engineering to assist them to keep current with changing technology in this field.

A department of sanitary engineering should be incorporated into the building and staffing of plants or planned expansions.

1.3.4 Raw Material and Packaging Material Tests

Short Term Recommendations -

Wherever international compendial standards are used the specifications for these materials should be updated to the current issue.

It should be forbidden for bench chemists to change any of the tests without the approval of senior quality control management.

Simple packaging material specifications and tests should be created at once.

The results of the tests on every batch of raw materials and packaging materials should be recorded on individual certificates of analysis.

Every batch of raw and packaging material should be assigned a receiving number on receipt at the plant. This receiving number should be entered on all documents pertaining to these materials.

Long Term Recommendations -

Since raw and packaging materials are stored under rather unfavourable conditions relative to temperature and humidity, stability testing should be performed on these materials to see if there is any adverse effect on the materials due to the improper storage.

Detailed specifications for every raw and packaging material should be created including caps, bottle, cartons, etc. and every lot of these materials received should be tested against the given specifications.

1.3.5 In Process Manufacturing and Quality Checks

Short Term Recommendations -

Starting immediately all master formulation documents from which manufacturing and packaging work orders are reproduced should be rewritten as they are withdrawn from the company's records to initiate production. To take a hypothetical example: If a company's inventory records indicate that the stock of tubes of Hydrocortisone Cream 0.5% with Neomycin is at its minimum level, instructions will go to the production department to initiate manufacturing of a new batch of this product. The

responsible person will extract the master formula and check it to see if it has all manufacturing detail which would enable any reasonably trained person familiar with the equipment but who has never previously manufactured this product to produce a new batch without depending on the memory or guidance of a second or third party.

If the existing master formulation cannot meet the above criterion then the master formula should be rewritten in a form similar to the formulae shown in appendix III to provide this information which should include:

- The names of the professional staff who will revise and check the old master.

- The date this revised formula was designed and the amendment number. (The first amendment would be No. 1; any future product changes which would result in changes to the master formula information would be called amendment No. 2 or No. 3, etc. and would necessitate the issuing of a newly typed master formulation embodying the approved changes.)

- The theoretical quantity of the batch size with the theoretical percentage deviation permitted when the actual yield produced was compared with the theoretical yield.

- The name of the person who will issue the production order based on this master formulation.

- The date that manufacture was started.

- The date manufacture ended.

- The name of the quality control person checking the cleanliness of the equipment before production is initiated.

- The name and standard quantity of each raw material used in the batch, with lot numbers.

- The initials of the person weighing each ingredient.

- The initials of the person checking the weight of each ingredient measured by the operator above.

- The initials of the person adding the measured raw material to the bulk mixing equipment.

- The initial of the person checking the addition of each quantum of ingredient to the bulk mixing equipment.

- Special instructions, e.g. protective wear for personnel; storage conditions for raw and bulk materials, etc.

- Complete manufacturing instructions in detailed step by step processing procedures including equipment to be used, mixing time, drying or melting temperatures, etc.

- The initials of each operator performing each step of the process.

- The signature of a supervisor indicating that the processing operation was completed satisfactorily.

- The signature of the quality control person who has sampled the finished bulk product.

- The signature of the production person charged with ensuring that the equipment used in the manufacturing process was cleaned according to written instructions.

- The signature of the Q.C. person checking that the equipment used has been cleaned satisfactorily.

- The signature of the Q.C. and production personnel releasing the bulk for packaging, with date shown.

The packaging section of the master formula which when reproduced becomes the packaging order will contain the information and specifications (please see specimen packaging specification card in appendix IV.

- Name of the product to be packaged.

- Date packaging started.

- The name of the supplier (the company which manufactured the bulk or supplying the bulk from outside the company).

- The container size, type and colour.

- The type of dessicator and filler.

- The type of cap and liner.

- The type of closure seals.

- Position of label (front/side/top of cap, etc.)

- Other packaging parameters outlined in example in appendix IV.

The same modifications could be revised on a product/batch basis for:

- In process quality control specification and test specimen document - See appendix V.
- Raw material specification and test specimen document - See appendix VI.
- Finished product specification and test specimen document - See appendix VII.
- Finished product permanent specification document - See appendix VIII.
- Label review specification - See appendix IX.

Please note that the simple photocopying of any of these master forms will give immediate working production or Q.C. documents on which the operators or laboratory staff can fill in findings or affix signatures to show that an activity is completed. These prototype masters with few modifications will meet the basic documentation required in a pharmaceutical operation.

Long Term Recommendations

Concomitantly with the activities advocated under short term recommendations the same review of documentation should be initiated on all company processing documents for all products irrespective of whether these products would be manufactured one month or one year into the future (because of existing warehouse inventories).

The review of this documentation should be closely integrated with other activities to upgrade GMP and checking systems in sanitation, maintenance of premises, equipment, product information, self inspection programmes, etc.

1.3.6 Finished Product Tests

Short Term Recommendations

The specifications against which all finished products are tested should be updated since in many instances products were being tested to old compendial standards.

Pharmaceutical companies should ensure that they have all supplements and addenda to the pharmacopeial standards that they are using as references.

All companies should purchase immediately United States Pharmacopeia, British Pharmacopeia and European Pharmacopeia reference chemical standard

materials, that is, standard reference materials against which laboratory personnel can compare their raw materials and finished products for identity, potency and purity.

Each and all finished product tests for products listed in the compendia should be performed. It should not be left to the discretion of the bench chemists to eliminate some of the tests because these tests are not considered important.

All bench reagents including volumetric titrating solutions should be standardized periodically.

Long Term Recommendations

Pharmaceutical companies should subscribe to more pharmaceutical scientific journals so that they are aware of changing methodology in finished product testing. Many more contacts should be established with international organizations in the field of pharmaceutical testing such as the Food and Drug Administration of the United States, the Canadian Health and Welfare Department, the World Health Organization, etc. to update the operations' technology. Visits should be paid to these organizations by senior laboratory staff to interface and establish valuable means of communication.

1.3.7 Quality Control Department

Short Term Recommendations

Declare a two year moratorium on the capital purchase of analytical laboratory equipment. Review present equipment and put them to work more effectively. It was the opinion of all the experts that equipment present in the pharmaceutical testing labs are very inefficiently used.

Since all pharmaceutical companies are in the public sector it should be possible to arrange that companies which may have tests to be performed but do not have the equipment can send the material to be tested to another company in the public sector which has that specific piece of equipment and ask that this test be performed.

Develop in-process manufacturing and packaging quality control procedures. These would include physical and chemical checks at various appropriate steps in the process.

Long Term Recommendations

Review and if necessary rewrite all manufacturing, packaging and testing procedures to ensure the maximum of GMP.

Arrange with other independent companies to test the quality of in house quality control department by sending out purposely incorrectly packaged product for testing to see whether the incorrect packaging will be detected.

Ensure by rotation of employees that all technical personnel are familiar with all equipment and every aspect of quality control in the plant. Utilize all equipment available and ensure that the proper materials, for example, glassware, colour indicators, etc. are available.

1.3.8 Stability Testing

Short Term Recommendations

Ensure that all new products marketed from here on be subjected to accelerated stability testing under the following conditions:

- Temperatures: 5°C, 40°C, 50°C and 60°C.

- Humidity: between 50% and 90% relative humidity usually in increments of 20%.

- Light exposure: ultraviolet or direct sunlight.

Where stability testing indicates that there is a problem expiration dates should be assigned to the product and stated on the label.

Since the public sector pharmaceutical industry seems to be moving away from bottles to foil and aluminum strip packaging all products packaged in these fashions should be subjected to accelerated and ongoing stability studies.

Stability studies and tests should be sensitive enough to detect degradation by-products.

Long Term Recommendations

At least one lot of each product per year should be subjected to stability studies. This type of testing may indicate that the same raw materials received from different sources may not have the same stability qualities.

If it is anticipated that a production process will be changed in the future stability testing should be initiated as soon as possible to ensure the bonaficity of the new process. For example, if the company is deciding to change the dosage form of a product from sugar coated tablets to a film coated tablet this change in procedure should be subjected to accelerated stability studies before full production is initiated, and the ongoing shelf life studies on the initial full production batches.

1.3.9 Recall System

Short Term Recommendations

A senior management committee chaired by the manager of quality control should be created to study and set up procedures for recalling a defective lot of product from the market should the need apply.

Long Term Recommendations

Companies should review their record keeping systems and where necessary make changes to ensure that should it be necessary to recall a defective lot of product it will be possible to trace each unit of this lot of product either through its accounting or inventory systems to the level of the retail pharmacy or hospital dispensary or field clinic.

1.3.10 Product Information Records

Short Term Recommendations

All companies should create for each of their products a product information record or monograph which should be the sum total of the entire information relative to this product. The product information should contain the following:

- Name of product.
- Ingredient or ingredients and the standard to which they conform.
- Chemistry and pharmacology.
- Indications which should include any abstracts from pharmacological or medical publications.
- Contraindications.
- Toxic effects, adverse reactions and precautions.
- Treatment of toxic effects.
- Storage conditions.
- Units per packaged dosage form.
- Recommended dosages.

For a specimen of a product monograph please see appendix I.

To this product information should be added from time to time any complaints from the medical or pharmacy professions relative to the efficacy of or adverse reaction to the product.

Long Term Recommendations

The continuous updating of the product information record will be essential. Information for this updating will come from within the plant and from a review of technical and pharmacopeial literature.

1.3.11 Self Inspection Programmes

Short Term Recommendations

Immediately in each plant a self inspection committee should be created with the head of quality control as the chairman. The committee should immediately begin the creation of a self inspection programme to be implemented in the company. The self inspection programme may follow the general headings outlined in this section of the report, 1.3.1 to .1.3.13, to ensure that all processing, packaging, quality control procedures and product specifications are routinely met in the company.

The committee should decide on the frequency of self inspections. It is our experience that twice a year is adequate.

Of considerable importance to the implementation of this programme is the fact that in subsequent inspections, great attention should be paid to see whether the faults found in previous inspections have been corrected.

Long Term Recommendations

Perhaps an inter-company self inspection procedure could be created to establish a common form of self insepction among existing companies in the Arab countries and in this way each company will assist the other to upgrade its GMP. This inter-company committee could also be reviewing good manufacturing practices around the world so that the process of upgrading is not only uniform but continuous.

1.3.12 Records and Samples

Short Term Recommendations

Records should be kept in one central locality so that all the documentation pertaining to a certain batch of product is readily at hand.

Samples wherever possible should be kept in environmentally controlled locations so that the quality of the sample remains constant. A sufficient quantity of units of each lot of product should be maintained so that the entire tests required for that product can be repeated at least three times. Samples should be complete final packaged dosage forms meeting all the company's requirements and should differ in no way whatever from samples of those lots of products on the shelves of the pharmacies and hospitals.

Long Term Recommendations

Attempts should be made to computerize all production records so that data could be easily collated relative to annual production figures, cost accounting, inventories, etc. to assist in long term projections and assessing of short term problem areas in the plant's operations.

1.3.13 Parenteral Operations

Short Term Recommendations

An immediate improvement in the protective clothing used in these operations is required. All parts of the skin should be covered. The hair should be totally covered and the feet obviously should be totally covered.

Ensure that all parenteral operations areas are under positive sterile air pressure.

Ensure that all personnel (especially mechanics) are properly clothed on entering these areas.

Conduct routine air testing during each production run.

Wipe all sterile areas with antiseptic solutions, spraying where necessary, before production runs.

Close all drains and remove all sinks from the sterile areas.

Attach temperature and pressure recording devices to all sterilizers; where such recorders are already in place ensure that they are working.

Check all air and water filtration systems.

Conduct routine medical examinations on all personnel working within the sterile areas.

Change the inspection personnel especially those working on the visual inspection for particulate matter frequently, such as every half hour.

Long Term Recommendations

It is suggested that in any future parenteral type of operation that completely new facilities be built away from crowded city environments in one storey prefabricated structures meeting the highest standard of GMP. A "Guide for Parenteral Drugs Manufacturing and Personnel Training" is included in appendix II.

Statistical methods for sampling large volume parenterals and large production batches of ampoules and vials should be brought in line with internationally accepted standards.

1.3.14 Importation of Finished Dosage Forms, Raw Materials and Pharmaceutical Machinery

1.3.14.1 Finished Dosage Forms

Short Term Recommendations

It is essential that a certified copy of the certificate of analysis for each lot of product imported into the Arab countries accompanying the product is a part of the required shipping documents.

All finished products should be packaged in light-resistant containers, well sealed against humidity, against specifications given by the purchaser to the supplier.

All products with known stability problems should carry expiration dates on the label. That is the date after which that particular product should not be used.

Long Term Recommendations

All foreign companies should be asked to supply to the competent authorities in Egypt (the other Arab countries should follow suit) evidence of the relative stability of all final dosage forms which they sell.

Buildings should be converted into environmentally controlled facilities to enhance the stability of products sotred therein.

Every effort should be made to import tinctures, salts, extracts in large quantities to save the very heavy freight costs. The bulk materials can then be filled into smaller containers by pharmaceutical processors in the Arab countries as a significant saving in cost. Eventually local companies should be making their own tinctures, disinfectants, surgical soaps, etc.

1.3.14.2 Raw Materials

Short Term Recommendations

Raw materials should be packaged in fibreboard, weather resistant containers or other suitable materials according to precise packaging specifications given to the supplier.

All raw material shipments should include the documents which accompany the material specifications or certificates of analysis to assist the final recipient (if it is a pharmaceutical, food or cosmetic company) to assess the quality.

Long Term Recommendations

All raw materials should be stored in environmentally controlled surroundings. All care should be taken to keep raw materials away from rodents and other types of vermin.

All raw material specifications should be updated to meet the latest compendial standards.

1.3.14.3 Pharmaceutical Machinery

Short Term Recommendations

All broken crates in the open (i.e. outside of buildings) which contain machinery should be covered by bags or wooden slats. Every effort should be made to clear machinery from holding areas as soon as possible.

Every effort should be made to see that equipment and critical materials are not ordered before they are ready for use.

Long Term Recommendations

Permit equipment to be shipped from dockside or airport directly to the plant or site of use and let the government agency process the paperwork only. The personnel in the plant ordering the equipment are the best judges of the quality of the shipment on arrival and are the best equipped to ensure careful storage of the equipment until they are put into use.

Enlarge storage facilities of the government agency engaged in purchasing raw materials and equipment.

2 Assessment of Production Capabilities and Capacities of Formulation Plants Visited and Recommendations to Upgrade Same

For the purpose of a comprehensive review of current production capabilities and capacities and consequent recommendations, comments will be made under the following headings:

2.1 Capabilities

2.1.1 General.
2.1.2 Processing Technology.
2.1.3 Management.
2.1.4 Research.
2.1.5 Manufacturing Equipment.
2.1.6 Quality Control Laboratory Equipment.
2.1.7 Packaging Equipment.
2.1.8 Physical Plant and Warehousing.
2.1.9 Marketing Organization.

2.2 Capacities

2.2.1 General.
2.2.2 Tablets - Uncoated.
2.2.3 Tablets - Coated.
2.2.4 Capsules - Hard Gelatin.
2.2.5 Ointments and Suppositories.
2.2.6 Powders and Granules.
2.2.7 Liquids.
2.2.8 Parenterals.
2.2.9 Packaging.
2.2.10 Labour.

2.1 Summary of Findings (F) and Recommendations (R) Relative to Capabilities

2.1.1 General

(F) ACDIMA has not assigned a level of priority concerning the immediate maximizing of present pharmaceutical operations' capabilities and capacities to improve the quantum of locally produced pharmaceuticals in the Arab countries.

(R) ACDIMA should as an order of first priority (concomitant with its other priorities) seek to exploit the unutilized capacities of present operating plants for increasing the quantity of pharmaceuticals produced locally. Furthermore, of equal importance, ACDIMA should immediately utilize a significant part of this excess capacity to have products processed to its own specifications (both product and GMP) and packaged under the ACDIMA name for sale by ACDIMA's marketing organization.

2.1.2 Processing Technology

(F) Basic technology to manufacture all types of dosage forms is available in the Arab countries.

(R) Updating of technology by introduction of modern operational techniques is recommended.

2.1.3 Management

(F) Absence of positive attitudes by management to GMP and delegation of authority was found.

(R) See comments under 1.1.1.

2.1.4 Research

(F) Most of the research appeared to be concentrated in the field of gastrointestinal bacterial and parasitic diseases.

(R) The base of research should be broadened and working contacts with international research bodies should be established.

2.1.5 Manufacturing Equipment

(F) - Excellent modern equipment which is improperly cleaned and maintained.
- Poor environmental control for equipment.
- Operated significantly below optimum capacities.
- Excellent machinery unused.
- Inadequate written operational procedures.

(R) Institute routine cleaning and maintenance of equipment to prevent breakdown and loss of efficient production. Increase the operating speed of equipment. Utilize all equipment in plants before purchasing additional equipment. Advertise to other pharmaceutical companies the availability of excess equipment or production capabilities. Introduce and establish routine written operational procedures.

2.1.6 Quality Control Laboratory Equipment

(F) Same as for 2.1.5.

(R) Same as for 2.1.5.

2.1.7 Packaging Equipment

(F) Same as for 2.1.5.

(R) Same as for 2.1.5.

2.1.8 Physical Plant and Warehousing

(F) Present plant and extensions under construction (but not completed) for production have:
- Crowded warehousing;
- Inefficient materials handling by employees;
- Inadequate record keeping and inventory control.

(R) Attempt to modify present manufacturing plants and projects under construction to meet acceptable operational standards.

2.1.9 Marketing Organization

(F) Marketing organization is not developed; modern marketing concepts are not used.

(R) Develop marketing organization and modern marketing concepts to enable production use of excess capacity. Merchandize under ACDIMA's label.

2.2 Summary of Findings (F) and Recommendations (R) Relative to Capacities

2.2.1 General

(F) Same as for 2.1.1.

(R) Same as for 2.1.1.

2.2.2 Tablets - Uncoated

(F) These were producing at about 40% of capacity.

(R) Increase speed of machines. Improve maintenance of equipment. Maximize the utilization of labour and equipment.

2.2.3 Tablets - Coated

(F) These were producing at about 35% of capacity.

(R) Increase coating pan loads. Document tablet coating procedures. Introduce film coating of tablets in lieu of sugar coating. Maximize the utilization of labour and equipment.

2.2.4 Capsules - Hard Gelatin

(F) These were producing at about 40% of capacity.

(R) Improve storage conditions for empty capsules. Increase speed of filling machines. Improve environment surrounding capsule making machines. Maximize the utilization of labour and equipment.

2.2.5 Ointments and Suppositories

(F) These were producing at about 30% of capacity.

(R) Utilize present mixing, milling and tube filling capacity more fully.

2.2.6 Powders and Granules

(F) These were producing at about 35% of capacity.

(R) Improve environment in the equipment area. Utilize present equipment more efficiently.

2.2.7 Liquids

(F) These were producing at about 35% of capacity.

(R) Utilize present equipment more efficiently.

2.2.8 Parenterals

(F) These were producing at 35% of capacity. Equipment was under utilized and there were improper quality control procedures.

(R) Increase the speed of equipment. Implement improved quality control procedures as outlined in the "Guide for Parenteral Drugs Manufacturing and Personnel Training" in the Appendices.

2.2.9 Packaging

(F) These were producing at about 35% of capacity. Tablet packaging equipment was unused. Bottles for liquids had poor closures and labelling was slow. Packaging lines were overcrowded with personnel. In all packaging operations equipment and personnel were operating below economical production levels.

(R) Increase the speed of operating equipment. Utilize unused equipment. Improve the quality of glassware. Increase strip-sealing capabilities of tablets, capsules, suppositories, etc.

2.2.10 Labour

(F) Abundance of labour were unused because present plant and equipment are under-utilized. Generally the direct labour personnel were under-trained.

(R) Operate all plants with two shifts. Improve the training of general labour. Decrease the number of employees on packaging lines.

2.3 Detailed Recommendations Relative to Capabilities

2.3.1 General

Short Term Recommendations

To assist the present pharmaceutical industry to improve its capabilities ACDIMA as part of its high priority to market products under ACDIMA's label and distribution control should, concurrently with the initiation of the indepth marketing programmes recommended in Section 3, establish contact with existing companies to initiate the formulation and production of a limited group of products under ACDIMA's label and according to ACDIMA's GMP.

This action would achieve three immediate objectives:

- The increased and efficient utilization of existing plants and equipment.

- Introduction of ACDIMA's name and products to the Arab market.

- By establishing specific standards for manufacturing, packaging and testing of ACDIMA's products by these companies, ACDIMA could set an example for improved GMP and other capabilities in these companies in a subtle and understated way.

Long Term Recommendations

It is crucial that ACDIMA's long term projections for pharmaceutical formulation products include as a high priority programmed cooperation with existing pharmaceutical (private and public sectors) manufacturers to utilize to maximum the capabilities and capacities of existing plants. It would be a disservice to the Arab countries to spend significant capital dollars for establishing new plants without attempting to upgrade and fully utilize present facilities. This does not mean that ACDIMA could not proceed with the immediate establishment of a model formulation plant for each of the following types of production: non-parenteral formulation plant, a parenteral formulation plant, a hard gelatin manufacturing and filling plant, etc. However, before authorizing the establishment of numerous plants in the Arab countries, the beneficial effect of improving efficiencies in present plants should be established.

2.3.2 Processing Technology

Short Term Recommendations

Implement the recommendations under 1.3.

Long Term Recommendations

Implement the recommendations under 1.3 as above.

2.3.3 Management

Short Term Recommendations

Implement the recommendations in 1.3.1 - short term recommendations.

Long Term Recommendations

Implement the recommendations in 1.3.1 - long term recommendations.

2.3.4 Research

Short Term Recommendations

Every public sector pharmaceutical company represents foreign principals which have extensive research facilities engaged in a broad range of research. The foreign principals' assistance should be sought in order to help Arab pharmaceutical companies to set up integrated research programmes especially in tropical diseases.

Foreign principals should also be actively encouraged to involve their Arab counterparts in clinical and pharmacological studies involving new and experimental pharmaceuticals and medical devices.

As a matter of fact the following requirement should be mandatory: Before any important therapeutic product or device can be introduced by foreign principals in the Arab market place either by importation of the finished product or through local manufacturing, that company should conduct clinical studies in the Arab countries to complement the studies made in the principal's country in order to show that the new product is therapeutically active and worthwhile in view of differences in the dietary habits and physiological make-up of the average Arab and the dispensing and administration practice of the local health practitioners. This requirement would serve two purposes, namely:

- The elimination of useless products in the market place [1/]
- Involving the local companies in a very important element of clinical and pharmaceutical research from which much valuable experience would accrue.

1/ See recommendations of the WHO Expert Committee on the Selection of Basic Drugs, Geneva, Oktober 1977.

Long Term Recommendations

In an effort to reduce the large number of duplications in pharmaceutical products which are imported into the Arab countries it should be a requirement that all foreign companies which have important therapeutic products on the Arab market prove through limited clinical studies conducted in the Arab countries on Arab patients the drugs' clinical efficacies.

This activity would not only utilize all research facilities in present plants to maximum capacity but may necessitate the expansion of these facilities (the costs of which would be partly paid for through the fees collected from the principals for the local clinical studies).

The beneficial experience gained by the local companies is self-evident.

Companies in the Arab countries should through visits of and correspondence by senior research personnel establish contact for the free interchange of data with such internationally known research institutes as:

- National Research Council, Ottawa, Canada
- Medical Research Council, Ottawa, Canada
- National Institutes of Health, Bethesda, Maryland, U.S.A.
- The Centre for Disease Control, Atlanta, Georgia, U.S.A.
- Stanford Research Institute, San Francisco, California, U.S.A.

etc. so that the base of research in the Arab countries may be broadened.

Increase significantly subscriptions to research oriented journals and encourage enrollment of senior personnel in international associations, institutions and organizations involved in various research activities.

2.3.5 Manufacturing Equipment

Short Term Recommendations

Immediately implement the short term recommendations in 1.3.2, Premises and Equipment.

Utilize the equipment in a limited second production shift starting at the conclusion of the first shift. It is appreciated that the pharmaceutical formulation plants are regarded as a labour intensive operation in the Arab world. However there is the contradictory factor, namely, that it seems very difficult to get labour in the Arab countries to work an afternoon or evening shift. If the present manufacturing equipment in the pharmaceutical plants can be put to maximum efficient use, they could be utilized as for a highly productive second shift with a minimum of supporting labour force. This hypothesis will be developed more fully in Section 2.4.10 - Labour, long term recommendations.

The present speed of operation of tabletting, encapsulation, liquid processing, and all packaging equipment should be increased immediately to improve productive capacity by at least 10-15%.

Detailed written production procedures showing all steps in processing operations will also increase the productivity of the equipment.

Long Term Recommendations

Implement the long term recommendations in 1.3.2 - Premises and Equipment.

Develop detailed production schedules to maximize the efficient utilization of equipment in general during the first shift and particularly during an implemented second shift which will be as automated as the company can make it resulting in minimizing the labour requirements for this second shift.

On a long term basis through time-motion studies establish the optimum operational speeds of equipment consistent with GMP and ensure that operators maintain these speeds.

Further comments will be made in Section 2.4.10 - Labour.

2.3.6 Quality Control Laboratory Equipment

Short Term Recommendations

It is suggested that a moratorium be placed on the purchase of all analytical equipment immediately. There is no question that the quality control laboratories in the companies visited had the most excellent instruments. All existing instruments should be immediately calibrated. All test solutions should also be standardized. A regular programme for future routine calibration and standardization should be instituted immediately. All equipment, for example, spectrophotometric, gas chromatographic, etc. should be immediately enclosed in a controlled environment relative to temperature and humidity.

Present equipment should be used for a significantly expanded programme in stability and production batch testing.

Long Term Recommendations

With the implementation of a second shift in production, the maximum utilization of the present equipment will take place.

It is essential for the best use of equipment that supplementary materials such as reference standard chemicals (U.S.P., B.P., E.P., etc.) be acquired and maintained under

ideal environmental conditions so that they may be used as reference materials against which raw materials and finished products can be measured to ensure the integrity of the latter.

2.3.7 Packaging Equipment

Short Term Recommendations

Same as for 2.3.5 - Manufacturing Equipment - short term recommendations.

Long Term Recommendations

Same as for 2.3.5 - Manufacturing Equipment - long term recommendations.

2.3.8 Physical Plant and Warehousing

Short Term Recommendations

Same as for 1.3.2 - Premises and Equipment - short term recommendations.

Institute immediately a programme among warehouse helpers in the handling of raw materials, finished products, and packaging materials in the careful handling of merchandise so as to cut down losses through damage from carelessness.

Long Term Recommendations

Ensure that all current and future expansions in the formulation plants meet with the highest standards of GMP. Much of the construction presently taking place in the industry has the capability of being altered at the present time to meet GMP.

Modern systems of inventory maintenance should be instituted to ensure that there is adequate stock rotation and lead times for the acquisition of raw materials, packaging materials, finished products, etc.

2.3.9 Marketing Organization

Short Term Recommendations

All companies in the public sector with the collaboration of ACDIMA should immediately institute market studies to indicate in which direction future marketing of products manufactured by the efficient utilization of their facilities will be going.

Public sector companies should be actively seeking the cooperation of ACDIMA to see how an integrated master plan could serve the immediate and future needs of the Arab countries.

Long Term Recommendations

In collaboration with ACDIMA undertake long term (five-year and ten-year) projections to establish market trends and the fulfillment of health needs of the Arab countries.

2.4 Detailed Recommendations Relative to Capacities

2.4.1 General

Short Term Recommendations

Please see 2.3.1 - General - short term recommendations.

Long Term Recommendations

Please see 2.3.a - General - long term recommendations.

2.4.2 Tablets - Uncoated

Short Term Recommendations

Immediately by increasing the operating speed of tablet manufacturing machines and improving the maintenance of these machines, capacity should increase about 15%.

Long Term Recommendations

The question of production on a second shift will be discussed in great depth under 2.4.10 - Labour - short and long term recommendations. However a second shift should add a further 20-25% increased capacity, resulting in a total increase of 35-40% in the production of uncoated tablets.

2.4.3 Tablets - Coated

Short Term Recommendations

In many plants unused coating pans were observed. It is conceivable that if one manufacturing operation does not have the capability or capacity to coat its tablets, arrangements can be made with another company in the public sector which has the excess capacity to do the necessary coating. This is a standard procedure utilized in other countries even among great rivals in the market place.

It appeared that coating pans were underloaded in several instances observed. Therefore careful studies to increase coating pan loads should be undertaken to cope with increases in cores coming from the faster operating tabletting machines.

Long Term Recommendations

Greater utilization should be made of improved technology in tablet coating. For example, film coating reduces the time of coating by significant man-hours and results in a more stable dosage form. It is the opinion of the experts that film coating is the ideal solution to problems of stability, friability, etc. encountered in tablet manufacturing in the Arab World.

Other comments relative to the improved production capacity will be made under the section of Labour, 2.4.10.

2.4.4 Capsules - Hard Gelatin

Short Term Recommendations

Enclose all equipment in facilities with very strict environmental controls relative to temperature and humidity.

Store all empty hard gelatin capsules in facilities which conform to the above environmental criteria. These two steps will immediately cut down lost production time due to the jamming of machines by capsules and bulk powders.

Increase speed of equipment and improve maintenance of equipment.

Long Term Recommendations

With the collaboration of ACDIMA immediately undertake feasibility studies to establish facilities for the manufacturing of hard gelatin capsules in the Arab countries. Local production will not only ensure a ready availability of empty capsules but will cut down the problems (friability, shrinkage, brittleness, clumping due to humidity, etc.) associated with the transportation of empty hard gelatin capsules over long distances with the varying climactic conditions.

The implications of increased capacity (about 30%) will be discussed under the section on Labour, 2.4.10.

2.4.5 Ointments and Suppositories

Short Term Recommendations

Increasing the speed of equipment will result in an enhanced capacity of 10-15%.

Long Term Recommendations

Greater utilization of equipment is required in this sector. A number of steam jacketed kettles which were obviously not in use or had not been in use for a significant period of time were observed lying idle.

With the implementation of a second shift discussed under "Labour", capacity of ointment and suppository production should increase by about 25-30%.

2.4.6 Powders and Granules

Short Term Recommendations

Increase the speed of filling equipment. Improve maintenance of the equipment.

Improve environmental controls of facilities so that there is less clumping and sticking of powder which reduces production time.

Long Term Recommendations

Implement second shift to utilize equipment more efficiently.

2.4.7 Liquids

Short Term Recommendations

Improve maintenance of equipment.

Increase the speed of filtration and filling equipment to give an immediate 15% increase in production.

Long Term Recommendations

Utilize double shift.

Clean and repair many of the large bulk containers seen lying around the plant so that they can be utilized for larger production batches.

2.4.8 Parenterals

Short Term Recommendations

Increase the batch size, i.e. the bulk of liquid manufactured for any one filling operation.

Operate equipment at an increased speed. Utilize equipment lying idle in the plant.

Long Term Recommendations

Implement the "Guide for Parenteral Drugs Manufacturing and Personnel Training".

2.4.9 Packaging

Short Term Recommendations

Increase the speed of packaging equipment and improve maintenance.

Long Term Recommendations

With the advent of a second shift, packaging equipment presently lying idle in the plant could be put to excellent productive use and be more fully automated. This increased automation would eliminate the necessity of large labor gangs on the second shift. It should be possible to package by automation in the second shift the same number of units that are packaged both by equipment and by hand in the first shift.

.2.4.10 Labour

Short Term Recommendations

Introduce formal training programs in processing and packaging operations to maximize efficiency of labour personnel.

Increase the number of blind personnel in the packaging operation. From observations they were significantly more productive than the operators who had their full vision. This was attributed to the fact that they were subject to no visual distractions. Secondly they are less likely to move from their work stations during production. Thirdly they appeared to be more highly motivated and proud of their labour.

Long Term Recommendations

It is strongly recommended that all plants immediately study the feasibility of implementing two shifts in all formulation plants.

It is suggested that the first shift would be:
7 a.m. to 2:30 p.m. - 7½ hours;
and the second shift would be:
2:30 p.m. to 7:30 p.m. - 5 hours.

It is recommended that the rate of hourly pay for the second shift should be such that an employee working 5 hours would receive the same financial remuneration as for an employee working 7½ hours. Thus if it was necessary to rotate employees between shifts there would be no loss of emoluments. There would also be the additional incentive of short working hours for an increased remuneration to encourage the employees to work the 2:30 to 7:30 shift.

If all the equipment existing in the formulation plants in the Arab World were operated according to their fully automated capacities, it is estimated that only about 50% of the number of employees utilized in the first shift would be necessary to

service, produce, and package an equal volume of product. This automation would reduce the problem of finding labour who would be willing to work the second shift. As previously indicated, employees who are prepared to work the second shift would be compensated by reduced hours for an increased wage. The end result may be summarized as follows:

- An increase of approximately 30% over and above present production.

- A greater return on capital plant and equipment investment for the Arab World pharmaceutical companies.

- Increased local production and a lessening of dependence on imported products.

- The realization of one possible avenue by which ACDIMA through the utilization of these increased production resources can enter the Arab market.

We reiterate that ACDIMA's future plans for the building of formulation plants should be most definitely contingent on and integrated with improved efficiency and increased production of the present pharmaceutical manufacturing plants in the Arab countries.

C. Findings and recommendations for the establishment of pharmaceutical formulation plants

3.2 Summary and Recommendations on the Establishment of Pharmaceutical Formulation Plants

In view of the fact that the existing pharmaceutical formulation plants in Arab countries produce only 50% of the Arab countries' pharmaceutical needs and as the forecast based on current annual production dollar volume outlined in Section 4.4 of this report indicates approximately 35 formulation plants capable of an annual production of $US 35 million should be built to provide approximately 44% of the Arab countries' pharmaceutical needs by 1985, it would appear that ACDIMA is in the ideal position to:

3.2.1 Create a master marketing plan and select the dosage form mix that would be produced under the ACDIMA label. (See Section 3.3.)

3.2.2 Create joint ventures with Arab and non-Arab countries. (See Section 3.4.)

3.2.3 Establish formulation plant profiles and construction projections. (See Section 3.5.)

3.2.4 Plan the location of formulation plants in the Arab countries (See Section 3.5.)

3.2.5 Establish standards of good manufacturing practices for its manufacturing plants. (See Section 1.3.)

3.2.6 Advise on the feasibility of regional bulk buying where applicable. (See Section 3.5.8.)

3.2.7 Establish a comprehensive integrated training programme for its initial and future plant personnel.

Recommendations

It is recommended that ACDIMA initiate feasibility studies at once to assess the implementation of the recommendations set out in 3.2.1 to 3.2.4.

With reference to 3.2.5 it is recommended that a committee of local Arab experts with perhaps the help of an expert in quality control management with considerable experience both in government and in the pharmaceutical industry from outside the Arab countries be invited to act as an advisor to this committee.

With regard to 3.2.6 since the members of the Board of Directors of ACDIMA are also often involved in the purchasing and control of pharmaceuticals in their respective countries it is suggested that perhaps the Board members would advise on the formation of small committees to examine the possibility of regional bulk pharmaceutical buying. More will be said on the subject in Section 3.5.8.

3.3 The Master Marketing Plan

The plan calls for the immediate creation of a marketing division of ACDIMA under the leadership of a Director who would report to the General Manager. A suitably qualified person should be hired at once to fill this position. His immediate activities would be:

3.3.1 After review of the reports of the pharmaceutical and medical appliance experts, to conduct indepth market surveys to identify areas in the Arab World where ACDIMA could immediately place its products (i.e. pharmaceutical and medical appliances) in the marketplace.

3.3.2 Invite proposals from Arab and foreign companies for joint ventures with regard to the immediate marketing of a complete range of multiple and single entity products under ACDIMA's label.

3.3.3 Initiate concurrently with 3.3.2 above and with the cooperation of Arab and non-Arab corporations, the actual marketing of a number of items known to have instant market acceptability under the ACDIMA label, without awaiting the results of 3.3.2.

3.3.4 Start the screening process of candidates who will eventually fill the roles of future territorial sales representatives for ACDIMA.

The activity outlined in 3.3.1 is self-evident.

The functions outlined in 3.3.2 will be covered in Section 3.4 which follows.

Point 3.3.3 requires some elucidation. These products would be standard products and would be manufactured by companies in Arab and non-Arab countries both to those companies' and ACDIMA's specifications. These products may or may not be sold in areas where they would be competitive to identical products of the custom manufacturer whether inside or outside the Arab countries small royalty may have to be paid on a per unit basis to the custom manufacturer for the use of his formulation and past expertise in developing the product formulation. However this royalty, usually 3-5%, will easily be covered by the selling price. In explanation of the above proposal, the following examples are given of the dosage forms which can be marketed immediately under ACDIMA's name.

Soft Gelatin Capsules

There is a place for soft gelatin capsules in the pharmaceutical marketplace of the Arab countries. There is only one company to the best of our knowledge making a small amount of soft gelatin capsules in the Arab countries. Bulk soft gelatin capsules are therefore important in final dosage form. ACDIMA should immediately begin negotiations with the many international companies as well as with the one company in the Arab countries regarding the supplying of standard products such as multi-vitamins, antihelminthics, barbiturates, sedatives, psychotropics, etc. in bulk form. The custom manufacturer of the capsules would then be informed as to which company the capsules should be shipped for custom packaging under the ACDIMA label. The finished product would then be introduced to the market by the ACDIMA sales force mentioned in 3.3.4 above.

Large Volume Parenterals, Vials and Ampoules

Companies with know expertise relative to these dosage forms both inside and outside the Arab countries should be invited to supply a final dosage form to ACDIMA and under ACDIMA's label or alternatively to supply the unlabelled final dosage form to a company of ACDIMA's selection within the Arab countries for final labelling under ACDIMA's label.

It is known that this group of products is readily marketable.

If necessary royalties would be paid. Again these products would or would not be offered for sale in the country of the manufacturer by mutual agreement.

Again as in the case of the soft gelatin capsules these products would be introduced in the marketplace by ACDIMA's sales force.

Hard Gelatin Capsules

Therapeutic agents such as antibiotics, psychotrophic agents, analgesics, antipyretics, antirheumatics, antihistaminics, antimalarials, vitamins and minerals, etc. can be packaged in hard gelatin capsules. Again as in the case of the soft gelatin capsules and the parenteral products ACDIMA will approach companies inside and outside of the Arab countries which do have the expertise to manufacture this type of product. Again royalties could be paid. The product would be supplied in bulk and would be repackaged under ACDIMA's label by one of the pharmaceutical companies within the Arab countries.

Standard Formulations

At the same time ACDIMA's Director of Marketing should select a number of therapeutic products in the following dosage forms: tablets, syrups (solutions), suspensions, powders/granules, and suppositories which are standard formulations already manufactured and sold in the Arab countries and surrounding territories. Again, a royalty would be paid to the existing companies to prepare identical units under the ACDIMA label for sale in areas where there would be no marketing conflict. It is suggest that four products from each of the therapeutic groups listed below be manufactured for sale in the dosage forms stated above:

Anaesthetics
Analgesics
Antipyretics
Antirheumatics
Antihelminthics
Antiinfectives (Chemical, e.g. Sulphonamides; Antimalaria
Antituberculosics
Antibiotics
Psychotrophics
Sedatives
Urogenital Antiinfectives
Orodentals
Antispasmodics
Antihistaminics
Vitamins
Vitamins and Minerals

Again these products would be introduced to the marketplace by ACDIMA's sales force. As stated before many of the companies custom manufacturing ACDIMA's initial products would be approached to participate in joint ventures for the creation of formulation plants under the ACDIMA umbrella.

Many of the companies which would be approached to fulfill the above programme of introducing ACDIMA's name to the marketplace would also be invited to tender on joint ventures. Therefore the above discussed activities of custom manufacturing and custom packaging some products for ACDIMA would serve as a means of getting to know possible future partners in joint ventures and also give ACDIMA personnel vitally needed multinational exposure and experience. At this point it is appropriate to discuss proposals and recommendations for joint ventures.

3.4 Joint Ventures with Corporations Inside and Outside the Arab

Corporations such as ACDIMA usually enter into joint ventures with other corporations and individuals for the following reasons:

1. The acquisition of new technology. (See 3.4.1 and 3.5.)
2. The acquisition of management skills. (See 3.6.)
3. The acquisition of financial direction and support. (See 3.7.)
4. The desire to share the inherent risks of a new venture. (See 3.8.)
5. The purchase of controlling interests in other corporations (acquisitions). (See 3.9.)

3.4.1 The Acquisition of New Technology

The acquisition of new technology will be accomplished mainly through partnerships with organizations inside and outside the Arab countries which will establish formulation plants in human and veterinary medicines, crop chemicals and medical appliances.

Joint ventures should immediately be sought among companies inside and outside of the Arab countries for the following groups of pharmaceutical entities:

3.4.1.1 Soft gelatin capsules.

3.4.1.2 Parenteral products, i.e. sterile large volume parenterals (LVP's), small volume parenterals (SVP's), ophthalmic and otic preparations for the human and veterinary fields.

3.4.1.3 Hard gelatin capsules (empty and filled), powders and effervescent granules.

3.4.1.4 Formulation plants - Human pharmaceuticals without parenteral operations to manufacture tablets, ointments and creams, liquids, powders and granules, suppositories, in the therapeutic groups shown in Phase I of ACDIMA's list of priorities, as well as to package and distribute from bulk finished product produced elsewhere, gelatin capsules and parenteral products.

3.4.1.5 Animal feed and veterinary premixes.

3.4.1.6 Veterinary pharmaceuticals without parenterals to manufacture the same dosage forms listed in 3.4.1.4 plus boluses and mastitis syringes.

3.4.1.7 Veterinary biologicals.

3.4.1.8 Packaging and labelling from bulk product.

3.4.1.9 Crop chemicals.

3.4.1.10 Medical devices.

The plant profiles which follow are suggested guidelines for the pharmaceutical formulation plants.

The management structure recommended for these plants is outliend in 3.6.3 and appendices X-XIV.

At this point it is our considered opinion that pre-feasibility studies for formulation plants are an absolute waste of time and money. ACDIMA's efforts from here on should be concentrated solely on feasibility studies. We reiterate that the recommendations following are for feasibility studies.

3.5 ACDIMA's Plant Profiles

3.5.1 Soft Gelatin Capsules

Modus Operandi

There is a distinct gap in the marketplace for soft gelatin capsules manufactured in the Arab countries. ACDIMA should communicate at once with the leading pharmaceutical companies involved in the manufacture of soft gelatin capsules; for example: R. P. Scherer, the Banner Corporation (both non-Arab companies) and the El Kahira Company of Cairo are three companies that come instantly to mind. We suggest a round table meeting to work out the mechanics of setting up a feasibility study for the mutual cooperation of the interested parties in establishing one or more soft gelatin manufacturing plants.

The Formula for Cooperation

The following contributions will be made by each party:

The non-Arab corporations - The latest technology and bridging or interim management skills.

The local Arab corporation - Knowledgeable manpower and the technology of producing soft gelatin capsules under local conditions.

ACDIMA - Will supply financing and permanent Arab management who have been trained under the bridge or interim management supplied by the non-Arab corporations (i.e. joint venture partners' project managers). Of course the above statement is rather succinct. The non-Arab joint partner corporation will supply other infra technology such as formulations, advice on equipment, setting up the operation and all the many factors that go into establishing a successful specialized pharmaceutical manufacturing "turnkey" operations.

For this corporation the following corporate mix initially is suggested.

ACDIMA -	40%
Arab corporation + foreign non-Arab corporations -	40%
Local health professionals -	20%

It would appear that ACDIMA would be acquiring a rather large share of the corporation solely for putting up the money. It should be clearly demonstrated however to all partners in the field of joint ventures that ACDIMA has a most unique position to assist in the marketing of the products of any company with which it is associated. By

virtue of the fact that ACDIMA is a corporation of the Council of Arab Economic Unity it is in an unique position to seek the active help of members of that Council to ensure that products manufactured by ACDIMA (always bearing in mind that these products must meet the highest level of international standards for good manufacturing practice) receive the sympathetic consideration of the Ministries of Health and professional bodies of Pharmacy and Medicine in the Arab countries, thus encouraging the local utilization of these products to dramatically enhance the success of ACDIMA and its associate corporations. In short, ACDIMA not only provides money but a most considerable marketing "clout" in the Arab pharmaceutical marketplace. This statement applies to all the other categories of joint ventures.

The products will be introduced to the marketplace by ACDIMA's sales force.

No attempt has been made at this time to prepare a precis or synopsis of the therapeutic groups, land and building costs, and equipment for this operation as none of the experts have any experience in this very specialized manufacturing operation. However, antimalarials and vitamins should have a high order of priority.

3.5.2 Parenteral Products (LVP's, SVP's, Ophthalmic and Otic Preparations) for the Human and Veterinary Fields

It is recommended that a formulation plant devoted solely to the manufacture of LVP's, SVP's and other sterile products (with the exception of biologicals) be developed at once. There is considerable theoretical and applied technology in these areas of specialty in Egypt and other countries. Many of the formulation companies in the Arab countries have operating departments with the most sophisticated equipment which, in theory, should be producing this group of products with the highest quality comparable to any product manufactured outside of the Arab countries. Unfortunately, because of inadequate management, maintenance, and lack of GMP there is considerable doubt regarding the quality of these end products manufactured locally. In this area ACDIMA could become the leader in creating parenteral operations which would conform to the highest international standards.

It is strongly recommended that the formulation plants created by ACDIMA should not include a parenteral operation in conjunction with tablets, liquids, ointments, etc. These are very specialized products which should be manufactured in a plant solely devoted to their production. Should each future ACDIMA formulating plant include a parenteral manufacturing

section the end result will be X number of plants producing products conforming to X number of different standards of quality as exists in the Arab World today. Whereas if one plant custom manufactured the parenteral requirements for all of ACDIMA's formulation plants (to be shipped unlabeled to these plants for labelling and finishing) then the quality of these products and the efficiency of the operation will be readily maintained and uniform.

Modus Operandi

ACDIMA would invite Arab and non-Arab corporations noted for their expertise in this area to form a consortium to conduct as quickly as possible a feasibility study for the establishment of the requisite number of facilities recommended in the projections given by the ACDIMA experts and recitified by the Director of Marketing, the senior management and Board of Directors of ACDIMA. It is quite conceivable that two formulation plants manufacturing parenterals could be conceived, planned and executed at the same time in different geographical regions.

The Formula for Cooperation

Non-Arab multinational - To supply the latest formulation technology; bridge or interim senior management; consultative services on construction, equipment, environmental resource, training, etc. etc.

Arab pharmaceutical company - To supply the land; the local formulation technology; the technical middle management; workers and the trainee technical senior management who will eventually take over fully from the expatriate managers.

ACDIMA - Will supply financing; liaison and ultimately general management who will liaise with ACDIMA's management; the sales force to distribute these parenteral products in the Arab countries under ACDIMA's name. ACDIMA will also assume that the standards of GMP are constantly maintained within the manufacturing operation.

The Corporate Mix Initially

ACDIMA -	40%
Foreign corporation -	40%
Local corporation -	10%
Local professionals -	10%

Therapeutic products to be manufactured in the parenteral product formulation plants for human consumption are as follows (unfortunately data are not currently available to the experts to advise on veterinary parenteral production):

Table 1. CAPITAL COSTS OF ESTABLISHING A MANUFACTURING FACILITY FOR PARENTERALS (SVP'S & LVP'S)**

DOSAGE FORM	INITIAL ANNUAL UNITS	EQUIPMENT COST CIF ARAB COUNTRY IN U.S. DOLLARS 1979	1980	1981	1982	1983	1984	1985
5 ml Ampoules SVP 10 ml Ampoules SVP 20 ml Ampoules SVP	20,000,000 20,000,000 20,000,000	*1,126,300	1,325,000	1,523,800	1,752,300	2,015,200	2,317,400	2,665,100
500 ml LVP 1,000 ml LVP	20,000,000 5,000,000	*2,975,000	3,500,000	4,025,000	4,628,800	5,323,100	6,122,000	7,040,300
COST OF LAND - 10 hectares (1,000,000 sq. meters) @ US 19.1¢ per sq. meter		191,000	224,700	258,400	297,200	341,700	393,000	451,900
COST OF BUILDING - 11,200 sq. meters @ $US 191.25 per sq. meter		2,142,000	2,520,000	2,898,000	3,332,700	3,832,600	4,407,500	5,068,600
		6,434,300	7,569,700	8,705,200	10,011,000	11,512,600	13,239,900	15,225,900

* Includes all support services.
**This manufacturing facility should produce $US 15,000,000 of product in 1979, with a 15% escalation per year to 1985.

Anaesthetics - Pentobarbital, Lidocaine.
Analgesics, Antipyretics - Metamizol.
Antirheumatics - Prednisolone, Hydrocortosone, other corticosteroids.
Analeptics - Methylphenidate HCl.
Antihelminthics
Antibiotics and Antiinfectives - Sodium Sulfadiazine, Streptomycin, Chlorpromazine, Benzathine, Penicillin G, Procaine, Oxytetracycline, Ampicillin.
Antidysenterics
Anticoagulants - Heparin, Coumarin.
Antihistaminics - Antazoline HCl, Hydroxyzine HCl.
Cardiovascular Agents - Dihydroxy propyl Theophylline.
Endocrine Products
Hepatobilinogenics
Vitamins - Single: B_1, B_6, B_{12}, C.
Vitamins - Complex: Vitamin B Complex.
Vitamins and Minerals
Uterine vasoconstrictors - Ergotamine.
Psychotrophics; Muscle Relaxants - Chlorpromazine, Diazepam, Imipramine, Trifluoperazine.
Sedatives and Hyponotics - Morphine, Phenobarbital.
Antispasmodics - Theophylline, Phenytoin.
Urogenital Antiinfectives
Antidiabetics - Insulin.
Hospital Products - Calcium Chloride, Dextran, Mannitol, Potassium Chloride, Sodium Chloride, Irrigation Solutions, Amino Acid and Electrolyte Solutions.
Long Acting Contraceptive Injectables

Size of Plant

Height - 10 meters to permit overhead services and mezzanines.
140 x 80 meters (11,200 square meters or 121,000 square feet).

Land

10 hectares (25 acres) which would allow for over 200% expansion.

Dosage Forms to be Manufactured in One 8-Hour Shift

Table 1 shows the projected number of units of each parenteral dosage form which will be made in one 8-hour shifts, and the projected capital costs depending on whether the equipment is obtained in 1979, 1980, 1981, 1982, 1983, 1984, or 1985.

3.5.3 Hard Gelatin Capsules (Empty and Filled), Powders and Effervescent Granules

It is our opinion that enough hard gelatin capsule sales (both empty and in filled dosage forms) exist in the Arab countries to warrant the creation of a unique complex for these types of dosage forms.

This complex would involve the creation of a hard gelatin manufacturing operation to supply empty hard gelatin capsules to all Arab countries. Concomitantly, a formulating plant would be built abutting on the capsule fabricating plant for the manufacture of filled gelatin capsules of antibiotics, analgesics and all other therapeutic groups for which the experts and the Director of Marketing agree that a market exists. Since it is necessary to have powder blenders, granulators, driers, and other supporting equipment for the encapsulating machines, these supporting machines can be more efficiently utilized if the production of effervescent granules and powders are included in this type of operation.

It is quite conceivable that ACDIMA's production of filled capsules would be of such a high standard that they could supply on a custom basis local manufacturers whose capsule filling capacities cannot keep up with their sales. Similarly ACDIMA's filled capsules could be shipped in bulk for packaging in final dosage forms to packaging facilities (in which ACDIMA may or may not have a financial interest) in other areas of the Arab countries where the density of population and other economic factors make it unfeasible at the present time to develop a formulation plant for encapsulation.

Modus Operandi

ACDIMA would invite Arab and non-Arab corporations noted for their expertise in gelatin making, hard gelatin capsule making, encapsulations of therapeutic products and perhaps formulators of very specialized products to form a consortium to establish a fully integrated capsule manufacturing complex.

Again from the reports of the experts and the studies by the Director of Marketing the product line would be established.

A word of caution should be inserted here. Any facility for the manufacture of antibiotics and steroid encapsulated products should be specially designed to separate these types of products from other encapsulated dosage forms. Since it takes some time to build gelatin extraction and capsulating plants, the companies involved could bring in bulk finished empty gelatin capsules in the interim for ACDIMA's use in their gelatin capsule formulation plant (which would be the

first facility built). Concurrently ACDIMA could be licensed as its partner's sole distributor for the empty capsules in the Arab countries. The next phase (i.e. Phase 2) of the operation would be the erection of the empty capsule manufacturing facility and after this facility was in operation (supplied by imported pharmaceutical gelatin) then the gelatin processing plant could be phased into operation. It may be necessary to divorce the gelatin extraction operation from the capsule fabrication and the formulating plant manufacturing the filled capsules for geographical and economic reasons.

The Corporate Mix Initially

ACDIMA -	35%
Foreign corporations -	49%
Local investors -	16%

Estimate of Cost to Set Up a Totally Integrated Hard Gelatin and Powdered Capsule Operation (i.e. the Manufacture of Both the Empty Shells and Filled Capsules)

Annual consumption in ACDIMA's Arab countries is approximately 2,034,000,000 capsules per annum (Egypt's production and imports 678,000.000 multiplied by a factor of 3). The average capsule making machine will manufacture 250 million empty capsules a year. From the point of view of efficiency, groups of 4 machines can be operated by 5-6 skilled operators under a foreman. One group of 4 machines will turn out approximately 1 billion, so that 8 machines would be required to produce 2 billion capsules annually. It is suggested that the feasibility of constructing 1 plant containing 8 capsule making machines each with a capacity of 250 million capsules be begun as soon as possible. In the same plant will be capsule filling operations for ACDIMA's powder and granule manufacturing formulation plants. The rationale for this unique design for gelatin capsules is as follows:

This process requires a highly sophisticated technology, very rigid in process quality controls with regard to viscosities, precise drying temperatures and times, and critical tolerances (within fractions of a thousandth of an inch) for the finished empty capsule. Inspection of the empty shells to remove imperfect capsules also require very sophisticated equipment.

Empty gelatin capsules on prolonged storage are highly sensitive to the effects of high temperatures and high humidities. Distortion, brittleness and shrinkage take place resulting in many problems when these capsules are placed in the capsule filling machines. By having the capsule filling operations in the same facilities as the empty capsule manufacturing, all of the problems associated with the shipping and storage of empty capsules in hot, humid environments would be eliminated.

Granules and Powders

Since the same rigid requirements regarding temperature and humidity are necessary for this type of product and the same blending and granulating equipment is used for the "fill" of capsules, it is suggested that this type of manufacturing be included with the capsule filling.

Location

The plant should be located away from densely populated urban centres, preferably in satellite cities or smaller centres of population which can provide the labour force and be an attractive residential area for middle and senior management.

Personnel and electricity sources should be dependable.

There should be easy access for transportation e.g. good roads, harbour, airport, river and canal systems.

Centres of higher learning e.g. technical schools and universities nearby would be beneficial.

The marketplace should be readily accessible.

Size of Plant

Area - 140 x 80 meters or 11,200 square meters (121,000 square feet).

Height - 10 meters to permit mezzanine for gelatin tanks, cone blenders, etc. as well as services (air conditioning, water and electricity) to be installed under the roof and above false ceiling.

Land - 10 hectares (25 acres) which will allow 200% expansion comfortably.

Production Schedule

Please note that the process for making empty hard gelatin capsules is a 24 hour a day operation for approximately 330 days per year (36 days for maintenance, shutdowns and checks).

Dosage Forms to be Manufactured

Empty capsule size	000 00 0 1 2 3 4	For veterinary and human use

Size 5 is most difficult to manufacture. If the quantity of active ingredient is very small, e.g. 2 mg Diazepam, use No. 4 capsule and increase the "filler" material.

Natural plus 6 basic colours will give 720 colour combinations of tops and bottoms.

Initial Annual Units of Empty Gelatin Capsules (7 Sizes)

2,000,000,000 (8 machines producing 250,000,000 each).

Equipment Costs for Establishing an Empty Gelatin Capsule Operation

Table 2 shows the costs of equipment required to set up such an operation.

Capital Costs for Support Services

Table 3 shows the capital costs for support services for an empty gelatin capsule operation, assuming that the support services are shared with a capsule filling, powders and effervescent granules operation. One-half of the costs of analytical laboratories, maintenance services (boilers, water purification, air conditioning, electricity, compressor, workshop, solvent room, etc.), administrative offices, land and building is charged to the empty gelatin capsule manufacturing operation, and one-half to the remainder.

Total Capital Costs for Establishing an Empty Gelatin Capsule Operation

The summary of capital costs shown in Table 4 includes both the equipment costs and costs of support services.

Equipment Costs for a Capsule Filling and Powders and Effervescent Granules Formulation Operation

Table 5 shows the capital costs of equipment required to set up such an operation.

Total Capital Costs for Establishing a Capsule Filling and Powders and Effervescent Granules Formulation Operation

The summary of capital costs shown in Table 6 includes both the equipment costs and costs of support services.

Total Capital Costs of an Integrated Empty Hard Gelatin Capsule Manufacturing, Capsule Filling, Powders and Effervescent Granules Formulation Facility

The overall capital costs for establishing an integrated facility for empty gelatin capsules, capsule filling and powders and effervescent granules are summarized in Table 7.

Table 2. CAPITAL COST OF EQUIPMENT FOR MANUFACTURING SEVEN SIZES OF EMPTY GELATIN CAPSULES

OPERATION & EQUIPMENT	AREA (m^2)	EQUIPMENT COST CIF ARAB COUNTRY IN U.S. DOLLARS 1979	1980	1981	1982	1983	1984	1985
Capsule Production - 8 Machines (250,000,000 capsules each). Each 4 machines and supporting equipment occupy an area of 842 sq. meters.	1,685	2,380,000	2,860,000	3,220,000	3,703,000	4,258,500	4,897,200	5,645,300
Hot Gelatin Tanks in mezzanine	1,000	Included above.						
Inspection and Yield - Scoops, scales, etc.	100	6,800	8,000	9,200	10,600	12,200	14,000	16,100
Check Imprint - 4 Machines and conveyor tables.	400	44,200	52,000	59,800	68,800	79,100	90,900	104,600
SUB-TOTAL	2,185	2,431,000	2,860,000	3,289,000	3,782,400	4,349,700	5,002,100	5,766,000

Table . CAPITAL COSTS FOR SUPPORT SERVICES FOR EMPTY GELATIN CAPSULE MANUFACTURING

SUPPORT SERVICE	AREA (m^2)	EQUIPMENT COST CIF ARAB COUNTRY IN U.S. DOLLARS 1979	1980	1981	1982	1983	1984	1985
* Analytical Laboratories:								
Instrumentation	100	127,500	150,000	172,500	198,400	228,100	262,400	301,700
Chemical/Physical	50	42,500	50,000	57,500	66,100	76,000	87,500	100,600
Microbiological	100	85,000	100,000	115,000	132,300	152,100	174,800	201,000
Animal Labs	50	21,300	25,000	28,800	33,100	38,000	43,700	50,300
SUB-TOTAL	300	276,300	325,000	373,800	429,900	494,200	568,400	653,600
* Boilers, water purification, air conditioning, electricity, compressor, workshop, solvent room. SUB-TOTAL	500	467,500	550,000	632,500	727,400	836,500	962,000	1,106,200
* Offices (Administrative)	550	212,000	250,000	287,500	330,600	380,200	437,300	504,800
Quarantine Area:								
Raw and packaging materials	300	42,500	50,000	57,500	66,100	77,000	87,500	100,600
Storage: Released raw materials	1,000	42,500	50,000	57,500	66,100	77,000	87,500	100,600
Storage: Released packaging materials	2,000	85,000	100,000	115,000	132,300	152,000	174,800	201,000
Storage: Manufacturing and finished products	2,185 815	85,000	100,000	115,000	132,300	152,000	174,800	201,000
SUB-TOTAL	6,300	255,000	300,000	345,000	396,800	458,000	524,600	603,200
* COST OF LAND - 10 hectares	1,000,000	191,300	225,000	258,800	297,600	342,200	393,500	452,600
* COST OF BUILDING	11,200	2,142,000	2,520,000	2,898,000	3,332,700	3,832,600	4,407,500	5,068,600

*One-half of these costs will be charged to the Empty Gelatin Capsule Manufacturing Facility and one-half will be charged to the Capsule Filling and Powders and Effervescent Granules Manufacturing Facility. This division may be oversimplified since each operation may require more of some of the support services than the other.

Table 4. SUMMARY OF CAPITAL COSTS FOR ESTABLISHING AN EMPTY GELATIN CAPSULE OPERATION

ITEM	COST IN U.S. DOLLARS 1979	1980	1981	1982	1983	1984	1985
Cost of Land (½ of total cost)	95,650	112,500	129,400	148,800	171,100	196,750	226,300
Cost of Building (½ of total cost)	1,071,000	1,260,000	1,449,000	1,666,350	1,916,300	2,203,750	2,534,300
Cost of Manufacturing Equipment	2,431,000	2,860,000	3,289,000	3,782,400	4,349,700	5,002,100	5,766,000
Analytical Laboratories (½ of total cost)	138,150	162,500	186,900	214,950	247,100	284,200	326,800
Boilers, Water Purification System, etc. (½ of total cost)	233,750	275,000	316,250	363,700	418,250	481,000	553,100
Offices (½ of total cost)	106,000	125,000	143,750	165,300	190,100	218,650	252,400
Services and Equipping Areas for Quarantine: Raw and packaging materials; Storage: Released raw and packaging materials, and manufacturing and finished products.	255,000	300,000	345,000	396,800	458,000	524,600	603,200
TOTAL COST	4,330,550	5,095,000	5,859,300	6,738,300	7,750,550	8,911,050	10,262,100

Table 5. CAPITAL COST OF EQUIPMENT REQUIRED FOR CAPSULE FILLING AND POWDERS AND EFFERVESCENT GRANULES FORMULATION

EQUIPMENT	AREA (m^2)	EQUIPMENT COST CIF ARAB COUNTRY IN U.S. DOLLARS						
		1979	1980	1981	1982	1983	1984	1985
4 Zanasi AZ 60	60	391,000	460,000	529,000	608,400	699,600	804,500	925,200
2 Hofliger & Karg Model 288	20	170,000	200,000	230.000	264,500	304,200	349,800	402,300
4 Parke Davis or Eli Lilly	80	68,000	80,000	92,000	105,800	121,700	139,900	160,900
2 Double Cone Blenders, 40 ft^3 PK, with liquid injection	40	170,000	200,000	230,000	264,500	304,200	349,800	402,300
2 Double Cone Blenders, 20 ft^3 PK, with liquid injection	40							
4 Quick Drying Granulators 100 kg	40	42,500	50,000	57,500	66,100	76,000	87,500	100,600
2 High Speed Fitz Mills	10							
1 Ribbon Mixer 100 ft^3	15	42,500	50,000	57,500	66,100	76,000	87,500	100,600
1 12-Compartment Drying Oven	20	12,800	15,000	17,300	19,800	22,800	26,200	30,200
2 Oscillator Granulators and stainless steel trays	20	51,000	60,000	69,000	79,400	91,300	104,900	120,700
4 Cleaning Pans for capsules	40	27,200	32,000	36,800	42,300	48,700	56,000	64,400
1 Hobart 50 kg Mixer	5	6,000	7,000	8,100	9,300	10,600	12,200	14,100
1 200-lb. Wet Steam Jacketed Kettle	10	3,400	4,000	4,600	5,300	6,100	7,000	8,000
SUB-TOTAL	400	984,400	1,158,000	1,331,800	1,531,500	1,761,200	2,025,300	2,329,300
Weighing Room - Floor and table scales, tables, benches, scoops, measuring containers, etc.	100	8,500	10,000	11,500	13,200	15,200	17,500	20,100
Clean Up Room	50	850	1,000	1,200	1,300	1,500	1,700	2,000
General - 2 electric hoists for loading blenders, etc.; misc. bins, containers, etc.		17,900	21,000	24,200	27,800	31,900	36,700	42,200
TOTAL	550	1,011,650	1,190,000	1,368,700	1,573,800	1,809,800	2.081,200	2,393,600

Table 6. SUMMARY OF CAPITAL COSTS FOR ESTABLISHING A CAPSULE FILLING AND POWDERS AND EFFERVESCENT GRANULES FORMULATION OPERATION

ITEM	COST IN U.S. DOLLARS						
	1979	1980	1981	1982	1983	1984	1985
Cost of Land (½ of total cost)	95,650	112,500	129,400	148,800	171,100	196,750	226,300
Cost of Building (½ of total cost)	1,071,000	1,260,000	1,449,000	1,666,350	1,916,300	2,203,750	2,534,300
Cost of Manufacturing Equipment	1,011,650	1,190,000	1,368,700	1,573,800	1,809,800	2,081,200	2,393,600
Analytical Laboratories (½ of total cost)	138,150	162,500	186,900	214,950	247,100	284,200	326,800
Boilers, Water Purification System, etc. (½ of total cost)	233,750	275,000	316,250	363,700	418,250	481,000	553,100
Offices (½ of total cost)	106,000	125,000	143,750	165,300	190,100	218,650	252,400
Storage Shelves and Equipment for:							
Raw Materials - Storage and Quarantine, 1000 m^2.	8,500	10,000	11,500	13,200	15,200	17,500	20,100
Finished Products - Storage and Quarantine, 1955 m^2.	8,500	10,000	11,500	13,200	15,200	17,500	20,100
TOTAL COST	2,673,200	3,145,000	3,617,000	4,159,300	4,783,050	5,500,550	6,326,700

Table 7. TOTAL CAPITAL COSTS OF ESTABLISHING AN INTEGRATED FORMULATION FACILITY FOR THE MANUFACTURE OF EMPTY HARD GELATIN CAPSULES, FILLED HARD GELATIN CAPSULES, POWDERS & EFFERVESCENT GRANULES

ITEM	COST IN U.S. DOLLARS 1979	1980	1981	1982	1983	1984	1985
Cost of Land	191,300	225,000	258,800	297,600	342,200	393,500	452,600
Cost of Building	2,142,000	2,520,000	2,898,000	3,332,700	3,832,600	4,407,500	5,068,600
Cost of Manufacturing Equipment:							
Empty Gelatin Capsules	2,431,000	2,860,000	3,289,000	3,782,400	4,349,700	5,002,100	5,766,000
Filled Capsules, Powders & Effervescent Granules	1,011,650	1,190,000	1,368,700	1,573,800	1,809,800	2,081,200	2,393,600
Analytical Laboratories	276,300	325,000	373,800	429,900	494,200	568,400	653,600
Boilers, Water Purification System, Air Conditioning, Electricity, Compressor, Workshop, Solvent Room, etc.	467,500	550,000	632,500	727,400	836,500	962,000	1,106,200
Offices	212,000	250,000	287,500	330,600	380,200	437,300	504,800
Services & Equipment for Storage & Quarantine Areas:							
Empty Gelatin Capsules	225,000	300,000	345,000	396,800	458,000	524,600	603,200
Filled Capsules, Powders & Effervescent Granules	17,000	20,000	23,000	26,400	30,400	35,000	40,200
TOTAL COST	6,973,750	8,240,000	9,476,300	10,897,600	12,533,600	14,411,600	16,588,800

3.5.4 Formulation Plants: Human Pharmaceuticals without Parenteral Operations

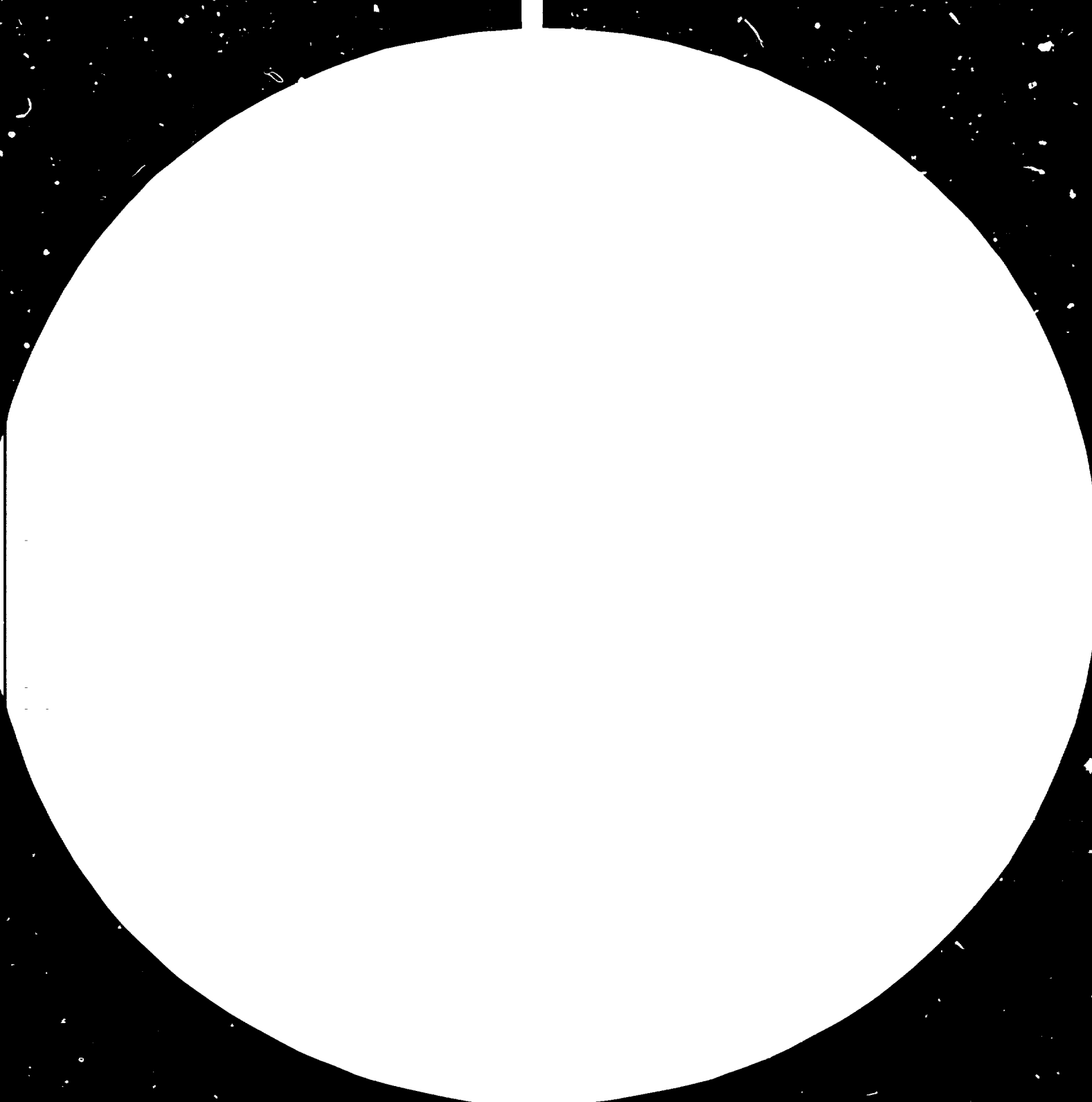
The creation of pharmaceutical formulation plants throughout the Arab countries participating in ACDIMA presents, in our opinion, the greatest challenge to ACDIMA from the point of view of intelligent decision making and the deployment of management and financial resources. However the detailed statistical data from which the projections could be made regarding construction of formulating facilities and other phases of the ACDIMA projects were often incomplete, in a non-usable format, or non-existent. However after considerable thought and discussion among the experts, ACDIMA personnel, and health discipline professionals in the Arab World, it was decided to base projections on the total annual consumption of Egypt and Iraq multiplied by a factor of two. In the absence of firm data from Iraq and other participants of ACDIMA's Arab countries, the total consumption in Egypt was multiplied by a factor of three. Despite the enthusiasm with which the ACDIMA's partners, the Arab Council for Economic Unity, the UNIDO experts and ACDIMA's staff view the creation of pharmaceutical and industrially related enterprises, a word of caution should be sounded at this point.

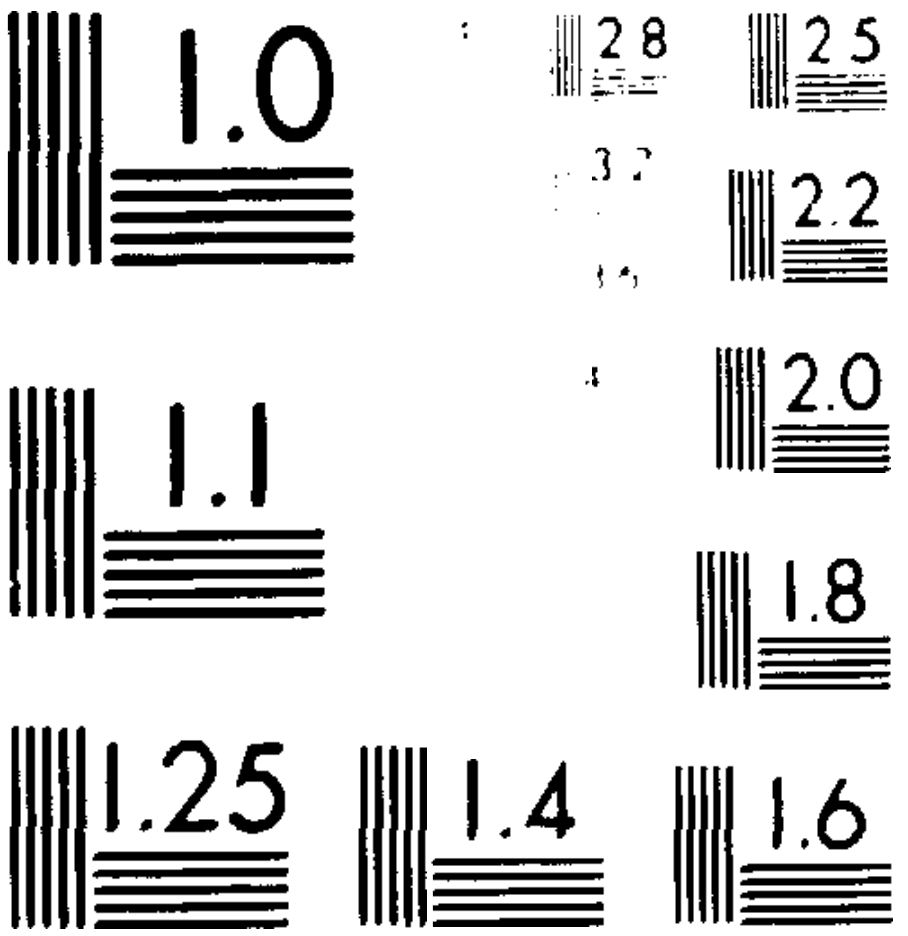
Foreign corporations are becoming increasingly disenchanted with the transfer of technology on a licensing or joint venture basis. Most foreign corporations are convinced that they cannot earn enough through licensing to recoup their capital costs in the joint ventures from the point of view of research and development of their products and their involvement in the joint project. Furthermore in their view, the legal systems in most countries are not strong enough to guarantee that their special "secret processes" will be protected or that their licensing fees will be truly accounted for or easily repatriated in the currency of their choice.

Predicated on the fact that ACDIMA will be in a position to ensure that the rights of joint venture partners (both in and outside the Arab countries) will be protected and guaranteed, the following projections are made.

Corporate Mix Initially

ACDIMA -	60%
Foreign corporation -	20%
Local corporation -	10%
Local professionals -	10%




1.0
2.8
2.5
3.2
2.2
2.0
1.1
1.8
1.25
1.4
1.6

Therapeutic Groups of Products to be Manufactured in ACDIMA's Model Formulation Plants which Do Not Contain Parenteral, Capsule (Hard and Soft), Powders and Granules Operations

Analgesics, Antipyretics and Decongestants
Antirheumatics
Antihistaminics and Antitussives
Dermatologicals (Systemic and Topical)
Endocrine Drugs
Gastrointestinals
Oto-Rhino-Laryngetics
Pneumothoracics (Pulmonary Drugs)
Vitamins, Single and Complex
Vitamins and Minerals
Psychotrophics, Antianxiety Drugs (Neurosedatives)
Hypnotics
Skeletal Muscle Relaxants
*Dental and Oral Hygiene Preparations
**Oral Hypoglycemics
***Disinfectants and Germicides
Specialty Products under Special Licence

* This group of products have been included because after discussion with the relevant authorities in the field of dental hygiene in ACDIMA's Arab countries, it was realized that there is a strong potential market in dental care and caries prevention among school children.

** We believe there is an extensive market for such products as Chlorpropamide and Tolbutamide.

*** We believe that surgical soaps, antirust cold sterilizing solutions and disinfectants for use in doctors' offices, clinics and hospitals have a large potential market.

The actual profile of the pharmaceutical plant will be as follows:

Location

General criteria - Away from densely populated urban centres, preferably in satellite cities such as Sadat City in Mohandessin, Giza, or smaller centres of population which can provide the labour force and be an attractive residential area for employees, middle and senior management.

Sources of good water and electricity should be dependable.

There should be easy access for transportation e.g. good roads, harbour, airport, river and canal system.

Centres of higher learning e.g. technical schools, universities are beneficial.

It should be easily accessible to the intended marketplace.

Size of Plant

Area: 140 x 80 meters = 11,200 square meters (120,000 square feet).

Height: 10 meters (49 feet) to permit mezzanine for liquid holding tanks, services (air conditioning, water and electricity) to be installed immediately under roof and between false ceiling and front office.

Land: 10 hectares (24.7 acres) which will allow for over 200% expansion comfortably.

Dosage Forms and Units to be Manufactured

The types of dosage forms to be manufactured and the initial annual units to be produced based on one 8 hour shift, 12 months a year are shown in TABLE 8.

The building and equipment outlined above and in TABLES 8, 9 and 10 is capable of increasing its capacity by 25% after 2 years of full operation and by an additional 25% within a further 3 years. If a second shift is instituted in this plant, the plant capacity could be increased an additional 50%. In other words, within 5 years of operation, 2 shift production of each group of product should have increased 2.5 times the first year's production.

Please note that the other dosage forms, viz. large volume parenterals, small volume parenterals, hard gelatin and soft gelatin capsules which will be manufactured in the other specialty plants will be brought in to this plant in bulk (in the case of capsules) for testing and packaging into final dosage form and labelling under ACDIMA's label, while the LVP's and SVP's will be brought in their labelled (ACDIMA's labels) final dosage form for testing and distribution to ACDIMA's customers.

Table 8. CAPITAL COST OF EQUIPMENT FOR FORMULATION PLANT OF DOSAGE FORMS
(Without Parenterals, Capsules, Powders and Granules)

DOSAGE FORM	INITIAL ANNUAL UNITS	AREA (m^2)	EQUIPMENT COST CIF ARAB COUNTRY IN U.S. DOLLARS 1979	1980	1981	1982	1983	1984	1985
TABLETS									
Compressed Sugar Coated	300,000,000	450	323,900	381,000	438,200	503,900	579,500	666,400	766,300
Enteric Coated Film Coated	100,000,000	250	85,000	100,000	115,000	132,300	152,100	174,900	201,100
Granulation Area	(Portable	450	143,700	169,000	194,400	223,500	257,000	295,600	339,900
Clean Up Area	Steam Gene-	200	21,300	25,000	28,800	33,100	38,000	43,700	50,300
Packaging Area	rators, Air Compressors)	800	153,000	180,000	207,000	238,100	273,800	314,800	362,000
LIQUIDS									
Syrups Suspensions Non Sterile Drops	200,000 litres	2 x 500	153,000	180,000	207,000	238,100	273,800	314,800	362,000
Disinfectants Liquid Surgical Soap Cold Sterilizing Solutions	200,000 litres								
Clean Up Area		200	21,300	25,000	28,800	33,100	38,000	43,700	50,300
Packaging Area		300	127,500	150,000	172,500	198,400	228,100	262,400	301,700
OINTMENTS & CREAMS									
Topical Therapeutic	75,000 kg	300	117,300	138,000	158,700	182,500	209,900	241,400	277,600
Topical Cosmetic (Includes Packaging & Mezzanine)	75,000 kg								
SUPPOSITORIES									
Adult (Includes Infant Packaging)	5,000,000 5,000,000	100	25,500	30,000	34,500	39,700	45,600	52,500	60,300
WEIGH UP AREA		400	12,800	15,000	17,300	19,800	22,800	26,200	30,200
TOTAL		4,450	1,184,300	1,393,000	1,602,200	1,842,500	2,118,600	2,436,400	2,801,700

Table 9. CAPITAL COST OF SUPPORT SERVICES FOR GENERAL FORMULATION PLANT
(Without Parenterals, Capsules, Powders and Granules)

SUPPORT SERVICE	AREA (m^2)	EQUIPMENT COST CIF ARAB COUNTRY IN U.S. DOLLARS 1979	1980	1981	1982	1983	1984	1985
ANALYTICAL LABORATORIES								
Instrumentation	100	127,500	150,000	172,500	198,400	228,100	262,400	301,700
Chemical, Physical	50	42,500	50,000	57,500	66,100	76,000	87,500	100,600
Microbiological	100	85,000	100,000	115,000	132,300	152,100	174,900	201,100
Animal Laboratories	100	85,000	100,000	115,000	132,300	152,100	174,900	201,100
Health Unit	50	21,300	25,000	28,800	33,100	38,000	43,700	50,300
Boiler, Water Purification, Air Conditioning, Electricity, Compressors, and Workshops	500	467,500	550,000	632,500	727,400	836,500	962,000	1,106,200
Quarantine Area: Raw and Packaging Materials	300	42,500	50,000	57,500	66,100	76,000	87,500	100,600
Storage: Released Raw Materials	1,000	42,500	50,000	57,500	66,100	76,000	87,500	100,600
Storage: Released Packaging Materials	2,000	42,500	50,000	57,500	66,100	76,000	87,500	100,600
Storage: Finished Product, 3 Month Inventory	3,000	85,000	100,000	115,000	132,300	152,100	174,900	201,100
Offices (Administrative) Includes Mezzanine	550	225,000	250,000	287,500	330,600	380,200	437,300	502,800
TOTAL	7,750	1,266,300	1,475,000	1,696,300	1,950,800	2,243,100	2,580,100	2,966,700

Table 10. SUMMARY OF CAPITAL COSTS FOR ESTABLISHING A GENERAL FORMULATION PLANT

(Without Parenterals, Capsules, Powders & Granules)

ITEM	COST IN U.S. DOLLARS 1979	1980	1981	1982	1983	1984	1985
Cost of Land	191,300	225,000	258,800	297,600	342,200	393,500	452,500
Cost of Building	2,142,000	2,520,000	2,898,000	3,332,700	3,832,600	4,407,500	5,068,600
Cost of Manufacturing Equipment							
Tablets	726,900	855,000	983,400	1,130,900	1,300,400	1,495,400	1,719,600
Liquids	301,800	355,000	408,300	469,600	539,900	620,900	714,000
Ointments and Creams	117,300	138,000	158,700	182,500	209,900	241,400	277,600
Suppositories	25,500	30,000	34,500	39,700	45,600	52,500	60,300
Weigh Up Area	12,800	15,000	17,300	19,800	22,800	26,200	30,200
Analytical Laboratories	340,000	400,000	460,000	[illegible],100	608,300	699,700	804,500
Health Unit	21,300	25,000	28,800	33,100	38,000	43,700	50,300
Boiler, Water Purification, Air Conditioning, Electricity, Compressors, and Workshops	467,500	550,000	632,500	727,400	836,500	962,000	1,106,200
Quarantine and Storage Areas	212,500	250,000	287,500	330,600	380,100	437,400	502,900
Offices	225,000	250,000	287,500	330,600	380,200	437,300	502,600
TOTAL	4,783,900	5,613,000	6,455,300	7,423,600	8,536,500	9,817,500	11,289,500

3.5.5 Animal Feed and Veterinary Premixes Plants

3.5.6 Veterinary Pharmaceuticals Formulation Plants

It is recommended that the same basic plant layouts and cost projections used in the human manufacturing (without parenterals) operations in the preceding monograph be applied to an animal feed and veterinary premixes plant and a veterinary pharmaceuticals formulation plant.

These comments are offered as a complement to the report of our colleague, Mr. N. Davidson, on a veterinary formulation and packaging operation.

3.5.7 Veterinary Biologicals Laboratories

Recommendations relative to the manufacturing facility required for this group of pharmaceutical products will be left to designated experts in the field of virology, bacteriology and immunology.

However, some suggestions will be made relative to their location on the basis of observations of the operations of some vaccine producing facilities in the Arab countries.

3.5.8 Packaging and Labelling from Bulk Product

It is recognized that there are some areas in the Arab countries, where it would not be feasible to construct a formulation plant because of small populations, current lack of technology, difficulty of accessibility to other parts of the Arab countries etc. However, a case could be presented for the establishment of facilities for packaging and labelling from bulk finished product.

After an indepth study is made ACDIMA could decide on the required complexity of the operations and by extracting the pertinent costs and projections from those given in Section 3.5.4 for the general formulation plant, arrive at a close approximation of establishing these plants.

However from the data available and the geographical configuration of the Arab countries, suggestions will be made under Section 4.5.8 relative to the location of this type of facility.

3.5.9 Crop Chemicals

3.5.10 Medical Devices

The preceding project monographs have dealt with the first reason outlined in Section 3.4 as to why ACDIMA should engage in joint ventures: "The Acquisition of New Technology". The rationale for the other reasons for ACDIMA's joint venture participation are now presented in Sections 3.6, 3.7, 3.8, and 3.9.

3.6 The Acquisition of Management Skills

It is clearly recognized that the most critical factor to ACDIMA's long term successful achievements is acquiring those technical and managerial human resources needed to operate their projects.

It is strongly recommended that ACDIMA immediately seek to form a joint venture with an international management consultant firm to acquire much needed management capabilities and access to vital technological resources around the world.

Modus Operandi

ACDIMA should invite proposals from management consulting firms around the World to form a joint venture with ACDIMA to perform the following services for operational divisions of ACDIMA on a short term basis. On a long term basis the same services would be supplied to other business organizations formed under the auspices of the Council of Arab Economic Unity. For a fee the joint venture Management Consulting Corporation would supply to the joint venture processing corporations the following services:

3.6.1 Consulting Preliminary Engineering and Economic Services

Pre-feasibility studies.
Feasibility studies.
Site evaluation.
Building design and planning.
Environmental control systems.
Material handling and distribution studies.
Assessment of the pros and cons of fixed priced - lump sum contracts.

3.6.2 Project Management Services

Engineering.
Planning and scheduling.
Estimating and cost control.
Procurement services.
Construction and construction management.
Equipment installation and start up operation.
Design of training programmes.

3.6.3 The Management Structures for ACDIMA Formulation Plants

The management systems for ACDIMA's formulation plants should follow internationally accepted management systems whereby policy and long term planning in each formulating plant is the function of the Chief Executive Officer and his senior executives based on guidelines or instructions issued by ACDIMA.

The implementation of the policy and operational plans are delegated to middle management who will oversee the day to day execution of the organisation's plans by the supervisors and workers.

Appendix X indicates the line authority from the chief executive officer (President or General Manager) to his first line management (Vice-Presidents or Directors or Assistant General Managers) through to the production, maintenance, plant, regional sales, personnel, office and financial managers. The titles given in Appendices 15, 18 and 19 are self-explanatory.

Appendix XI outlines the line authority of the Vice-President or Director of Quality Control and Research.

Appendix XII indicates the structure of the line authority of the Vice-President (or Assistant General Manager), Operations, reporting to the President or General Manager.

Appendix XIII indicates the Marketing division line authority.

The VP's or AGEM's whose units are outlined in the above appendices will form an Administrative Advisory Committee to assist the Chief Executive Officer in executing the policies handed down by the Chairman of the Board of ACDIMA.

3.7 The Acquisition of Financial Direction and Support

This is the third factor listed for joint ventures involving such corporations as ACDIMA and financial institutions. It is noted that apart from an administrative manager on the staff of ACDIMA and a member of the Board of Directors of ACDIMA who is an Assistant Deputy Minister of Finance of his government there appears presently to be no person or authority directly connected with ACDIMA who is in a position to advise the Board of Directors or the General Manager routinely on the complexities of the financial aspects of joint ventures and international investments.

In addition although ACDIMA may have access to very significant funds for investment in its projects, it is conceivable that ACDIMA at some time in the future may have to seek additional funds over and above its available subscribed capital because of the magnitude of the fiscal demands as various pharmaceutical projects are initiated.

It is therefore of primary importance that ACDIMA strengthens its financial advisory resources immediately.

Modus Operandi

ACDIMA's Board of Directors should immediately consider the proposal to invite Arab and/or international banks to participate in a minority equity participation in ACDIMA. It may not be necessary for these financial institutions to contribute actual dollars immediately. Instead we see the participating banking institution contributions as follows:

- Providing a "line of credit" if and when the magnitude of ACDIMA's projects exceeds the corporation's capital.
- Assessment of the financial validity of project forecasts.
- Advising on the establishment of accounting systems and procedures for ACDIMA's projects.
- Provision of independent auditing facilities of operational projects.
- Provision on a short term basis from their own resources, personnel for interim financial management or to initiate or monitor accounting procedures, and assistance in the training of permanent financial and accounting personnel for ACDIMA's projects.
- Advising on long term planning and budgeting.
- Assessment of financial status and credibility of potential joint venture partners.

ACDIMA should invite the financial institutions of choice to put forward proposals concerning the ways in which the institutions and ACDIMA could work together for their mutual benefit.

When an agreement was reached regarding the terms and conditions of this joint venture the financial institution(s) would nominate (subject to ACDIMA's Board approval) two Directors to the Board as ex officio members. These Directors would have voting privileges only on financial matters concerning the utilization of any financial resources required from their institutions.

All services rendered by these institutions would of course be on a fee basis payable by ACDIMA or its subsidiary corporations where applicable.

3.8 The Desire to Share the Inherent Risks of a New Venture

The fourth factor for joint ventures is the desire to share the inherent risks and benefits of new ventures. One of the principal objectives of ACDIMA is to engage in scientific research. Since this activity involves high risk on the return on investment of capital dollars, it is recommended that ACDIMA undertake joint ventures in this field.

Modus Operandi

ACDIMA through its office of scientific research and in collaboration with Arab countries and reputable international researchers would identify such areas of scientific research in the field of pharmaceutical synthesis, fermentation, bioengineering (especially as this discipline applies to medical appliances) and applied pharmacological and clinical studies which are relevant to the socio-economic well being in the Arab countries and form joint ventures in research with internationally known research institutes such as the Stanford Research Institute, the National Research Institute of Canada, etc. to proceed along carefully planned paths of scientific research, e.g. in tropical parasitology, diseases of the eye, carcinogenisis, etc.

A formula could easily be worked out for the licencing of any product entity arising out of this research and the sharing of accrued financial gains.

The Corporate Mix Initially

ACDIMA	50%
International Research Institute	40%
Academic	10%

3.9 The Purchase of Controlling Interests in Other Corporations

This activity is highly recommended to ACDIMA to permit access to readily available technology and markets.

Modus Operandi

ACDIMA arter establishing its order of priorities in the master marketing plan should offer, through discreet advertisements in international financial publications, confidential communications with the investment departments of international banking institutions inside and outside the Arab countries and subsequently through ACDIMA appointed foreign representatives, to acquire major equity control of viably sound existing operating manufacturing companies.

There are many small and intermediate sized corporations which are prepared to surrender majority control because of the death ot the majority shareholder; the lack of capital for expansion; the shrinkage of sales through unimaginative marketing policies or aggressive competition from larger corporations; unwise capital investment for carelessly researched building expansion, etc.

Acquisition of this type of company is strongly recommended in the field of:

- Human and veterinary pharmaceutical formulation plants.
- Veterinary feed mix plants.
- Crop chemical plants.
- Chemical synthesis plants.
- Specialized medical appliance operations.

It is not recommended that these plants be dismantled and moved to sites within the Arab countries for the following reason:

- A break in the continuity of production.
- The loss of key personnel who may not wish to relocate in the Arab countries for personal reasons.
- Damage to equipment while in transit.
- Capital costs to adapt equipment to local power and environmental requirements.

These acquisitions by ACDIMA could supply ready sources of bulk and finished product for distribution under ACDIMA's label. The pricing would be competitive with corporations shipping bulk and finished product into the Arab countries. Again ACDIMA could make local arrangements for the packaging and finishing of these goods supplied from their foreign acquisitions.

Corporate Mix Initially

ACDIMA	51-60%*
Foreign Corporations	49-40%

*Unless majority control prevented by local corporation laws.

D. The location of pharmaceutical formulation plants and the rationale for selecting the sites

4.1 Summary of Findings

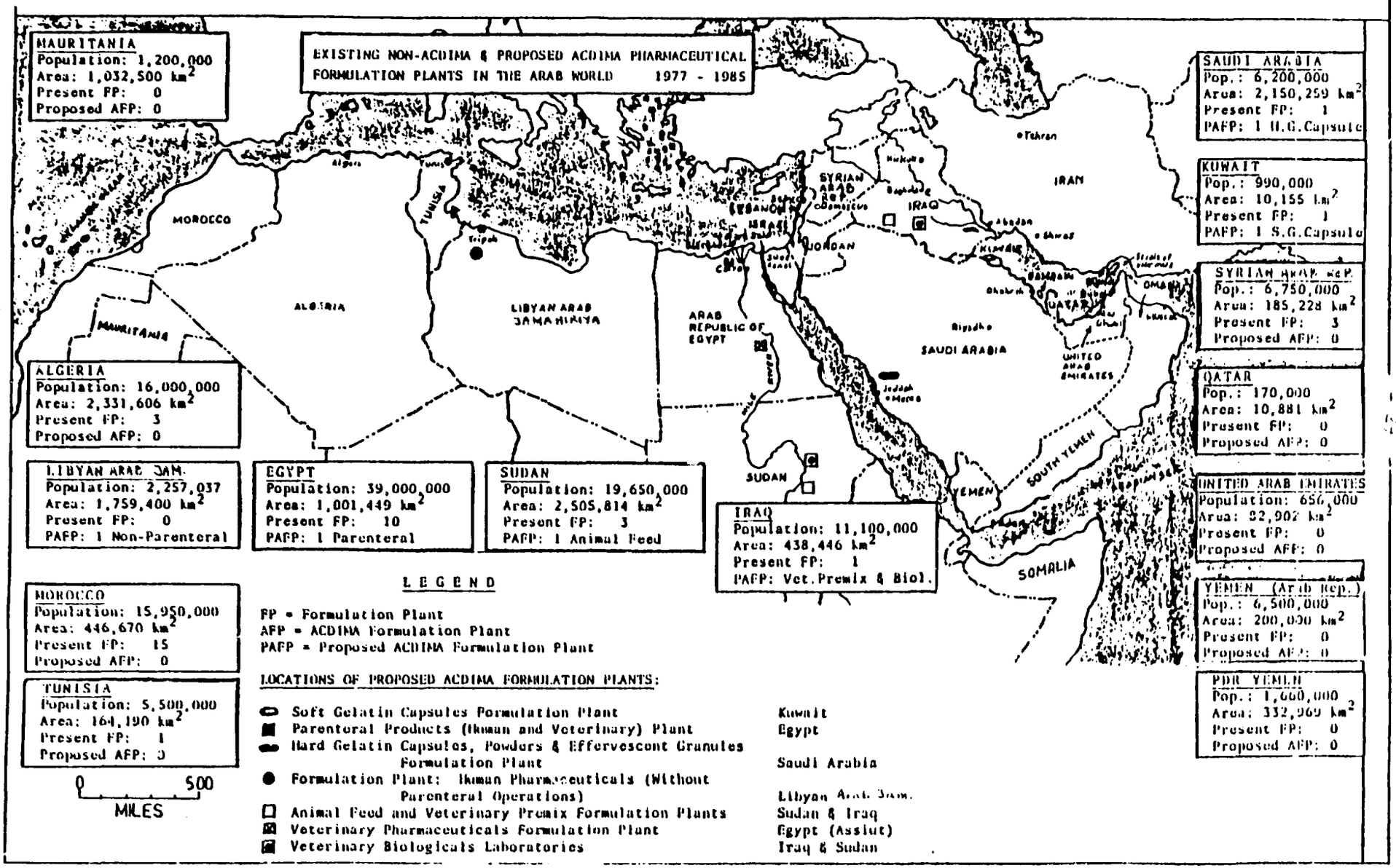
4.1.1 The indepth marketing, social and economic data were not available in the Arab countries or from other sources to permit accurate numberical projections of the numbers and types of formulation plants which should be constructed or their locations, in order to achieve ACDIMA's objective of ensuring that the Arab countries be as self-sustaining as possible in the health products field.

4.1.2 Vital requirements, namely highly skilled multi-disciplined professionals, management expertise and other infrastructures do not exist currently in the Arab countries to support an immediate massive expansion of the pharmaceutical formulation industry.

4.1.3 The current management of ACDIMA with the exception of the Chairman of the Board and Managing Director does not have the broad experience in business and government necessary to oversee the simultaneous implementation of multi-product formulation plants as part of a totally integrated pharmaceutical production complex without substantial short term expatriate managment assistance at all levels of ACDIMA.

4.1.4 The location of new plants should be complementary to improving existing plants as recommended in other parts of this report. The simplified map in Figure 1 illustrates the location of present formulation plants and summarizes the recommendations for the locations of the proposed ACDIMA plants.

The boundaries shown on this map do not imply offical endorsement by the United Nations.



4.2 Summary of Short Term Recommendations

4.2.1 The production of the present facilities should be improved so that the average production of all pharmaceutical plants in the Arab countries average $US 25,000,000.

4.2.2 Until an indepth Pan Arab marketing study is made, and because of immediate needs, ACDIMA should embark on feasibility studies to establish one model for each type of formulation plant outlined below in the following suggested geographical areas:

Soft gelatin capsules formulation plants	Kuwait
Parenteral products (human and veterinary) plant	Egypt (Near Cairo or Alexandria)
Hard gelatin capsules, capsule filling, powders and effervescent granules formulation plant	Saudi Arabia
Formulation plant: Human pharmaceuticals (without parenteral operations)	Libyan Arab Jamahiriya
Animal feed and veterinary premix plants	Sudan and Iraq
Veterinary pharmaceuticals formulation plant	Egypt (Assuit)
Veterinary biologicals laboratories	Iraq and Sudan
Facility for packaging and labelling from bulk finished product	United Arab Emirates Qatar PDR Yemen

4.3 Long Term Recommendations

No long term recommendations will be made in this report. Long term recommendations for further plant location can only be based on indepth studies throughout the Arab countries.

4.4 Discussion of Findings

Despite exhaustive research and repeated requests from the industry for recent production figures in the form of dosage units (a questionnaire was sent to all Egyptian formulation plants and distributed to ACDIMA board members representing other Arab Countries without a single response) no such data were provided. Instead it was suggested by the Arab professionals that the latest (1975) dollar volume of pharmaceuticals produced in the Arab countries (with an estimated 15% increase in production per year to 1985) be used as a basis for estimating the number of formulation plants needed to make the Arab countries self reliant.

From discussions with government officials, representatives of the Council of Arab Economic Council and senior executives of the pharmaceutical companies visited, it appeared that the average annual production dollar volume of a formulation plant in Egypt was $US 15.5 million.

On a projection that consumption of drugs in the Arab countries would increase on an average of 15% per annum and therefore production should increase in a similar percentage it appeared that from a base of $US 786 million in 1975 through $US 1,581 million in 1981, the $US production of pharmaceuticals would reach $US 3,180 million in 1985.

To meet 100% of these consumption needs (or production expectations) would require (on a directly proportional mathematical projection) the following numbers of formulation plants each producing $US 15.5 million.

In the year	1975 -	50.7 plants;
	1980 -	102.0 plants;
	1985 -	205.2 plants.

However as can be seen from data in Table 11, if the formulation plants could have been made to produce an annual average of $US 25 million in pharmaceuticals theoretically 100% of the consumption needs of the Arab countries would have been (or would be) met with the following numbers of plants:

In the year	1975 -	31.4 plants;
	1980 -	63.2 plants;
	1985 -	127.2 plants.

In actual fact based on the data presented to the team, the formulation plants in the Arab countries currently produce 47% of the products consumed locally. On the basis of this statistic let us look at the 1977 projections in Table 11. Using the annual average production of $US 15.5 million in theory it would have taken 67.1 plants to produce locally 100% of the Arab countries' consumption in the year 1977. However, if the annual production could have been raised

Table 11. PROJECTIONS OF ANNUAL $US PRODUCTION IN MILLIONS 1975-1985 AND THE NUMBERS OF FORMULATION PLANTS REQUIRED TO ACCOMPLISH THIS PRODUCTION

Section	Item	1975*	1976	1977	1978	1979	1980	1981	1982	1983	1984	1985
1	Annual Production in the Arab countries - in $US Million	786	904	1040	1196	1375	1581	1818	2091	2404	2765	3180
2	No. of Formulation Plants Producing $US 15.5 Million** per Annum to Satisfy Arab Countries' Requirements 100%	50.7	58.3	67.1	77.2	88.7	102.0	117.3	134.9	155.0	178.4	205.2
3	No. of Formulation Plants Producing $US 25 Million per Annum to Satisfy Arab Countries Requirements 100%	31.4	36.2	41.6	47.8	55.0	63.2	72.7	83.6	96.2	110.6	127.2
4	No. of Formulation Plants Producing $US 35 Million per Annum to Satisfy Arab Countries Requirements 100%	22.5	25.8	29.7	34.2	39.3	45.2	52.0	59.7	68.7	79.0	91.0

*Updated Report on "Arab Pharmaceutical Consumption and Industries", p. 12.

**The average production in $US of the 10 Egyptian formulation plants.

to $US 25 million (instead of $US 15.5 million), the number of plants required would have been 41.6.

Interestingly enough, from data gathered from various sources it would appear that there are approximately 39 formulation plants now producing pharmaceuticals in the Arab countries (see appendix XIV). That is, approximately 39 formulation plants with an annual production of $US 15.5 million each are responsible for —% of the current Arab countries' production/consumption.

However if the present operating plants (39) in 1977 could have raised their average production to $US 25 million then the annual production for that year would have been approximately $US 975 million or almost 94% of total local requirements.

From a review of Table 11, it would appear that if the average pharmaceutical plant could have increased its production to $US 35 million the current requirements of the Arab countries may have been exceeded with the probability of available products for export.

However in view of the current shortage of expertise in the Arab countries a formulation plant designed to produce $US 35 million appears to be rather impractical.

4.5 Detailed Short Term Recommendations

In view of the foregoing statement it seems of paramount importance that a very high order of priority should be given to the creation of double shifts in the present drug companies so that the formulation plants producing an average of $US 15.5 million can in the short term increase its production by $US 9.5 million (or 61.3% of average current production) to $US 25 million. Therefore each of the present 39 formulation plants can be producing as soon as possible $US 25 million for a grand annual total of $US 975 million. If this improvement in production can be achieved by the present plants in 1979 then they would have achieved 70% of the production projected for 1979.

We do not believe that the foregoing mathematical projections can take the place of indepth marketing and plant productivity studies to establish Pan Arab pharmaceutical needs to 1985. In addition it is crucial that every effort should be made to gather meaningful statistics of past production figures as well as present ones and to establish an integrated system of data retrieval relative to production and consumption of pharmaceuticals so that realistic projections can be made concerning the location and types of formulation plants which will be needed in the future.

However on the basis of the meagre statistics available and the known lack of certain pharmaceutical products in the Arab countries it is recommended that feasibility studies be initiated to assess the viability of establishing the following plants in the stated geographical regions.

4.5.1 Large Volume and Small Volume Parenteral Plant

The reasons for establishing a separate plant for these dosage forms have been given in a preceding section and will not be repeated here.

Location

It is recommended that this plant be located near Cairo or Alexandria in Egypt.

Rationale

The sites were selected for the following reasons:

a. The existence already of the very sophisticated technology necessary to produce satisfactory products.

b. The presence in Egypt of many international corporations which have licensed Egyptian firms to produce their pharmaceutically advanced products and whose continuously

7.5.2 Formulation Plant (Without Parenteral or Capsule Manufacturing Operations)

Location

It is recommended that this plant be located near Tripoli in Libyan Arab Jamahiriya.

Rationale

a. Since over 90% of the raw and packaging materials currently used in the manufacture of pharmaceuticals in the Arab countries are imported into the region, the strategic location of Tripoli cannot be ignored. In addition the shipping of finished product to other Arab countries is easily facilitated by using the shipping lanes of the Eastern Mediterranean, Red and Arabian Seas and the Persian Gulf.

b. Again because of the location of the Libyan Arab Jamahiriya a formulation plant located in this area can readily draw on the technology of Europe as well as of the Arab countries. Currently the Libyan Arab Jamahiriya draws heavily on foreign sources for its skilled manpower. About 40% of the work force are from outside the country, especially from Arab countries with Egypt being by far the greatest contributor of technologists.

   The entire economy is based on the oil industry which is not labour intensive. The Libyan Arab Jamahiriya should be encouraged to broaden its industry base by the introduction of labour intensive industries such as pharmaceutical manufacturing, and through the use of short-term expatriate expertise establish the necessary infrastructure to operate labour-intensive industries.

c. The Libyan government is actively planning the building of a formulation plant in Tripoli and this would be an ideal opportunity for ACDIMA to offer to participate in its planning and execution.

d. The Libyan Arab Jamahiriya abuts geographically on Egypt and the Sudan which as stated previously represent over 66% of the Arab consumers.

e. The presence of abundant energy and other natural resources necessary for the production of pharmaceuticals.

4.5.3 Hard Gelatin Capsule, Powders and Effervescent Granules Formulation Plant

Location

It is recommended that this operation be initiated in Saudi Arabia near the port of Jeddah.

Rationale

a. The production of empty and filled hard gelatin capsules is one of the most mechanized production operations in drug manufacturing. If the recommendations for the manufacturing of empty hard gelatin capsules are reviewed it will be seen that a group of 5-6 skilled technicians per shift can operate a "bank" of four capsule making machines each capable of manufacturing 250 million capsules a year. In other words, 6 persons in one 8 hour shift for 330 days in one year can manufacture approximately 80 million capsules.

b. Similarly one operator using a Zanasi AZ 60 machine can fill approximately 1000 capsules a minute, 60,000 capsules an hour or 400,000 capsules in an 8 hour shift (allowing off time for meals, etc.)

c. The making of powders and effervescent granules are also highly mechanized blending and packaging operations.

   Because of the high degree of mechanization involved placing this industry in a densely populated country will not contribute significantly to reduction of unemployment.

d. This industry requires considerable amounts of power, absolute reliability of power supply and critical tolerances in raw material, equipment and environment controls (temperature, humidity, etc.)

   Saudi Arabia appears to have the necessary power requirements.

e. Located near Jeddah raw materials can be readily received and the finished product readily accessible to Egypt and the Sudan (containing the bulk of the Arab population) across the Red Sea, and through common borders, the Persian Gulf, and the Arabian, Red and Mediterranean Seas easily accessible to the other Arab countries.

f. Technologists can be brought in from Egypt and Europe on short term consultancies until Saudi technicians are trained.

g. Since water requirements are extremely minimal in this type of plant, the high cost of producing potable water in Saudi Arabia is not a serious deterrant.

improving technology and product research can be drawn upon (through joint venture arrangements) to aid significantly in the establishment of a modern model plant with the highest standards of GMP.

c. The presence of some of the most sophisticated Arab organizations for higher education in the health and scientific supportive disciplines e.g. pharmacy, chemisty, engineering, microbiology, etc.

d. Large volumes of fair quality water which can be easily treated to produce the highest grade of water for injection.

e. The existence of base industries in glass, polyvinyl chloride polypropylene and other polymer producing industries to provide containers.

f. As the "hub" of the Arab countries, can readily export finished product overland and through Mediterranean and Red Seas to every Arab country. Similarly importation of the very complex and costly equipment and materials used in the manufacturing of these products can be readily brought in through Alexandria or Port Suez.

g. Egypt and its immediate neighboour to the South, the Sudan, account for approximately 66% of the population of the Arab countries and are therefore significantly susceptible to the diseases which are treated by parenteral drugs. This type of operation because of its high transportation costs should be located as near as possible to its potential "market place".

For a geographic depiction of the above please see map, on page 297.

4.5.4 Soft Gelatin Capsule Formulation Plant

Location

It is recommended that the state of Kuwait be the location of this operation.

Rationale

a. See rationale (a) in the preceding section on Hard Gelatin Capsule, Powders and Effervescent Granules Formulation Plant.

b. See rationale (c) in the same preceding section 4.5.3.

c. See rationale (d) in section 4.5.3 concerning the similar availability of power requirements.

d. By means of the availability of excellent air, sea and land transportation goods manufactured in Kuwait have easy access to the other Arab countries. Because of the unit size of soft gelatin capsules large quantities can be packaged and air-freighted very economically.

4.5.5 Animal Feed and Veterinary Premix Formulation Plants

Location

Because of the large animal population in the Arab countries and the abundance of basic raw materials available, it is recommended that two plants be built simulataneously with ACDIMA participating in the equity of each but with different expatriate corporations for each plant. One manufacturing operation should be located in Central Sudan, the second in Iraq.

Rationale

a. The presence of huge quantities of molasses and by-products from crops such as sorghum, millet, wheat, rice, groundnuts, sesame, and cottonseed in the Sudan and Egypt, and the by-products of the date fruit and the petrochemical industries in Iraq provide the major ingredients for the proposed Animal Feed/Veterinary Premixes and Pharmaceuticals Formulation plants.

b. From data provided by ACDIMA's Arab Pharmaceutical Consumption and Industries - A Brief Report, Livestock and Veterinary Pharmaceuticals Section, page 9 (reproduced as appendix XV, it will be shown that of the Arab nationa participating in ACDIMA, Iraq, the Sudan and Egypt are the largest meat producers.

Egypt is the largest producer of cattle and poultry and the second largest producer of sheep, goats and other types of livestock. The Sudan is the largest producer of sheep and goats and the second largest producer of cattle and other kinds of livestock and the third largest producer of poultry. Iraq is a very significant producer of cattle, sheep, goats, poultry and other types of livestock. Therefore the proposed plants would be located in areas of greatest livestock activity. (Please see appendix XVI)

c. The presence of highly skilled veterinary medicine laboratories and faculties of animal husbandry in these countries viz. The Veterinary Laboratory and Research Institute at Aboughrab, Iraq; The Faculty of Animal Husbandry at Assuit, Egypt; and the State Veterinary Biological Laboratories in the Sudan.

d. The strategic location of these two countries would permit the marketing and distribution of products to other Arab countries.

e. The countries selected have the largest areas of arable land and therefore the potential to produce in the future large quantities of basic animal feeds and significantly increased numbers of every type of livestock.

4.5.6 Veterinary Pharmaceuticals Formulation Plant

Location

Assuit, Egypt.

Rationale

a. The location of an extensive and largely underdeveloped branch of the Chemical Industries Development Co. (C.I.D.) with excellent land and building areas for developing and expanding a veterinary pharmaceutical formulation plant.

b. The presence of an excellent Faculty of Agriculture and Animal Husbandry at Assuit University with imaginative, innovative scientists in the applied, agricultural and veterinary sciences to supply (1) the technology required, and (2) testing and research facilities.

c. The very good location of Assuit vis á vis the Sudan and the Nile Valley where some of the largest animal populations of the Arab countries exist.

d. Easy means of transportation by road, rail, water and air between Assuit, Luxor and Cairo permit the easy entry of raw materials to the plant site and the shipping of finished products.

4.5.7 Veterinary Biologicals Laboratories

Location

It is recommended that ACDIMA, through participation with the government departments concerned and the collaboration with expatriate expertise assist in developing and expanding the present facilities in Iraq and the Sudan.

Rationale

a. The present existence of basically well structured producing laboratories for veterinary vaccines in the Sudan and Iraq (see Section 4.5.5 c) will provide excellent foundations.

b. Large animal populations in these countries and neighboring territories provide an easibly accessibl, market.

c. The availability of highly skilled technologists in the Arab countries in this discipline will be invaluable.

d. Short and long term projects of the respective governments indicate that planned expansion of existing laboratories in the Sudan and Iraq enjoy a high priority. ACDIMA should approach these governments to offer participation to ensure that consideration is given to the greater needs of the Arab countries as opposed to the narrower requirements of the individual countries concerned.

4.5.8 Facilities for Packaging and Labelling from Bulk Finished Product

Location

Undoubtedly further studies will indicate additional areas where this type of operation can be located, however it is suggested that the initial small packaging and labelling operations be established in Abu Dhabi, United Arab Emirates; Qatar; and Democratic Yemen. No attempt has been made to locate these facilities on the map on page 97.

Rationale

a. The location of Abu Dhabi and the related Emirates States Dubai, Shariah, Ajman, etc. with a population of approximately 750,000 is in an ideal position to service the Truncated States, Western Saudi Arabia, Oman, Bahrain, etc. Similarly bulk products can be received from plants in nearby Iraq, Saudi Arabia (hard gelatin capsules), Kuwait, and distally by sea from Egypt and the Sudan.

b. Technologists can be drawn from Iraq, Kuwait and Egypt.

c. Since large volumes of potable water and very expensive and elaborate environmental control systems are not necessary, there would be no need for a highly skilled manufacturing and maintenance infrastructure.

d. The local population could be serviced with products manufactured under labels printed almost completely in Arabic as opposed to imported products labelled in foreign languages.

e. As the population and health needs in these areas expand, additional physical plant can be added to the existing facilities.

The rationale stated in (a) to (e) above is applicable to Qatar and Democratic Yemen.

Appendix I

PRODUCT INFORMATION RECORD

PREDNISONE TABLETS B.P. 5 mgm.

1. Specification, Processing and Testing Information

See product file

2. Complaints and Regulatory Actions

See product file and complaints records

3. Chemistry and Pharmacology

Other names: Prednisonum (I.P.); Deltacortisone; Deltahydrocortisone; 1,2-Dehydrocortisone; Metacortandracin. 17x,21-Dihydroxypregna-1,4-diene -3,11,20-trione

Chemical formula: $C_{21}H_{26}O_5$

M.W. = 358.4

A white or almost white, odourless, crystalline powder, with a persistent bitter after-taste. M.p. about 230° with decomposition.

Almost insoluble in water; soluble 1 in 190 of alcohol, 1 in 300 of dehydrated alcohol, and 1 in 200 of chloroform; soluble in dioxan and methyl alcohol.

The metabolism of prednisone is similar to that of prednisolone.

Corticosteroids, with the exception of deoxycortone, are absorbed from the gastro-intestinal tract. When given by topical application particularly under an occlusive dressing, or as a rectal enema, sufficient corticosteroid may be absorbed to give systemic effects. Administration by mouth may give a more rapid response than intramuscular injection of an insoluble corticosteroid. Water-soluble forms of corticosteroids giving a rapid response are used for intravenous injection.

Corticosteroids in the circulation are highly bound to plasma proteins, mainly to globulin and less so to albumin. The corticosteroid-binding globulin has high affinity but low binding capacity, while the albumin has low affinity but large binding capacity. Only unbound corticosteroids diffuse into tissue fluids and cerebrospinal fluid but transplacental diffusion in significant amounts has not been demonstrated.

Corticosteroids are metabolised in the liver and kidney and excreted in the urine. Urinary excretion of 17-hydroxycorticoids is used as an index of adrenal function. The slower metabolism of the synthetic corticosteroids with their lower protein-binding affinity may account for their increased potency compared with the natural corticosteroids.

4. Indications

Prednisone is a synthetic glucocorticoid with the general properties of Corticosteroids.

Five mg. of prednisone is about 25 mg of cortisone acetate. In equivalentdoses it causes less sodium and fluid retention than cortisone and for this reason it is usually preferred to cortisone in the treatment of such conditions as rheumatoid arthritis, rheumatic fever, status asthmaticus, and ulcerative colitis but it is not used in the treatment of nephrotic oedema as it produces diuresis. Prednisone is used as an immunosuppressive agent, often with azathioprine, during and following surgery for organ transplantation involving the kidney, liver, and heart.

Prednisone may be administred by mouth in doses adjusted according to the needs of the patient and the disorder being treated. In rheumatoid arthritis or for long-term suppressive therapy, dosage should be maintained at not more than 8 mg daily as side-effects inevitable occur with higher dosage. In conditions dangerous to life, such as pemphigus vulgaris, leuknemia, and acute haemolytic crises, a much higher dosage is permissible, up to 100 mg daily if necessary. In status asthmaticus up to 60 mg daily may be given, though in severe crises hydrocortisone or corticotrophin administered intravenously may be preferred.

Ten patients being rea-ed for either the neph-otic syndrome or lupus glomerulonephritis and receiving alternate-day therapy with prendisone 25 to 120 mg were compared with 8 patients with other conditions, receiving average daily doses of 56 mg of prednisono or its equivalent, and 10 health men. Side-effects of alternate-day therapy were less than with daily treatment and suppression of the pituitary-adrenal axis was lesa. Moderate depression of the resting concentration of plasma 17-hydroxycorticosteroids occurred, but the response to hypoglycaemia was similar to that shown by health control subjects.--G.L. Ackerman and C.M. Nolan, New Engl. J. Med., 1968, 278, 405.

There were no data to show that patients made a better response to alternate-day than to continuous corticosteroid therapy, and there responses of groups receiving different doses could not be compared.--R.B. Stoughton (letter), New Engl. J. Med., 1968, 278, 915; a reply.--G.L. Ackerman, ibid.

Intermittent administration of prednisone 60 mg per m^2 body-surface on 3 day per week, following initial daily administration of the same dose for 3 weeks, was given to 8 children. One other child was given prednisone on alternate days, and another daily. Suppression of the hypothalamic-pituitary-adrenal axis was evident in all the children, but growth was inhibited only in the child receiving continuous daily treatment.--M.M. Martin et al., New Engl. J. Med., 1968, 279, 273.

Prednisone 20 to 100 mg was given in a single dose by mouth on alternate mornings to 12 patients with inflammatory disorders. In 7 patients a change from daily to alternate-day therapy was made and was found to be followed by increased delayed hypersensitivity to experimental allergens. Patients started on alternate-day therapy retained their prior skin sensitivity to allergens. Alternate-day therapy successfully reduced inflammation and produced relatively mild side-effects.--R.R. MacGregor et al., New Engl. J. Med., 1969, 280, 1427.

Allergic Disorders. Prednisone, 25 mg or more daily, suppressed the symptoms of allergic vasculitis in 7 patients.--C. Ramsay and L. Fry, Br. J. Derm., 1969, 81, 96.

Arteritis. Two elderly patients with giant-cell arteritis responded promptly to prednisone therapy. The symptoms of peripheral neuropathy, muscle wasting, and anaemia had suggested malignant disease.--D.A. Warrell et al., Lancet, i/1968, 1010.

A persistently high sedimentation-rate and anaemia might be indicative of arteritis in a patient with symptoms of a stroke and, if infection was absent, should be treated with prednisone, 15 mg thrice daily.--L.J. Hurwitz, Br. med. J., iii/1969, 699.

Asthma. Long-term treatment with steroids for an average of 27 months was given to 71 patients with asthma. The usual dose was 40 mg of prednisone daily for 9 days, but if there was no response after the first 5 days the dose was increased to 60 mg daily for 3 to 5 days. After 8 to 10 days' treatment, the dose was reduced by 5 mg every other day to the smallest dose which controlled the wheezing, usually 7.5 to 12.5 mg daily. Results were very good in 34 patients, moderate in 26, and prednisone was considered to have failed in 11.--J.L. Livingstone and J.P. Davises, Lancet, i/1961, 1310.

Blood Disorders. Anaemia. Treatment with prednisone (initially 80 and 100 mg daily) in conjunction with fluid balance, and peritoneal dialysis in 1 patient, resulted in completed reversal in 2 patients of a syndrome of acute microangiopathic haemolytic anaemia and severe oliguric renal failure.--C.M. Shapiro et al. J. Am. med. Ass., 1970, 213, 567.

In a woman with primary macroglobulinaemia, severe anaemia responded to treatment with prednisone 40 mg and azathioprine 150 mg daily, and folic acid 5 mg twice daily, when therapy with other cytotoxic drugs had failed. Normal peripheral blood counts were obtained after 4 months' therapy, when the dosages of azathioprine and prednisone were reduced to 100 mg and 20 mg daily, respectively.--R.C. Heading et al., Br. med. J., iii/1970, 750.

Leukaemia. A trial to assess the value of prednisone given in conjunction with mercaptopurine in the treatment of acute leukaemia.--Second Report to the MRC of the Working Party on the Evaluation of Different Methods of Therapy in Leukaemia, Br. med. J., i/1966, 1383.

Treatment with prednisone or prednisolone in a dose of 40 mg per m^2 of body-surface area had produced remissions in about 60% of patients with acut lymphocytic leukaemia. Remissions in about 82% of cases could be achieved by concomitantly giving mercaptopurine, 2.5 mg per kg body-weight. Remissions of the same order could be expected by substituting vincristine sulphate, in a dose of 2 mg per m^2, and remissions approaching 100% could be reached with doses of 120 mg per m^2 of prednisone. Hyperuricaemia and uric acid nephropathy were potential dangers of corticosteroid therapy. Adequate fluids should be given to maintain urinary output at about 3 litres daily and the urine should be kept alkaline with sodium bicarbonate, 10 to 20 grains four times daily initially and acetazolamide, 250 to 500 mg each night.--per R.A. Kyle and J.E. Maldonado, Mayo Clin. Proc., 1966, 41, 383.

Four dosage regimens of prednisone were given to 223 previously untreated children with acute leukaemia; 86 had 2 mg per kg body-weight daily in 3 divided doses; 85 had 4 mg per kg daily in 3 divided doses; 28 had a single dose of 8 mg per kg on alternate days; and 24 had a single dose of 16 mg per kg every fourth day. Bone-marrow remissions occurred in 72%, 60%, 21%, and 12% respectively. Intermittent therapy was less effective than continuous dosage but side-effects were reduced.--S.L. Leikin et al., Cancer, N.Y., 1968, 21, 346, per Abstr. Wld Med., 1968, 42. 897.

Thrombocytopenic purpura. Treatment with prednisone alone sufficed to restore the blood-platelet count to normal within 17 days in a patient with brucellosis with peripheral bleeding and thrombocytopenic purpura. The prednisone was started in a daily dosage of 60 mg, then progressively reduced to 30 mg daily.--S.E. Halpern and S.G. Wolf, J. Am. med. Ass., 1968, 204, 679.

Coeliac Disease. Prednisone, in a dose of about 30 mg daily for 7 days, in conjunction with a gluten-free diet, produced clinical improvement in a 36-year-old woman with coeliac disease and restored lymphocyte transformation.--O.Popovic et al. (letter), Lancet, ii/1970, 725.

Exophthalmos. In 2 patients with malignant exophthalmos, in whom the prognosis had been regarded as hopeless, the advanced eye changes were successfully treated with prednisone, 120 to 140 mg daily. Neither patient improved on daily doses of 45 mg but improvement quickly followed the higher dosage. The improvement was maintained, despite a short relapse in 1 patient, during the slow withdrawal of prednisone.--S.C. Werner, Lancet, i/1966, 1004.

Haemangioma. Six infants with extensive haemangiomas were treated for about 2 weeks with 20 to 30 mg of prednisone daily by mouth, tapered off over 2 to 4 weeks. In 5 there were remissions, but 3 of them relapsed and were controlled by a second course. In the other child, who had extensive scarring from earlier surgery, there was little response to prednisone.--N.C. Post and N.B. Esterly, J. Pediat., 1968, 72, 351, per

Abstr. Wld Med., 1968, 42, 616.

An infant aged about 3 weeks, with hepatic haemangioma and congestive cardiac failure, was treated with prednisone 40 mg every other day, reduced to 25 mg after 4 weeks, andthen progressively reduced and discontinued. The liver size and scan, heart size, and ECG were normal 6 months after discontinuing treatment. Treatment with corticosteroids should be considered in patients with haemangioma which threatened life.--S.J. Goldberg and E. Ponkalsrud, J. Am. med. Ass., 1969, 208, 2473.

Herpes Zoster. Sixteen patients, average age 71 years, with severe herpes zoster accompanied by very severe pain were successfully treated within 1 to 10 days of the appearance of the rash with large doses of prednisone. Fourteen patients received 60 mg daily for a week, 30 mg daily for a second week, and 15 mg daily for a third week, and 2 patients had cortisone acetate, 300 mg daily, for the first week. Pain was abolished within 12 to 36 hours when treatment was initiated within 1 to 2 days of the onset of the rash but lasted 5 to 8 days when treatment was started on the fourth day or later; the average duration of pain after starting treatment was 3½ days. In 8 of a control group the average duration of pain was 3½ weeks. F.A. Elliott, Lancet, ii/1964, 610. Experience gained in treating an additional 38 patients had confirmed the value of corticosteroids for the relief of pain in the postherpetic neuralgia. It was most important that treatment should start within a few days of the appearance of the rash.--P.A. Elliott (letter), ibid., ii/1968, 170.

Immunosuppression. Immunosuppressive therapy in a patient who had received a liver allograft included azathioprine, prednisone, and antilymophocytic globulin, which were given in maximum daily dosages of 100 mg, 200 mg, and 21 ml respectively. The patient was able to return to work 6 weeks after operation.--R. Y. Calne et al., Br. med. J., iv/1968, 541.

The use of prednisone in the course of bone-marrow transplantation. --F.H. Bach et al., Lancet, ii/1968, 1364.

In 17 patients receiving azathioprine daily after renal transplantation, prednisone given on alternate days instead of daily maintained stable renal function with reduced antihypertensive therapy in 10 patients, stabilised cataracts in 2 patients, promoted healing of a non-healing infected flank-nephrectomy incision in 2 months in 1 patient, reduced proteinuria in 1 patient, and migratory arthritis in another, and allowed growth to continue in an 8-year-old girl who did not grow in the first 7 months after transplantation.--W.P. Reed et al., Lancet, i/1970, 747.

Influenza. Corticosteroids in sufficient doses given either by mouth or intravenously for 6 days suppressed the febrile and inflammatory reactions due to virus diseases. The reactions were not resumed when the steroid treatment was discontinued. Acute febrile infections of the upper respiratory tract, presumably of virus origin, had been aborted by doses of 80 mg of prednisone

taken at bedtime on the day the infection started.--G.E. Brown (letter), Lancet, i/1967, 1277.

Liver Disorders. Prednisone accelerated bilirubin excretion and, used prophylactically, prevented the hyperbilirubinaemia usually present in kernicterus of prematurity. The usual dose was 2.5 mg four times daily but in rare cases when jaundice persisted a daily dose of 2 to 5 mg could be given for 2 to 3 weeks.--H.Wiesener, Mschr. Kinderheilk., 1960, 108, 1, per Abstr. Wld Med., 1960, 28,245.

A 5-day course of prednisone, 15 mg four times a day, served to distinguish successfully between extrahepatic jaundice due to malignancy and intrahepatic jaundice of viral infection. A fall of 50% or more in the serum-bilirubin concentration occurred only in patients with viral inflammatory disease of the liver.--L.D. Wruble et al., J. Am. med. Ass., 1966, 195, 184.

Prednisone was effective in improving liver-function tests in patients with cirrhosis of the liver and sprionolactone reduced oedema. The 2 drugs given together had a reliable natriuretic effect.--J. Lintrup et al., Acta med. scand., 1966, 179, 13, per Abstr. Wld Med., 1966, 40, 261.

A controlled study in 334 patients with cirrhosis of the liver showed that treatment with prednisone, minimum dose 10 mg daily, did not affect the death-rate. Patients with ascites and patients suffering from alcoholism who were treated with prednisone had a significantly higher death-rate than an untreated control group.--A Report from the Copenhagen Study Group for Liver Diseases, Lancet, i/1969, 119.

Lupus Erythematosus. Prednisone, 60 to 120 mg daily, was recommended for the treatment of acute systemic lupus erythematosus. As the condition remitted the dose was reduced gradually to a maintenance dose of about 5 to 15 mg daily.--N.R. Rowell, Br. med. J., ii/1969, 427.

Muscular Dystrophy. Prednisone, 20 to 30 mg daily, would relieve or abolish the symptoms of myotonia in muscular dystrophy.--J.N. Walton, Br. med. J., iii/1969, 939.

Myastenia Gravis. Prednisone, administered in a single 100 mg dose by mouth on alternate days, greatly improved the condition of a 44-year-old man with myasthenia gravis. No side-effects had occurred 3 months after the start of treatment.--J.R. Warmolts et al, (letter), Lancet, ii/1970, 1198.

Nephrotic Syndrome. In children with the nephrotic syndrome who were given 60 mg or more of prednisone on alternate days the therapeutic effect was equivalent to that of daily administration. Steroid side-effects were reduced and there were resumption of of growth.--L.F. Soyka, Am. J. Dis. Child., 1967, 113, 693, per Abstr. Wld Med., 1968, 42, 246.

Another similar report.--L.F. Soyka, Clin. Pediat., 1967, 6, 77, per J. Am. med. Ass., 1967, 200 (Apr. 10), A241.

Of 125 adult patients with the nephrotic syndrome admitted to a multicentre trial, 64 acted as controls and 61 received prednisone, usually in a dosage of 20 to 30 mg daily, for at least 6 months. Patients were classified, according to biopsy specimens, as having minimal glomerular change, membranous nephropathy, or proliferative glomerulonephritis. In the patients with minimal glomerular change, prednisone usually caused an early marked decrease in proteinuria, hypoproteinanemia, and oedema. Renal function was not significantly improved. In the other groups, prednisone had no marked effect on proteinuria or renal function. Though statistically insignificant, mortality was higher in the prednisone-treated group (17 of 61 patients) compared with the control group (12 of 64 patients). Mortality due to cardio-vascular disease was significantly greater in the patients receiving prednisone but that due to renal failure was not significantly different in the 2 groups. In patients with the nephrotic syndrome, apart from those with minimal glomerular change, the risks of continuous steroid therapy might outweigh the possible benefits.--D.A.K. Black et al., Br. med. J., iii/1970, 421.

Pyoderma Gangrenosum. Prednisone was effective, if given early in the course of the disease, in controlling pyoderma gangrenosum. In the fulminant, rapidly developing disorder, a dose of 60 to 100 mg daily was given.--per J. Am. med. Ass., 1968, 206, 2229. See also G.M. Stathers et al., Archs Derm., 1967, 95, 375, per J. Am. med. Ass., 1967, 200 (Apr. 24), A190.

Reiter's Disease. In a 20-year-old woman with Reiter's disease who developed extensive keratodermia blennorrhagica, administration of prednisone 40 mg daily by mouth led to a rapid improvement in her condition with cessation of pyrexia and healing of skin lesions.--A.J. Richards, Br. med. J., iv/1970, 723.

Rheumatic Fever. In 122 patients with rheumatic fever given prednisone 50 to 62.5 mg daily, tapered off over 12 weeks, together with penicillin and sulphadiazine, and given either bed rest or early ambulation treatment, about 20% in each group had heart murmurs after 1 year. Activity as soon as the ESR had returned to normal did not influence damage to the heart.--B.J. Grossman, Am. J. Dis. Child., 1968, 115, 557, per Abstr. Wld Med., 1968, 42, 880.

Sarcoidosis. A total of 106 patients with proved pulmonary sarcoidosis were treated with prednisone without any harmful side-effects. Corticosteroids did not alter the ultimate prognosis of the disease but they shortened the attacks and prevented irreparable damage to the heart and lungs. Once fibrotic changes had occurred prednisone produced no functional improvement.--H. Drobny, A. Tuberk., 1964, 1212, 147, per Abstr. Wld Med., 1964, 36, 426.

Trichinosis. Prednisone, 10 to 15 mg every 6 hours, was recommended for the treatment of trichinosis. Prednisone could be given parenterally if necessary. Treatment should be continued for 5 to 7 days, but if continued for longer the doses should be

tapered before withdrawal.--W.E. Herrell, Clin. Med., 1968, 75 (May), 92.

Ulcerative Colitis. Sixty-two patients who had had attacks of ulcerative colitis that were considered to be symptomatically and sigmoidoscopically in remission were given either prednisone, 5 mg thrice daily, (32 patients), or a placebo (30 patients). In both groups 12 patients remained in remission for 6 months and the remainder, with the exception of 3 patients (2 treated and 1 given the placebo) who stopped treatment because of side-effects, relapsed. In all, 7 patients receiving prednisone experienced side-effects which included dyspepsia in 4. Side-effects also occurred in 2 receiving the placebo. Prednisone was considered not to be superior to the placebo in preventing relapses of ulcerative colitis.--J.E. Lennard-Jones et al., Lancet, i/1965, 188.

Seven children with ulcerative colitis were successfully maintained on prednisone, 40 to 80 mg, given on alternate days; therapy was administered daily until the acute symptoms were controlled. The symptoms reappeared when attempts were made to stop treatment or lower the dosage.--A. Sadeghi-Nejad and B. Senior, Pediatrics, Springfiled, 1969, 43, 840, per Abstr. Wld Med., 1969, 43, 959.

Ulcerative Oesophagitis and Colitis. A 15-year-old boy had severe ulcerative oesophagitis. He had chest pain on swallowing, bloody diarrhoea, and gross bleeding with oedema and friability of the rectal mucosa. Prednisone, 60 mg daily, together with sulphasalazine, was given because of the progressive condition. There was prompt reduction of fever and improvement in well-being, dysphagia, and diarrhoea. Nine months later the boy was free of dysphagia and the diarrhoea had lessened but hepatosplenomegaly persisted. A further 7 months later the oesophagus was normal.--K. A. Knudsen and M. Sparberg (letter), J. Am. med. Ass., 1967, 201, 140.

5. Contraindications

Systemic administration of corticosteroids is contra-indicated in patients with peptic ulcer, osteoporosis, psychoses, or severe psychoneuroses, and they should be used only with great caution in the presence of congestive heart failure, in patients with diabetes mellitus, infectious diseases, chronic renal failure, uraemia, and in elderly persons. Patients with active or doubtfully quiescent turberculosis should not be given these hormones except as adjuncts to treatment with tuberculostatic drugs.

Because of interference with antibody formation, systemic administration of corticosteroids is usually contra-indicated in the presence of acute bacterial infections, herpes zoster, herpes simplex ulceration of the eye, and other viral infections. There are, however, in the following pages, reports of their successful use in adequate dosage and with appropriate antibiotic cover in the treatment of some life-threatening infections.

There is normally an increased secretion of corticosteroids by the adrenals in response to stress caused by anaesthesia, surgery, or trauma; patients receiving corticosteroids or who have been given corticosteroids in the previous 2 years may have insufficient

adrenal reserve and should be given supplementary corticosteroids. Cortisone acetate by mouth or intramuscularly or hydrocortisone sodium succinate intravenously or intramuscularly may be given for 1 to 2 days before an operation and continued until stress has ceased before tapering off the dose.

Concurrent administration of barbiturates or phenytoin may enhance the metabolism and reduce the effects of cortiosteroids. Response to anticoagulants may also be affected by corticosteroids.

Topical applications of cortiscosteroids should not be made with an occlusive dressing to large areas of the body because of the increased risk of systemic toxicity and should not, in general, be used in the presence of infection, particularly that of the eye. Occasionally they may be used with the addition of a suitable antimicrobial substance in the treatment of infected skin but there is a risk of sensitivity reactions occurring. Corticosteroids should not be applied to ulcers of the leg.

6. Toxic effects, Adverse reactions and Precautions

The side-effects associated with the use of corticosteroids in the large dose often necessary to produce a therapeutic response result from excessive action on electrolyte balance, excessive action on other aspects of metabolism including gluconeougenesis, the action on tissue repair and healing, and an inhibitory effect on the secretion of corticotrophin by the anterior lobe of the pituitary gland.

Disturbance of electrolyte balance is manifest in the retention of sodium and water, with oedema and hypertension, and in the increased excretion of potassium with the possibility of hypokalaemia alkalosis. In extreme cases, cardiac failure may be induced. Disturbances of electrolyte balance are common with the naturally occurring corticotrophin, cortisone, deoxycortone, and hydrocortisone, but are less frequent with many synthetic derivatives, such as betamethasone, dexamthasone, methylprednisolone, prednisolone, prednisone, and triamcinolone. Most topically applied corticosteroids may, under certain circumstances, be absorbed in sufficient amounts to produce systemic effects.

Other excessive metabolic effects lead to mobilisation of calcium and phosphorus, with osteoporosis and spontaneous fractures, nitrogen depletion and hyperglycaemia with accentuation or precipitation of the diabetic state. The insulin requirements of diabetic patients are increased. Increased appetite is often reported.

The effect on tissue repair is manifest in peptic ulceration with haemorrhage and perforation, delayed wound healing, and increased liability to infection. The topical application of corticosteroid preparations to the eyes has produced corneal ulcers, raised intraocular pressure, and reduced visual function and systemic administration has caused posterior subcapsular cataract. Increased susceptibility to all kinds of infection, including sepsis, fungous

infections, and viral infections, have been reported in patients on corticosteroid therapy; for example, Candida infections of the mouth in patients treated with corticosteroids, especially if these are given conjointly with antibiotics, are not uncommon. Application of corticosteroids to the skin has led to loss of skin collagen and subcutaneous atrophy.

The dose of corticosteroid required to diminish corticotrophin secretion with consequent atrophy of the adrenal cortex and the time required for its occurrence vary from patient to patient. Acute adrenal insufficiency, with loss of consciousness, may occur during prolonged treatment or on cessation of treatment and may be precipitated by an infection or trauma. Growth retardation in children has been reported and attempts have been made to overcome it by using intermittent dosage.

Large doses of corticosteroids, or of corticotrophin, may produce symptoms typical of hyperactivity of the adrenal cortex, with moonface, sometimes with hirsutism, buffalo hump, flushing, increased bruising, striae, and acne, sometimes leading to a fully developed Cushing's syndrome. If administration of the hormone is discontinued immediately on the appearance of these symptoms they are usually reversed, but such sudden cessation may be dangerous.

Other toxic effects include amenorrhoea, mental and neurological distrubances, intracranial hypertension, and, on sudden reduction of dosage during the treatment of rheumatoid arthritis, fatalities have been attributed to lesions of small arteries and arterioles similar to polyarteritis.

Infections may be masked since corticosteroids have marked anti-inflammatory and anti-pyretic properties, and may produce a feeling of well-being.

The administration of corticosteroids may also cause a reduction in the number of circulating lymphocytes.

Muscular weakness is an occasional side-effect of most corticosteroids, particularly when they are taken in large doses, and it is most evident with fludrocortisone and triamcinolone. It has been suggested that this effect is more pronounced when a fluorine atom is present in the 9x-position in the steroid molecule.

Toxic effects occur, in general; fairly equally with all corticosteroid preparations and their incidence rises steeply if dosage increased much above 8 mg daily of prednisolone or its equivalent.

Prednisone is less likely than cortisone or hydrocrtisone to cause sodium retention, electrolyte imbalance, and oedema, but gives rise more frequently to dyspepsia and peptic ulceration.

The phenomenon of muscular wasting was not confined to the newer corticosteroids with a fluorine radical. Prednisone could cause

wasting of the same type. Wasting of the leg muscles, with consequent weakness and difficulty in walking occurred in 2 patients but improved on reduction or cessation of prednisone.--J.R. Harman (letter), Lancet, i/1959, 887.

A 39-year-old woman with acute leukemia, who was given 1 g of prednisone daily for 36 days, developed leucopenia and severe infection. The patient recovered after treatment and was still alive and well, though obese, 7½ years after the onset of symptoms. --W. Dameshek and W.J. Mitus, New Engl. J. Med., 1963, 268, 670.

A 29-year-old Negro with pulmonary sarcoidosis who was given prednisone in a final maintenance dosage of 20 mg daily developed severe hyperglycaemia, ketonuria, and acidosis which responded to discontinuance of the steroid and treatment with fluids, sodium lactate, and insulin.--R.P. Blereau and C.M. Weingarten, New Engl. J. Med., 1964, 271, 838.

Aseptic Bone Necrosis. Intravascular fat emboli in a necrotic femoral head developed in a young man during 3 years of treatment with prednisone, 35 to 45 mg daily, and azathioprine, 150 to 200 mg daily, given as immuno-suppressive therapy following renal transplantation.--D.E. Fisher et al., Mayo Clin. Proc., 1969, 44, 252.

Avascular necrosis of bone in 6 patients who had undergone renal transplantation could have been associated with treatment with prednisone.--M.C. Hall et al, J. Am. med. Ass., 1969, 308, 1325.

Leucoctyosis. Of 18 patients with the nephrotic syndrome, 12 received prednisone treatment. Polymorpho-nuclear leucocytosis developed in all patients treated with prednisone and the mean white-cell count, ranging from 8370 to 13,700 per mm^3, was linearly related to the prednisone dosage of 0 to 30 mg daily.--M. Floyd et al, Lancet, i/1969, 1192.

Pancreatitis. Prednisone, 200 mg daily, caused acute pancreatitis in a 13-year-old girl who was being treated for idiopathic thrombocytopenic purpura.--R. W. Schrier and R.J. Bulger, J. Am. med. Ass., 1965, 194, 564.

Renal Failure. A 20-year-old woman with polyarteritis nodosa received prednisone initially in a dosage of 40 mg daily increased up to 100 mg daily. At a dosage of 75 mg daily hypercalciuria occurred with a fall in creatinine clearance and a rise in blood urea. Renal function improved when the prednisone dosage was gradually reduced under cover of immunosuppressive therapy.--J.R. Condon and J.R. Nassim, Br. med. J., i/1971, 327.

Adrenal suppression. There was a danger of adrenal suppression even with doses as low as 5 mg daily.--J.A. Hicklin and M.R. Willis, Ann. rheum. Dis., 1968, 27, 33, per Abstr. Wld Med., 1968, 42, 676.

In 43 patients with pulmonary sarcoidosis treated with prednisone for at least 2 years in doses gradually reduced from 40 mg daily, tests of adrenocortical function indicated that basal function

returned to normal while prednisone treatment was continued at a low dosage. At a dosage level of 7.5 mg of prednisone daily, a definite nyctohemeral rhythm was evident, indicating that pituitary secretion of corticotrophin was resumed in a rhythmical manner. The response to tetracosactrin stimulation was not normal when prednisone 2.5 mg daily was being taken, and was normal in only about one-half the patients on cessation of treatment.--L. Westerhof et al., Br. med. J., iv/1970, 534.

Neuropathy. From a study of 18 patients on prednisone therapy for chronic obstructive lung disease, it was suggested that patients receiving prednisone should be watched carefully for signs and symptoms of peripheral neuropathy.--per J. Am. med. Ass., 1970, 212, 2034.

Panniculitis. An unusual form of panniculitis occurred in a 16-month-old boy following the rapid discontinuation of large doses of prednisone administered by mouth for an episode of acute nephritis. The literature concerning 16 other cases was reviewed.-H.H. Roenigk et al., Archs Derm., 1964, 90, 387, per Int. pharm. Abstr., 1965, 2, 905.

Strongyloidiasis. Four patients, aged 5 to 32 years, taking prednisone 40 or 60 mg daily for the nephrotic syndrome, and a 23-year-old woman taking dexamethasone 20 mg daily for eczema, developed fatal strongyloidiasis during or shortly after treatment. Strongyloides stercoralis was responsible in each instance. Corticosteroid therapy might have altered the host-parasite equilibrium.--T. Cruz et al., New Engl. J. Med., 1966 275, 1093.

7. Treatment of Toxic Effects

Toxic effects are nearly always signs of overdosage and should be treated symptomatically and dosage reduced or the drug slowly withdrawn. During long courses of treatment, laboratory and metabolic studies should be made; measurement of the fluid intake and output, and daily weight record, may give early warning of fluid retention. Sodium intake may need to be reduced to less than 1 g daily and potassium supplements may be necessary.

To reduce skin, bone, and muscle changes during treatment with corticosteroids, patients should receive a high-protein diet and those on high doses should receive anabolic steroids such as nandrolone phenylpropionate or decanoate and methenolone enanthate in addition. The dose of corticosteroid must be increased during infection, surgical operations, or accidents.--D. Ferriman, Practitioner, 1965, 194, 43.

Perioral dermatitis due to rebound exacerbation of the condition when topical corticosteroids were withdrawn could be successfully treated with tetracyclines taken by mouth.--A.J. Rook and D.S. Wilkinson (letter), Br. med. J., ii/1970, 481.

Symptomes of adrenal insufficiency may occur for several days following cessation of a prolonged course of steroid therapy and though adrenal function then becomes adequate for the usual daily needs, 6 months or more may be required for the return of function adequate to meet the stress of infection, surgical operations, or trauma. Deaths due to adrenal insufficiency have occurred. Withdrawal of corticosteroids should therefore always be gradual; when prednisone for example, has been used for long-term suppression of chronic inflammatory disorders, its dose should not be reduced by more than 0.5 or 1 mg daily every 2 to 3 weeks. If sudden withdrawal is necessary, corticotrophin, 20 units given daily by intravenous infusion during 8 hours for 3 to 5 successive days, is usually sufficient to prevent withdrawal symptoms.

8. Storage - In airtight containers, away from light.

9. Supplied - 100's, 500's, 1000's, 5000's

10. Dose - 10 to 100 mg daily in divided doses. Children, twice daily; up to 1 year, 1 to 2.5 mg; 1 to 5 years 2.5 to 10 mg; 6 to 12 years, 5 to 20 mg.

Appendix II

GUIDE FOR PARENTERAL DRUGS MANUFACTURING AND PERSONNEL TRAINING

I. INTRODUCTION

Definition - "Parenteral use" means administration of a drug by means of hypodermic syringe, needle or other instrument through or into the skin or mucous membrane.

Parenteral preparations must be as nearly perfect as possible with respect to purity, freedom from toxicity and freedom from contamination. This is especially true of intraspinal (intrathecal) and intracisternal (thoracic duct) injections.

II. ADMINISTRATION OF PARENTERALS

Five general categories of injections are:

1. Solution.
2. Dry soluble.
3. Suspension.
4. Dry insoluble.
5. Emulsions.

III. ADVANTAGES OF INJECTIONS

- Immediate physical action.
- Can modify formulation or choice of route of injection to prolong effect.
- Therapeutic response more controlled and reliable because it is not dependent on intestinal absorption.
- Confidence of certainty and accuracy of administration if performed by a professionally trained person.
- Can be administered to unconscious or uncooperative patients.

IV. DISADVANTAGES OF INJECTIONS

- Ensuring asepsis of administration (to prevent systemic infection).
- Nearly impossible to correct an error of medication or dosage.
- Real or psychological pain factor.
- Daily or frequent administration may pose problems for outpatients.
- Infection, irritation or necrosis around injection site.
- Damage to veins (collapse).
- Danger of accidental intravenous injection when not wanted.

V. PARENTERAL COMBINATIONS

When large volumes of electrolytes or nutrients are administered intravenously, physicians often combine other parenteral preparations to reduce the number of injections.

Incompatibilities may be physical, chemical or therapeutic. Physical changes provide immediate warning (e.g. color changes or precipitates) and should not be used because:

1. Solid particles may occlude blood vessels;
2. Therapeutic agent may not be absorbed; and
3. Drug may be degraded to toxic substances.

Invisible changes could be equally or more dangerous because of (2) and (3). Parenteral combination results are altered by the order of mixing, proportions in mixtures, and time lapse before use. The extent of degradation may be predicted by pH and reaction rates.

Ideally no combinations should be used unless they are thoroughly evaluated for physical, chemical and therapeutic compatibility.

VI. GENERAL REQUIREMENTS

The onus is on manufacturers regarding:

1. High moral and professional ethics and attitude.
2. Full application of pharmaceutical knowledge.
3. Alertness in using and updating specialized techniques.
4. Use of ingredients of highest quality.
5. Establishing stability and effectiveness, especially if changes are made in ingredients and techniques.
6. Establishing rigid and vigilant quality assurance programs for evaluation of ingredients, equipment, production procedures, finished product testing, storage, and distribution.
7. Compliance of labelling, advertising and manufacturing procedures with existing legislation and good manufacturing practices.

VII. GENERAL PROCESS

The general process emcompasses four general areas:

1. Accumulation and selection of components and containers.
2. Production facilities and procedures.
3. Quality control.
4. Packaging and labelling.

1. Components and Containers

a. Components

Vehicles - Water for injection is the most widely used vehicle for injections. Water for parenterals must be distilled (see also U.S.P. XIX requirements).

Distillation of water

Conventional stills in general consist of boiler (evaporator) with baffles, etc.; a source of heat: process steam, gas, or electric; and condenser.

Construction can be of metal coated with pure tin, 304 or 316 stainless steel or chemically resistant glass (Barnstead, American Sterilizer Co., Corning).

Design features include raw water filtration to remove solids and deionizers to remove salts (prone to microbial growth and pyrogens), drainage of evaporator to reduce scale deposit, and conductivity metercells in distillate line.

Capacities range from 1.4 to 11.4 litres per hour for glass stills and up to 135 litres per hour for metal stills.

Compression distillation with vapor compression stills can produce large volumes of distillate and provide for high purity water if properly constructed.

Their main features of construction and operation are:
- evaporator with a core of tubes running internally (vertically) through the middle (which are sealed off externally to form a steam chest);
- baffles at top of evaporator (leading to compressor) to separate the entrained feed water from vapor;
- compressor which compresses the vapor and raises its temperature to approximately 107°C (224°F);
- steam chest where compressed vapor condenses on the outer surface of the vertical feed water evaporator tubes and is drawn off as distillate;

- heat from the distillate raises the feed water to boiling;
- once started little energy is required except for the operation of the compressor (driven by electric motor or diesel engine).

Storage of distilled water

Water for injection should be used immediately but this is not usually possible.

Water for injection should be collected in scrupulously clean, closed systems with inlet and outlet connections to the storage tank sealed. A vent with filter capable of preventing entry of microorganisms or chemical vapors should be installed to allow for changes in pressure when filling or emptying the tank.

Storage tank and connections should be of chemically resistant glass or 304 or 316 stainless steel or metal internally coated with pure tin.

Polyvinyl chloride is not recommended because it is more likely to contaminate and softens above 21°C (70°F).

During storage (which should not exceed 24 hours) the water should be kept about 80°C (176°F) or under ultraviolet light if storage is at room temperature.

For small quantities seal and store in containers at 80°C (176° F) or under refrigeration or autoclave to sterilize.

Water for injection can contain no added substances such as bacteriostatic agents, maximum total solids of 10 ppm, but need not meet U.S.P. sterility requirements because products will be sterilized.

Sterile water for injection must meet U.S.P. sterility requirements, can have bacteriostatic agents added, be of maximum 30 ml volumes in containers, have total solids of up to 40 ppm according to ratio of surface area of container to unit volume of water.

Types of Vehicles

Aqueous vehicles are usually isotonic and drugs are added at time of use. Examples are Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, and Lactate Ringer's Injection.

Water miscible vehicles consist of ethyl alcohol, polyethylene glycol, propylene glycol, etc. used as solvents as portions of complete vehicles and are mostly used intramuscularly and only occasionally intravenously.

Non-aqueous vehicles consist of fixed oils of vegetable origin, e.g. corn, cottonseed, peanut, sesame. (See U.S.P.)

The oils must be metabolizable (therefore not mineral oil), must be liquid at room temperature (therefore not animal origin), and must not become rancid (therefore not animal origin).

Fixed oils must contain esters of unsaturated fatty acids but must not be too unsaturated or will cause tissue irritation. Therefore the U.S.P. stipulates upper and lower iodine and free fatty acid limits.

Tocopherols in fixed oils prevent rancidity.

Fixed oils are used chiefly as vehicles for hormone preparations.

Type of fixed oil used must be stated on label.

Active Ingredients

The medicinal compounds used in injections must:

- be of highest purity;
- free from metallic contamination;
- free from microbial contamination;
- free from pyrogenic contamination;
- and free from gross dirt.

Other Added Substances

U.S.P. includes in this category all substances added to preparations to improve or safeguard the quality of product. They may:

- improve solubility (e.g. sodium benzoate in Caffeine and Sodium Benzoate Injection);
- make solution isotonic;
- enhance chemical stability (e.g. antioxidants, inert gases, buffers, chelating agents);
- "preservatives" as added substances may mean not only antimicrobial agents but include all substances that act to retard or prevent the chemical, physical, or biological degradation of a preparation.

Antimicrobial agents as per U.S.P. must be added in bacteriostatic or fungistatic concentrations to multiple dose containers to prevent multiplication of microorganisms inadvertently introduced by hypodermic needles when withdrawing a dosage portion.

Frequently employed antimicrobial agents are:

- For aqueous injections
  Phenylmercuric nitrate at 0.01% maximum but usually 0.002%.
  Thimerosal at 0.01%.
  Benzethonium chloride at 0.01% (Hyamine 1622, Solamine, Quatrachlor, Phemeride, etc.)
  Benzalkonium chloride at 0.01%.
  Phenol or cresol at 0.5%.
  Chlorobutanol at 0.5%.
  Methyl p-hydroxybenzoate 0.18% + propyl p-hydroxybenzoate 0.02%.

- For oleaginous injections (oils)
  No antibacterial agents are really effective but hexylresorcinol 0.5% and phenylmercuric benzoate 0.1% are moderately bacteriostatic.

Pyrogens are not predetermined components but may be present as unwanted contaminants. They adhere strongly to glass.

The presence of pyrogens indicate microbial contamination since they are products of microbial growth. Most potent ones are from Gram negative bacteria but they are also produced by fungi. Pyrogens are chemically lipopolysaccharides which may be associated with proteins and can contain phosphorus.

Pyrogens are very difficult to remove, but may be destroyed by the following means:

- Dry heat at high temperatures, e.g. for glassware and equipment: 250°C for 45 minutes; 650°C for 1 minute; or 180°C for 4 hours.

- Autoclaving does not destroy pyrogens.

- Heating with strong alkalis (but not 100% pure).

- Heating with oxidizing agents, e.g. hydrogen peroxide.

- Anion exchange resins adsorb pyrogens from water.

- Distillation is the most reliable method because pyrogens are not volatile.

- Asbestos filters can adsorb pyrogens from solutions but they also adsorb chemical constituents.

- In process destruction of pyrogens also possible by careful heating of pharmaceuticals in dilute alkali, dilute acid or oxidizing agents.

- Solutes may be a source of pyrogens. Purification by recrystallization, precipitate washing or other means should remove the pyrogens.

b. Containers

Containers are an integral part of the formulation and no container, even glass, is totally insoluble. Selection of containers must be based on consideration of component of container as well as the solution.

Plastic Containers

Thermoplastic containers are presently limited to components of disposable injection uits, a few selected sterile products and ophthalmic solution. They are still relatively new and there is insufficient history regarding reactivity with drugs. Absorption and adsorption of drug molecules can occur especially with polyamides and nylon.

These containers cannot be thermally sterilized in most cases but are sterilized by ionizing radiation and ethylene oxide, which may produce toxic ethylene oxide residues.

They must be tested for pyrogenicity.

For ophthalmic preparations low density polyethylene is used because flexibility of these tubes allows dropwise use.

Plastic containers should be tested for biological toxicity as per the U.S.P. and not exceed chemical limits.

Glass Containers

The container of choice for most injections is glass, which is composed principally of silicon dioxide with varying amounts of other oxides such as Na, K, Ca, Mg, Al, B, and Fe. Boric oxide permanently combines with the silicon dioxide tetrahedron network structure but most of the other oxides are loosely bound in the network interstices and tend to leach out into solutions especially during thermal sterilization and hydrolyze to raise pH of the solution, catalyze reactions, or enter into reaction.

Ampoules (thinner walls, optically clearer) and cartridges of up to 100 ml are drawn from glass tubing. Other vials and bottles are molded and are more uniform and strong.

Types of glass - for U.S.P. classification and tests see U.S.P. XIX. Types I, II, and III are for parenterals. Type NP is not for parenterals.

Type I - for all products, expensive. Borosilicate glass (chemically resistant, low leaching, also low thermal coefficient of expansion).

Type II - below pH 7, buffered solutions, etc. Soda lime, treated (SO_2 dealkalized internal surfaces and less leaching than Type III).

Type III - anhydrous liquids, dry substances. Soda lime, higher proportion of sodium and calcium oxides. Leaches more.

Type NP - general purpose soda lime. Not for parenterals.

Rubber Closures

Rubber closures permit introduction of needle from a hypodermic syringe into a multiple dose vial and provide resealing of the vial as soon as the needle is withdrawn.

They are also used for single dose cartridge type vials.

Aluminum caps hold the rubber closures in place.

Composition of rubber closures:

- Natural rubber (latex).
- Synthetic polymer (e.g. butyl).
- Combination of natural rubber and synthetic polymer.

Other ingredients used in manufacturing rubber closures include:

- Vulcanizing agent (usually sulfur).
- Accelerator (organic, e.g. Mertax, Thiotax or 2-mercaptobenzothiazole).
- Activator (usually zinc oxide).
- Fillers (e.g. carbon black or limestone).
- Miscellaneous ingredients e.g. antioxidants and lubricants.

All ingredients are compounded together, then vulcanized into shape in molds using high temperature and pressure.

Requirements of rubber closures:

- Elasticity: (i) to make snug fit between the closure and neck and lip of vial; (ii) to allow needle to pass through without undue force; and (iii) to spring back and close hole when needle is withdrawn.

- Hardness: (i) sufficiently firm to hold shape and fit tight; and (ii) not too hard or needle would not go through or the hollow needle may cause fragmenting.

- Nonreactive with solution (none are completely nonreactive because compounding ingredients leach).

- Provide complete vapor barrier (none does this completely especially after being used as in the multiple-dose vial).

Physical shapes of rubber closures:

- Most have a lip and protruding flange to go into the vial.

- Disk closures are used especially for high speed packaging of antibiotics.

- Slotted closures are used for freeze-dried products to let vapor out.

- Flexible lip types are for large volume intravenous hospital use.

2. Production Facilities and Procedures

Production facilities and procedures are very important as a product having the best quality components can be ruined if environment contaminated or if manufacturing procedures are improperly carried out. Therefore standards for production facilities and processing procedures must be as close to perfection as possible.

a. Production Facilities for Parenterals - are normally divided into five areas:

(i) Clean-up area - does not need to be aseptic but ceiling, walls and floors must be constructed of materials impervious to moisture, steam, detergents, etc. for cleaning.

Clean-up area must be adequately ventilated and exhausted to control heat and humidity for personal comfort and minimize microbial growth.

Clean-up area is used in particular for containers equipment before sterilization and subsequent routing to aseptic area for filling.

Ultraviolet lights should be installed in clean-up area.

(ii) Preparation area - Ingredients are formulated and compounded and equipment assembled in preparation for filling.

This area does not need to be aseptic but controls are more stringent than for clean-up area.

Ceiling, walls and floor should be sealed with a continuous intact vinyl or epoxy "spray-on-tile" sealing coat free of crevices, etc.

Adequate sink, counter and cabinet space preferably of stainless steel should fit snugly into walls.

All surfaces should be kept clean by regular, thorough washing.

Ultraviolet lights should be installed in preparation area.

(iii) Aseptic area - Construction is designed for maximum security.

Ceiling, walls, floor are sealed (germicidal paints are used by some) so that they can be washed and be treated with antiseptic wipe or spray before each use.

Counters should be of stainless steel and hung from the walls so as to provide no legs for dirt accumulation.

Light and ventilation fixtures and utility service lines should be recessed in walls or ceiling to eliminate ledges, joints, etc. where dirt and dust can accumulate.

Tanks containing products and mechanical equipment should be kept outside aseptic area and product fed in through hose lines.

Mechanical equipment in aseptic area should be housed in stainless steel cabinet to seal off operating parts from aseptic environment.

Mechanical parts in contact with parenteral product should be demountable to allow sterilization.

For small fills use a hood with armhole fitted with sterile gloves for the operator to use.

Airlocks are essential for traffic in and out of aseptic area. There should be no traffic in and out when filling and any movement while filling should be kept at a minimum.

Personnel should:

- enter and leave the filling area only through the gowning room airlock door;
- be dressed in sterile gowns or coveralls, sterile hats, face masks and foot cover put on in separate gowning room;
- be neat, orderly and reliable;
- receive physical examination at regular intervals and not be permitted into aseptic area if they have colds or illnesses;
- receive intensive instructions regarding aseptic techniques;
- put on fresh sterile uniforms after breaks before entering aseptic area;
- wear sterile gloves or scrub hands with hexachlorophene soap or another bactericidal solution;
- wear Dacron or use air showers since lint is a problem.

Equipment - Laminar Flow Environment

Laminar flow provides marked improvement in environmental control. There is total air sweep of confined area with uniform air velocity along parallel lines with minimum of eddies originating from a high efficiency particulate air (HEPA) filter occupying one entire side of confined area and circulates entire area with air with 99.97% or better of particles greater than 0.3 um particles removed.

Laminar flow can be horizontal or vertical and air velocity should be 100±10 feet per minute. Vertical flow is considered best where danger is possible to operators from viable microorganisms, penicillin powder, etc.

Vertical flow is recommended for sterility testing procedures. It provides a protective "blanket" of air between the operator's face and body and the work area.

Laminar flow work areas necessitate protection from disturbing air currents and turbulence or movements that exceed the velocity of the HEPA air flow.

Air Cleaning

Air conditioning and humidity control for the comfort of personnel and protection of sensitive products should be incorporated.

Prefilters are usually glass wool which removes large particles from outside air.

Electrostatic precipitators induce electrical charge of a given polarity on remaining particles and precipitate them on oppositely charged plates.

HEPA filters remove 99.97% of particles greater than 0.3 um.

Final passage around ultraviolet lights will kill any remaining viable organisms.

"Kathabar System" - chemical scrubbing of air through antiseptic (lithium chloride) solution to remove dust, microorganisms and control humidity is a more recent development.

Ultraviolet Radiation

Ultraviolet radiation is produced by a cold cathode mercury vapor lamp putting out 20 uW/cm^2 at 253.7 nm wavelength. It is used to continually maintain sterile air since there is always some microbial contamination from personnel and equipment.

Ultraviolet radiation is irritating to eyes and skin of personnel; therefore ultraviolet absorbing goggles should be used and lamps should be installed about 7 feet from the floor with a deflector to direct the rays above the heads of well-clad personnel.

Ultraviolet lamps have a special silica (96% Vycor) glass tube which absorbs shorter wavelengths that enerate undesirable ozone. The crystal structure gradually changes and absorbs the desired ultraviolet radiation so periodic checking is required; (20 uW/cm^2 is required for effective antibacterial activity).

Clean lamps are essential because dust and grease drastically reduce effectiveness.

Limited penetration of ultraviolet light give only surface sterilization and rays only travel in straight lines so obstructions should be eliminated.

Direct radiation of a room when personnel are not present is a valuable way of reducing bacterial counts on working surfaces and floors (e.g. before and after filling, etc.)

Ultraviolet radiation should also be installed in at least the clean-up and preparation areas in addition to the aseptic areas.

Maintenance of Aseptic Area

Careful cleaning and maintenance are very important. Crews should have special instruction by qualified supervisor.

Equipment should be effective and free of lint-producting tendencies.

Clean-up should be after completion of day's work to allow adequate interval of time for direct ultraviolet radiation prior to next aseptic filling.

Environmental Control Tests

These are required to monitor the sterility of aseptic areas because contamination can occur in spite of elaborate precautions.

Air sampling and/or sterile fill tests are in general use, i.e. (i) drawing air sample through sterile membrane, etc.; (ii) exposing nutrient agar culture plates; or (iii) fill sterile medium with same equipment used for product.

(i) Forced air sampling - involves a vacuum pump (preferably located outside sterile area) fitted with flow gauge to draw a given volume (e.g. 10 cu.ft.) of air through a sterile membrane filter during an aseptic operation. Sampling locations are chosen for sites with high potential for contamination e.g. filling and sealing area, next to personnel, next to moving equipment, near doorways and other openings, etc. Filters are examined microscopically for particulate matter (lint, dust, etc.) or incubated on culture media and examined for growth. To avoid dehydrating microorganisms the air may be drawn into a measured volume of sterile nutrient agar and the nutrient agar run through a sterile membrane which is incubated. Air sampling tests should be done at planned intervals with standards and locations set up from experience regarding level of contamination permissible (if any).

(ii) Air plates - Plates exposed to air can be nutrient agar or blood agar if pathogens are suspected. Locations of plates should be carefully planned. Exposure is usually one hour or more but should be uniform each time so there can be meaningful comparisons among tests. These tests are useful regarding checking of cleaning and production personnel, air cleaning equipment failure, and human carriers of disease.

(iii) Monitoring of filling equipment - by filling and sealing sterile ampoules with sterile fluid thioglycollate or trypticase soy broth is a more stringent test. The entire lot is incubated. Since this is a total sterility test it is the best indicator of the efficiency of the entire aseptic filling process.

Instrumental methods for particle counts are based on light scattering when beams are passed through an optical system to detect the level of particles present. Consistent results are difficult to get but the methods may be useful for routine monitoring of an environment.

Standards for clean rooms are developed by General Services Administration of the U.S. Government and are based on standard methods developed by A.S.T.M.

(iv) Quarantine area

This is a holding area for products after aseptic filling and/or sterilization pending results of testing etc. before packaging and labelling. There are no specific location requirements but the quarantine area should bear logistical relationship to other areas in the production of sterile products.

(v) Packaging and finishing

After testing is completed and satisfactory the product goes to the finishing area for final labelling and packaging and examination before going to storage and shipping.

Examination includes inspection for:
- Floaters - use black and white background and oblique light.
- Discoloration.
- Imperfect or improper sealing or closures.
- Imperfect containers (with bubbles or deformation).
- Foreign material (e.g. broken glass, dust, dirt, etc.)
- The wrong product (especially a different sized bottle).

b. Production Procedures for Parenterals

(i) Cleaning

Containers and equipment in contact with parenteral products must be scrupulously clean; otherwise all other precautions are useless.

Even new containers and equipment can be contaminated by dust, fibres and chemical films from the atmosphere and human hands, etc.

Previously used containers and equipment require especially thorough cleaning to remove contaminants.

Equipment should be reserved only for parenterals and where required only one type of product.

Selection of cleaning equipment depends on physical types of containers.

Regardless of type of cleaning machine certain fundamental operating characteristics are required:

Internal liquid or air treatment must be introduced directly as a jet stream that strikes the bottom of the inside of the inverted container and spreads in all directions without splashing. The jet stream must flow smoothly down the sides with a sweeping actions and out the opening without accumulating and without turbulence (splashing may fail to clean all areas and turbulence may redeposit loosened dirt).

Outside rinse of the container should occur concurrently.

Treatment cycle should alternate very hot (thermal shock treatment) and cool treatment to loosen debris adhering to the container wall.

Final treatment should be an effective rinse with good quality (filtered) distilled water and optional final filtered air blast.

Metal parts in contact with containers should be of stainless steel (or other noncorroding or noncontaminating material).

Reused containers must have adequate hot detergent treatment at sufficiently high temperature and pressure to remove contaminants from previous use which may be microbiological, pyrogenic, chemical or physical.

Decision to reuse containers must be made only after careful consideration because of difficulty of cleaning.

Rubber closures

(Reference: Bull. Parent. Drug Assoc. 25: 65-67, 1971.)

The problem of washing parenteral closures is of major importance.

Removal of particulate matter is difficult as the mechanical action of cleaning tends to produce small pieces of rubber matter especially if the cleaning cycle is carried too far.

Initial treatment suggested is boiling the stopper in distilled water in a vacuum autoclave. This treatment is considered effective because it breaks the electro-mechanical bond holding dirt on the surface of the rubber.

Subsequent mechanical washing with a hot detergent e.g. 0.5% sodium pyrophosphate is desirable but excessive mechanical action is to be avoided to prevent particles of rubber being produced by abrasion.

Thorough rinsing of the stopper is required to remove not only particles but detergent residue and a spray rinse is preferable.

A check of the cleaning effectiveness can be made by filtering aliquots of the water from each major cleaning step through an 8 um membrane. After drying the membrane a count and visual observation indicates how thorough the cleaning has been. The membranes can be mounted on slides for better observation and to provide a permanent record.

After cleaning the closures are usually sterilized by autoclaving in water of injection aseptically drained and stored in closed containers until used. The water for injection sometimes has a bacteriostatic agent added if used in the final product.

If the closures must be dry for use they may be vacuum-dried at 100°C.

(ii) Machinery for cleaning containers

Cleaning equipment vary in mechanics but all embody good cleaning principles.

Rotary rinser - Jet tubes are arranged on arms like the spokes of wheel which rotates around a centre post through which treatments are introduced. The same operator loads and unloads the containers.

Conveyor rinser - Rows of jet tubes mounted on a conveyor belt move rows of containers past the treatment stations and discharge the clean containers out the end of the machine (usually through a wall into a clean room). Two operators are required.

Cabinet-type washer - A rack of jet tubes is loaded with containers and is pushed inside a cabinet for treatment. Small load but different sized containers can be handled.

Conveyor chain - Chain conveyor drags rows of loaded jet tubes through a long tunnel for various treatments. Clean containers return to loading point for removal. This can process a large number of containers.

Rack-loading washer - This has the advantage of not requiring individual loading. Racks fit into open containers in shipping cartons. The shipping carton and racks are inverted and the containers are transferred to the washer without individual handling.

(iii) Product processing

iiia. Product preparation

- Measurement should wherever possible be made by weight (determine weight experimentally from volume initially if required). Weight is more accurately measured than volume and no adjustments for temperature is required.
- Equipment should be sufficiently dry before use to avoid any significant dilution not accounted for and incompatibility with anhydrous products.
- The order of mixing is important expecially where large volumes require considerable mixing time to become homogeneous.
- pH adjustment may be critical if not conducted gradually, e.g. addition of even a dilute acid too fast may cause excessive local pH reaction and induce adverse and irreversible effects before dispersion throughout the entire volume is complete.

- Parenteral dispersions (e.g. colloids, emulsions, suspensions) require particular care to achieve and maintain proper reduction in particle size under aseptic conditions and keep uniform state of dispersion throughout the entire process (i.e. preparation, transfer, packaging, etc.)
- Formulation of a stable product is of utmost importance, e.g. during terminal sterilization the high autoclave temperature may initiate or acturally complete chemical reactions of constituents.

iiib. Filtration - enhances the impression of high quality e.g. clarity of especially a parenteral solution. It is used to clarify solutions after compounding.
- High degree of filtration is termed "polishing" by removing particulate matter down to 2 um.
- Removal down to 0.2 um eliminates microorganisms and accomplishes "cold" sterilization.
- Filters function by:
  - Sieving or screening, i.e. particles retained on surface of the filter.
  - Entrapment of particles smaller than the pore size of the filter in folds or turns or ledges of the filter (entrapped particles may be forced through if pressure is too high or prolonged.)
  - Electrostatic attraction of particles of opposite charge are adsorbed to the filter surface.
- Filters can cause adverse effects (especially on initial portion of solution) by reacting with constituents in the solution.
- This can be avoided or reduced by conditioning the filter prior to use e.g. neutralizing of alkaline filters with acid.
- Types of filters:
  - Asbestos pad - the most reactive and fibres may get into filtrate.
  - Unglazed porcelain - less reactive; fine particles may come off into filtrate.
  - Sintered glass - less reactive; fine particles may come off into filtrate.
  - Cellulose ester membranes - Millipore, etc. and now more widely used especially for final filtration; less reactive and low shedding of particles.
- Selection of a filter includes such factors as:
  - Flow rate desired (unglazed porcelain and sintered glass are slow).
  - Loss of vehicle by absorption of solution - higher with asbestos and membrane filters.
  - Loss of vehicle by evaporation - higher with slow filtering sintered glass.
  - Cleanability - more important if filter is

to be reused. Fittings that hold and support the filter may be difficult to clean. One type of solution only is recommended to be filtered using the same filter if it is to be reused and cleaning is a problem.

iiic. Filling

General - Filling requires stringent control to avoid contamination of the product when being transferred from "bulk" to final dosage containers.

This especially applies to "aseptic fills" of products previously sterilized by e.g. filtration that will not be sterilized in final containers.

Contamination can come from the environment, equipment and personnel performing the operation. During filling the open container and closures are exposed to contamination until sealed.

For maximum protection filling is done in aseptic filling areas in a laminar flow workbench or under a hood with ultraviolet lights.

Compounded products are usually in liquid or solid forms.

Liquids - are easier to transfer than solids and can be transferred more readily into narrow mouth containers.

Viscous, sticky liquids are more difficult to subdivide and usually require specialized heavy-duty machinery for rapid filling.

All liquid filling equipment has certain characteristics in common, e.g. a repetitive measured quantity is forced through the orifice of a delivery tube into the container. The size of deliver, tube depends on characteristics of the liquid, speed of delivery and inside diameter of container neck.

Delivery tube must enter well into the neck to avoid spillage, have sufficient clearance to permit air to leave the container without blowing the liquid out the neck, and have as large a diameter as possible concomitant with the above to minimize resistance to flow for accurate and rapid filling.

Excess volume is required in delivery apparatus for liquids (see U.S.P. XIX).

For small volume of mobile liquids usually a set stroke of a syringe plunger using a two-way ball valve for alternate filling and delivery is used.

For small volumes of viscous liquids usually stainless steel syringe (for strength) and a sliding piston valve are used.

For short runs hand operation can be used but for a large number of containers an automatic set-up gives faster filling.

For large volume containers filling is usually measured to a given level of fill in the container by gravity, pressure or vacuum using an overflow tube and usually allowing a liberal excess.

To avoid remaining drops of liquid wetting narrow container necks after delivery most delivery systems have a mechanism to draw back the last drop into the delivery tube.

Delivery system in contact with the liquid must be non-reactive material such as boro-silicate glass or stainless steel and easily demountable for cleaning.

Solids - such as sterilie antibiotics in solid form are more difficult to package from bulk to final dosage containers.

The rate of flow of solid material is slow and irregular (better if granulated).

Accuracy of the dosage desired is harder to control than liquids.

Filling is difficult even with large mouthed containers. Spillage is hard to avoid (therefore cross-contamination is a problem).

Wider tolerances are allowed (see U.S.P. XIX) for solid dosage forms.

Individual weighing is the most accurate but very slow.

Granular solids flow more easily and can be filled with automated equipment.

Measurement of the fill is usually by volume corresponding to a given weight.

Equipment used for mechanical filling are of two general types:

- Wheel with adjustable cavities in the rim filled by vacuum until drug is discharged into the containers using sterile air.
- Auger in the stem of a funnel (and fed by a hopper) is fed into a container. Regulated volume can be delivered by controlling the size and speed of rotation of the auger.

iiid. Sealing

Ampoules - are purged with inert gas e.g. nitrogen or carbon dioxide before sealing when sensitive products are filled to prevent decomposition. Ampoules must be sealed as soon as possible after filling to prevent contamination, oxidation or hydration or loss of inert gas. Sealing involves melting the glass neck. Two types of sealing are used: tip-sealing (bead-seals) and pull-sealing.

Tip-seals (bead-seals):
- Made by melting enough glass evenly and all around the tip of the neck to form a bead and close the opening of the ampoule.
- High-temperature gas-oxygen flame used and the heat of the flame and time of heating must be properly adjusted to get complete closing of the ampoule neck.
- Insufficient heat leaves an open capillary through the bead and causes leakers.
- Over-heating expands gases in the ampoule and forms a bubble in the soft bead. If the bubble bursts the seal is broken - if it does not burst the wall of the bubble will be thin and easily broken.

Pull-seals:
- The neck of the ampoule is heated by rotating in a single flame leaving sufficient tip to allow gripping and pulling with forceps or other mechanical device.
- When the glass has softened the tip is pulled quickly while the body of the ampoule continues to rotate and a small capillary tube is formed and twisted closed.

- Pull-sealing is slower but more sure than tip-sealing and usually done by machine.
- Wide-mouthed ampoules (for powders, etc.) must be pull-sealed because the large bead if tip-sealed would cause glass strain resulting in a fracture where the bead and neck wall join.
- Wet necks must be avoided to prevent bubble formation and unsightly carbon deposits from heat of sealing if the product is organic in origin.
- Wet necks tend to fracture when heated during sealing.

Vials and bottles - are sealed with rubber stoppers or closures. The larger opening of vials and bottles make it imperative that sealing is done quickly and carefully after filling to prevent contamination of the product. Containers should be protected from contamination during filling and sealing with covers or preferably within a closed hood in an aseptic area.

Rubber stoppers must be:
- Elastic enough to completely seal any slight irregularities of the lip and neck of the container.
- Firm enough to seal snugly and stay in place.
- Sized properly to avoid difficulty when being inserted into the neck of the container and yet seal well.
- Stoppers can be inserted (always under aseptic conditions) directly by hand using sterile gloves with sterile forceps or mechanically by a sorting and stoppering device for high speed production by means of a tool connected to a vacuum line operated by hand using sterile gloves.

Aluminum caps are used to hold the rubber stoppers in place. The caps are crimped under the lip of the vial or bottle to hold the stoppers firmly in place. The closure or stopper cannot be removed without destroying the aluminum cap; therefore intact cap is proof of unopened container.

The inner aluminum cap consists of an aluminum band with open centre. This holds the closure in place after crimping. The inner cap allows withdrawal of the contents of the container (e.g. multiple-dose vials) with a hypodermic syringe or intravenous needle without removing the stopper which protects the contents from exposure to the atmosphere.

The outer aluminum cap covers the inner cap and the usual set-ups found are:
- A single layered cap with "tear-off" centre.
- Double layered caps with the outer cap having a "tear-off" centre.
- Triple-layered caps (e.g. for intravenous solutions) in which the rubber closure has a permanent hole protected by a thin rubber disk overlaid with a solid aluminum disk, which are sandwiched between the inner and outer aluminum caps.

A hand crimper can be used for single-layered aluminum caps. Double or triple-layered caps require mechanical crimpers which can apply more force. The capping components are usually put over the rubber stopper as a combined unit and one crimping operation is performed.

iiie. Sterilization

- is defined as the inactivation or removal of all viable organisms.

General - Preferably parenteral products should be sterilized in their final containers (terminal sterilization) immediately after sealing but terminal sterilization usually involves a thermal process which may adversely affect many pharmaceutical and biological products by the elevated temperatures required. For these thermolabile products a nonthermal process must be used such as filtration, radiation, gaseous ethylene oxide, etc. Filtration is widely used for many thermolabile liquids and oleaginous solutions but aseptic conditions are required at each processing stage and these are difficult to maintain.

Sterilization methods

Steam under pressure (autoclaving).
Saturated steam under pressure is one of the most reliable and widely used methods for aqueous liquids or substances that can be reached or penetrated by steam. It is ineffective for anhydrous oils or anhydrous conditions such as dry solids sealed in ampoules. Moist heat sterilizes by coagulating proteins in the microbial cells.

It is essential that entrained and entrapped air is removed from the autoclave or proper

temperature cannot be attained. Recent techniques for this provide for a pulsing system using alternate vacuum and steam purging, or evacuation to 15 mm Hg within 4 minutes before steaming.

Normal cycle is for the liquid product to be autoclaved at 121°C (250°F) for 15 minutes after the exhaust is at 121°C. For large bottles or large loads a longer cycle would be needed depending on the time required for the centre of the liquid to reach 121°C (and be maintained for 15 minutes).

For products that can withstand a higher temperature for a short time one can use a high-vacuum high-pressure cycle e.g. 135°C (275°F) for 3 minutes instead of 121°C for 15 minutes.

Modern autoclaves may be obtained with a variety of controls that can be pre-set, e.g. thermocouples at various locations in the autoclave; automatic times to control the time of sterilizaiton after the proper temperature is reached and automatically terminate the sterilizing period; controlled slow or fast exhaust depending on the type of load, i.e. slow exhaust for full bottles of liquid that could overflow if the pressure were suddenly reduced. Some autoclaves employ water-cooled jackets for faster cool-down.

Dry heat - Also see Appendix II. Dry heat kills microorganisms primarily by an oxidation process. It is used for materials that cannot withstand moist heat such as dry glassware, petroleum jelly, mineral oil, greases, waxes, talcum powder, etc.

For parenteral use the main applications would be for sterile powders not adversely affected by the high temperature and long heating period required; and associated glassware and metalware (e.g. hypodermic needles and glass syringes).

Various time-temperature combinations are used depending on the material being sterilized and some examples would be:

- 170°C (340°F) for 1 hour (glassware, etc.)
- 160°C (320°F) for 1 or 2 hours (peanut oil solutions - 2 hours)
- 150°C (300°F) for 2½ hours
- 140°C (285°F) for 3 hours
- 125°C (257°F) for up to 24 hours (sulfonamides).

Filtration - is a means of sterilizing solutions that cannot be heated. Aseptic techniques are required. Several types of bacterial filters are available including: Leitz filters, porcelain filters, and membrane filters.

Leitz filters - asbestos pad type of filter.
- Available in sizes ranging from the small Swinny filter to large plate type filter.
- Leitz pads are available in several porosities and are relatively inexpensive sc new pads are used each time.
- One disadvantage is that fibres may get in the solution unless the filter is backed by nylon mesh or sintered stainless steel.
- Models are available for either vacuum or pressure operation.
- The asbestos pad is the most reactive filter and may adsorb some pharmaceuticals and have adverse effects.

Porcelain filters - unglazed porcelain.
- All porcelain types are useful where metallic contact might damage the product.
- One disadvantage is that they become plugged with microorganisms and debris and must be cleaned with strong acid or burned out at high temperatures which can change the pore size.
- Another disadvantage is that the severe cleaning methods especially high temperatures can result in shedding of fine particles after repeated cycles and contaminate the product.
- Porcelain filters should be checked for efficacy from time to time using a test organism (e.g. Serratia marcescens) easily identified.

Membrane filters - commonly of cellulose and cellulose derivatives (e.g. cellulose ester).
- Ultrafiltration using membrane filtration has become increasingly popular in recent years due to improvement and refinement of the various membranes.
- Large number of pore size grades are available from 8 um down to 0.22 um.
- Liquid to be sterilized is forced through the membrane filter by vacuum, pressure or centrifuging. Approximately 80% of filter volume is composed of the pores. Therefore the filter acts primarily as a simple screen and retains all particles whose size exceeds the filter pore size.

- Combined forces of gravity and van der Waals forces (effects of both volume occupied by and attractive force between molecules) cause particles to adhere to the filter in a single microscopic plane with little overlapping.

- Membrane filters allow a flow rate 40 times faster than other filters having the same pore size but obviously can be clogged by an excess amount of particles in the solution.

- Membrane filters are generally less reactive and have lower shedding of fibres than other types of filters.

- Newer types of membranes available which can withstand alcohols, reactive monomers, strong acids and alkalis with only 15% to 25% swelling and no loss of filtration efficiency extend their usefulness.

- Sterilization can be by autoclaving or dry heat such as at 200°C.

- Membranes tend to be thin and brittle.

- Supporting filter holders available include stainless steel screens, silver screens, glazed porcelain, porous carbon discs, sintered glass, porous earthenware, etc.

Gas sterilization - Various gases have germicidal properties. For parenterals the chief usage is ethylene oxide, for antibiotics and associated equipment such as plastic bottles, etc.

Ethylene oxide penetrates dry materials quite well but has limited ability to penetrate and diffuse in liquids except for a shallow layer.

Ethylene oxide in air is highly explosive but in a mixture of 10% with 90% carbon dioxide it is not combustible. (Carboxide is the commercial name of the mixture.)

It is essential to aerate treated material for at least 5 days at room remperature to detoxify (under aseptic protection of course).

Radiation - is generally classified into two types:

- Electromagnetic radiation e.g. UV, gamma, X-rays, cosmic rays. These are photons of energy (gamma and X-rays produce indirect ionizing radiation).

- Particulate radiation .g. electrons, beta particles, etc., also known as corpuscular radiation (producing direct ionizing radiation).

Electromagnetic radiation

Ultraviolet

- Non-ionizing and main disadvantage is limited penetrability (the 254 nm wavelength is screened out by most materials).

- UV light is germicidal at 254 nm and has been used for 30 years for destroying microorganisms.

- Principal use of UV - maintaining sterility of aseptic areas rather than sterilization purposes.

- Inactivation by UV is a function of radiant energy dose, i.e. application of an effective radiation intensity over a proper interval of time.

- Dose requirements vary widely for microorganisms e.g. vegetative bacteria are most susceptible.

- Bacterial spores more resistant by 3 to 10 fold than vegetative bacteria (e.g. 800 uW-min/cm^2 for inactivation).

- Fungal spores are 100 to 1000 times more resistant than vegetative bacteria (e.g. 5000 uW-min/cm^2 required to inactivate Aspergillus niger spores).

- Clean UV lamps are essential (clean periodically with alcohol and test output).

- Germicidal UV requires protection for exposed personnel and eye protection is particularly important.

- It is generally stated that 20 uW/cm^2 of UV radiation is required for effective antibacterial activity.

Gamma rays

- Considered electromagnetic and produce ionizing

radiation indirectly by ejection of orbital electrons.

- Main source of gamma rays is radioisotopes such as cobalt 60 and cesium 137.

- Cobalt 60 is the source most used by pharmaceutical and medical devices firms for radiosterilization.

X-Rays

- Also electromagnetic and produce ionizing radiation indirectly.

Particulate radiation

- Beta particles and electrons are the best known particulate or corpuscular radiation sources and are generally produced in the linear accelerator.

- They are charged particles that interact directly with matter giving direct ionizing radiation and in general penetrate better than UV radiation.

Miscellaneous radiation facts

- High energy radiation is thought to affect organisms either by the formation of free radicals or changing a vital cell structure such as chromosomal nucleoprotein and probably is a combination of both these effects causing complete and irreversible inactivation of the microorganisms.

- The unit of radiation dosage most recently used is the rad arbitrarily defined as 100 ergs/g absorption. Sterilization dosages are usually given in megarads.

- 2.4 megarads is sufficient to kill the most resistant microorganisms with an adequate safety factor under most conditions. Vegetative forms are the most sensitive to radiation followed by molds, yeasts, spore-formers, and viruses in decreasing order of sensitivity.

- Ionizing radiation has been successfully used to sterilize hospital supplies, vitamins, antibiotics, steroids, hormones, bone and tissue transplants and medical devices such as plastic syringes, needles, surgical blades, plastic tubing, catheters, prostheses, petri dishes and sutures.

- Ionizing radiation is effective but the main disadvantage is presently the high cost of equipment and its installation.

- The intensity of ionization (specific ionization) is a function of linear energy transfer (LET).

- LET is defined as the energy lost/um of path of the ionizing particle.

Alternate methods of sterilization - Also known as marginal methods of sterilization:

Fractional sterilization or "Tyndallization"

- Used for substances e.g. nutritive, without bacteriostatic or inhibiting agents that cannot tolerate dry heat or steam autoclaving etc. and cannot be filtered.

- The procedure involves the following process carried out on 3 successive days:

  1. Heat in free-flowing steam for 1 hour to kill vegetative bacteria.
  2. Place in incubator so bacterial spores can germinate.
  3. Repeat (1).

Heating with a chemical agent to some temperature below 100°C.

- Use spores in similar containers as indicators (which are subsequently incubated to test for growth) to establish the time and temperature required for sterilization.

Boiling

- No longer an acceptable method for sterilizing since it does not kill all spores.

- Instruments, hypodermic syringes and needles can be rendered aseptic but if spores are present sterility is not guaranteed.

Direct flame

- A minimum of 20 seconds sterilizes (by incineration of microorganisms) such items as: forceps, needles, metal spatulas, etc.; also lips of beakers, flasks, test tubes, etc.

- Disadvantages include local overheating which may break glassware and destroy the temper of metallic instruments.

- Direct flame also used to sterilize (incinerate) contaminated material e.g. cotton swabs and pledgets, inoculating loops used in transferring bacterial cultures.

- Not to be used to sterilize greasy oily materials or tubercular swabs as spattering may spread rather than eliminate contamination.

Sterilization indicators

Chemical

- Some are small melting-point tubes that may indicate the temperature reached but not the length of time at that temperature.

- More satisfactory are those that indicate by progressive colour change that both the time and temperature of sterilization was satisfactory (e.g. made with chromate solution).

Biological

- Some biological indicators also incorporate a chemical indicator.

- Biological indicators make use of prepared bacterial spores.

- Bacillus stearothermophilus spores are the most adequate indicators of steam sterilization and are now widely used. It is an obligate thermophile that will not grow at 30-35°C but grows at 55-65°C. It is nonpathogenic, nontoxic, nonpyrogenic and therefore aesthetically acceptable.

- Other spore-formers used include Bacillus subtilis var. niger (Bacillus globigii) for wet and dry heat and ethylene oxide sterilization; B. pumilus and Streptococcus faecium for radiation; Clostridium novyi for catgut and Clostridium sporogenes for canning.

iiif. Freeze-Drying (Lyophilization)

The basis of this process is due to the fact that ice will sublime at pressures below 3 mm Hg.

Essentially freeze-drying steps involve:

- Freezing an aqueous product at a temperature below its eutectic temperature (i.e. below the lowest melting point of the mixture);

- Evacuating the chamber to 0.1 mm Hg or lower;

- Subliming ice on a condensing surface colder than the product in the same or a connecting chamber;

- Heating the product (with controlled conditions) sufficiently to sublime the product but still keep it under its eutectic temperature.

Advantages of freeze-drying include:

- Biologicals and pharmaceuticals usually unstable in aqueous solution can be processed using the advantages of handling liquids, dried without adverse thermal effects of high temperature, and stored in a relatively stable state.

- Freeze-dried products often are more soluble or dissolve faster.

- Dispersions are more stable throughout their shelf life.

- Products degraded by oxidation have improved stability since the process is carried out under vacuum.

Disadvantages of freeze-drying:

- Increased time (a slow process) and handling are required.

- Specialized equipment are of high cost.

- Maintenance of aseptic conditions during processing and sealing after drying is essential (slotted rubber closures are helpful as they can be sealed in the chamber while still under vacuum and the product is protected from subsequent exposure to outside air).

3. Quality Control

a. Sterility Test

For details please see USP XIX or BP 1973. In general sterility testing should be conducted by suitably qualified and experienced personnel.

The use of laminar flow hoods is strongly suggested to avoid "false positive" and protection of personnel and other plant areas from contamination and/or cross-contamination. A separate area is required, i.e. not part of parenteral processing area.

Membrane filtration used in sterility testing as per USP XIX gives more reliability in products which are expected to have extremely low bacterial count or none.

b. Pyrogen Test

For details please see USP XIX. Rabbits are used as the test animals since they show a physiological response to pyrogenic substances similar to that of humans.

Pyrogen testing is usually performed on vehicles since medicinal ingredients may have pharmacological effects that mask a fever response in the test animal or cause a spurious pyrogenic response.

Temperature recording devices and thermocouples should be checked and calibrated on a fixed routine schedule.

c. Clarity Test

Visible "dirt" is not only aesthetically undesirable but indicates the presence of particulate matter that could cause serious harm to the circulatory system and vital organs of man and animals.

Inspection is usally perfomed by trained inspectors using good light baffled against reflection into the eye against a black and a white background to reveal light and dark matter respectively. Frequent changes or rests for the inspectors are required to prevent eye fatigue and subsequent reduced efficiency.

Particles as small as 10 um can be seen due to light scattering (Tyndall effect) by a trained inspector (50 um is the limit for the unaided eye).

It has been stated that a maximum of 5 um should be strived for since erythrocytes have a diameter of 4.5 um but mechanical scanning (e.g. Coulter or another particle counter) would be required for this.

Microscopic examination following collection of sample on a membrane filter can yield both count and identification. This requires care and experience but is useful in detecting contamination sources or failure of filtering apparatus.

d. Leaker Test

This is conducted on glass ampoules to detect imprefect "bead-seals" or "pull-seals". The test is usually done with the ampoules submerged in a coloured dye, e.g. 1% methylene blue, solution under negative pressure in a vacuum chamber. After thoroughly rinsing the dye solution off the outside the dye will be visible inside a leaker which is discarded.

Vials and bottles are not given a leaker test since the rubber closures are not meant to withstand such a test.

4. Packaging and Labelling

This aspect is a part of standard good manufacturing facilities and controls.

STERILIZATION SCHEDULE

EQUIPMENT	METHOD	PRE-VACUUM (Min)	TEMP. (°C)	TIME (Min)	POST-VACUUM* (Min)	MAXIMUM STORAGE	WRAPPING
Aluminum Foil	Autoclave	5	121	30	30	72 h	Kraft Pape
	Dry Heat	—	250	60	—	72	Stainless Steel Con
Ampoules	Dry Heat	—	250	60	—	24	S.Steel T
Bags, Dacron	Autoclave	5	121	30	90	72	S.S. Container
Basket, Centrifuge	Autoclave	5	121	60	30	72	Kraft Pape
Beakers, Stainless Steel	Autoclave	5	121	45	30	72	Kraft Pape or S.S.
Blow Tank, S.S. with Bottom Valve & Tubing	Autoclave	5	121	45	30	72	Kraft Pape
Bottles (2½, 5, and 12 gal)	Dry Heat	—	250	60	—	24**	Alum. Foil
Bottles, Infusion	Dry Heat	—	250	60	—	72	Alum. Foil
Bottles, Mayonnaise Type	Dry Heat	—	250	60	—	24**	Alum. Foil
Bottles, Sampling	Autoclave	5	121	30	30	48	Kraft Pape
Brewer Machine Assembly	Autoclave	5	121	45	30	72	S.S. Containers
Bulk Bottle Caps	Autoclave	5	121	60	30	72	S.S. Containers
Bulk Trays	Dry Heat	—	250	60	—	72	—
Burettes	Autoclave	5	121	30	30	72	S.S. Cans or Kraft Paper
Cans, Blend	Dry Heat	—	250	60	—	24	Alum. Foil
Caps (Mayonnaise Type Bottle)	Autoclave	5	121	30	30	24	S.S. Containers
Caps, Dispensing	Autoclave	5	121	30	30	72	S.S. Containers
Caps, Glass	Autoclave	5	121	30	30	72	Kraft Pape

*Follow by drying in oven at 105°C for 30 minutes if necessary.
**Prior to capping or stoppering.

STERILIZATION SCHEDULE (Cont'd)

EQUIPMENT	METHOD	PRE-VACUUM (Min)	TEMP. (°C)	TIME (Min)	POST-VACUUM* (Min)	MAXIMUM STORAGE	WRAPPING
Centrifuge Basket	Autoclave	5	121	45	30	72 h	S.S. Containers
Connecting Lines	Autoclave	5	121	45	30	72	S.S. Containers
Covers, Dacron, Cotton, Glass, or S.S.	Autoclave	5	121	45	30	1 wk	Kraft Pape
Cylinder, Graduated	Autoclave	5	121	30	30	72 h	Kraft Pape
Dispensers	Autoclave	5	121	45	30	72	—
Dispensing Caps	Dry Heat	—	170	60	—	72	S.S. Containers
Eye Dropppers	Autoclave	5	121	30	30**	24	S.S. Trays
Filter Pots	Autoclave	5	121	45	30	72	Kraft Pape
Filter Press	Autoclave	5	121	45	30	72	Kraft Pape
Filter, Cambridge (Micro-atomizer)	Autoclave	5	121	90	30	72	Kraft Pape
Filters, Sintered glass, porcelain, asbestos, etc.	Autoclave	5	121	30	30	72	Kraft Pape
Funnels, S.S.	Dry Heat	—	250	60	—	72	S.S. Container
Gaskets	Autoclave	5	121	30	30	72	S.S. Container
Glassine Paper	Autoclave	5	121	30	30	72***	S.S. Container
Gloves, Rubber	Autoclave	5	121	15	30	4 d	Glove Pocket
Homogenizer	Autoclave	5	121	30	45	72 h	Kraft Pape
Hopper, Accofil or Die Wheel	Dry Heat	—	170	60	—	72	S.S. Container
Kettles							
First Run	Autoclave	5	121	15	—	0	Alum. Foil
Second Run	Autoclave	5	121	60	30	72	Alum. Foil

*Follow by drying in oven at 105°C for 30 minutes if necessary.
**Follow by drying in oven at 105°C for 2 hours.
***Not to be resterilized.

STERILIZATION SCHEDULE (Cont'd)

EQUIPMENT	METHOD	PRE-VACUUM (Min)	TEMP. (°C)	TIME (Min)	POST-VACUUM* (Min)	MAXIMUM STORAGE	WRAPPING
Knife	Autoclave	5	121	30	45	72 h	Kraft Paper
Mortar & Pestle	Autoclave	5	121	30	30	72	Kraft Paper
Petri Dishes	Dry Heat	—	170	60	—	72	Canister
Pipes, S.S.	Dry Heat	—	250	60	—	72	Alum. Foil
Pipettes	Dry Heat	—	170	60	—	72	Kraft Paper
Powder, Talcum	Dry Heat	—	170	2 h	—	8 d	Talcum Can.
Recrystalliz. Equipment	Autoclave	5	121	60 min	30	72 h	Kraft Paper
Scoops, S.S.	Dry Heat	—	250	60	—	72	Any
	Autoclave	5	121	30	30	72	
Screens, S.S.	Autoclave	5	121	30	30	72	Kraft Paper
Spatula	Autoclave	5	121	30	45	72	Kraft Paper
Stoppers, Rubber, Dry	Autoclave	5	121	30	30 + 2 h at 105°C Dry Heat	72	S.S. Container
Stoppers, Rubber, Wet	Autoclave	5	121	30	—	24	S.S. Container
Syringes	Autoclave	5	121	45	30	72	S.S. Cont. & K. Paper
Tank, Blow	Autoclave	—	121	45	—	72	Alum. Foil
Tank, Holding	Autoclave	5	121	60	30	72	Alum. Foil & K. Paper
Tank, Seed	Autoclave	5	121	45	30	72	Alum. Foil & K. Paper
Test Tubes	Autoclave	5	121	30	30	72	Cotton Plug & K. Paper
Towels, Wrapped	Autoclave	5	121	30	30	72	Kraft Paper
Towels, Unwrapped	Autoclave	5	121	30	30	72	—
Trays, Bulk	Dry Heat	—	250	60	—	72	S.S. Container
Tubing, Rubber	Autoclave	5	121	30	30	72	Kraft Paper
Vials	Dry Heat	—	250	60	—	24	S.S. Trays

*Follow by drying in oven at 105°C for 30 minutes if necessary.

STERILIZATION SCHEDULE (Cont'd)

EQUIPMENT	METHOD	PRE-VACUUM (Min)	TEMP. (°C)	TIME	POST-VACUUM (Min)	MAXIMUM STORAGE	WRAPPING
VEHICLES							
Tween #20 in 50 ml Vials	Autoclave	5	121	30 min	—	48 h	Cotton or Urethane Plugs and Kraft Paper Hoods
Water - to 500 ml Volume	Autoclave	5	121	30 min	—	48	
Water - 500 to 5000 ml	Autoclave	5	121	1 h	—	48	
Water - 5 to 20 liters	Autoclave	5	121	2 h	—	48	
PRODUCTS							
Procaine HCl	Dry Heat	—	120*	8 h	—	Indefinite	
Polyvinyl Pyrrolidone	Dry Heat	—	120 60	2 h 8	—	Indefinite	
Sodium Carboxy-methyl Cellulose	Dry Heat	—	150*	2 h	—	Indefinite	
Sodium Citrate	Dry Heat	—	150*	2 h	—	Indefinite	
Sodium Hydroxide in 100-500 ml	Autoclave	5	121	1 h	—	Indefinite	
Fat Emulsion	Autoclave	5	121	30 min	—	Indefinite	

*Check with thermocouple.

Appendix III

MASTER FORMULATIONS (SPECIMEN ONLY; NO WORKING FORMULATIONS)

Manufacturing Work Order ☐

Formulated by Mr. X, B.Sc.

Checked by Mr. Y, B.Sc.

A. Product Benzalide Cold Anti-Rust Germicidal Solution Concentrate

Amendment _____ Dated _____

Lot No. _____ Quantity: Theoretical 90 gallons / 409.05 litres % Deviation ±5%

Issued by _____ Actual Yield _____

All Equipment Checked for Cleanliness by _____

Manufacture Started _____

Manufacture Ended _____

	RAW MATERIAL	LOT NO.	WEIGHT Metric	WEIGHT Avoir lb-oz-gr	WB[1]	CB[2]	AB[3]	MC[4]
1	Hyamine 3500 Benzalkonium Chloride 50%		16.330 kg	36-0-0		2b / 2a		
2	Sodium Nitrite USP		8.165 kg	18-0-0				
3	Methylene Blue USP		1.166]	0-0-18				
4	Isopropyl Alcohol USP		67.734 ℓ	14 gal 144 fl.oz.				
5	Distilled Water USP to produce		409.050 ℓ	90 gallons				
	Total Theoretical Yield							

Total Actual BULK Yield _____ % Deviation 5

Total Actual FINISHED PRODUCT Yield _____ % Deviation 5

Special Instructions:

1. Keep drums of in-process materials tightly closed and away from light.
2. Make sure all containers and equipment are clearly identified by lot.

Manufacturing Instructions:

1. Dissolve Item 3 in Item 4 in 50 litre stainless steel dixie. _____
2. Dissolve Item 2 in 20 gallons of water in 125 gallon polyethylene tank. _____
3. Add Step 1 to same tank and mix for 10 minutes. _____
4. Add Item 1 while mixing with hand paddle. _____
5. Add sufficient water to bring to 90 gallon volume and mix for 15 minutes with tank covered. _____
6. Filter and package. _____

(WB^1_{2a} - Initials of person weighing material;
CB^{2a}_3 - Initials of person checking the weighing;
AB^3_{2b} - Initials of person adding material to bulk batch;
CB^{2b}_3 - Initials of person witnessing addition to batch;
MC^3 - Material cost (for accounting purposes).)

Processing Completed: _____ Sampled by Q.C.: _____

CLEAN EQUIPMENT as per Instructions at End of Run: _____ Checked by: _____

Released for Packaging: _____ Date: _____

Quality Control Department

Manufacturing Work Order ☐
Formulated by _____
Checked by _____
Amendment _____ Dated _____

3. Product C.T. Biosulkol S.A.

Lot No. _____ Quantity: Theoretical 35,500 tabs ±2%
Actual _____ % Dev. _____

Issued by _____
All Equipment Checked for Cleanliness by _____

Manufacture Started _____
Manufacture Ended _____

	RAW MATERIAL	LOT NO.	WEIGHT Metric	WEIGHT Avoir lb-oz-gr	WB*	CB*	AB*	MC*
1	Phthylsulfacetamide NF		5783.4 g	12-12-0				
2	Sulfaguanidine BPC		5783.4 g	12-12-0				
3	Sulfathiazole BPC		2296.35 g	5-1-0				
4	Kaolin (Colloidal) NF		4613.95 g	10-2-328				
5	F.D. & C. Lake #5		119.0 g	0-4-85				
6	Starch USP		368.55 g	0-13-0				
7	Distilled Water USP		3693 ml	130 fl. oz				
8	Dried Wt Potassium Chloride USP		2268.0 g	5-0-0				
**9	Streptomycin Base = Streptomycin Sulphate BP		1000 g	2-3-119				
10	Pectin NF		2268 g	5-0-0				
11	Starch USP		609.54 g	1-5-219				
12	Sterotex HS		226.8 g	0-8-0				
13	Magnesium Stearate BP		56.7 g	0-2-0				
	Total Theoretical Yield		25,393.69 g	55-15-315				

**Weight adjusted based on actual quality control assay results of raw material.

Total Actual BULK Yield _____ % Deviation _____
Total Actual FINISHED PRODUCT Yield _____ % Deviation _____

Special Instructions:
1. Keep drums of in-process materials tightly closed and away from light.
2. Make sure all containers and equipment are clearly identified by lot.

Manufacturing Instructions:
1. Place 1, 2, 3, 4, and 5 in ribbon blender and mix for 10 min at reg. speed. ____
2. Add 10% starch paste and mix at reg. speed for 10 min. _____
3. Pass through No. 4 screen, place on paper lined trays in the drier at 40°C for 24 hours. _____
4. Screen through 12 mesh into tared container and weigh _____ Gross _____ Tare _____ Net _____
5. Screen 8 and 10 through No. 12 mesh, 9 through No. 24 mesh and add Items 11, 12, and 13 to Step 3. Mix in ribbon blender. Blend at reg. speed 10 min. _
6. Tablet on stokes single using ½ inch Standard Concave Punch and Die.
   Thickness: 0.215" ±5%
   Hardness: 2-4 kg
   Disintegration: Less than 30 min.
   Tablet Weight: 11.0388 grains ±5%; or 715.315 mg ±5%

Processing Completed: _____ Sampled by Q.C.: _____
CLEAN EQUIPMENT as per Instructions at End of Run: _____ Checked by: _____
Released for Packaging: _____ Date: _____
Quality Control Department

*See explanation on page

Manufacturing Work Order ☐

Formulated by Mr. X, B.Sc.

Checked by Mr. Y, B.Sc.

C. Product *Hydrocortisone Ointment 0.5% with Neomycin* Amendment _____ Dated _____

Lot No. _____ Quantity: Theoretical 59-15-239 % Deviation 5

Actual _____

Issued by _____

All Equipment Checked for Cleanliness by _____

Manufacture Started _____

Manufacture Ended _____

	RAW MATERIAL	LOT NO.	WEIGHT Metric	Avoir lb-oz-gr	WB*	CB*	AB*	MC*
1	White Petrolatum USP		18378.5565 g	40-8-119.7				
2	Mineral Oil Heavy USP		7722.0864 g	17-0-168				
3	Paraffin Wax USP		555.9775 g	1-3-267.4				
4	Aracel-C Atlas		272.403 g	0-9-266				
5	Hydrocortisone USP		136.2132 g	0-4-352				
6	Neomycin Base USP + 14% overage		108.983 g	0-3-369.3				
7								
8								
9								
10								
11								
12								
13								
	Total Theoretical Yield		27,203.1372 g	59-15-239	MC/G x4			

*See explanation in Appendix 3A.

Actual BULK Yield _____ % Deviation _____

Actual FINISHED PRODUCT Yield _____ % Deviation _____

Special Instructions: 1. Keep all bulk containers tightly closed.
2. Store all materials in light resistant containers, in cool dry place.
3. Personnel to wear protective heat resistant gloves and eyeglasses in case hot waxes splash.

Manufacturing Instructions:

1. Place Items 1, 2, and 3 in a 100 litre stainless steel steam jacketed kettle with Lightning No. 2 agitator.
2. Apply steam until temperature reaches 90°C and all ingredients melted.
3. Start agitator and mix ingredients at regular speed for 15 min while maintaining temperature at 90°C.
4. While mixing, add Item 4 and agitate for an additional 5 min at 90°C.
5. Reduce heat to 70°C and add Items 5 and 6 and continue mixing for 10 min.

Processing Completed: _____ Sampled by Q.C.: _____

CLEAN EQUIPMENT as per Instructions at End of Run: _____ Checked by: _____

Released for Packaging: _____ Date: _____

Quality Control Department

Appendix IV

SPECIMEN OF PACKAGING SPECIFICATION CARD

PACKAGING ORDER

Prepared by_____ Date_____
Checked by_____ Date_____

Date Packaging Started_____ Bulk Quantity_____

Product_____ Lot No._____

Supplied by_____

% Deviation_____ Special Precautions_____

SPECIFICATION	UNIT SIZE				UNIT QUANTITY ISSUED				ADDITION ISSUED
Container Size									
Tube and Colour									
Dessicator									
Filler - Cotton									
Cello									
Cap and Liner									
Celloseal									
Label - Front *									
Side *									
Shipping Label									
Brochures									
	ACTUAL YIELD								

Warning Stickers*_____ Price Stickers_____ % Loss/Gain_____

Boxes_____ Labelled_____ Printed_____ No. of Labels Destroyed_____

Size of Boxes_____ Brochures*_____ No. of Finished Product Units Damaged or Destroyed_____

Group Wrapping_____ Promotional Literature_____ No. of Units Sampled by Q.C._____

Special Additions_____

Shipping Carton: Size_____ Number_____ Released by:

Carton Labelled_____ Lot No._____

_____
Signature, Manager of Q.C.

Special Packing Instructions_____

_____
Date

Special Storage Instructions_____

Special Shipping Instructions_____

_____

Date Entered Inventory_____ Date First Shipment Made_____
Amount Received by Warehouse_____
Signature of Receiver_____ Date Last Shipment Made_____

*Samples attached to the back of this packaging order.

Appendix 7

IN-PROCESS QUALITY CONTROL SPECIFICATION AND TEST SPECIMEN DOCUMENT

Master prepared by _____
Checked by _____
Amendment No. _____ Date _____

Product _____ Lot No. _____

Theoretical Quantity _____ Date _____ Issued by _____

Date

SPECIFICATIONS

TEST	Report Results as Average of:	FREQUENCY OF TESTING		THEORETICAL DEVIATION	ACTUAL DEV.
		Production	Q.		
Average Weight	10 tablets	Every 15 min	Every 2 hours		
Hardness	5 tablets	Every 15 min	Every 2 hours		
Mean Tablet Thickness	5 tablets	———	Every hour		
Disintegration (Compendial Standard)	6 tablets	———			
Disintegration (Company Standard)	6 tablets	———			

TEST RESULTS

No.	Time	Average Weight	By	Hardness	By	Mean Tablet Thickness	By	DISINTEGRATION Compendial	By	Company	By
1											
2											
3											
4											
5											
6											
7											
8											
9											
10											
11											
12											
13											
14											
15											
16											
17											
18											
19											
20											
21											
22											
23											
24											
Mean Value											

Appendix VI

RAW MATERIAL SPECIFICATION AND TEST SPECIMEN DOCUMENT

OUR LOT _____

CERTIFICATE OF ANALYSIS

SUPPLIER LOT _____

RAW MATERIAL (OUR NAME) _____

FIRST SUPPLIER _____ OUR STANDARD _____

SECOND SUPPLIER _____ OTHER STANDARD _____

TESTS	SPECIFICATIONS	RESULTS
APPEARANCE		
ODOUR		
SOLUBILITY		
IDENTITY		
MELTING POINT ° C.		
LOSS ON DRYING/WATER		
RESIDUE ON IGNITION		
PH/ACIDITY/ALKALINITY		
HEAVY METALS		
I R SCAN		
CHLORIDE		
SULFATE		
1. MICROBIAL LIMITS		
2. OPTICAL ROTATION		

ASSAY REFERENCE

ASSAY LIMITS

STORAGE INSTRUCTIONS

CATEGORY ☐ RELEASED ☐ REJECTED

APPROVALS Control Chemist _____ Q.A. Manager _____

Date _____ Date _____

Appendix VII

FINISHED PRODUCT SPECIFICATION AND TEST SPECIMEN DOCUMENT

Product: Date:

Supplier: House Lot No.:

Appearance: Supplier's Lot:

Expiry Date:

Identification: (Bulk and Final Product Dosage Form) Method:

ASSAY:

Ingredient (s)	Label Claim	Assay Results	Percent Limits	Percent Claim	Method Used

CONTENT UNIFORMITY:

Run Number	Label Claim	Assay Results	Limits
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			

DISSOLUTION:

Run Number	%Claim	Limits
1		
2		
3		
4		
5		
6		

Mean Disintegration (Food & Drug):_____ Average Weight(Gross) (Net)

Mean Disintegration (Compendial_____/House:_____ Hardness: _____

Weight Variation: _____ Mean Tablet Thickness: _____

Other Tests: House/Compendial

Date Released for Packaging_____Finished Product For Sale _____ Released to Warehouse_____

_____ _____

Manager, Quality Control Vice-President, Quality Control

Appendix VIII

FINISHED PRODUCT PERMANENT SPECIFICATION DOCUMENT

Label Sample

PRODUCT _____

SUPPLIER _____

A-TABLETS or CAPSULES

APPEARANCE _____

SIZE _____

THEORETICAL WEIGHT _____

WEIGHT VARIATION _____

DISINTEGRATION _____

DISSOLUTION _____

CONTENT UNIFORMITY _____

HARDNESS LIMITS _____

B-LIQUIDS, INJECTIONS & OINTMENTS

APPEARANCE _____

SPECIFIC GRAVITY _____ R-OH CONTENT _____

PH _____ TOTAL SOLIDS _____

STERILITY _____ PYROGENS _____

EXPIRATION DATE (if required) _____

STABILITY TESTS _____

WARNINGS _____

STORAGE _____

OTHER INTRUCTIONS _____

Gum Label Here

INGREDIENTS ASSAYED	LABEL CLAIM	ADDED OVERAGE	% LIMITS	ASSAY METHOD	IDENTIFICATION METHOD

Appendix IX

LABEL REVIEW SPECIFICATION

SAMPLE TO PRINTER

FINISHED LABEL RECEIVED FROM PRINTER

Product:-

LABEL CHECK LIST

☐	Name & Dosage: Main Panel	☐
☐	Pharmacological Classification: Side Panel	☐
☐	Standard: NF, USP, BP, CF, DS, Other - Main Panel	☐
☐	Lot No.: Side Panel	☐
☐	Content: Side Panel	☐
☐	Exp. Date: USP, DS, Vitamins - Side Panel	☐
☐	DIN: Main Panel	☐
☐	Caution or Warning: Main Panel	☐
☐	Dose & Route of Administration; Oral, Parental, Rectal, External, Sublingual - Side Panel	☐
☐	Symbols: Pr, N, C, Blank - Main Panes	☐
☐	Contraindications & Indications: Side or Main Panels	☐
☐	Prescribing Information: Side Panel	☐
☐	Storage: Side Panel	☐
☐	Vitamin Minimums: If in Excess label to carry Caution-Therapeutic Use Only - Main Panel	☐
☐	Spelling	☐

Quantity: Date:

Approved by Vice-President Q.C. _____

Date: _____

No. of labels required

Date sent _____

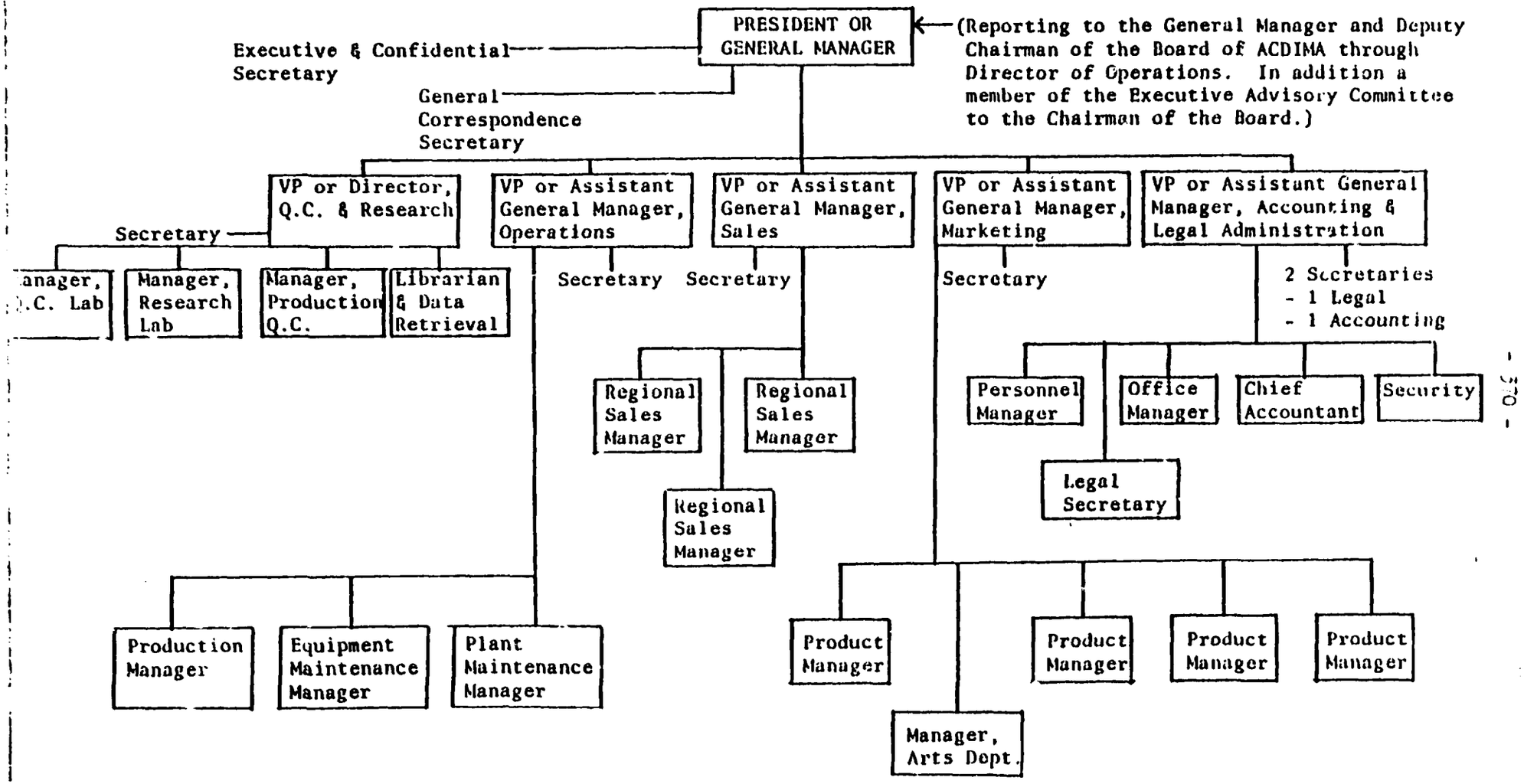
No. of labels received _____

Date _____

Lot No. assigned _____

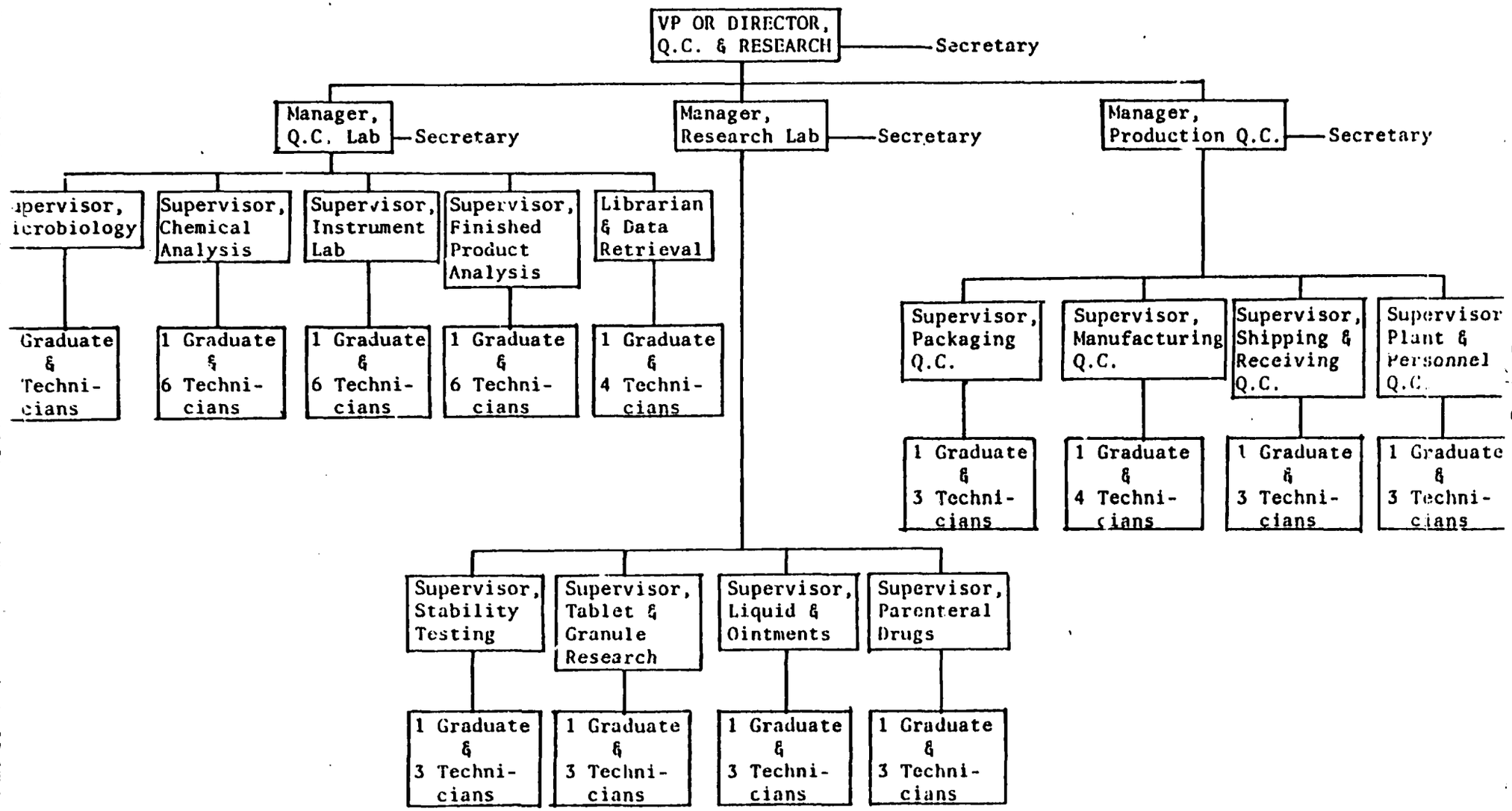
Appendix X

MANAGEMENT STRUCTURE FOR ACDIMA FORMULATION PLANTS



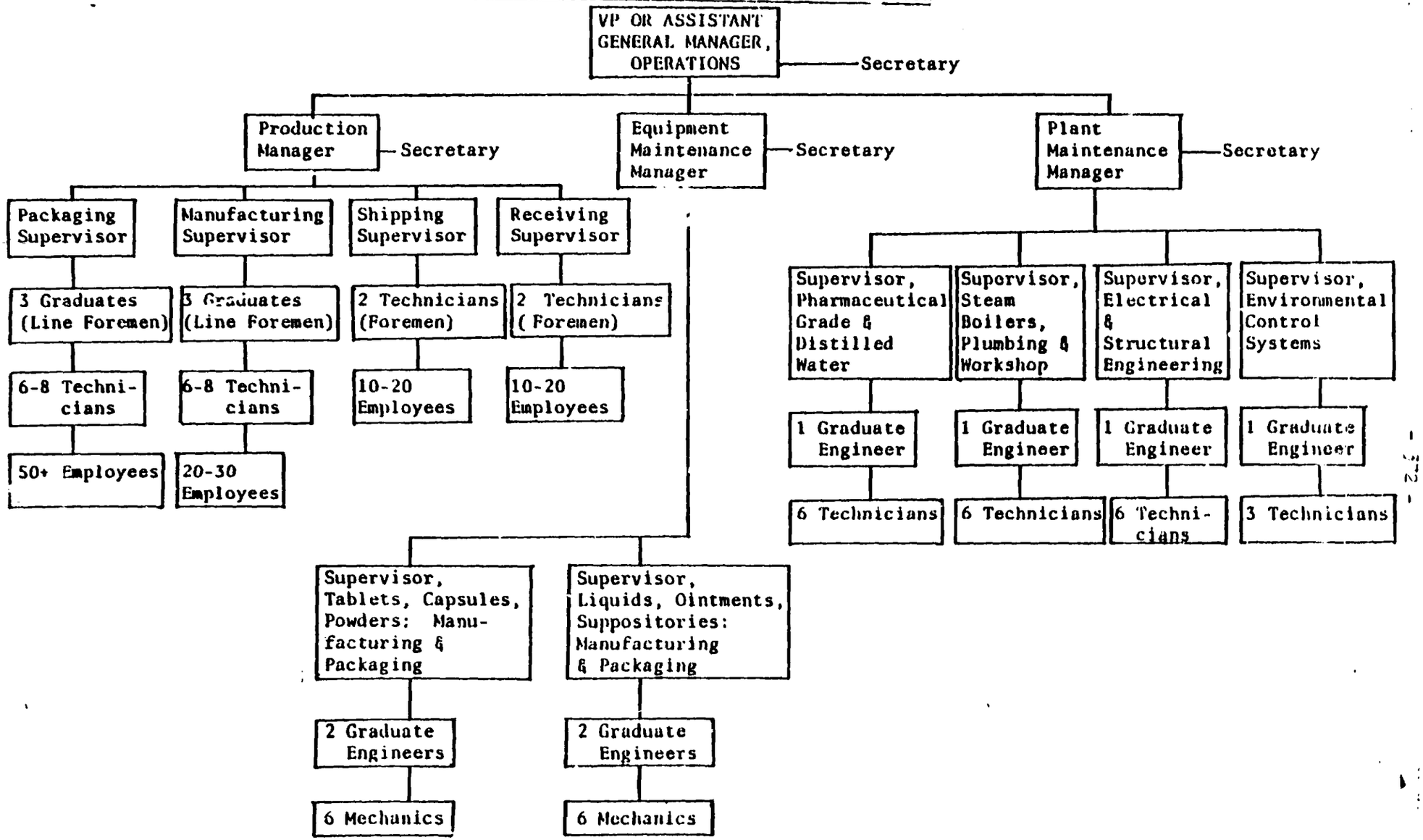
Appendix XI

MANAGEMENT STRUCTURE OF QUALITY CONTROL AND RESEARCH DIVISION



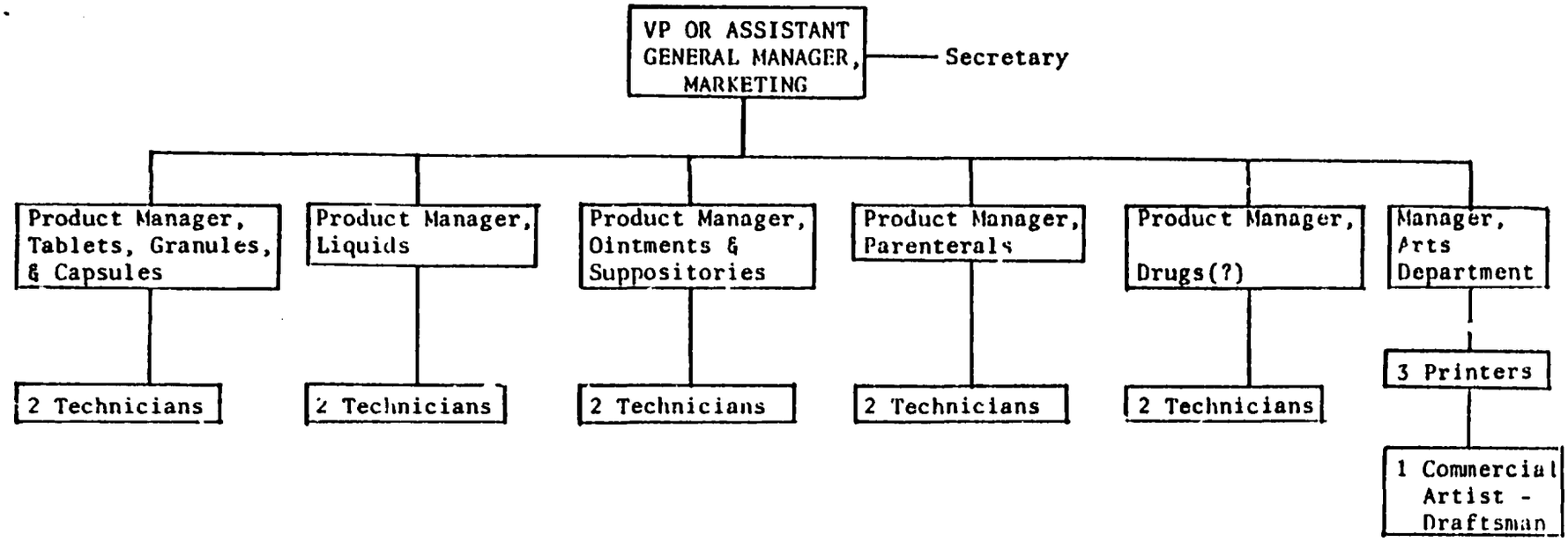
Appendix XII

MANAGEMENT STRUCTURE OF OPERATIONS DIVISION



Appendix XIII

MANAGEMENT STRUCTURE OF MARKETING DIVISION



Appendix XIV

NUMBER OF FORMULATION PLANTS IN ARAB COUNTRIES AND PERCENTAGE OF LOCAL CONSUMPTION PRODUCED BY THESE PLANTS*

COUNTRY	NO. OF PLANTS IN PRODUCTION IN 1977	% OF LOCAL CONSUMPTION PRODUCED
Morocco	15	75
Egypt	10	86
Algeria	3	35
Sudan	3	15
Syrian Arab Republic	3	15
Iraq	1	30
Tunisia	1	25
Jordan	1	20
Kuwait	1	10
Libyan Arab Jamahiriya	0	7
Saudi Arabia	1	3
Yemen	0	0 (1 underway
United Arab Emirates	0	0
	39	

The total number of plants in operation in the Arab countries = 39.

These plants produced 44% of the pharmaceutical dosage units consumed in the Arab countries.

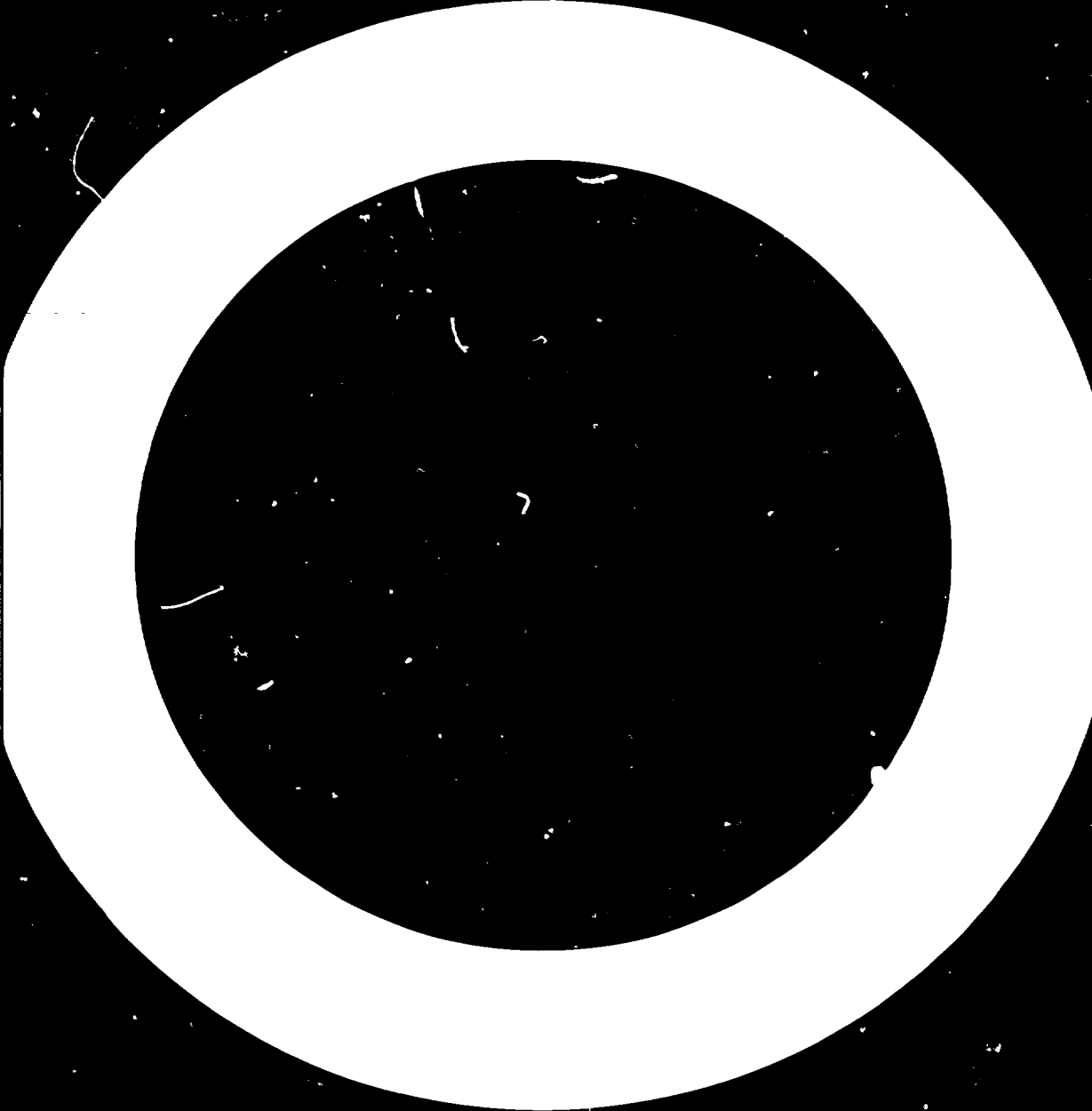
*The information was supplied by ACDIMA personnel.

Appendix XV

AVERAGE ANNUAL MEAT PRODUCTION (in Thousands of Metric Tons)
IN ARAB STATES AND THE RESPECTIVE IMPORTANCE FOR EACH STATE, 1971-1973

STATE	CATTLE		SHEEP & GOATS		POULTRY		OTHERS		TOTAL	
	Amount	%	Amount	%	Amount	%	Amount	%	Amount	%
Bahrain	—	—	—	—	1	0.4	1	0.6	2	0.1
Iraq	54	7.9	89	15.2	9	3.7	8	5.0	160	9.6
Jordan	1	0.1	6	1.0	4	1.5	1	0.6	12	0.7
Kuwait	—	—	1	0.2	5	2.0	2	1.3	8	0.5
Lebanon	6	0.9	10	1.7	22	10.1	5	3.1	43	2.6
Saudi Arabia	4	0.6	28	4.8	5	2.0	25	15.7	62	3.7
Syrian Arab Republic	15	2.2	58	10.0	10	4.1	—	—	78	4.7
Yemen	14	2.1	49	8.4	1	0.4	2	1.3	66	3.9
Democratic Yemen	1	0.1	6	1.0	1	0.4	1	0.6	9	0.5
Algeria	27	3.9	47	8.0	28	11.5	7	4.4	100	6.5
Egypt	219	31.9	47	8.0	80	33.0	21	13.3	367	21.9
Libyan Arab Jamahiriya	3	0.4	15	2.6	3	1.2	2	1.3	23	1.4
Mauritania	20	2.9	14	2.4	2	0.8	8	5.0	44	2.6
Morocco	85	12.5	70	11.9	45	18.5	12	7.5	212	12.7
Somalia	31	4.5	37	6.3	2	0.8	27	17.0	97	5.8
Sudan	189	27.6	93	15.8	11	4.4	31	19.5	324	19.4
Tunisia	16	2.3	22	2.8	13	5.2	6	3.8	57	3.4
TOTAL	685	100.0	587	100.0	242	100.0	159	100.0	1,673	100.0

Source: From ACDIMA's "Arab Pharmaceutical Consumption and Industries - A Brief Report", Livestock and Veterinary Pharmaceuticals Section, Page 9.



XIII OPOTHERAPEUTICS

A. Summary

I: Present:

(a) Develop the Bio assay method of testing insulin in the State Drug Control Laboratories in Iraq, Syrian Arab Republic and Sudan to check imported as well as locally produced insulin.

(b) Take up formulation of insulin from the imported insulin in crystal form for reasons of economy. A start can be made in Egypt and Iraq to be extended to Sudan and Syrian Arab Republic.

(c) Organize collection of pancreas from slaughterhouses and freezing. For this purpose, the slaughterhouses should be provided with deep freezer units; till adequate quantity of pancreas becomes available for taking up commercial production of insulin, the frozen pancreas can be exported.

(d) Expand the catgut manufacturing facilities at Nile Co. in Cairo to process the entire quantity of sheep intestine from slaughterhouses in Egypt for export. Also collect sheep intestine in Sudan for the above expansion programme.

(e) Organize laboratory and pilot plant scale experiments on the extraction of insulin, isolation of heparin, preparation of rennet in Egypt, Sudan and Iraq.

(f) Use the blood from all slaughterhouses in Egypt, Iraq, Syrian Arab Republic and Sudan as fodder for animals, (blood meal,).

II: Future:

(a) Plan for the establishment of an insulin plant in Egypt or Iraq, preferably in the latter. For viable production, there should be at least 200 tons of Pancreas per annum. The limitations on the use of pancreas of sheep such as allergic factor and the low yield of insulin should be investigated and the proportion in which sheep pancreas can be used along with cattle or camel

pancreas has to be worked out before the feasibility of establishing a plant for the commercial production of insulin can be considered. The world resources of cattle pancreas are limited and as such the possibilities of import have to be explored before hand.

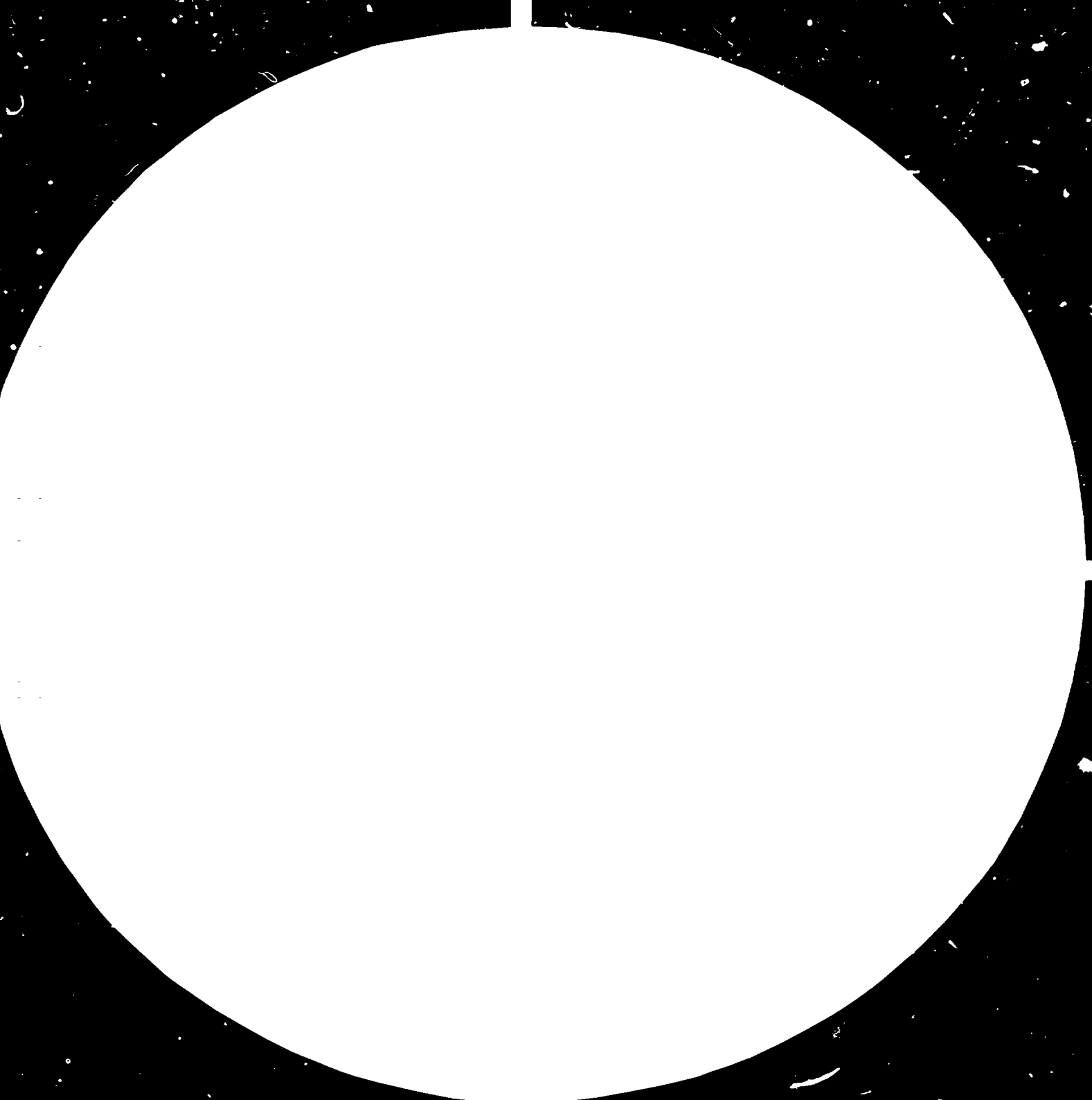
(b) Requirements of rennet, catgut, heparin, blood plasma and albumin and blood meal in Arab countries are to be worked out in order to assess the need to establish manufacturing facilities for the same.

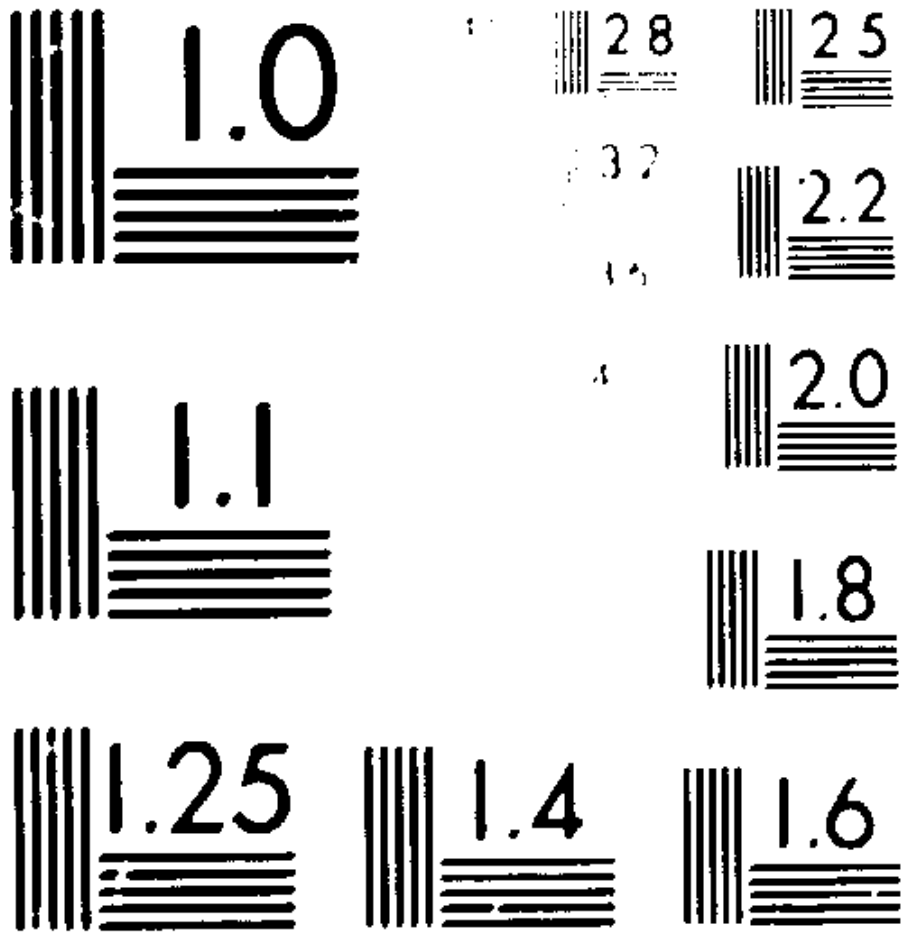
(c) Organize the processing of plasma and albumin from blood in Baghdad and Khartoum.

(d) Plan for the erection of plant facilities for rennet in El Nasr Co, Cairo.

(e) Build a new catgut factory in Sudan.

(f) Carry out feasibility studies for the production of heparin.




1.0
2.8
2.5
3.2
2.2
2.0
1.1
1.8
1.25
1.4
1.6

B. Livestock in ACDIMA countries

Information was collected on the livestock population in different Arab States and is shown in tables 1 to 3.

C. Slaughter houses in ACDIMA countries

Prior to visit to dif erent slaughterhouses, data was collected. Dr. Fahmy Awad of the Faculty of Veterinary Science, Cairo University visited as U.N. Expert different Arab States. The information furnished by him on the livestock slaughtered in different States is given in table 4.

Visits to slaughterhouses

1. Cairo, Egypt

The Cairo slaughterhouse was built fifty years ago and is too small at present. It is old fashioned with slaughter partly outside, without the possibility of collecting the blood properly, and with cooling facilities out of order. It is evidently too small for a city of about nine million inhabitants like Cairo. The slaughterhouse houses the catgut factory of Nile Co. Department, for collecting and cleaning of sheep intestine as raw material. Figures about animal slaughtered were given by the slaughterhouse director and the head of the catgut department.

2. Alexandria (Egypt)

Although the Alexandria slaughterhouse is old and seemingly too small, nevertheless it is bigger than the one in Cairo and the working conditions are better. It has not been possible to see the cooling facilities. Also in this slaughterhouse there is a department of the Cairo catgut factory. Data about Alexandria slaughterhouse was given by the head of catgut factory department.

3. Mansura (Egypt)

In Mansura there is a completely new and modern slaughterhouse with good cooling facilities, but the capacity is very small. Figures were obtained from the Slaughterhouse Director and a Veterinarian. The data

Table 1. AVERAGE ANNUAL NUMBER OF ANIMALS IN ARAB COUNTRIES, 1971-1973 (THOUSANDS)

COUNTRY	Sheep	Goats	Total	Cows	Gamoos	Total
Bahrain	—	9	9	—	—	—
Iraq	15,333	2,453	17,786	1,983	293	2,276
Jordan	412	366	778	39	—	39
Kuwait	91	73	164	6	—	6
Lebanon	227	334	561	87	—	87
Qatar	37	43	80	—	—	—
Saudi Arabia	3,091	1,822	4,913	307	—	307
Syrian Arab Republic	5,402	692	6,094	511	1	512
Yemen	3,487	8,169	11,656	1,223	—	1,223
Democratic Yemen	220	885	1,105	94	—	94
Algeria	8,188	2,290	10,478	903	—	903
Egypt	2,010	1,234	3,244	2,126	2,097	4,223
Libyan Arab Jamahiriya	2,552	1,083	3,635	109	—	109
Mauritania	3,425	2,623	6,048	2,183	—	2,183
Morocco	16,925	7,923	24,848	3,523	—	3,523
Somalia	3,900	5,000	8,902	2,866	—	2,866
Sudan	12,733	9,800	22,533	14,067	—	14,067
Tunisia	3,133	573	3,706	673	—	673
TOTAL	81,166	45,372	126,538	30,710	2,291	33,101

Source: AFAO Statistics 1976.

Table 2. **Livestock in Sudan**

Reference	Sheep	Cattle (oxen, cows, bulls)	Goats	Camels
Ministry of Animal Resources and Agriculture	15 000 000	41 000 000	11 000 000	3 000 000
Kadaro slaughterhouse director	16 229 000	15 365 000	11 229 000	2 361 000

Table 3. Average annual meat production in Arab countries during 1971-73 (in 000 tons)

Country	Cattle		Sheep & Goats		Poultry		Others		Total	
	amount	%	amount	%	amount	%	amount	%	amount	%
Bahrain	-	-	-	-	1	.4	1	.6	2	.1
Iraq	54	7.9	89	15.16	9	3.7	8	5.0	160	9.6
Jordan	1	.1	6	1.02	4	1.5	1	.6	12	.7
Kuwait	-	-	1	.16	5	2	2	1.3	8	.5
Lebanon	6	.9	10	1.7	22	10.1	5	3.1	43	2.6
Saudi Arabia	4	.6	28	4.77	5	2.0	25	15.7	62	3.7
Syrian Arab Republic	15	2.2	53	9.95	10	4.1	-	-	78	4.7
Yemen	14	2.1	49	8.35	1	.4	2	1.3	66	3.9
Democratic Yemen	1	.1	6	1.02	1	.4	1	.6	9	0.5
Algeria	27	3.9	47	8.01	28	11.5	7	4.4	100	6.5
Egypt	219	31.9	47	8.01	80	33.0	21	13.3	367	21.9
Lybian Arab Jamahiriya	3	.4	15	2.60	3	1.2	2	1;3	23	1.4
Mouritania	20	2.9	14	2.40	2	.8	8	5.0	44	2.6
Morocco	85	12.5	70	11.92	45	18.5	12	7.5	212	12.7
Somalia	31	4.5	37	6.30	2	0.8	27	17.0	97	5.8
Sudan	189	27.6	93	15.80	11	4.4	31	19.5	324	19.4
Tunisia	16	2.3	22	2.75	13	5.2	6	3.8	57	3.4
T O T A L	685	100	587	100	242	100	159	100	1673	100

Ref: "Arab Pharmaceutical Consumption and Industries, Brief Report, 1975".

Table 4. Data on slaughter in Arab countries

Slaughterhouse	Sheep		Cattle		Camels		Pigs		Donkeys	
	per day	per year	per day	per year	per day	per year	per day	per year	per day	per year
Cairo (3 days per week, 156 days per year)	2 000	310 000	500	77 500	25	3 880				
Alexandria (3 days per week, 156 days per year)	200	31 000	100	15 600			50	7 750		
Khartoum (7 days per week, 365 days per year)	600 to 700	average 235 000	200 to 300	average 80 000						
Baghdad (7 days per week, 365 days per year)	200	73 000	100	36 500						
Damascus (about 200 days per year)	200 to 300	average 50 000	50	10 000						
Tunisia (about 200 days per year)	200 to 300	average 50 000	100	20 000					100	20 000
Kuwait (about 200 days per year)	200	40 000	100	20 000						
Total per year		789 000		259 600		3 880		7 750		20 000

compiled from the slaughterhouses visited in Egypt are shown in tables 5 to 7.

4. Khartoum, Omdurman (Sudan)

Khartoum has two slaughterhouses. An old one in Omdurman and a new one in Kadaro, near Khartoum.

Omdurman slaughterhouse is functioning well but not too modern. It was not possible to see the cooling facilities. They worked only by night. Data was given by slaughterhouse staff and by the Ministry of Animal Recourses and Agriculture (See table 8).

5. Kadaro near Khartoum (Sudan)

A new, completely modern slaughterhouse, built a year ago, exclusively for export, is situated in Kadaro about 25 km from Khartoum. It has good cooling facilities at 4°C for 50 tons and at 20°C for 10 tons. The slaughterhouse uses many refrigerated trucks for transport. But this slaughterhouse has been out of operation since the end of May 1977. According to the Slaughterhouse Director they hope to start the work again in September 1977. In addition, they expect an expansion during next year. The Slaughterhouse Director provided figures of slaughter, and he informed about a new private slaughterhouse that would be built in 1979 in Khartoum and the slaughter expected there. According to data obtained from him and from the Ministry about the animal stock in the Sudan, figures about slaughter expected in next two years seem realistic.

6. Damascus (Syrian Arab Republic)

Damascus has a new, well run slaughterhouse. They have good cooling facilities at 4°C. Figures are furnished by the Slaughterhouse Director who informed about Aleppo slaughterhouse as well and are shown in table 9.

Table 5. Data on Cairo Slaughterhouse

Reference	Period	Sheep	Calves	Cattle (oxen, cows, bulls)	Buffaloes	Camels	Pigs
Slaughterhouse director --	July 1977	25 600	4 296	6 517	1 302	2 005	2 000
	per annum	307 200	55 462	78 204	15 624	24 060	24 000
The head of cat gut factory department in Cairo slaughterhouse --	1976	269 436	63 594	92 460	16 371	25 875	40 801
	First six months 1977	143 577	27 897	45 358	8 508	1 497	20 220
	per annum 1977	287 154	55 794	90 716	17 016	2 994	40 440
Selected	per annum	287 200	55 800	90 700	17 000	24 000	40 400

Table 6. Data on **Alexandria slaughterhouse**

(Figures collected from the head of cat gut factory department in Alexandria slaughterhcuse)

Period	Sheep	Calves	Cattle (oxen, cows, bulls)	Buffaloes	Camels	Pigs*
18.2.to 27.2.1977	329	497	260	253	1	
28.2.to 5.3.1977	296	297	374	216		
6.3.to 17.3.1977	57	477	592	438		
18.3.to 8.4.1977	171	670	870	634		
9.4.to 23.4.1977	954	426	470	386		
24.4.to 10.5.1977	1 064	214	531	375	1	
73 days	2 862	2 581	3 117	2 302	2	
Per annum	14 400	13 000	15 600	11 500	8	1 500

*Pigs: - in summer per month: 100 . 6 = 600
- in winter per month: 150 . 6 = 900
- per annum: 1 500

Table 7. Data on Egyptian Slaughterhouses

Slaughterhouse	Sheep	Calves	Cattle (oxen, cows, bulls)	Buffaloes	Camels	Pigs
Cairo	287 200	55 800	90 700	17 000	24 000	40 400
Alexandria	14 400	13 000	15 600	11 500		1 500
Mansura*			12 000			
Total	301 600	68 800	118 300	28 500	24 000	41 900

*The figure obtained from the slaughterhouse director and a veterinarian: oxen 200 to 250 per week.

Table 8. Data on Khartoum Slaugherhouses

Slaughterhouse	Figures collected from	Perood	Sheep	Cattle (oxen, cows, bulls)
Omdurman	Omdurman slaughterhouse staff	per day	1 000	200
		per annum (300 working days)	300 000	60 000
	Ministry of Animal Resources and Agriculture	per annum 1975/76 (July to June)	211 000	64 600
		per annum 1976/77 (July to June)	250 000	66 000
	Selected	per annum	250 000	60 000
Kadaro	Kadaro slaughterhouse director	per annum 1977 (out of operation)	300 000	75 000
		per annum 1978	450 000	120 000
New private slaughterhouse	Kadaro slaughterhouse director	per annum 1979	210 000	120 000
Total 1979		per annum	910 000	300 000

Table 9. Data on slaughterhouses in the Syrian Arab Republic

Reference	Slaughterhouse	Period	Sheep	Cattle (oxen, cows, bulls) and camels
Damascus slaughterhouse director --	Damascus	per day	1 300 to 1 400	10
		per annum (300 working days)	400 000	3 000
	Aleppo	per day		30 to 35
		per annum (300 working days)		10 000
Total		per annum	400 000	13 000

Slaughter in Saudi Arabia during three days in November (once per year)

Reference	Total	Sheep and goats	Cattle (oxen, cows, bulls)	Camels
The Arab Company for Livestock Development, Damascus --	1 000 000 to 1 500 000 average 1 200 000	85% or 1 020 000	10% or 120 000	5% or 60 000

7. Baghdad (Iraq)

In Baghdad there are four slaughterhouses and one of them was visited and data was given by the Director of Al-Risapha slaughterhouse. This slaughterhouse is modern, built three years ago. According to the General Director of Veterinary Services in Iraq and the Slaughterhouse Director, the new slaughterhouse that will cover the needs of Baghdad, will be completed in 1979. The General Director of Veterinary Services provided figures about slaughter in Iraq in bigger slaughterhouses in 1976 and these are shown in table 10.

8. Slaughter in Saudi Arabia

According to suggestions of the Arab Co. for Livestock Development in Damascus, it would be possible to arrange the collecting of pancreas from animals slaughtered in Saudi Arabia during the three days in November. They could request the Saudi Government to decree such a collection. In this case the Saudi Government would borrow the necessary deep freezers from private owners.

A resume on the data collected on slaughterhouses in different Arab states is given in tables 11, 12 and 13.

Collection of pancreas in slaughterhouses

In all slaughterhouses visited, the method of collecting pancreas and at what stage of slaughter the cleaning procedure and the need to freeze forthwith were explained. There are no deep freezer units in the slaughterhouses, except in the slaughterhouse in Kadaro.

According to the Veterinarians in many slaughterhouses, the price of frozen pancreas will be about half of the cost of meat.

Table 10. Data on Baghdad slaughterhouses

Figures collected from	Slaugterhouse (260 working days per annum)	Sheep		Cattle (oxen, cows, bulls) and buffaloes		Camels	
		per day	per annum	per day	per annum	per day	per annum
Al-Risapha slaughter-house director	Al-Risapha	2 000	520 000	250	65 000	40	10 400
	Al-Kerh	1 800	468 000	180	46 500		
	Al-Shulla	1 500	390 000	150	39 000		
	Fourth (old)	200	52 000	20	5 200		
Total per annum			1 427 000		155 700		10 400

Slaughter in Iraq in 1976 in bigger slaughterhouses

Figures collected from	Sheep	Goats	Cattle (oxen, cows, bulls)	Buffaloes	Camels
Director General of Veterinary Services in Iraq	1 864 000	860 000	374 000	53 800	13 400

Table 11. Animals slaughtered per annum in slaughterhouses in Arab Countries.

Year	Country	Sheep	Calves	Cattle (oxen, cows, bulls)	Buffaloes	Camels	Pigs	Donkeys
1977	Egypt	302 000	68 800	118 300	28 500	24 000	41 900	
	Sudan	250 000		60 000				
	Syrian A.R.	400 000		13 000				
	Iraq	1 427 000		155 700		10 400		
	Grand total	2 379 000	68 800	347 000	28 500	34 400	41 900	
1980	Egypt	302 000	68 800	118 300	28 500	24 000	41 900	
	Sudan	910 000		300 000				
	Syrian A.R.	400 000		13 000				
	Iraq	1 864 000		374 000	53 800	13 400		
	Tunisia	52 000		20 000				20 000
	Kuwait	40 000		20 000				
	Total	3 560 000	68 800	865 300	32 300	37 400	41 900	20 000
	Slaughter in Saudi Arabia during three days in November	1 020 000		120 000		60 000		
	Grand total	4 588 000	68 800	985 300	82 300	97 400	41 900	20 000

Table 12. Pancreas collected in slaughterhouses per annum

Year	Sheep	Calves	Cattle (oxen, cows, bulls)	Buffaloes	Camels	Pigs	Total of cattle, calves, buffaloes, camels, and pigs (sheep excluded)
1977							
Egypt Sudan Syrian A.R. Iraq	71 tons	11.7 tons	59 tons	4.9 tons	12 tons	2.5 tons	90.1 tons
1980							
Egypt Sudan Syrian A.R. Iraq Tunisia Kuwait	108 tons	11.7 tons	147 tons	14 tons	13 tons	2.5 tons	186.2 tons
Including slaughter in Saudi Arabia during three days in November	137 tons	11.7 tons	167.5 tons	14 tons	34.1 tons	2.5 tons	229.8 tons

Calculated according to number of animal slaughtered and weights of pancreas of several kinds of animals

Table 13. Mucous membrane available in slaughterhouses per annum

Year		Sheep	Cattle (oxen, cows, bulls), Calves, Buffaloes	Pigs	Total percentage
	A viable production of heparin requires minimum*	24 000 000	1 800 000	3 000 000	
1977	Number of animals slaughtered	2 379 000	347 000 68 800 + 28 500 444 400	41 900	
	Percentage of animals required	10%	24.6%	1.4%	36.0%
1980	Number of animals slaughtered	3 568 000	865 300 68 800 + 82 300 1 016 400	41 900	
	Percentage of animals required	14.9%	55.2%	1.4%	71.5%

D. Insulin

As regards by-products from slaughterhouses, insulin is the most important. Diabetics need it to survive. Insulin is the only medicine for more difficult cases of diabetes mellitus. The raw material is pancreas from slaughterhouse animals, except sheep and goats, kept deep-frozen.

1. Imports of insulin:

Egypt imports insulin in the crystalline form as well as injections. Iraq, Syrian Arab Republic and Sudan import only the final product insulin in vials. The total imports of insulin by the Arab states amount to 17 kg. per annum expressed in insulin crystals of 25 units per mg. and the figures are shown in table 14.

2. Formulation of insulin in Egypt:

One formulation unit - C.I.D. Co. in Cairo was at one time formulating insulin in vials at the rate of about 300,000 vials annually which was equivalent to 2.5 kg. of crystalline insulin of 25 units per mg. However this operation was stopped on account of losses apparently due to price control on insulin formulations. The formulation of insulin should be possible in Iraq and Sudan too.

3. Biological assay of insulin:

The biological assay of insulin is an essential pre-requisite for the production and formulation of insulin. In Egypt, biological assay is carried out in the State Control Laboratory of Drugs and C.I.D. Co., where there are the necessary animal house facilities. The convulsion test is used and every batch of insulin injection produced in C.I.D. Co., is checked. At S.D.I., Samarra, Iraq the biological assay is carried out in collaboration with Samarra Hospital. The

Table 14. Insulin imports in Egypt, Iraq, Syrian Arab Republic and Sudan

Country	Reference	Insulin in vials		Crystalline insulin of 25 I.U. per mg	Total insulin in grams of 25 I.U. per mg	Population	Insulin units per capat
		units	expressed in grams of 25 I.U. per mg				
Egypt	- For insulin in vials: Egyptian State Drug Corp., average of 1976 and 1977	157 116 000	6 550				
	- For crystalline inculin: C.I.D.Co., Cairo, for 1976			2 000	8 550	37 000 000	5.54
Iraq	-Ministry of Health, average of 1974 and 1975	24 819 000	1 034				
	- Hospitals	18 250 000	766		1 800	11 000 000	3.92
Syrian Arab Republic	- Ministry of Health for 1976	21 976 000	916		916	8 000 000	2.75
Sudan	- Ministry of Health, average of 1975 and 1976	132 000 000	5 500		5 500	18 000 000	7.33
Grand total					16 766		

biological assay will also be organized in the Drug Control Laboratory of Ministry of Health in Baghdad in the near future.

4. Raw Material:

The most important is quality and quantity of pancreas.

Quality: Pancreas must have at least 30% of dry matter and 70% of water, but less than 10% of fat. According to literature and working experience one can get from pancreas of:

- cattle to 5 years: 2,500 units of insulin per kg.
- baby beef (18 to 30 months): 3,500 to 4,000 units.
- calves: 8,000 units
- pigs: 2,500 to 3,000 units
- sheep: 1,000 to 1,200 units

Quantity: At least 200 to 300 tons of pancreas per annum are necessary for economic viability of insulin production. One ox pancreas weighs about 170 gr; in one kg. there are six pieces of pancreas. For 200 tons of pancreas that means 1,200,000 heads of cattle. If there are 300 working days per year, that means 4,000 cattle per day.

If one pig pancreas weighs 60 gr. the same calculation gives 16 pieces of pancreas in one kg. For 200 tons that means 3,200,000 pigs or 10,700 per day.

As to camel we may put that the weight of its pancreas is about twice as much as ox pancreas, about 350 gr. In one kg. there would be about three pieces of camel pancreas. For 200 tons of pancreas that amounts to 600,000 camels or 2,000 per day. Concerning sheep one must be careful, as sheep pancreas is a poor source for insulin and sheep insulin causes allergic reactions in patients. According to informations obtained from Yugoslavia and India, the sheep pancreas is excluded as source for insulin production.

Standard preparation of crystalline insulin has 24 to 25 International Units (I.U.) per mg. but it will be better to calculate with purity of 20 units per mg. although many manufacturers obtain 25 to 27 units per mg.

Thus, with a purity of 20 units per mg. and yield of 2,000 units per kg. of pancreas it means 400,000,000 units or 20 kg. of insulin, or 1,000,000 vials of insulin of 400 units, from 200 tons of pancreas of cattle or pigs.

The price of raw material is important because it has a comparatively big influence on the final product. The total cost of raw material for economical production (pancreas and chemicals)can not exceed 30% of total price of insulin. Some prices on world market (obtained from "Pliva" Drug Factory, Zagreb):

- for frozen pancreas:

Argentina, $1 - per kg. it is the best pancreas from young cattle with only 5% of fat. Can obtain 3,500 units per kg. with a purity of 27 units per mg. Argentina pancreas was not available in the last two years on world market.

France, (firm collector Gene), about $1.90 per kg. of pancreas.

Italy, $2.84 per kg. of pancreas.

- for insulin crystals.

Denmark, $1.36 for 1,000 units of insulin with purity of 24 units per mg. One gr. of insulin (= 24,000 units) will cost $32.50.

CSSR, $1.30 for 1,000 units of insulin with same purity. One gr. of insulin will cost $31.20.

- for insulin solution in vials:

Novo, Denmark, protamin-zinc-insulin, 1 vial of 400 units costs $1.20, or 1,000 units amounts to $3. The cost of one gr. of insulin (=24,000 units) will be $72.

Novo, Denmark, insulin lente or monoinsulin, 1 vial of 400 units is $2, or 1,000 units amounts to $5. The cost of one gr. of insulin will be $120.

5. Technology:

The technology adopted depends on the capacity of production. In any case, pancreas must be transported to the production plant deep-frozen. For smaller plants one usually combines well known prescriptions.

The first step is always the extraction with acidified alcohol and short alkalization for the removal of protein hydrolysates. After repeated acidification the extract is treated with vacuum distillation or absorption of insulin from alcoholic extract, for instance, on alginic acid. Further steps are usually precipitation with sodium chloride, removal of fat, isoelectric precipitation, clarification with acetone, and finally crystallization. Larger factories can buy the complete equipment including the technology of production from specialized firms, for instance, Alfa Laval or Westfalia. Assay of insulin is possible only by biological test on rabbits or mice. The method is expensive and rather difficult. It requires a specially trained research worker.

Use: Difficult cases of Diabetes mellitus.

6. Production of insulin on laboratory scale:

C.I.D. Co. in Cairo has just commenced experiments on the extraction of pancreas. The Research and Consultancy Institute in Khartoum is interested in the laboratory scale extraction of insulin. Advice was given by the author to both these institutions on this subject. Dr. Waleed Ohan-Denho studied the possibility of producing insulin in Iraq for S.D.I., Samarra along with a team of workers at S.D.I. and Medical Research Centre in Baghdad.

7. Viable Production of insulin:

A viable production of insulin nowadays needs at least 200 tons of pancreas per year. The availability pancreas for insulin production is indicated in table 12. One kg. of pancreas of cattle and pigs is enough for the production of at least 2,000 units of insulin. As indicated earlier, the pancreas of sheep and goats is not used for insulin production. According to figures obtained from Egypt, Iraq, Syrian Arab Republic and Sudan, only about 90 tons of pancreas can be collected and this is not adequate for a viable production.

By 1980 after the completion of new slaughterhouses, in Khartoum and Baghdad and on the basis of information available on Tunisia and Kuwait, it may be possible to collect about 185 tons of pancreas per year which may be the minimum viable capacity. Further, if there is a possibility of collecting the pancreas of animals slaughtered in Saudi Arabia during the three days in November, one could obtain 230 tons of pancreas for insulin production. For the collection of animal by-products, the slaughterhouses must be provided with suitable cooling facilities. Small deep freezers such as ice-creamers can be installed for this purpose. It is desirable to arrange for the collection and freezing of pancreas from all slaughterhouses. Frozen pancreas is exported mainly by South America. The price of Argentine pancreas is $1 per kg. and that of France is $1.90. In view of shortage of pancreas in the world market, the possibility of export from Arab States is worth investigating.

8. In the light of the above, the following recommendations are made:-

(a) Short term basis:

1. Biological assay:

It is recommended that the biological activity testing of insulin be developed at the State Drug Control Laboratories in Iraq, Syria and Sudan. This assay, as indicated earlier, was being carried out in Egypt. A good animal house and trained personnel are required for this assay.

2. Formulation of insulin:

Import of insulin crystals is cheaper than import of injections. If 1 gr. of crystalline insulin, with a purity of 24 units per mg. costs $32.50 and 1 gr. of insulin solution in vials costs $72., the difference for 1 gr. of insulin will amount to $39.50. This is more than the price of 1 gr. of crystalline insulin.

The difference in cost of insulin in vials and insulin crystals amounts to:

- Egypt besides C.I.D. Co., for 6,550 gr. of insulin	- $258,725.
- C.I.D. Co. for 2,000 gr. of insulin	$ 79,000.
- Iraq for 1,800 gr. of insulin	$ 71,100.
- Syrian Arab Republic for 916 kg. of insulin	$ 36,100.
- Sudan for 5,500 gr. of insulin	$217,250.
- Total	$662,175.

There is an attractive margin after allowing for the vials, caps and other production expenses. Further insulin solution is not stable at higher temperatures and has to be kept at 4°C, while insulin powder is comparatively more stable even up to 50°C. The formulation of insulin solution in vials from insulin powder can be carried out in the injection department of every drug factory. It is also desirable to recommence production at C.I.D. Co. and expand the production. Similarly, the formulation can be taken up at S.D.I. Samarra. This can also be included in the production programme of Sudan in the proposed injectible solution plant.

3. Preparation of insulin on a laboratory and pilot plant scale:

It is recommended that Egypt and Sudan develop the method of insulin extraction and purification on a laboratory scale with pancreas collected locally. Similar work can be carried out in Iraq. It is also desirable simultaneously to import crude insulin and purify in the laboratory to gain experience in production in a shorter time. It is also recommended that a pilot plant for this purpose may be erected preferably in Iraq where some work, as indicated earlier has been carried out. A pilot plant to handle about six tons of pancreas per annum or 20 kg. per day will cost about US$50,000 as indicated below

The price for all equipment for insulin processing for about 6 tons of pancreas per annum (or 20 kg. per day) was in 1975	US$20,000
- If added the same figure for buildings and some existing equipment	US$20,000
- Taken into consideration a 20% price increase	US$10,000
- Total about	US$50,000

(b) Long term basis:

Based on the experience gained in the pilot plant, it is recommended that large scale insulin plant be built. The quantities of pancreas available in Arab States will become adequate for viable production of insulin in the next three years. Efforts may also be made to purchase pancreas from abroad at the initial stages to have adequate quantity for viable production.

As regards location, it is more economical to build such a plant as a part of a big pharmaceutical plant in view of the availability of facilities such as utilities. As large pharmaceutical plants are in existance in Egypt and Iraq, these should be the logical choice. A reference has already been made to the preliminary work carried out at both these places. The laboratory/pilot plant scale experiments carried out in Egypt and Sudan will also help train personnel. The assistance of an outside expert may be sought and few persons from the concerned Arab states may be sent abroad for training e.g. in 'Pliva' drug factory, Zagreb, Yugoslavia. The approximate cost of such a training would be the following:

- UNIDO fellowhip in Yogoslavia per mongh (including travel expenses)	US$	750
- Additional 10%	US$	75
- Total	US$	325
Total for six months, approx	US$	5,000

The technology and training in insulin production are also available free of charge from Canada. There are examples wherin insulin production was started in smaller plants not considered as viable. In India, the Government had to subsidize insulin production. It is the same case with Yugoslavia. Now insulin production is viable in both these countries. Similarly, the Arab states may consider subsidizing insulin production in the initial stages in view of the essential nature of this drug.

E. Pancreatin

Pancreatin is a multi-enzymic preparation from pancreas. However, pancreatin prepared from sheep lacks lipase. Sheep pancreas of about 70 tons at present and about 100 tons in 1980 could be used for pancreatin production. The processing consists of an extraction in 20% methanol removal of the tissues and spray drying the clear extract. However, due to the absence of lipase in pancreatin prepared from sheep, such production is not carried out in Yugoslavia. However, in India sheep pancreas is the main source for pancreatin production. A smaller production can also be viable.

F. Heparin

Heparin is another interesting drug derived from the by-products of slaughterhouses. It is used in modern therapy as a physiological anti-coagulant. The price of heparin on the world market dropped rather suddenly. There is no satisfactory assay available for this drug. The availability of mucous membrance is indicated in table 13. The total supply of raw material is hardly 36% of the quantity required for viable production of heparin. By 1980, the availability is expected to go up to 70%. In view of this, the viability of heparin is questionable.

In the case of heparin, it is desirable to gather experience on a laboratory scale. It must be noted that the manufacture of heparin is possible subject to the following conditions:

(1) Adequate quantity of raw material for viable production.

(2) The price on the world market is stable and

(3) The assay problem is resolved.

Data available is not so reliable as in the case of insulin, because heparin production in Yugoslavia does not exist. The Veterinary Institute and Production Plant in Subotica intends to start the production of heparin in the near future.

Raw Material: Cattle lungs and liver, pig mucous membrane of thin intestine. Cattle and sheep may be used too. About 50 to 100 mg. of heparin can be obtained from 1 kg. of cattle lungs, and 240 mg. of heparin from 1 kg. of pig mucous membrane. From cattle or sheep mucous membrane the yield is less, maybe from 1 kg. about 100 to 150 mg. of heparin.

The pure heparin has 100 to 140 units per mg.

One pig has 1 kg. of mucous membrane, one ox 4 kg. and sheep 300 gr. One ox has 5 kg. of lungs and 7 kg. of liver, and one sheep has 300 gr. of lungs and 500 gr. of liver. Liver is a poor source for heparin. Pig mucous

membrane is considered as the best raw material for heparin production.

A production of 700 kg. of heparin per annum is regarded as being economically viable. However, this figure depends on the price of the raw material and prices of the final product on world market. For production of 700 kg. of heparin from mucous membrane of pigs, one must use 3,000,000 pigs per annum or 10,000 per day, with 300 working days per year.

As cattle and sheep are not as good a source as pigs, it must be used 2.4 times more. For sheep that means 24,000,000 per annum or 79,000 per day. For cattle 1,300,000 per annum or 6,000 per day. For cattle lungs the rate is less favourable and requires about three times more than pig mucous membrane. That means 2,100,000 cattle per annum or 7,000 per day, and 30,000,000 sheep per annum or 100,000 per day.

An ampoule of heparin contains 25,000 I.U.

The price of heparin fell rapidly during the last year. In summer, 1976 it was US$4.6 per 100,000 units (or one gr.), in October, 1976 it was US$2.6 and at the beginning of 1977 only US$2.0.

Production procedure: Fresh raw material is preserved with sodium bisulphite ($NaHSO_3$). It is transported in this state to manufacturers. It is produced through precipitation or extraction with acetone followed by the digestion with proteolytic enzymes, usually pancreatin. The final product cannot contain more than 1% of protein. Then absorption in column and elution takes place. The product obtained is sodium heparin, pale-white, amorphous powder, odourless, hygroscopic.

The method of assay is a biological test of prevention of blood clotting according to U.S. Pharmacopeia XVII to XIX. This procedure is evidently out of date. Some new procedures are recommended, for instance, chromatographic or photometric determination, protonmagnetic spectra (p.r.m.), but the last method is not a quantitative one. All in all the problem of heparin assay is open now.

Uses: Quick interventions for prolonging the clotting time of blood.

G. Gelatin

Gelatin is another useful product manufactured from slaughterhouse waste. However, the pharmaceutical grade gelatin suitable for the manufacture of capsules and is produced only by a few manufacturers in the world as the processing is complicated. In view of this, it is not recommended for manufacture at this stage in the ACDIMA countries.

Raw materials are bones, connective tissue and skin.

Gelatin is obtained by partial hydrolyse of collagen. There are Type A gelatin obtained by acid treatment, and Type B gelatin by an alkaline process.

Cattle bones or pork skin are normally used for gelatin production. A variety of products with desirable properties are available and special processing is required in each case. The steps in manufacture involve isolation and refincement of the insoluble collagen, followed by its hydrolytic conversion to soluble gelatin. The gelatin is further processed by chemical adjustment, filtration for clarification, and then dried to yield a product of some predeterminated quality. A vacuum evaporation is required, because after hydrolysing the solution has only 3 to 8% of gelatin. With further drying, the product with 10% of moisture is obtained.

There exists a special treatment for preparation of pharmaceutical gelatin. To get pharmaceutical gelatin as final product 5 to 6 different sorts of gelatin must be mixed and specially treated. There are only a few such manufacturers in the world, for instance, Scherer in W. Germany. There is no production of pharmaceutical gelatin in Yugoslavia.

Assay: According to U.S. Pharmacopoeia, a special Bloom rating with gelometer, viscosity, ash, pH, moisture, arsenic, bacteria number. This assay is not complicated.

Uses: Food industry, photographic industry, capsules for pharmaceutical industry. Capsules are made in big quantities. Gelatin is widely used nowadays as matrix for water soluble vitamins particularly. It preserves degradation during an application per os.

H. Blood

Blood is one of the most important raw materials of animal waste from the slaughterhouse. Fodder for animals can be prepared from blood. Plasma and albumin are two other important products from blood. As blood is unstable at high temperatures, transport becomes a bottleneck. So only blood from one slaughterhouse which is big enough can be used for obtaining the above products. At present, blood is utilized in several slaughterhouses in Arab states for fodder as blood meal. In all the slaughterhouses larger or smaller parts of blood are collected, depending on the working conditions. In older slaughterhouses as in Cairo, Alexandria and Omdurman a smaller part and in modern slaughterhouses in Mansura, Kadaro, Damascus and Baghdad, practically the whole blood is collected. No other animal by-products are collected at present.

It is desirable to arrange for the processing of plasma and albumin, the most profitable products from blood, in all Baghdad slaughterhouses put together. The quantity of about 1,700 tons per year will be adequate for viable production. Plasma and albumin manufacture does not require expensive equipment but only a good centrifuge unit and a spray dryer are needed.

The quantity of blood in the new big slaughterhouses built in Baghdad will reach 3,300 tons in the next three years and in Khartoum. In a similar period, after the completion of the new slaughterhouse and expansion of the Kadaro slaughterhouse, the quantity will reach 2,050 tons. In Baghdad the plasma and albumin production may be continued in a larger plant and in Khartoum such a production with blood from three slaughterhouses may be commenced..

There is a great quantity of blood in slaughterhouses and it is usually disregarded. After slaughter, it can be collected from:

- ox about 5 kg.
- pig about 1 kg. and
- sheep about 600 gr.

One thousand to two thousand tons of blood per year are considered as viable for processing with 300 working days per annum, it amounts to 3,300 to 6,600 kg. of blood per day.

That means about 650 to 1,300 cattle per day or 200,000 to 400,000 per annum.

As to pigs this will amount to 3,300 to 6,600 per day or 1,000,000 to 2,000,000 per annum, and for sheep it means 5,500 to 11,000 per day or 1,650,000 to 3,300,000 per annum.

The blood has 7 to 9% of dry matter and about 3% of albumin in total.

The technology of production of plasma or albumin is the most interesting. In any case, sodium acetate or oxalate as anticoagulant is added to the fresh blood. Centrifugation by special type centrifuge for blood (may be Alfa Laval or Westfalia) is easy and effective. Dried blood plasma is widely used in the food industry for canned or tinned preparations.

Capsules, the mass of erythrocyte may be used in many ways. It is usually dried. If it is hydrolysed enzymatically, the product is dark coloured. By acidic hydrolyse, which is recommended, sodium chloride of about 40% is produced and it must be removed after hydralysing. Ion exchange is expensive.

Further processing of plasma includes defibrination with more anti-coagulant and calcium and second centrifugation. The resulting serum is spray-dried and the product obtained is blood albumin. It is used widely for cosmetics. With the above capacity of production one can obtain 30 to 60 tons of albumin per year, or 100 to 200 kg. per day.

I. Rennet

Rennet is another common enzyme preparation used widely for clotting of milk for cheesemaking process. El Nasr Co. in Cairo carried out research work on the possibility of rennet extraction from the stomachs of the calves on a laboratory scale. The collection of calf and lamb stomachs for rennet production is possible only in Egypt because of the slaughter of young

calves and lambs. The slaughter of young animals is not allowed in Iraq, Syrian Arab Republic and Sudan. It is recommended that the experiments at EL Nasr Co. be continued and a production plant be erected in the same factory based on the laboratory experience. A smaller rennet plant can yield a viable production too.

Raw material: Calf stomachs from suckling animals, also lamb stomachs. Normally dried stomachs are processed. The production procedure is easy. A small plant may be viable too. For larger factories the viability depends on raw material, the cost of calf and lamb stomachs. Only this is important and decisive, because the raw material cost depends on stomachs to the extent of 90%. Assay is easy too, but bacteriological control is required. According to the new technology of production, the first step is desintegration or perfect crumbling of the cell-walls of fresh stomachs. The procedure includes evaporation of clarified rennet extract as liquid film. The last step is spay-drying of concentrate extract. About one to two tons of product per year with an activity of 100,000 units are viable.

Grades (or kinds of product): Powder with activity of 50,000 and 100,000 units, tablets of 10,000 units (one tablet for clotting of 10 litres of milk), also liquid rennet of 5,000 to 10,000 units.

J. Catgut

There is technologically a satisfactory production of catgut in Nile Co., Cairo and the departments of the same company in the slaughterhouses at Cairo and Alexandria. This Company uses only 20% of the intestines of sheep slaughtered in both these slaughterhouses. It is recommended that the catgut factory of Nile Co., Cairo be expanded to process the whole quantity of sheep from the slaughterhouses in Egypt. This should be economical and it may be possible to export this item. Similarly it would be useful to collect the sheep intestines in the slaughterhouses in Sudan and a new catgut factory may be built in Sudan initially for the local need and possibly for export.

XIV. ECONOMICAL ASPECTS OF MEDICINAL PLANTS

A. Summary

A study was undertaken to explore the possibility of setting up pharmaceutical industry tc produce vegetable drugs in Arab countries.

Analysis of the available information indicated that phytochemicals and crude extracts from medicinal plants are used extensively in different Arab states about 20, pure chemicals and more than 80 crude extracts were found to be used in formulations : markated in the Arab countries.

Survey of the raw material showed that only six species of medicinal plants are found in large quantities. These include, senna (Cassia acutifolia) liquorice (Glycyrrhiza glabra), Egyptian henbane (Hyoscymus muticus) Ammi majus, Ammi visnaga and Acacia senegel.

There are eight other plants which are either found growing wild or have been cultivated on experimented scale, but the available quantity is small. This group of plants consist of peppermint (mentha piperita), Datura (D. metel, D. stramonium) belladone (A. belladone) solanum lacinatum, Papaver somniferum, and Digetalis lanata. Cultivation of these plants has been recommendes on large scale.

Four other plants which are important for a pharmaceutical industry and which are not found in Arab states have been recommended for introduction. These include Mexican yam, (Dioscorea floribunda), japanese mint (Mentha orvensis), Ergot of rye (Claviceps purpurea) and pyrethrum (Chrysanthemum cineraraefolium)

Survey of existing industry indicated that only Egypt and Iraq have some phytochemical industry. The processing units in Egypt produce xanthotoxin, khellin and crude extract. In addition. Egypt has also a well developed essential oil industry producing jasmine concrete and geranium oil for export. Other industrial units produce crude extracts.

It has been suggested that ACDIMA should set up a separate organization under its control to develope a medicinal plants industry in Arab countries. It is also proposed that the new unit should also establish drug farms for cultivation of vegetable raw material on commercial scale.

The proposed organization should process, Senna (C. acutifolia), liquorice (G. glabra), (A. majus), and H. muticus in the first stage. other plants like A. belladona, D. floribunda, M. piperita, C. purpurea, M. arvensis have been suggested to be taken up in the second phase.

Recommendation has also been made for taking up research work to utilize Rouwolfia vomitoria Cathranthus roseus and Belanite eagyotica.

3. Requirements of Phytochemicals for the Arab pharmaceutical industry

As a result of survey of assisting pharmaceutical industries and personal discussion with scientists and technologists it was found that active constituents and crude extracts from the vegetable kingdom are used extensively in different Arab countries. An analysis of the various formulations produced by the leading drug companies in Egypt, Sudan, Syrian Arab Republic and Iraq indicated that more than 25 % of the trade items marketted by them contain either one or more plant products. This does not include the formulation which are imported directly from other countries.

More than 20 pure chemicals and about 80 different crude extracts are used in the four countries menticned above. A large number of crude extracts are being used primarily on the basis of old traditions and at least 80 % of these are not required for a modern health service.

An estimate of requirements of important alkaloids, glycosides, steroids, coumarines, essential oils and crude extracts for all Arab countries is presented in the appendix. The estimates are based on import of these items in Egypt in 1975 and requirements for the all countries have been

calculated by multiplying the Egyptian export figures by 3. This is a very crude estimate as imports give only approximate idea about the need, and these imports do not include the phytochemicals imported in form of formulations from abroad.

Considering the current use of vegetable drugs in the world, the health needs of the Arab people, the export potential, and the availability of raw material in different countries, 19 different plant drugs which includes pure chemicals, essential oils and crude extracts, are considered important for a medecinal plant industry to be established by ACDIMA. The list of these drugs along with their possible source is presented in Table 1.

Table 1. Phytochemicals Required for Arab Pharmaceutical Industry

Serial No.	Active constituent	Name of the plant
1.	Steroidal Sapogenins and glycoalkaloids (Raw material for steroidal Drugs)	Dioscorea sp. Solanum lacinatum S. aviculare Agave sisaliana
2.	Calcium sennoside	Cassia acutifolia c. angustifolia
3.	Xanthotoxin (Ammodin)	Ammi majus
4.	Khellin	Ammi visnaga
5.	Glycyrrhitic Acid liquorice extract	Glycyrrhiza glabra
6.	Tropane Alkaloids, Hyoscine, Hyoscymin Atropine*	Hyoseymus muticus Datura metel, D. stramonium
7.	Opium Alkaloids-Codeine, Morphine, Papavarine	Papaver sommiferum
8.	Digitalis glycosides-Digoxine, lanatosides	Digitalis lanata
9.	Ergot alkaloids-Ergometrine, Ergotamine	Clviceps purpurea
10.	Menthol	Mentha grvensis

* Atropine is now a days obtained from synthetic sources, but can be also manufactured from plants if a economic source like H. muticus is available.

Serial No.	Active constituents	Name of the plants
11.	Euelyptol (Cineol)	Euelyptus globulus
12.	Pyrethrins	Chrysanthemum- cinerarae-folium
13.	Pepperanint oil	Mentha piperita
14.	Euclyptus oil	Euclyptus globulus
15.	Gum Arabic	Acacia senegel
16.	Extract Belladona and total Belladona alkaloid.	Atropa belladona
17.	Extract hysocymus	Hyoscymus muticus
18.	Extract Stramonium	Datura stramonium
19.	Psyllium husk	Psyllium Plantago ovata P. Psyllium

This list does not include some of the important materials like Quinine, Quinidine, Caffeine, Reserpine, Colchicine, Ephedrine, Emetine and Camphor, which are very important for medical use allover the world. These items have been excluded, as some of these like Ephedrine and Camphor are mostly obtained from Synthetic sources and for the rest there is no possibility for obtaining the raw material in any Arab country.

The list also does not contain, those chemicals which are required mostly for perfumery, cosmetic, food and leather industry, as these are beyond the scope of a pharmaceutical complex. A large number of essential oils and food flavours are already being produced by the essential oil industries in Egypt. This industry is in a good shape, and it is suggested that ACDIMA should confine its activities to only those essential oils which are used exclusively for medicine or which are very important for pharmaceuticals. ACDIMA can help the essential oil industry in Egypt to increase their production of those aromatic oils and oleorosine which are in short supply or which have substantial export market. The only improvement which the existing aromatic plant industry needs is the intensification of research and development work for increasing the yield and active constituents of plants like Geranium, spearmint, peppermint and rose.

Only a limited number of crude plant extracts have been included as others are either not required in significant quantities or there is no raw material available in the Arab countries. Moreover there is a number of large pharmaceutical companies like CHEMICAL INDUSTRIES DEVELOPMENT Co. and MEMPHIS Co. in Egypt and STATE DRUG Co. of IRAq at Samara with sufficient equipment and facilities to satisfy the crude extract requirement of all Arab countries. As already indicated, according to modern medical science, a large number of these plant extracts are not essential for medicine and can be easily dispensed with.

C. Availabiligy of raw materials

The Arab countries, which cover a vast area in the Middle East and North Africa, are very rich in vegetable resources which can be exploited for industrial purposes. Because of wide variety of climatic and soil conditions, all types of medicinal plants of tropical, subtropical, temperate and mediterranean region can be profitably cultivated in one or the other Arab country.

A perusal of the survey report produced by AC DIMA in "ARAB PHARMACEUTICAL INDUSTRIES", shows that about 106 different species of medicinal plants have been reported to occur in 13 different Arab countries. A close study of this list

shows that only 21 can be classified as medicinal plants according to current international use of plants in modern medicine in the world. Out of these only 10 can be considered to be of use as raw material for a modern pharmaceutical industry. Unfortunately the list gives an erroneous impression about the availability of raw material in Arab states, as even plants like onion, garlic, groundnut, and common lawngrass have been included in this list.

A scientific survey carried out on the basics of this list indicated that only six of the plants are available in sizable quantities and that too from wild sources. The distribution and availability of these plants along with their active constituents is given below in Table 2.

Table 2. Medicinal Plants available in large quantities in Arab countries.

Serial No.	Name of the plant	Active constituents	Location & source	Quantity* in Metric /Tons
1.	Liquorice (Glycyrrhiza glabra)	Glycyrrhizitic Acid Liquorice extract	Iraq, Syrian A.R. (wild)	7728.00
2.	Senna-podsand leaves (Cassia acutifalia)	Calcium sennosides	Sudan (wild)	1751.00
3.	Gum Arabic (Acacia senegel)	B.P. grade Gum Arabic	Sudan (wild)	28347.00
4.	Ammi majus	Xanthotoxin (Ammodin)	Egypt (wild & cultivated)	100.00
5.	Ammi visnaga	Khellin	Egypt (wild & cultivated)	200.00
6.	Henbane (Hyoscymus muticus)	Hyoscine, ,Hyoscymine, Atropine	Egypt Sudan (wild)	Exact figure not known.

* estimate based on export of these raw materials in 1975 (Bureau of statistics Egypt, Sudan, Syrian Arab Republic, Iraq)

Chammomile.(Matricaria chammomila) is cultivated on large scale in Egypt, but the dried flowers are exported to Europe, and there is no scope for processing this material.

Seven different plants which are required for medicine have been tried on experimental scale and these can be cultived on commercial scale after further improvement of agrotechnology and pilot scale trial. The plants along with their main active ingredients and area for cultivation are given below in Table 3.

Table 3. Medicinal Plants which can be cultivated in different Arab countries

Serial No.	Name of plants	Active constituent	Area for cultivation
1.	Belladona (*Atropa belladona*) *	Belladona extract Total alkaloids	Mountains of Syrian A.R. Iraq, Egypt
2.	Solanum (*Solanum lacinatum*) *S. aviculare*	Solasodine	Egypt
3.	Opium Poppy (*Papaver somniferum*)	Codeine, Morphine papaverine	Iraq
4.	Peppermint (*Mentha piperita*)	Peppermintoil	Egypt, Syrian A.R. Iraq
5.	Datura (*Datura metel*)	Hyoscine, Hyoscymine	Egypt, Sudan
6.	Stramonium (*Datura stramonium*)	Hyoscymine Stramonium extract	Egypt, Syrian A.R. Iraq
7.	Digitalis (*Digitalis lanata*)	Digoxine	Mountains of Iraq & Egypt

* *A. belladona* is a temperate plant and as such optimum yield and alkaloid content is obtained only in temperate areas. If cultivated in Egypt both yield and alkaloid content would be low.

In addition the above seven plants efforts will have to be made to organise large scale cultivation of Ammi majus, Ammi visnaga, Hyoscymus muticus and Cassia acutifolia in Egypt and Sudan, in order to support a sizable phytochemical industry. The quantity of these drugs available from wild sources is not sufficient, and no industry can be based only on vegetable raw materials from wild growth unless the quality is guaranteed and raw material supply is not exhausted by continuous collection.

As no Arab country has a good source of stercidal sapogennis, Ergot alkaloids, Pyrethrins, and Menthol, the proper species of plants used for these chemicals would have to be introduced in order to grow these raw materials to feed the industry. The list of such plant materials along with the area for introduction is given below in Table 4.

Table 4. Exotic plants which are required to be introduced in Arab countries

Serial No.	Name of plants	Active constituents	Area suitable for introduction
1.	Japanese mint (*Mentha arvensis*)	Menthol	Egypt, Sudan
2.	Ergot of Rye (*Claviceps purpurea*	Ergometrine Ergotamine	Mountains of Syrian A.R. and Iraq
3.	Pyrethrum (*Chrysanthemum cinerariaefolium*)	Pyrethrins	Mountains of Iraq, Syrian A.R., and Sudan
4.	Mexican yam (*Dioscorea floribunda*)	Diosgenin	Egypt and Sudan

There is no alternate source for the first three plants and very little research work has been done on cultivation of these plants in Arab states. Some preliminary work was carried out at "CAIRO COMPANY OF FOOD FLAVOURS AND ESSENCE" which indicates that Japanese mint grows well in Egypt. However, the plant has been introduced on a very small scale and no data about yield or oil content are available.

As regards the fourth plant, The Mexican Yam (Dioscorea Floribunda), it is the most widely used source of Diasgenin in the world today. About 60 % of the total requirement of steroidal drugs are obtained from Diosgenin isolated from tubers of this plant and related species like D. composita and D. spieuliflora growing wild in Mexico and other central American countries. D. floribunda has been cultivated successfully in India, Mexico and U.S.A. (Puertorico) and the climatic as well as soil conditions are ideal for optimum growth of this plant in light soils of Egypt and Sudan. As steroidal drugs consisting of corticosteroids, sex hormones, anabolic steroids and oral contraceptives, are the most important chemicals obtained from vegetable sources, introduction of the proper species of plant is essential for development of any large size pharmaceutical industry in Arab countries.

These drugs are the costliest among the phytochemicals and their wide use as antiarthritic, antiinflammatory and oral contraceptive agents gives them a prominent place in health program of any developing or developped country. Steroidal drugs are the most commonly imported items by all the Arab countries and in most of the cases only formulations are imported at an exorbitant price. The basic raw material, Diosgenin has a considerable market in the world. It is estimated that the present requirement of Diosgenin in the world is about 1,000 tons annually (valued approx. 80.00 million $ Dollars). This requirement is expected to reach 2000 tons during the next 3-5 years specially because of intensification of family planning program in heavily populated countries of Asia.

The second alternate source for steroids is the glycoalkaloid, solasodine isolated from leaves and fruits of Solanum lacinatum an S. aviculare. Considerable research work has been done in Egypt on S. lacinatum, specially by the medicinal plant section of the National Research centre at Cairo Headed by Dr. Faiza Hammouda and by Dr. Jamal Mohd. Ghorab of Memphis Co. The plant contains about 1.5 % solasodine which has been used commercially to a very limited extent in East European countries and U.S.S.R. The plant has been cultivated successfully by the scientist at National

Research centre and at the Medicinal Plant Research Station of "General Organization of Drug Research and Control" near the pyramids. Although different scientists differ in their estimates the average yield obtained thus far does not exceeded 500 kg per acre (600 kg per feddan). Similarly no scientific study has been made to work out the actual cost of production of Solasodine. On the basis of discussion with Dr. Ghorab, Dr. Hammouda and Dr. Fardaus of C.I.D. Co. it can be concluded that the cost of chemicals and raw material comes to 50-60 Egyptian pounds (75 to 90 U.S. Dollars). Taking the overhead expenditure interest on capital and depreciation, the actual cost would come to more than 100 U.S. Dollars. On the basis of this calculation the cost of production exceeds the current international price of Diosgenin or Solasodine which is approximately 80 U.S. Dollars per kg and it is expected that it would stabilize at about 50 U.S. Dollars per kg in the next two to three years. The prices of this product have fluctuated from 40 dollars to 120 Dollars per kg during the last 3 years. It is therefore suggested that further research should be carried out specially to increase the yield of dry leaves up to 1.5 tons per acre. which may be possible if the job is given to a competent agronomist. In the mean time effort should be made to introduce mexican yam (D. floribunda) and to work out indigenous agrotechnology in order to have the ideal raw material for

steroidal drugs in the Arab countries.

During the tour in Sudan another interesting raw material was found growing throughout semiarid and humid parts of Sudan. The common "Helig" tree (Belanite eagyptica) as it is called in Sudan forms approximatly 25 % of the tree population of Sudan. It is distributed widely in all those areas in clay and sandy soils of Sudan where rainfull exceeds 350 mm annually. It is found growing along the rivers and streams in association with Acacia senegel. Although most of the parts of the tree contain saponins, mesocarp, the fleshy portion of the fruits contain 1-1.5 % total sapogenin which mainly consist of diosgenin, yamogenin and some other minor genins. The fruit of the tree which has a sweet acrid taste is eaten by children allover Sudan and the dried fruits, often called soapnuts, are used for washing clothes by poor villagers. The seed of Belanite fruit has been found to contain more than 40 % of a fixed oil of good quality which can be used as an edible oil and in soap industry. In fact the people in the villages have been using the seed oil for cooking for several centuries. The cake left after removal of oil is a rich source of a protein, the nutritive value of which has been found to be comparable to soyabean protein.

Considering all the qualities of this fruit as a potential raw material for medicine and food, there is an immediate need to work out technology for manufacture of Diosgenin, fixed oil and protein from this plant. The raw material is available in huge quantities, and the only cost involved is the labour used in collection of fruits, even at present the dried fruit is available at 50 Sudanese pounds per ton and the cost would come down to about 30 S.P/ton if an organization takes up collection work on a large scale. Dr. Ibrahim Mohamed Abu Al Futuh, Senior Consultant and Head of the division of pharmaceutical sciences at the Industrial Research and Consultancy Institute has already taken up the project. However he needs help and encouragement to develope a viable technology.

In addition to the plants mentioned above there is good possibility for cultivation of cathranthus-roseus and cymbopogen citratus (lemon grass) in Egypt and Sudan. These plants should be tried on experimental scale.

During the discussion with scientists in Sudan it was found that Rauwolfia vomitoria, a good source of Reserpine is found growing wild in certain parts of southern Sudan. It is worth while to investigate the possibility of explanting this valuable drug.

D. Processing of medicinal plant

1. The existing phytochemical industries in Arab countries.

A survey of existing industries indicated that some kind of phytochemical industry exists only in Egypt and Iraq. The industry which is much well developped in Egypt can be classified into two types. The first category of industry which is in a fairly advanced stage of development is the "Aromatic plant Industry" producing essential oils, and oleoresins used in perfurmery, cosmetic and food flavours. There is one large state owned company "The CAIRO COMPANY OF FOOD FLAVOURS AND ESSENCE" and several other private units which produce sizable quantity of Geranium (Pelargonium-graveolens) oil, jasmine (jasminum-grandiflorum) concrete and absolute, small quantities of peppermint (Menta piperta) oil, spearmint (Mentha-spicata) oil, Bitter orange oil, Neroli oil, Fennel oil, Carraway oil, Thyme oil, Garlic oil and a number of other food flavours. Today Egypt is one of the major exporters of Geranium oil and jasmine concrete in the world. The production of important essential oils is presented in Table 5.

The estimated figures have been obtained by taking average yield of oil per feddan and the area under

cultivation. The figures for areas have been produced by department of Economics and statistics, Ministry of Agriculture, Egypt. Production figures for spermint , Peppermint, Bitter orange and Neroli oils have been given by Cairo Company of Food Flavour and Essenes.

Table 5. Production of Important Essential oils in Egypt (1977)

Serial No.	Name of the Oil	Area Under Cultivation in Feddan	Estimated production of oil in Tons
1.	Geranium oil	11,000	210.00
2.	Jasmine concrete	2876	11.54
3.*	Peppermint and Spearmint oil	446	2.0
4.	French Basil oil	75	1.50
5.	Bitter orange oil	80	0.50
6.	Neroli oil	80	0.50
7.	Majoram oil, Rosemary oil, Rose concrete, Aniseedoil, Fennel oil, Dill oil, Thyme oil, Cumin oil,& Garlic oil.		Small quantities

* Only a part of Peppermint herb is distilled for oil and a major portion is exported as dried herb for medicinal tea.

The essential oil industry is in a fairly good shape except for the fact that it needs a good Research and

Development service to improve the agrotechnology. The distillation equipment also needs improvement. The recovery of oil can be improved if the present coil type condensers can be replaced by tubular condensers.

The second type of industry existing in Egypt consists of the medicinal plant Industry. There is only one company, "THE MEMPHIS Co." which has a plant for isolation of Ammodin (xanthotoxin)(500 kg annually) from Ammi majus seeds and khollin (1.000 kg annually) from Ammi visnaga seeds. The company has an old extraction plant which is being replaced by a new continuous extraction plant of a much larger capacity. The authorities of the company were not prepared to show their new plant. They were also not agreable to discuss their technology. Although recovery of khollin is good, the recovery of xanthotoxin is only 50 % than normal recovery in any modern plant. Since the company is not prepared to discuss their methods of extraction hence no improvement can be suggested. The low recovery may be due to poor quality of raw material, or the defect in technology. There is only one other company in Egypt, C.I.D. company which makes crude extracts from plants. Approximately 60,000 litres of crude extracts are prepared. The most important extracts produced by the company consist of liquorice extract, Belladona extract, Valeriana extract,

Gentian extract, Rhubarb extract and a number of minor plant extracts and tinctures. The company in collaboration with National Research Centre has also produced solasodine on pilot plant scale. However, the commercial production has not been started because the cost of production is very high. As the extraction plant is producing only crude extract, there is an idle capacity of at least 50 %.

There is only one industrial unit "The Samara pharmaceutical complex" under the STATE DRUG Co. of IRAQ which has a large size (4 batteries of 7 extractors) solvent extraction plant with all the accessories. The plant which was imported from U.SS.R sometimes back was meant for processing more than two dozen medicinal plant suggested by Russian experts. A farm for production of various plants was started in 1961, but it was closed down, after initial experiments were completed on about 40 medicinal plants. At present the equipment is being used for a small quantity of crude extracts mostly for consumption in company's own formulations. It is processing about 1.6 tons of belladona, 5.6 tons of liquorice, 5.3 tons of valeriana roots, and small amount of minor vegetable drugs like ginger and cardamum. Thus the plant has an idle capacity of about 80 %. The size of the plant is sufficient to supply crude extracts to four other Arab countries. It is suggested that the medicinal plant farm at Abughrab should be restarted and the

crude drugs produced at the farm should be processed at Samara to supply vegetable drugs to Syrian Arab Republic Lebanon, Jordan, Saudia Arabia and Kuwait.

Recently a project for production of liquorice powder has been taken up by the ministry of Industry in Iraq. However, the exact condition of the project and the rated capacity of the plant is not known.

2. Need for Setting up of New Industries

A study of the available raw material, present and future requirements and the products already manufactured by existing industry shows that a large size phytochemical industry would have to be established to fulfil the requirements for internal use and export.

It is suggested that ACDIMA should take immediate action for manufacture of the following chemicals from the raw material already available in commercial quantities:

1. Calcium sennoside from Sennaleaves and pod. (C. acutifolia) available in Sudan .
2. Glyeyrrhizitic Acid and Liquorice extract and powder from Liquorice (G. Glabra) available in Iraq and Syrian Arab Republic
3. Xanthotoxin (Ammodine) from Ammi majus, available in Egypt.

4. Hyoscine and Hyoscymine from Hyoscymus muticus, available in Egypt and Sudan.

There is considerable demand for senna glycosides in the world and at present all the senna collected from wild growth in Sudan is being exported to European countries. In order to produce a large quantity of sennosides it is desirable that cultivation of this plant should be taken up in Sudan. As the plant grows well even in salt affected areas in Sudan, it can be easily produced even on wasteland.

At present most of the liquorice collected from the desert areas of Iraq and Syrian Arab Republic is exported in crude form. As there is considerable demand for liquorice extract, and powder allover the world, it is advisable that the entire quantity (approx. 30, 000.00 tons) should be processed in Arab countries and only finished products should be exported. In addition to concentrated extracts, glycyrrhizitic acid can be also produced from the roots. There is appreciable demand for this chemical, as it is being used widely for treatment of peptic ulcers.

Although some xanthotoxine (Ammodine) is being produced by Memphis Company, the quantity (500 kg) is not sufficient for meeting the world demand. The demand for this chemical has increased considerably during the recent year because if its use for treatment of Psorasis and as

a cosmetic in suntan lotion.

Similarly there is a sizable market for hyoscine and hyoscymine in the Arab countries. Both these products can be also exported. There is acute shortage of hyoscine in the international market (present price approx. 800.00 U.S dollars per kg). The raw material (H. muticus)is found growing wild all over Egypt and some parts of Sudan. Initially the processing can be started from the drug obtained by collection. However in order to have a consistent supply of good quality of the drug, a good strain of the plant would have to be cultivated on large scale. Another alternate raw material (Datura metel) can be also used for processing if sufficient quantities can be obtained by organized cultivation.

Production of khellin from A. visnaga should be left to Memphis Co., as it is able to meet the world demand and it has capacity to meet any increase demand of the chemical in the market.

In addition to above four plants ACDIMA should also consider the possibility of refining and bleaching of the large quantity of Gum Arabic (A. Senegel) exported from Sudan in crude form. Sudan has the monopoly of this gum in the world, and it can fetch much better price if the crude product is refined bleached and exported in a presentable form.

Production of the following chemicals should be taken up after arrangement have been made for production of plant material in large quantities at a price which is economic for processing.

1. Diosgenin from Mexican yam (D. Floribunda)
2. Solasodine from Solanum sp. (S. lacinatum)
3. Menthol from japanese mint (M. arvensis)
4. Codeine, Morphine and Papaverine from opium poppy (P. somniferum)
5. Ergotamine and Ergometrine from ergot of rye (C. purpurea)
6. Belladona alkaloids and extract from Belladona (A. belladona)
7. Peppermintoil from peppermint (M. piperita)
8. Euclyptol from Euclyptus (E. globulus)
9. Citral from lemon grass oil (C. citratus)
10. Digoxine from Digitalis (D. lanata)

In the third phase of the project, the industry should take up production of formulations based on phyto-chemicals. It could also think of making steroidal drugs from diosgenin.

Production of diosgenin from "Helig" fruits (B. aegyptica), total alkaloids of cathranthus (C. Roseus)

or reserpine from rauwolfia vomitoria can be also considered if the research work proves these processes as economically feasible.

E. Proposed outline for the execution of the project

The method of approach for establishing a pharmaceutical industry for producing vegetable drugs would be quite different than synthetic chemicals or antibiotics. In this case ACDIMA itself would have to take up production of necessary raw materials. Not only the plants have to be produced commercially, but any organization which intends to take up production would have also to take up pilot scale trials and use the existing data for large scale cultivation of drug plants.

It is therefore suggested that ACDIMA should set up an organization under its control to carryout this project. The organization can be designated "ARAB COMPANY OF MEDICINAL PLANTS" or "ARAB PHYTOCHEMICAL CORPORATION". This organization should have two main divisions; the raw material production division and the processing division.

The first unit which would be responsible for development of necessary agrotechnology as well as large scale production of the plants required by the processing unit. It should be headed by a qualified agricultural

scientist, with considerable experience in research, and development, and large scale production of economic crop plants. He should be assisted by people who are also able to carry out their research work for commercial cultivation of medicinal and related plants. There is no need to separate research using and the production, as it would prove expensive for any commercial undertaking.

In order to start this unit it is suggested, that at least 1,000 acres of land should be acquired in Egypt and Sudan, for setting up ACDIMA'S own farms. Similarly about 200 acres of land should be obtained in the montains of Syrian Arab Republic and Iraq. These farms would serve as nucleus for cultivation of medicinal plants . The farms would encourage the private farmers in the area to take up cultivation on their individual farms. The drug produced by the farmers would be purchased by the company. The company would also help the farmers by providing necessary seed, agricultural inputs and advanced technology.

The processing unit should be under a competent phytochemist, pharmaceutical chemist, or chemical engineer who has at least 10 years experience in research and production of phytochemicals from plants. In this case also the research, development and commercial processing should go together. The unit should be equipped with a good size

pilot plant to update the technology acquired by ACDIMA. The processing factory in the initial stages should have enough equipment to handle about 2,000.00 tons of senna, 1000 tons of ammi majus seeds, 20,000 tons of liquorice and 1,000 tons of hyoscynues or datura leaves. The same machinary can be used for taking up production of items proposed to be taken up in the second phase.

Before making the final selection of land for drug farms is made an international or local agricultural expert should be consulted, as the choice of land is very important for the project, Necessary technology expertise including planting material would be available from India if ACDIMA approaches council of scientific and Industrial Research through UNIDO.

The feasibility reports along with flow sheets and list of equipment and machinery would be included in the final report.

F. Recommendations

1. ACDIMA should take immediate step to set up a separate organization under its control to start a new medicinal plant industry in Arab countries.

2. The proposed company should not only process existing raw materials but should also have a unit for producing medical plants on commercial scale.

3. Both the processing well as well as cultivation units should carry out applied research and development to produce important vegetable drugs for internal consumption and control.

4. The commercial unit established by ACDIMA should take up processing of Senna leaves and pods, lequorice roots, ammi majus seeds and henbane leaves in the first phase of its project.

5. ACDIMA should help the existing industries, specially C.I.D. Co. in Egypt and State Drug Company in Iraq to utilize their idle capacity for production of crude extracts for all Arab countries.

6. As soon as a medicinal plant organization is formed steps should be taken to start drug farms in Egypt (1000 acres) Sudan (1000 acres) Syrian Arab Republic (200 acres) and Iraq (200 acres) to start work on research. on cultivation and commercial production of medicinal plants.

Services of an international expert may be obtained for selection of land and training of staff to run the forms.

Appendix

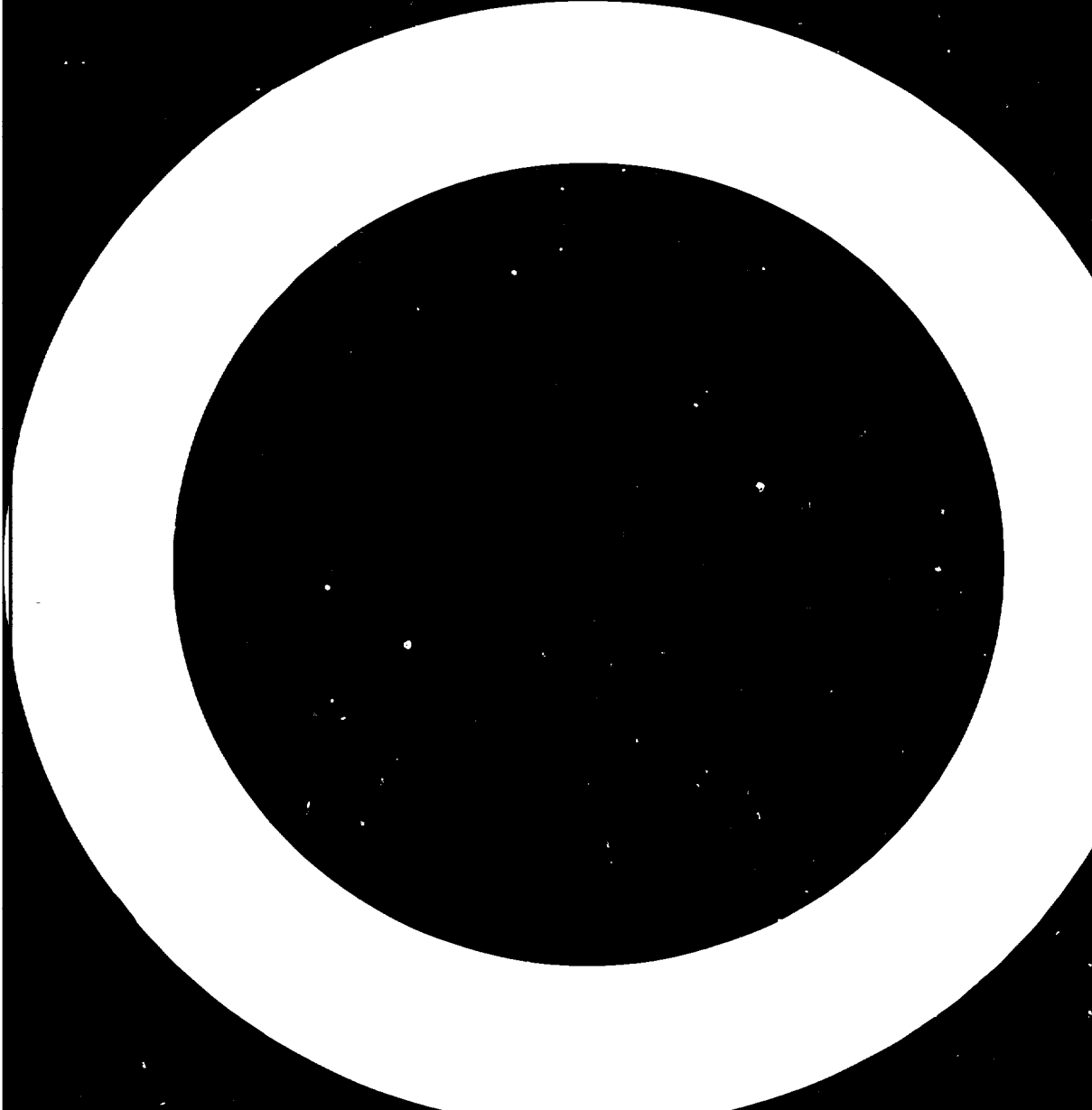
ESTIMATED REQUIREMENTS OF PHYTOCHEMICALS AND CRUDE EXTRACTS IN ARAB COUNTRIES

Serial No.	Name of the chemical or extract	Actual Import in Egypt in kgms	Estimated requirement of Arab countries
1.	Steroidal drugs (conticosteroids, sex hormones)	553.37	1665.00
2.	Codeine salts	2750.1	8250.00
3.	Papaverine salts	2060.28	6180.00
4.	Caffeine salts	10689.77	32067.00
5.	Ergotamine tartarate	81.16	258.00
6.	Ergometrine maleate	7.73	23.00
7.	Hyoscymine sulphate	20.00	60.00
8.	Hyoscine hydrobromide	129.4	388.00
9.	Reserpine	12.70	38.00
10.	Colchicine	7.50	22.00
11.	Digoxine	3.44	10.00
12.	Quinine salts	1049.5	3148.00
13.	Quinidine salts	126.5	379.00
14.	Menthol	2303.9	6911.00
15.	Camphor (natural)	1273.5	3820.00
16.	Camphor (synthetic)	2153.1	6459.00
17.	Thymol	8161.5	24484.00
18.	Euclyptol (cineol)	78.16	234.00

Serial No.	Name of the chemical or extract	Actual Import in Egypt in kgms	Estimated requirement of Arab countries
19.*	Pyrethrum extract (23 %)	——	5,000.00
20.	Euclyptus oil	2303.1	6909.00
21.	Peppermint oil	3800.4	11401.00
22.	Extract Belladona (all types)	8043.00	24129.00
23.	Extract buchu	13125.00	39375.00
24.	Cascara sagrada dry	5,000	15,000.00
25.	Extract gentian	21500.00	69500.00
26.	Extract rhubrab	34990.00	104970.00
27.	Extract senega	23000.00	69000.00
28.	Extract lobelia	5080.00	15210.00
29.	Extract hyoscymus	3140.00	9420.00
30.	Extract Ipec	3854.00	11562.00
31.**	Extract stramonium	——	2000.00
32.	Extract liquorice (liquid)	2700.00	7100.00
33.	Extract liquorice (dry)	2100.00	6340.00
34.	Syrup tolu	16,000.00	48,000.00

* Data based on consumption in Sudan

** Data based on consumption in Sudan



XV. PRODUCTION OF GLAS CONTAINERS FOR THE PHARMACEUTICAL INDUSTRY (GLASS VIALS. BOTTLES ETC.)

A. Summary

A survey of the glass container industry in Egypt reveals that the local glass container manufacturers have not been able to satisfy the demands of the pharmaceutical companies in the ACDIMA countries, most probably on account of the poor quality of the glass containers manufactured locally.

The analysis done in this study indicates that there is sufficient demand for pharmaceutical blown glass containers in the ACDIMA Countries to justify a small plant devoted to the manufacture of Type II and III pharmaceutical blown glass containers. This is based on the assumption that the proposed glass plant would be able to achieve an 80% share of the pharmaceutical blown glass container market in the ACDIMA Countries.

The proposed plant with a 100 tons per day furnace would require an investment of about $19 million[1/] and would show an internal rate of return of about 9% with a payback period of about 8½ years.

1/ All financial and sales figures shown in current 1977 dollars. The exchange rate used in this chapter is LE 1 = $US 2.5.

B. Product form analysis and packaging of pharmaceutical products

The level of demand of blown glass containers is sufficient to justify a small blown glass container plant with a 100 tons per day furnace. The economic analysis shows that such an operation would break even at about 13,000 to 14,000 tons, based on a selling price equal to international glass container prices. A plant such as this would require an investment of about $19 million and would show an internal rate of return of about 9% with a payback period of about 8½ years.

Therefore the options available to ACDIMA management are:-

(a) Pursue the developments at both El Nasr Glass and Middle East Glass to see if with their new capacity, a supply of quality glass can be assured for the pharmaceutical industries in the ACDIMA countries, or

(b) Invest $19 million in a glass plant to manufacture pharmaceutical containers if the 9% return estimated for the glass plant is acceptable.

There are 30 pharmaceutical plants in the ACDIMA Countries, with a total production value of about $200 million, of which the majority (80%) is accounted for by Egypt. Therefore, the current market for pharmaceutical glass is in Egypt and most of these plants are located in and around Cairo.

1. Product Form Analysis

As no significant correlation between therapeutic class and type of packaging used was found, the analysis has been done by product form only.

Distribution by product form of the unit production of pharmaceutical products in Egypt is shown in Table 1.

The figures in Table 1 indicate that shifts are occurring in the share of pharmaceuticals sold by product form. Comments made by respondents during the survey also indicated that shifts between product form are occurring and will continue to occur in the Egyptian market. These shifts are occurring for a number of reasons:

- Introduction of new drugs into the market; for example, Tetracycline, an antibiotic which can be administered orally versus the more established antibiotics which are injected

- Ease and convenience of administering capsules and tablets versus liquids and injectables

The distribution by product form of pharmaceutical production when measured in dollars is compared below for Egypt and the U.S.A.:

	U.S.A. 1972	Egypt 1973
Solid Oral	63%	44%
Liquid	21%	21%
Injectables	9%	25%
Ointments	4.6%	5.7%
Suppositories	0.9%	1.9%
Powder & Granules	0.6%	3.2%
Other	0.6%	3.6%

Sources: Federation of Egyptian Industries Yearbook
Market Study of Pharmaceutical & Drug Packaging - Technomic

Table 1. Distribution of pharmaceutical production in Egypt by product form

Product Form	1973		1974		1975		1976	
		%		%		%		%
Ampoules	165	4.1	139	3.1	187	4.0	206	3.7
Vials for Injectables	60	1.5	45	1.0	72	1.5	74	1.3
Tablets	3,520	87.4	3,924	87.6	3,952	85.5	4,596	83.8
Capsules	178	4.4	264	5.9	279	6.0	470	8.5
Liquids	58	1.4	50	1.1	62	1.3	64	1.2
Powders & Granules	9	0.2	14	0.3	15	0.3	15	0.3
Ointments & Pastes	25	0.6	23	0.5	34	0.7	29	0.5
Suppositories	11	0.3	18	0.4	19	0.4	31	0.5
Total	4,027	100	4,478	100	4,622	100	5,485	100
% Increase	-4.3%		11.2%		3.2%		21.3%	

Source: Federation of Egyptian Industries Yearbook

Production in Millions of Units

2. Packaging of Pharmaceutical Products

Pharmaceutical products in Egypt are packaged in the following types of containers:

Glass Ampoules and Vials
Blown Glass Bottles and Jars
Plastic Vials, Bottles Jars and Pouches
Metal Cans
Blister Packs
Aluminum Foil Strip Packaging
Metal Tubes

Information on the other ACDIMA countries is not available but it is believed that the types of packaging used is similar to that in Egypt.

Blister and Strip packaging are popular forms of packaging for tablets, capsules and suppositories. There is no statistical data available on the use of the various types of packaging materials. Rough estimates arrived at by consulting industry personnel are shown in Table 2. Source and availability of these various packaging materials is discussed further in the section on the Packaging Industry.

Packaging machinery used by the Egyptian pharmaceutical manufacturers range from hand filling and capping to completely automated washing, filling, labelling and capping lines. However, most of the lines are a combination of machine and manual operations. The filling and capping operations are most often done on slow speed machines, the other operations of labelling and packaging are manually performed.

Table 2. Type of packaging used by product form

	Estimates 1975/1977					Forecast 1980					1985				
	Glass	Plastic	Metal	Strip or Blister	Tubes Metal or Plastic	Glass	Plastic	Metal	Strip or Blister	Tubes Metal Or Plastic	Glass	Plastic	Metal	Strip or Blister	Tubes Metal or Plastic
Ampoules	100					95	5				90	10			
Vials for Sterile Solutions Etc.	100					90	10				85	15			
Tables	10	40	20	30		10	35	15	40	-	10	35	10	45	
Capsules	25	55	15	5		15	55	15	15		10	50	10	30	
Syrups & Solutions	100					80	20				70	30			
I.V.Solutions Large Vol. Parenterals	50	50				40	60				30	70			
Droppers	95	5				75	25				60	40			
Powders & Granules	98		2			80	10	10			60	20	20		
Ointments & Pastes	10				90	5	5			90	5	5			90
Suppositories		20		80					100					100	

Some of the pharmaceutical manufacturers mentioned that their plans to install faster and more automated filling lines cannot be implemented because of the problems encountered with glass containers. The glass containers they receive are usually off specifications as to shape and dimension and therefore create problems in the high speed filling machines.

They are attempting to switch from glass to plastic wherever possible because of these problems plus the inherent advantages of plastic bottles such as lightweight, non-breakability etc. However, this is not possible for all products, because of non-compatibility of plastics with the product packaged.

The role of packaging as a merchandising tool is not as important in Egypt, as say in North America, because:

a) The pharmacies are not self serve type operations, even for non-ethical products, therefore, packaging does not have to play a role in merchandising

b) The pharmaceutical industry is owned largely by the government and the number of competing drugs allowed on the market is limited by the government

For these reasons the need to update or change packaging for marketing or esthetic reasons is not important. Changes in packaging are considered mainly if there are problems with existing packaging or for economical/technical reasons.

However, most of the Egyptian pharmaceutical manufacturers are interested in exporting to other middle east countries. Exports allow them to earn valuable foreign exchange which in turn allows them to import needed equipment or materials. For the export markets, they are more conscious of their product image, since in those markets their products have to compete with products of international firms. Hence the search for better quality packaging for export products.

C. The packaging industry

Very little published information is available on the packaging industry in Egypt or the other ACDIMA countries. The dollar value or volume of production of this industry is not known. However, it is known that most of the larger ACDIMA countries such as Egypt, Syria and Iraq have some form of packaging industry. The plastic, metal and glass container industries have been discussed briefly below.

1. Plastic Container Industry

Most of the ACDIMA countries are manufacturing a limited amount of injection molded and blow molded plastic containers. However, no information was available on the quantity or quality of their production.

In Egypt there are a small number of private and public sector companies fabricating plastic products. Of these, Medical Packaging Company (in the public sector) is the largest manufacturer of plastic packaging for the pharmaceutical industry. Medical Packaging manufactures:

Injection Molded Plastic Vials
Blow Molded Bottles
Injection Molded Closures and
Compression Molded Closures

PRICES OF PLASTIC BOTTLES (Provided by Medical Packaging Co.)
1 LE = $2.5 U.S. Prices for 1000 bottles

Size	Price
1000 cc	$ 152.5
60 cc	$ 37.5
15 cc	$ 19.8

El Nasr Pharmaceutical Chemicals Co. has an in-house facility for manufacturing plastic blow molded bottles for large volume parenterals. Their production is about 2 million per year.

A small number of plastic squeeze bottles for nose drops etc. are imported into Egypt. A number of the pharmaceutical companies have in-house machines for blister packaging of capsules and tablets. The plastic sheet/strips for these operations is produced by Medical Packaging Co.; the aluminum foil is imported.

2. Metal Container Industry

In Egypt, metal containers are used for bulk packaging 1000 tablets or capsules for hospitals and clinics. A considerable amount of metal cans are produced in Egypt and Iraq for the food processing and canning industries. A limited number of small aluminum containers are imported for packaging effervescent granules for the export market.

Metal tubes are used in Egypt for pharmaceuticals, cosmetics and toiletries. There are two companies producing metal tubes, of which one is a captive (in-house) plant producing about 2 million tubes for shaving cream. The major producer is Medical Packaging Co., with an annual output of about 45 million aluminum tubes and about 10 million tin tubes.

3. Glass Container Industry

3.1 General

Demand for glass containers in the ACDIMA countries far exceeds supply. Even in countries such as Egypt and Iraq, with local production capacity, glass is imported from countries such as Lebanon, Czechoslovakia, France, India, Turkey, Singapore etc. For example, Iraq, in 1975, imported 15,400 tons of glass containers valued at $7.8 million and Egypt imported about 19,000 tons of glass in 1976.

Information on the total consumption of glass in these countries is not known.

The major end use market for glass containers is the soft drink industry. The other end use markets are relatively small in comparison to soft drinks. In some of these countries where liquor, wine and beer are prohibited and no food processing or cosmetics industry exists, such as in Saudi Arabia, soft drinks is the only market for glass containers.

Comments received from people interviewed, suggest that production in some end use industries is restricted at times due to unavailability of glass or other suitable packaging. It is expected that with rising incomes and increasing industrialization, the demand for glass containers will increase substantially.

3.2 Glass Container Manufacturers

Table 3 below shows the number of glass plants by country and their location, with particulars where known.

Table 3. Glass container manufacturers in ACDIMA countries

Country	Location	No. of Plants	Description
Egypt	Cairo	4	1 Automated Plant (30,000 ton caps); 3 Semi-automated/ manual plants
	Alexandria	1	
Saudi Arabia	Daman	1	
Syrian A.R.	Damascus	1	
Iraq	Baghdad	1	3 furnaces, nine - 6 section single gob machines
Tunisia	Tunis	1	
	Tripoli	1	
Sudan	Khartoum	1	
Total		11	

Very little information is available on these plants; for example, it is not known whether they are modern plants producing glass using automatic machines or producing the glass manually or with semi-automated machines. Neither is there any information available on their capacities or the quality or type of glass containers manufactured.

Lebanon, a non-ACDIMA, Arab country reportedly has two relatively modern glass companies, Saliver Glass and Malibon Glass producing good quality glass containers. Both companies are believed to have been aggressively exporting glass to the Arab countries in the middle east.

3.3 Problems with Locally Produced Glass Containers

Information on locally produced glass containers was available only for Egypt.

The quality of Egyptian glass containers, especially those made by the manual or semi-automated process, is poor, when compared to international standards.

The glass containers are not made to rigid standards and there seems to be considerable variance in the internal and external dimensions of the containers. The neck finishes (that is the threads) are not consistent. These cause problems in the end use industry plants, especially with the filling and capping machines. Because the glass containers in Egypt are not coated to reduce friction on the filling lines, they limit the speed at which they can be filled, ruling out high speed filling machines.

Glass containers are packed in jute bags with straw filling, and these bags are loaded and unloaded manually. Because they are loosely packed in jute bags, the containers have to be washed and cleaned prior to use at the customers' plant. Also, there is considerable breakage in shipment reported by customers, due to the use of the jute bags.

3.4 Supply Situation

As mentioned earlier, both Iraq and Egypt are net importers of glass containers. Even with these imports, the demand for glass containers in Egypt at least is not fully satisfied, for only those firms or industries can import glass who either:

a) have an independent source of foreign exchange (usually only through export earnings) or

b) are classfied as a priority industry (such as pharmaceuticals)

In 1976, Egypt imported the following quantities of glass containers:

Importing Industry	Type of Container	Approx Tons (metric)	Approx Cost to User* $000s	$/ton
Pharmaceutical	Vials	2,460	$2,818	$1,145
	Ampoules	1,200	1,912	1,593
	Plasma Bottles	1,300	740	570
	Dropper Bottles	1,380	2,024	1,466
		6,340	$7,494	$1,180
Wine		5,000	n.a.	
Beer		4,000	n.a.	
Soft Drinks		4,000	n.a.	
Total		19,340		

* The User Cost includes customs tariffs, inland transportation, storage and handling and the mark-up of the importing company.

Glass Container importation figures for other years were not available. It seems that based on other available information (non statistical) glass imports in 1976 were considerably higher than those of past years.

Iraq, in 1975, imported 15,450 tons of glass valued at about $7.8 million. (equivalent to an average price of $505 per ton). The major exporting countries were Lebanon, Turkey and Czechoslovakia.

D. Glass container industry in Egypt

1. General

There are a number of glass container plants in Egypt, in both the public and private sectors. However, only El Nasr Glass and Crystal Co. has production facilities of any significant size.

Overall planning for the glass container industry in Egypt is under the auspices of the Chemical and Building Industries section of the General Organization for Industrialization (GOFI). According to GOFI, glass container consumption in 1976 in Egypt was about 72,200 tons and expected to increase to 106,000 tons by 1980. Based on 72,200 tons, the per capita consumption of glass containers in Egypt is about 2 kg; this is very low when compared to 53 kg for the U.S.A. It would seem, however, that the GOFI figures underestimate the 1976 glass container consumption because it presumes that only 1,570 tons of glass containers were used by the cosmetics and pharmaceutical markets.

GOFI has given its approval for the following expansion of the glass container industry:

a) Increase in El Nasr Glass and Crystal capacity from 36,000 to 72,000 tons through increased productivity (1978/79)

b) A joint venture between Cairo Beverages and Industrial Co. and a foreign glass manufacturer to put up a 35,000 to 40,000 ton plant, sometime in 1978/79

c) Increase capacity of other private sector firms to 17,000 tons by 1980/81

d) A small project of 600 tons for Neutral Glass sometime in 1980.

If all these expansion plans are implemented, the capacity of the Egyptian glass container industry would increase from about 60,000 tons to about 125,000 tons by 1980. This would mean that there would be sufficient capacity, at least according to GOFI's forecasts of glass container demand.

The following are the major blown glass container plants in Egypt:

Company	Estimated Capacity
1. El Nasr Glass & Crystal Co. (Cairo)	
Mostorod Plant	36,000 tons
Shaubra El-Kheima Plant	12,000 tons
2. Middle East Glass Factories (Cairo)	6,000 tons
3. Medical Packaging Co. (Cairo)	3,000 tons
4. Egyptian United Co. for Glass Industry (Alexandria)	3,000 tons *

(* guesstimate by author)

2. El Nasr Glass and Crystal Co.

A government owned and operated diversified glass manufacturer, that produces flat glass, glass wool, pressed glass, housewares, and crystal glass in addition to blown glass containers.

El Nasr is currently negotiating with an international glass container manufacturer for a technical assistance program. Such a program could improve the productivity of the Mostorod plant considerably and increase its capacity from the existing 36,000 tons annually to between 70,000 to 100,000 tons.

The Mostorod and Shoubra plants are located in the vicinity of Cairo. During a very brief tour of the Mostorod plant, it was observed that the plant has modern four section Hartford I.S. machines and feeders and Zeppa automatic weighing and batching equipment. However, what was not obvious was on line quality control equipment.

The plant also fabricates about 70 million ampoules annually from imported European Type I glass tubing.

Table 4 shows an analysis of El Nasr's production for 1973 and eleven months of 1974.

3. Middle East Glass Factories

A privately-owned firm located in the heart of Cairo produces between 5,000 to 7,000 tons of glass containers a year.

There are six very small oil fired furnaces. The forming process is manual. Gobs of glass are manually taken from the furnace to the parison mold, from where they are manually transferred to the blow mold, where compressed air is used for blowing the container to final shape. The container is then manually transferred to the lehr.

The company has two old single-section Belgian automatic forming machines; however, these were not operational at the time of the visit.

Table 4. Glass container production of El Nasr glass and crystal company

Type of Container	Total Quantity in 000's	%	Total Tons	%	Avg. Price per 1000 $	Total Sales in $ 000's	Avg. Price per ton/$
1973							
Pharmaceutical	8,485	13	1,512	6	46.6	395.4	261
Cosmetic	2,595	4	545	2	59.8	155.2	285
Food & Beverage	55,095	83	25,285	92	87.3	4,809.4	190
Total 1973	66,175	100	27,342	100	81.0	5,360.1	196
1974 (11 mths only)							
Pharmaceutical	16,360	44	2,416	20	49.3	806.8	334
Cosmetic	463	1	78	1	80.0	37.0	475
Food & Beverage	20,107	55	9,659	69	105.4	2,120.0	220
Total 1974 (11 months)	36,930	100	12,153	100	80.3	2,963.8	244

Prices: 1974 prices for pharmaceutical bottles ranged from $42 to $62 per 1000

Source: ACDINA

For environmental pollution reasons, the government has directed the company to relocate in the industrial suburbs of Cairo. The Company approached a firm in Germany for technical assistance, and plans to install one furnace with a capacity of about 9,000 to 10,000 tons annually.

According to them, lack of financing prevents them from putting up a larger furnace even though they feel that there would be a market for their products.

However, the materialization of these plans is uncertain since

The Government has yet to provide them with an alternate site

4. Medical Packaging Co.

This is another government owned firm which specializes in the manufacture of packaging materials and containers for the medical and pharmaceuticals industry. Besides its extensive plastics operations, it operates a small manually/semi-automated glass plant with an annual capacity of about 3,000 tons. The plant manufactures only pharmaceutical containers.

Management of the company consider the plant obsolete and plan to operate the plant only until such time as demand for their product exists.

5. Egyptian United Co. for Glass Industry

Is a small glass container manufacturer located in Alexandria. No information is available on this company. It is guesstimated that its annual production is in the 3,000 tons range.

6. Proposed New Glass Container Capacity

Cairo Beverages and Industrial Co. is a new soft drink bottling firm that plans to start marketing some soft drink and some flavours sometime in 1978.

This firm is planning a joint venture with an international glass container manufacturer to construct a 35,000 to 40,000 ton per year glass container facility in Cairo, to be called Middle East Glass. The output of this plant would be mainly soft drink and wine bottles. The plans of this company are well advanced and they expect to be able to supply glass containers by late 1979 or early 1980.

They expect that this new plant's capacity would be utilized as follows, at least in the first few years:

Local Soft Drink Market	13,500 tons
Local Wine Market	10,000 tons
Export of Soft Drink Containers	10,000 tons
Surplus Capacity	6,500 tons
Total	40,000 tons

The commissioning of Middle East Glass would add considerably to Egypt's glass container facility. And, if the improvements at El Nasr Glass & Crystal Co. were to take place as planned, Egypt's glass container capacity by 1980 would be:

1.	El Nasr Glass & Crystal Co., Mostorod	70,000 tons
	Shaubra El Kheima	12,000 tons
2.	Middle East Glass Factories	6,000 tons
3.	Medical Packaging Co.	3,000 tons
4.	Egyptian United Co. for Glass Industry	3,000 tons
5.	Middle East Glass	40,000 tons
	Total	134,000 tons

The capacity would then be in excess of the 1980 needs of the market, as forecasted by GOFI.

7. End Use Markets for Glass Containers

Very little information was available on other end use markets for glass containers in ACDIMA countries, except Egypt. Table 5 shows the 1970/74 production statistics of the glass container end use markets in Egypt; these have been discussed further below.

7.1 Cosmetics and Toiletries

During the period 1970 to 1974, cosmetics and toiletries industry shipments increased by almost 100%. Since 1973/74, when the government liberalized import regulations, considerable amounts of toiletries and cosmetics are being imported into Egypt. Data on the glass container consumption of this industry is not known. In 1973 and 1974, El Nasr Glass produced 545 tons and 78 tons

Table 5. Production statistics of end use industries of glass containers in Egypt

(in millions) 1 LE - $2.5

Industry	Units	1970	1971	1972	1973	1974
Cosmetics	$	12.5	14.7	20.4	22.7	25.0
% Change			18.2	38.4	11.1	10.0
Pharmaceuticals	$	83.0	100.0	114.7	135.0	148.0
% Change						
Soft Drink Bottles	Million Bottles	590	618	660	586	660
% Change		16.1	4.4	6.8	-11.2	12.6
Beer	Litres	24	28	30	32	29
% Change		14.3	16.6	7.1	6.6	- 9.4
Wine	Litres	5.9	5.4	5.6	3.4	1.4
% Change		0.4	-8.0	3.1	-38.9	
Liquor	Litres	7.3	11.8	15.5	12.6	
% Change		-27.3	62.5	31.1	-18.2	
Vinegar	Litres	4.0	5.0	5.6	6.7	6.4
% Change		33	25	20	16	-4.5
Pasteurized Milk	Litres	29	33	31	38	42
% Change		2.5	13.8	-6.1	22.5	9.0

respectively of cosmetic glass containers. It seems that the smaller glass plants supply some of the needs of the cosmetics industry and that the industry is unsatisfied by the quality and quantity of glass available to it.

7.2 Beer

Sales of beer increased from 24 million litres in 1970 to about 44 million in 1977, an average increase of about 10% a year. They are expected to reach 63 million litres in 1980 and 117 million in 1985.

The industry uses returnable bottles of two sizes 2/3 litre and ½ litre. However, the predominant size is the 2/3 litre bottle.

The industry purchased about 10.2 million bottles (6000 tons) in 1973.

7.3 Wine Industry

Wine production has decreased during the period 1970 to 1974 from 5.9 million litres to 1.4 million litres respectively. The wine industry uses non-returnable 2/3 litre bottles. Its 1973 purchases amounted to about 10,000 tons.

7.4 Milk & Food

Most of the pasteurized milk is now being packaged in plastic containers. There is almost no food being packaged in glass containers except for vinegar. However, information on this market is not available.

7.5 Soft Drinks

Consumption of soft drinks has increased from 590 million bottles (200 ml) in 1970 to about 660 million in 1974. The level of consumption is expected to increase substantially for the following reasons:

- improvement in quality of drinks
- increased supply
- better distribution
- increase in living standards

The industry uses returnable 200 ml bottles, and experiences a trippage of between 20 to 70 trips. However, the large number of trips is partly a function of the quality of used bottles considered acceptable by the soft drink companies. It can be expected that, with increased availability of glass containers and increasing competition within the soft drink industry, the soft drink companies will become more selective in re-using the bottles. This would reduce the number of trips achieved, and hence increase the requirements for new glass bottles.

Industry sources estimate the consumption in 1980 and 1985 to be 1.53 billion and 3.8 billion bottles respectively. This will increase the demand for glass containers substantially.

7.6 Pharmaceuticals

The pharmaceutical market has been discussed in detail in Section B. In this section, the market for pharmaceutical glass containers for the years 1980 and 1985 has been developed.

The glass container demand forecast has been developed based on:

a) the distribution of pharmaceutical production by product form as shown in Table 1. However, because some of the 1975 figures appeared very low in comparison to those quoted by other industry sources, they have accordingly been modified by the author and shown in Table 2.

b) the revised figures have been used to forecast the share of the different product forms for the year 1980 and 1985, taking into account the trends noticeable in Egypt and in the international pharmaceutical market. These forecasts are shown in Table 6.

c) The forecast of Table 6 was used in conjunction with the forecast for type of packaging by product form developed in Table 2 to develop the glass container requirements of the Egyptian market for 1980 and 1985 as shown in Table 7.

The tonnage shown for tubing and blown glass consists of a mixture of different types and colours of glass.

The majority of the ampoules are of Type I glass and are of both flint and amber colour. The vials are mainly Type III flint glass.

Table 6. Revised 1975 distribution of pharmaceutical production in Egypt and forecasts for 1980 and 1985 by product form

(in millions of units)

Product form	1975		1980		1985	
		%		%		%
Ampoules	400	8.1	540	6.7	800	5.0
Vials	80	1.6	128	1.6	224	1.4
Tablets	4,000	81.5	6,190	77.4	12,220	76.4
Capsules	280	5.7	920	11.5	2,080	13.0
Liquids	80	1.6	96	1.2	176	1.1
Powders & Granules	15	0.3	24	0.3	48	0.3
Ointments & Pastes	34	0.7	48	0.6	110	0.7
Suppositories	19	0.4	40	0.5	96	0.6
Other			16	0.2	240	1.5
Total	4,908	100	8,000	100	16,000	100

Note: Annual growth rates for total production have been assumed at 10% for the years 1975 to 1980 and 15% for the years 1981 to 1985.

Table 7. Glass container needs of Egyptian pharmaceutical industry

Product Form	Avg. Container Weight in Gms.	Estimate 1975		Forecast 1980		1985	
		Qty.in Millions	Weight In Ton	Qty in Millions	Weight In Ton	Qty In Millions	Weigh In Ton
Ampoules	4.25	400	1700	510	2165	720	3060
Vials	17.0	80	1360	115	1955	190	3230
Total Tubing			3060		4120		6290
Tablets *	75	20	1500	31	2325	61	4575
Capsules *	75	5	375	9	675	13.8	1035
Liquids	75	75	5620	72	5400	108	8100
Powders & Granules	180	14.7	2645	19	3420	28.8	5180
Ointments & Pastes	100	3.4	340	2.4	240	5.5	550
Total Blown Glass			10,480		12,060		19,440

*, Assumed that on the average 20 tablets or 15 capsules packed per container

The blown glass containers are mainly Type III amber glass; however, the Plasma and Dropper bottles, which are mainly imported, are of Type I and Type II[2/] glass respectively.

2/ Type II glass is Type III glass treated with either a Fluoride or Sulphur treatment to reduce the alkalinity of the glass, and thus bringing Type III glass closer to the characteristics of Type I glass.

E. Analysis of ACDIMA market and alternative solutions

1. ACDIMA Countries Glass Container Market

Because no information was available on the ACDIMA market, it was decided that the following assumptions would be made:

a) That the total requirements of the ACDIMA market for pharmaceutical glass containers would be twice the requirements of the Egyptian market. This factor was provided by the ACDIMA staff, as a reasonable method of judging the size of the ACDIMA market.

b) That the distribution of pharmaceutical product form usage for ACDIMA countries would be the same as that for the Egyptian market.

c) It was suggested by the ACDIMA staff that because the supply of locally produced pharmaceutical glass was inadequate in most ACDIMA countries and because very little information was available on the glass container industries in those countries, it could be assumed that 100% of the pharmaceutical glass container market would be open and available to the ACDIMA glass plant.

d) However, in this report it has been assumed that the proposed ACDIMA pharmaceutical glass plant would achieve 80% market share. This would bring the ratio between the ACDIMA pharmaceutical glass market and the Egyptian pharmaceutical glass market to 1.6. The 1.6 ratio is also more in line with the 1985 ratio of forecasted local pharmaceutical production between total ACDIMA countries and Egypt ($745: $484 million) as shown in Table 8.

e) The forecasts of pharmaceutical glass for Egypt as shown in Table 7 were multiplied by 1.6 to arrive at the forecast for the ACDIMA countries as shown in Table 8.

This report does not consider the glass tubing products - only the blown glass container requirements have been further analysed.

The blown glass container requirements of ACDIMA increase from 19,200 tons in 1980 to 31,000 tons in 1985. Of this total tonnage, about 15% consists of Type I glass used for large size parenterals such as plasma bottles and for small dropper bottles. The requirements of Type I glass are too small to justify the additional capital

Table 8. Forecast of pharmaceutical glass container requirements of the ACDIMA countries

Product Form	Average Wt. in Gms.	1980		1985	
		Qty. in Millions	Weight in Tons	Qty. in Millions	Weight in Tons
Tubing Products					
Ampoules	4.25	815	3,460	1,150	4,885
Vials	17.0	180	3,130	300	5,100
Total Tubing			6,590		9,985
Blown Glass for:					
Tablets	71	52	3,720	102	7,250
Capsules	71	15	1,080	23	1,650
Liquids	75	115	8,610	173	12,950
Powders & Granules	190	28	5,400	43	8,250
Ointment & Pastes	100	4	400		900
Total Blown Glass	91	214	19,200	350	31,000

expenditures involved and the associated operational problems of formulating and forming Type I glass containers. It is, therefore, recommended that these containers continue to be imported. Also, the international trend to plastic squeeze type bottles for nose and eye droppers etc., and for some of the large size parenterals will reduce the long term demand for glass containers for these applications. The remaining Type II and Type III tonnage has been further analysed by approximate container size in Table 9 for 1980 and 1985.

These forecasts have been used as the basis for designing the glass plant discussed in the following section.

2. Future Demand and Supply

As mentioned earlier, no statistical information is available on the glass container demand/supply situation in the ACDIMA countries except Egypt.

It is presumed from comments received from ACDIMA staff and other sources that demand for pharmaceutical glass and glass in general, exceeds the local supply. Expansion plans for the glass container plants of the ACDIMA countries, except Egypt, are also not known.

However, it can be assumed with reasonable certainty that the demand for glass containers in general will exceed supply in ACDIMA countries until 1985 at least.

Table 9. Analysis of blown glass pharmaceutical container requirements of the ACDIMA countries

Glass Type	1980	1985
Type I (Plasma & Dropper Bottles)	3000 tons	4500 tons
Type II and Type III	16200 "	26500 "
Total Blown Glass	19200 tons	31000 tons

ANALYSIS OF TYPE II AND TYPE III GLASS CONTAINERS

Bottles For	Avg. Wt. In Gms.	Nominal Size Ml.	1980 Quantity Millions	1980 Weight Tons	1985 Quantity Millions	1985 Weight Tons
Tablets	25	20	9	225	18	450
&	50	50	25	1,250	45	2,250
Capsules	75	75	15	1,125	30	2,250
	100	100	10	1,000	17	1,700
	150	150	8	1,200	15	2,250
	71		67	4,800	125	8,900
	35	30	6	210	10	350
Liquids	75	75	16	1,200	24	1,800
&	100	100	20	2,000	31	3,100
Syrups	200	200	11	2,200	16	3,200
	105		53	5,610	81	8,450
Powders	125	125	14	1,750	22	2,750
&	250	300	11	2,750	16	4,000
Granules	300	500	3	900	5	1,500
	192		28	5,400	43	8,250
Jars for	50	50	1.4	70	3	150
Pastes &	125	125	2.6	325	6	750
Ointments						
	100		4	400	9	900
Total Type II & III			152	16,200	258	26,500

Pharmaceutical glass containers because of their relatively small size, present special manufacturing problems to the normal glass plant that is geared mainly for the larger sized wine, beer and soft drink bottles. This special problem, coupled with the general excess of demand over supply of glass containers has been the cause of the glass container shortage for the pharmaceutical industries in the ACDIMA countries.

3. Alternative Courses of Action

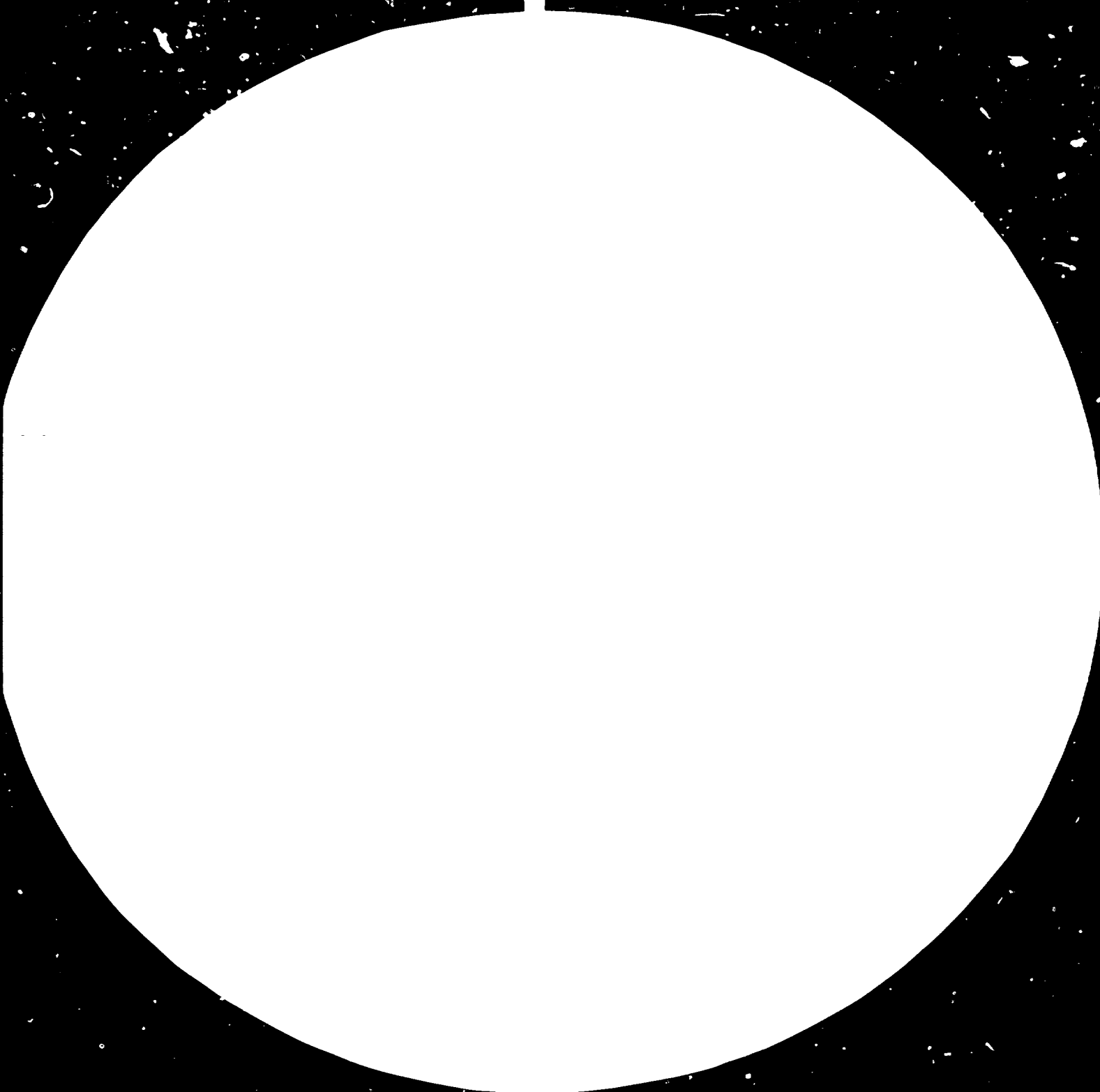
It is the opinion of the author that based on the forecasts of pharmaceutical glass requirements to 1985, and the known expected expansions in the glass container industry, it seems that ACDIMA will have to take some form of action to ensure the pharmaceutical industry of locally produced glass containers.

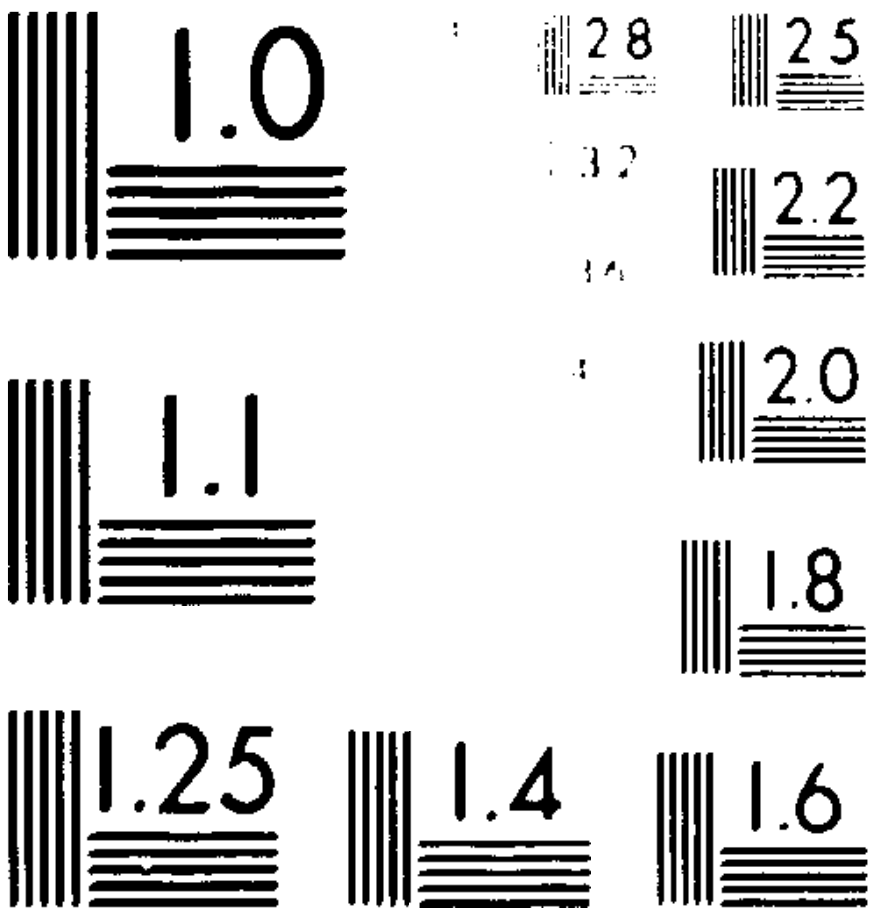
This action could take either of the following forms:

a) Establish an independent glass container plant

b) Tie-on with proposed new glass plant of third party (i.e. Middle East Glass Co.) either through equity or some other vehicle that would provide the required management control, to ensure that the demands of the pharmaceutical industry are not neglected

c) The purchasing power of the individual pharmaceutical plants is small due to their relatively small requirements of glass containers in money terms. This weakness in relation to other end users is also one of the causes of the problems of the pharmaceutical industry in the ACDIMA countries




1.0
2.8
2.5
3.2
2.2
1.1
2.0
1.8
1.25
1.4
1.6

c. Joint purchasing of the pharmaceutical industries' total requirement through a common vehicle, such as ACDIMA, might increase the pharmaceutical industries' bargaining power and help improve their supply situation

The current period might be an opportune time to negotiate a supply contract with El Nasr Glass & Crystal Co. who are planning a 100% expansion of their capacity. The validity of such a strategy would depend upon whether a contract specifying quality, quantity and punitive clauses for non-performance can be enforced legally.

In this study, only the first option of a new glass plant has been further explored.

Based on the preferences stated by ACDIMA staff and also because of insufficient data on other end use markets, this study has focused exclusively on producing pharmaceutical containers and not considered the very real possibilities of producing other ware for markets such as cosmetics, food, soft drinks etc.

F. Glass plant design and operations

1. Location

No analysis has been done to determine the optimum location of the glass plant. For the purposes of this pre-feasibility study, it has been assumed that the plant would be located in Cairo or its vicinity, since over 70% of the current pharmaceutical production in the ACDIMA countries is produced in Cairo.

However, location of the plant near the market is not an important criterion for small containers such as pharmaceuticals. A more thorough analysis would be required with consideration given to labour, and raw materials availability and prices.

2. Design

It has been assumed that the earliest the plant would be operational would be early 1981; therefore, 1981 has been used as the base year of operation.

The plant has been designed based on the sales forecast shown for the years 1980 and 1985 in table 9.

The plant would consist of one 100 ton/day oil (heavy oil) fired furnace with recuperator with capacity for expansion to two furnaces. The furnace would produce both flint and amber glass, until the second furnace is installed at which time the furnaces could be devoted to a single colour. Based on the present sales forecasts, the second furnace would be required in 1985/86, which would also coincide with the rebuilding of the first furnace, assuming a 5 year life span for the furnace. The furnace would have six forming machines attached to it.

Forming equipment would be of the Hartford Individual Section type. In the first year - 1981 - 5 single gob and one double gob, 6 section machines would be required, of which one single gob machine would be a Press and Blow and the others all Blow and Blow. The machine complement would change to one single gob and 5 double gob by 1985. This would be achieved by converting the single gob machines to double gob machines. (See schedule in table 10.) Production levels are not expected to achieve the total sales potential in years 1981 to 1984 because it is assumed that until the production staff acquires the necessary expertise, the furnace output will be lower than capacity for the first few years. Also, because double gob machines are more complex to operate, it would be necessary to introduce them slowly as experience is gained on the single gob machines.

Each of the I.S. forming machines would have a 1.2m (wide) by 20m (long) annealing lehr.

Cartons would be assembled and stitched on the floor and would be fed to the packers at the cold end of each lehr.

Table 13. Schedule of machines and glass tonnage

	1981	1982	1983	1984	1985
Bottles Required (Millions)	168	185	205	225	258
Tons Equivalent	17,900	19,750	21,800	24,050	26,500
Efficiency (T Packed)	64%	71%	77%	82%	85%
No. of S.G.Machines	5	4	3	2	1
No. of D.G.Machines	1	2	3	4	5
Bottles Packed (S.G.) (Millions)	109	96	79	56	28
Bottles Packed (D.G.) (Millions)	36	80	126	169	230
Bottles Packed Total (Millions)	145	176	205	225	258
Tons Packed	15,450	18,789	21,800	24,050	26,500
Tons Pulled	24,140	26,463	28,310	29,330	31,176
% of Furnace Capacity	71%	78%	83%	86%	91%

The batch house would have automatic weighing and mixing equipment. The batch would be transferred by conveyors to the furnace. There would be 10 storage silos, each about 7m in diameter and about 16m high. Because of the problems in transportation and general unreliability of raw materials suppliers, it was considered necessary to provide for more than adequate covered storage:

Raw Material	Storage Requirements
Sand	4 weeks
Soda Ash	8 weeks
Lime	12 weeks
Feldspar	18 weeks
Salt Cake	40 weeks

Cullet could be stored outdoors. Facilities have also been provided for both oil and water storage. A preliminary plant layout is shown in Figure I.

3. Capital Costs

Prices used throughout have been based on 1977 price levels or on the latest available information. With regards to costs to be incurred in Egypt, the information provided by ACDIMA staff has been used.

The 7200 sq. m. plant would require about 85,000 sq. m. of industrial land; this would allow for future expansion of the buildings to house an additional furnace and storage space.

Figure I

Proposed Pharmaceutics Glass Container Plant

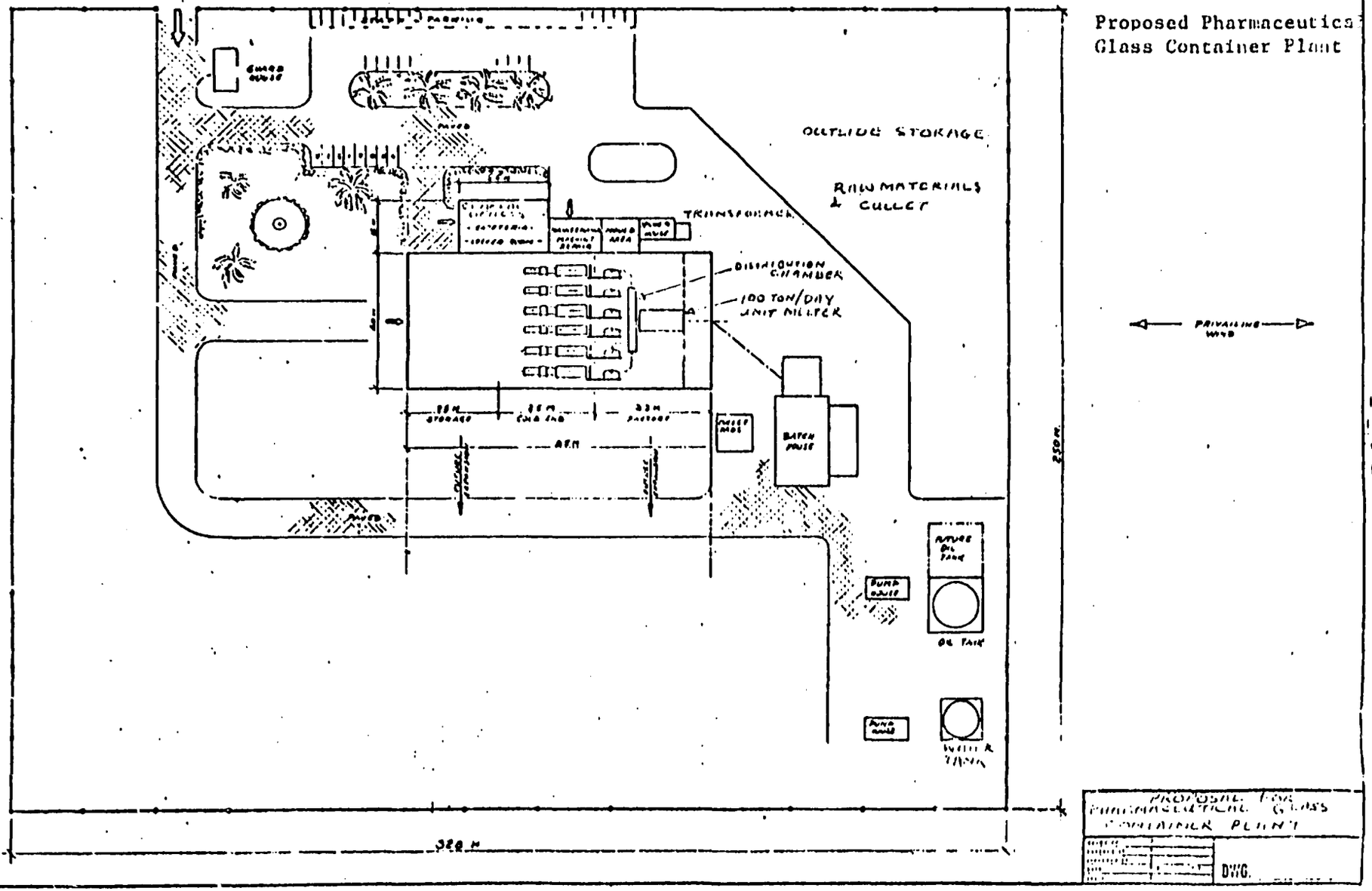


Table 11. Capital expenditure for pharmaceutical glass plant in $000's

1.	Land	85,000 sq. m. @ $2.00/sq.m.	$ 170	
	Site preparation		150	$ 320
2.	Utilities			
	Water	$ 50		
	Sewage	50		
	Gas	60		
	Electricity	300		460
3.	Buildings			
	Batch House (7m Ø x 16 m H)		$1,000	
	Furnace Bldg. 1450 sq. m.		1,305	
	Cold End 1950 sq. m.		351	
	Factory Offices 500 sq. m.		150	
	Power House 560 sq. m.		196	
	Mold, Maint., M/C Repair 1500 sq. m.		525	
	Offices, Cafeteria 1400 sq. m.		420	3,947
4.	Services			
	Compressed Air 50 psi (6000 SCFM)		$ 425	
	" " 100 psi (360 SCFM)		75	
	M/C Cooling Fans (250 HP)		270	
	Fire Protection		75	
	Oil Storage & Pumping (50,000 gal)		200	
	Water (Cullet, Process, Domestic)		150	
	Lighting		110	
	Power Distribution		395	
	Control & Instrumentation		180	1,880
5.	Batch System			
	Raw Materials Handling		$ 110	
	Batch Preparation		660	
	Cullet Handling		150	
	Batch Transfer (Conveyors)		100	
	Elevator		50	1,070
6.	Furnace			
	Refractories		$ 700	
	Steel		255	
	Recuperator		150	
	Combustion System		150	
	Cooling		60	
	Batch Chargers		50	1,365
7.	Forming Machines			
	Feeder Mech (144)		$ 180	
	6 Sec. I.S. M/C S.G. x 5)		1,110	
	6 Sec. I.S. M/C D.G. x 1)			
	Variable Equip.		220	
	Gang Stackers		120	
	Lubrication		40	
	Machine Services		140	1,810

cont'd

8.	Lehrs		
	Six, (1.2m x 20m) Lehrs	$ 750	
	Cold End Sprays	120	$ 870
9.	Spare Parts		300
10.	Carton Forming and Hand Packing		
	Stitching, Hand Pack Stn., Shrink Tunnel & Conveyor		90
11.	Miscellaneous Equipment		
	Batch & Tank Laboratory	$ 80	
	Quality Control	100	
	Offices	100	
	Mould Shop	500	
	Maintenance & M/C Repair	150	
	Lift Trucks	25	955
12.	Transportation		
	Ocean Freight, Insurance		2,000
	Inland Freight, Handling		
13.	Engineering & Construction Management		
	Engineering Costs, Fees, Commissions		2,000
14.	Engineering Contingency		900
15.	Training and Start-up Costs		1,200
	Total		$ 19,167

The details of the land buildings and equipment costs are shown in table 11.

The capital costs are estimated at $15 million plus $2 million for engineering design and construction managements' costs and an additional $0.9 million for engineering contingencies, bringing the total capital costs to about $18 million.

4. Training and Start-Up

Approximately $1,200,000 is estimated as the cost of training the local staff and start-up which would bring the new plant to the first year's targeted level of efficiency.

At this stage, no further details have been worked out for the training program, as to whether it would be conducted in Egypt or in the plants of the company providing the technical assistance.

5. Plant Manning

The plant manning has been based on the machine and tonnage schedule shown in table 10. It is estimated that the plant would operate on a 3 shift basis for 340 days a year.

The direct labour complement required is shown below for skilled, semi-skilled and unskilled categories.

5. Plant Manning

The direct labour rates used include fringe benefits at 20% of base pay and were taken on a basis higher than the current Egyptian rates, on the assumption that a premium would be necessary to attract a better class of worker.

The rates used are shown in the appendix.

The direct labour complement for 1981 is projected at 212 persons, not including supervisors and management. The schedule is shown in table 12.

The staffing is heavier than at comparable North American plants because of the assumption that all packing operations would be done manually.

6. Raw Materials

Prices assumed for raw materials have been based on available information, and are shown in the appendix.

The raw material batch cost is based on the assumption that 65% of output will be Amber glass and 35% will be Flint.

Based on the following batch composition for Amber glass:

Sand	58.6%
Soda Ash	20.0
Limestone	14.5
Feldspar	5.3
S. Sulphate	1.0
Carbicites	0.2
Pyrites	0.2

Table 12

GLASS PLANT MANNING

$ in 000's

Direct Labour Category	1981		1982		1983		1984		1985	
	Persons	$	Persons	$	Persons	$	Persons	$	Persons	$
Unskilled	100	276	105	290	122	336	128	353	142	392
Semi-Skilled	63	217	70	242	82	283	86	296	95	328
Skilled	49	203	50	207	53	219	55	228	55	228
Total Direct	212	696	225	739	257	838	269	877	292	948

Indirect & Overhead Labour Category	Plant Persons	Office Persons	Total Persons	Total $
Managerial	6	5	11	103
Foreman/Supervisors	18	10	28	114
Clerical/Secretarial	11	12	23	62
Total	35	27	62	279

Note: Direct labour costs include fringes of 20%

Indirect and Overhead Labour Costs include fringes of 30%

The average cost of the batch is $46.60 per ton of glass. To this has been added the cost of transportation which has been assumed at $13.00 per ton to arrive at a total cost of $59.60 per ton of glass.

7. Inventory of Raw Materials and Finished Goods

Because of the high costs for cartons, carton inventory has been assumed at one weeks level. This may need to be increased based on prevalent supply conditions.

Other raw materials inventory has been based on figures shown in Section F, . 2 on Design.

It has been assumed that it would be necessary to carry 1.5 months of production in finished goods in inventory.

8. Mould Shop and Machine Repair

Provisions have been made for a completely equipped mould shop to ensure that moulds of the necessary specifications and tolerances are available. It is believed that the necessary grey iron castings for the moulds are available in Egypt. It would be necessary, however, to purchase an initial set of moulds until the mould shop becomes operational. It is estimated that the initial set of moulds would cost about $225,000.

The plant has also been equipped to overhaul and modify the I.S. forming machines.

9. Source of Technology

It would be necessary for ACDIMA to acquire the necessary glass manufacturing technology from an established and reputable glass container manufacturer. This source would provide the initial design and start-up management. It has been assumed that a technical assistance agreement would also be negotiated for at least the first 10 years of operation, so that local management can fully acquire and absorb the technology of glass manufacture and also continue to benefit from new developments in the field. It has been assumed that the cost of such an ongoing agreement would be about 3% of sales.

G. Financial analysis

1. Major Assumptions

Earnings and Return on Investment are dependent on the financial structure of the company. Though it is more than likely that debt capital would be utilized, it is beyond the scope of this study to suggest an appropriate mix of debt and equity capital. For purposes of presenting an investment analysis it has been assumed that the project would be financed solely from equity capital. Debt capital if available at favourable rates, would obviously improve the return on equity capital.

Depreciation has been calculated on a straight line basis, with periods ranging from 40 years for buildings to 5 years for furnace lining. Based on the different rates used, the average period for the total capital investment in buildings and equipment works out to about 16 years.

It has been assumed that the 5 year tax holiday allowable to new enterprises in Egypt, would be applicable to this project. A tax rate of 40% has been used for the years 1986 to 1990.

For purposes of the return on investment analyses the project is assumed to have a life of 10 years with a liquidation value of $5 million plus working capital.

2. Sales Forecasts

Sales have been forecast using international prices for pharmaceutical glass bottles. It has been assumed that prices would have to be competitive to international prices to be able to export to the pharmaceutical companies in the other Arab countries.

Based on the distribution of sizes, the average selling price is $480 per ton (including carton costs of $15/ton) f.o.b. the glass plant.

3. Packaging Costs

It has been assumed that glass would be packed in corrugated cartons with suitable dividers. The cost of corrugated cartons, which are expensive in Egypt, account for about 33 percent of the sales dollar. Profit levels could obviously be improved if suitable and cheaper alternate methods of packaging could be used, such as shrink wrapping etc. This needs to be investigated further.

4. Financial Projections

Pro forma Income Statements, Balance Sheets and Cash Flow Statements are shown in tables 14, 15 and 16 for the years 1981 to 1985.

Table 13 shows the financial highlights.

The project shows an Internal Rate of Return of 9% with a payback period of about 8.5 years. It has been assumed in the Return on Investment calculations (and contrary to the cash situation shown on the Balance Sheets) that the cash generated by the operations would either be paid out in dividends or invested elsewhere.

Because of the assumed tax holiday for the years 1981 to 1985 net income peaks at $3 million in 1985. It has been assumed for purposes of ROI calculations, that for the years 1986 to 1990 the same level of sales and costs would be maintained. However, a 40% income tax factor has been applied reducing the net income to $1.8 million.

Figure II shows a plot of sales against total costs. The operations achieve a breakeven point at about 13,000 packed tons or sales of about $6.2 million.

Table 13. Financial highlights

Total Investment	$ 19,000,000	
Payback period	8.4 years	
Rate of Return on Investment	9%	
Net Income		
1981	$ 422,000	(tax holiday)
1985	3,010,000	(tax holiday)
1986 to 1990	1,806,000	annually (40% tax)

FIGURE II.

OPERATIONAL BREAKEVEN

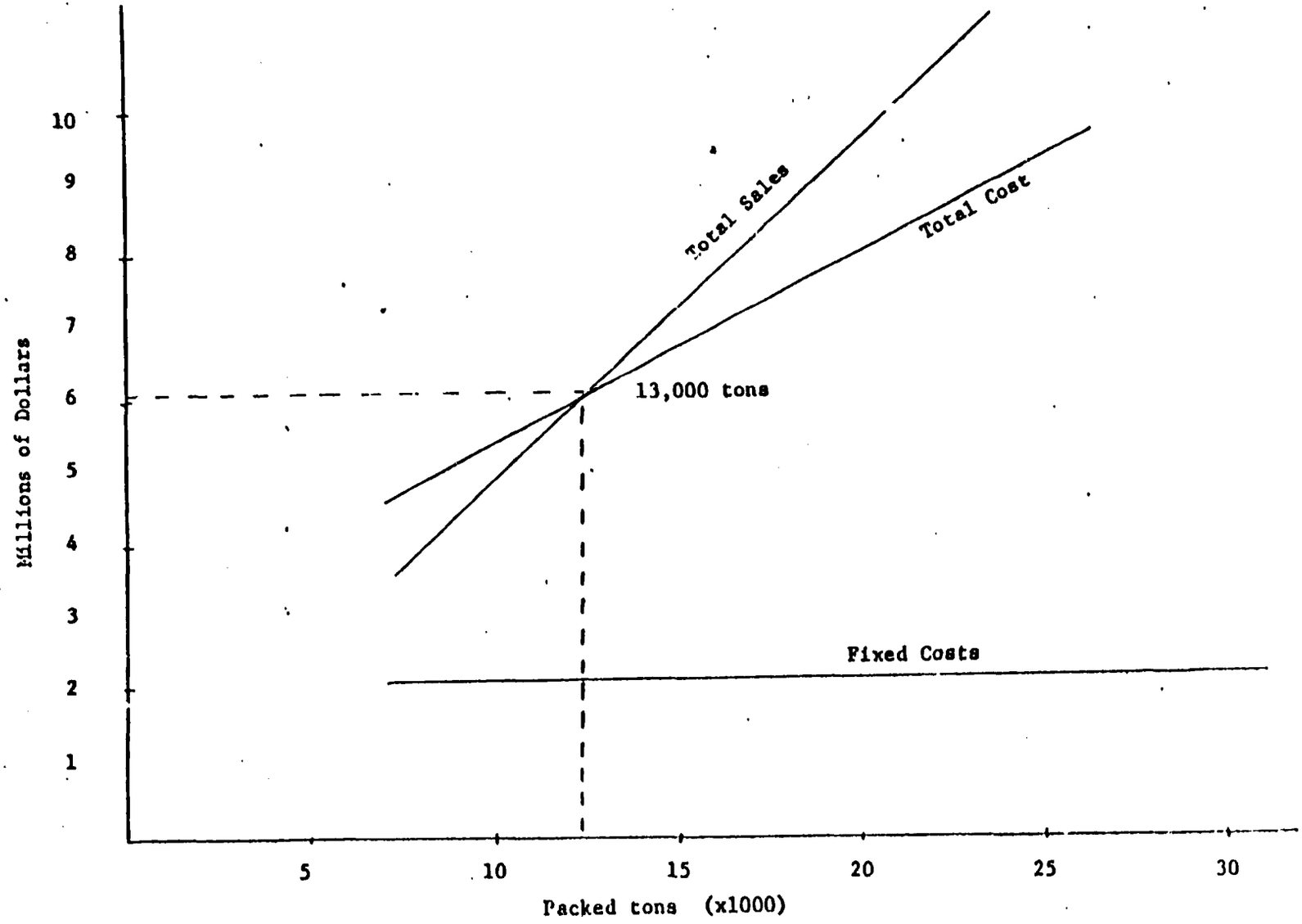


Table 11. Pro forma income statement

	1981	1982	1983	1984	1985
Sales @ $480/ton	7,416	9,019	10,464	11,544	12,720
Cost of Goods Sold					
Batch Materials @ $59.6/ton	941	1,127	1,311	1,448	1,591
Direct Labour	696	739	838	877	948
Fuel & Utilities @ $14.5/ton	350	384	410	425	452
Mould Costs	350	150	120	120	150
Carton Costs	2,412	2,930	3,420	3,745	4,300
Misc. Materials & Supp. @ $5/ton	121	132	142	147	156
Total Direct Costs	4,870	5,462	6,241	6,762	7,597
Maintenance & Repairs @ $5.5/ton	133	145	156	161	171
Indirect Labour	169	169	175	175	180
Depreciation	1,100	1,105	1,110	1,115	1,120
Total Indirect Costs	1,402	1,419	1,441	1,451	1,471
Total Cost of Goods Sold	6,272	6,881	7,682	8,213	9,068
Gross Profit	1,144	2,138	2,782	3,331	3,652
Administrative Costs					
Salaries	110	115	125	135	150
Expenses	90	95	100	105	110
Amortization of Start-up Costs	300	300	300	300	
Tech. Asst. Fees @ 3% of Sales	222	271	314	346	382
Total Administrative Costs	722	781	839	886	642
Profit	422	1,357	1,943	2,445	3,010
Tons Packed	15,450	18,789	21,800	24,050	26,500
Tons Pulled	24,140	26,463	28,310	29,330	31,176

N.B. Income tax holiday assumed for the first 5 years of operation.

Table 15. Pro forma balance sheet

	1980	1981	1982	1983	1984	1985
Assets						
Cash	208	93	2,558	5,611	9,229	13,112
Accounts Receivable		927	1,127	1,308	1,443	1,590
Inventory		955	1,082	1,211	1,288	1,428
Land, Bldgs. & Machinery	17,967	17,967	18,017	18,067	18,117	18,167
Less Accumulated Dep'n		1,100	2,205	3,315	4,430	5,550
		16,867	15,812	14,752	13,687	12,617
Pre Production Expenses	825	1,200	1,200	1,200		
Less Amortization		300	600	900		
	825	900	600	300		
Total Assets	19,000	19,742	21,179	23,182	25,647	28,747
Liabilities						
Accounts Payable		320	400	460	480	570
Shareholders Equity	19,000	19,000	19,000	19,000	19,000	19,000
Retained Earnings		422	1,779	3,722	6,167	9,177
	19,000	19,742	21,179	23,182	25,647	28,747

Table 16. Pro forma cash flow analysis

	1980	1981	1982	1983	1984	1985
Sources of Funds						
Equity	19,000					
Operating Income		422	1,357	1,943	2,445	3,010
Depreciation		1,100	1,105	1,110	1,115	1,120
Amortization Preproduction Exp.		300	300	300	300	
Accounts Payable		320	80	60	20	90
Total Inflow		2,142	2,842	3,413	3,880	4,220
Uses of Funds						
Preproduction Expenditure	825	600				
Capital Expenditures	17,967		50	50	50	50
Accounts Receivables		927	200	181	135	147
Inventory		955	127	129	77	140
Cash	208	(340)	2,465	3,053	3,618	3,883
Total Outflow	19,000	2,142	2,842	3,413	3,880	4,220

H. Conclusions

The major reasons that prompted ACDIMA to consider investing in a pharmaceutical glass container plant are:

a) The inability of local glass container manufacturers to satisfy the demands of the pharmaceutical companies in the ACDIMA countries, and

b) The poor quality of the glass containers manufactured locally

These conditions which have existed for some time, have hindered the production of pharmaceuticals and have also been a negative factor in the Egyptian pharmaceutical industry's efforts to increase pharmaceutical exports.

The analysis done in this study shows that there is sufficient demand for pharmaceutical blown glass containers in the ACDIMA countries to justify a small plant devoted to the manufacture of Type II and III pharmaceutical blown glass containers. This is based on the major assumption that the proposed glass plant would be able to achieve an 80% share of the pharmaceutical blown glass container market in the ACDIMA countries. This assumption is based on the information provided to the author by the ACDIMA staff. It is not possible to comment on the validity of this assumption as the author had no opportunity to judge the reactions of the pharmaceutical industries in the other countries.

Based on the assumptions shown earlier in the report, a discounted cash flow analysis shows that the return on investment would be about 9%, with a payback period of about 8½ years. The attractiveness of this rate of return on investment could of course only be judged by ACDIMA.

The two current developments in the Egyptian glass container industry (vis a vis El Nasr Glass & Crystal Co. and Middle East Glass Co.) are likely to substantially increase the glass container production capacity of Egypt. It is possible that either one or both of them could produce the necessary pharmaceutical glass for the ACDIMA countries, thus increasing the options open to the pharmaceutical industry and to ACDIMA management.

It is also possible that this increase in glass manufacturing capacity may produce increased competitive activity in the market place, resulting in:

a) Lowered glass prices in the initial years 1979 to 1981, and

b) Increased pressure on the sources of raw materials such as soda ash

However, this study has not taken these factors into consideration.

Appendix

SCHEDULE OF ASSUMED PRICES

1. Major Raw Materials

Treated Sand	$ 20.00 per ton
Limestone	12.50 " "
Feldspar	107.50 " "
Soda Ash	100.00 " "
Sodium Sulphate	45.00 " "

2. Utilities & Fuel

Heavy Oil - Mozout	$ 20.00 per ton
Electricity	0.03 per kw. hr.
Water	0.075 per cubic meter

3. Labour

Unskilled	$ 1.25/hour including 20% fringes
Semi-skilled	1.55/hour including 20% fringes
Skilled	1.90/hour including 20% fringes
Supervisory	$340/month including 30% fringes
Clerical	225/month including 30% fringes
Managerial	780/month including 30% fringes

4. Cartons

Average size 0.04 cubic meters	$1.20

5. Land & Buildings

Serviced Industrial Land	$2.00/sq. m.
Industrial Building:	
Heavy Construction	$900/sq. m.
Light Construction	180/sq. m.
Office Construction	300/sq. m.

XVI - PRODUCTION OF PLASTIC AND METAL TUBES FOR THE PHARMACEUTICAL INDUSTRY

A. Summary

1) Plastic Tubes:

a) Present:

The Medical Packaging Company (MPC) of Cairo has facilities for the production of plastic vials or tubes. It is necessary to improve the precision of the molds to ensure satisfactory quality of the products.

b) Future:

The consumption of the plastic tubes is on the decline owing to the increasing popularity of blister packing. In view of this a market survey is warranted before further investments are made to augment production of plastic tubes for the pharmaceutical industry.

2) Metal Tubes:

a) Present:

There are facilities available at MPC for the manufacture of metal tubes. However, the quantum of production as well as quality are not up to the mark due to improper working of the machines. The points requiring immediate attention to obtain optimum output have been highlighted.

b) Future:

It is necessary to carry out market research to find out the actual requirements of metal tubes for the pharmaceutical industry as well as for cosmetic and other uses. After establishing the need for higher output and after ensuring proper functioning of the existing machines, it is recommended that ACDIMA may erect a new plant outside of Egypt. Guidelines are laid down for consideration prior to the establishment of new manufacturing facilities.

c) Suppliers of Equipment:

The names of the leading suppliers of equipment for the manufacture of metal tubes along with their product lines are indicated.

B. General

A survey of the manufacturing facilities for Plastic and Metal tubes in Egypt was carried out. It is understood that there are no facilities for the manufacture of tubes in other Arab States. In Egypt there is only one tube manufacturing plant located in Cairo known as Medical Packaging Company (MPC) in the Public Sector. This unit has three divisions viz. Plastic vials (tubes, closures and different containers), metal tubes and glass bottles.

The requirements of metal tubes by the pharmaceutical plants are indicated in tables 1 and 2. The output of metal tubes at the Medical Packaging Company is shown in table 3 along with their future plans and the distribution of the products.

Table 1. ANNUAL REQUIREMENTS OF METAL TUBES BY THREE PHARMACEUTICAL UNITS IN EGYPT

Name of the Unit	Requirements in Millions	
	Aluminium Tubes	Tin Tubes
C.I.D. Co., Cairo *	8.0	2.0
Nile Co., Cairo	0.35	0.4
Hoechst Orient S.A. +	0.95	0.5

* 15% of the requirements imported from France and Germany

\+ Part requirements covered by imports from El Maaden in Tunisia.

Table 2. REQUIREMENTS OF METAL TUBES BY PHARMACEUTICAL PLANTS (IN MILLIONS)

Year	Aluminium Tubes	Tin Tubes	Imports of Aluminium or Tin Tube:
1977	26	3.9	1.5
1978	39	4.2	
1979	45		
1980	55		

Table 3. Output of Metal Tubes at Medical Packaging Co., Cairo

(in Millions)

Year	Aluminium Tubes						Tin Tubes				
	13.5 mm	19 mm	22 mm	25 mm	30 mm	Total	10 mm	13.5 mm	16 mm	19 mm	Total
1975		2.2	8.6	5.5	3.8	20.3	0.6	8.1	0.2	0.4	9.3
1976		3.3	9.1	5.3	3.3	21.0	0.4	7.5	1.0	0.3	9.6
1977	2.0	5.0	12.0	5.5	3.5	28.0	0.0	7.0	0.5	0.5	8

Notes to table 3:

I: Tin tubes, as well as 13.5, 19, and 22 mm aluminium tubes, are exclusively used for pharmaceutical products.
1977 production of 25 mm aluminium tubes is expected to be distributed between pharmaceuticals, cosmetics and toothpastes at the rates of 20%, 55% and 25% respectively, while 30 mm aluminium tubes are expected to be distributed between cosmetics and toothpastes at the rates of 70% and 30% respectively.

II: Sources of raw materials and amount:

a) Aluminium slugs
170 tons imported from France and Federal Republic of Germany (the local production of aluminium slugs being below the required standards).

b) Zinc stearate
200 kgs. to be purchased locally.

c) Lacquer for inside protection
5000 kgs. imported. Consumption rather high.

III: Planning for future facilities for production of aluminium tubes (and aluminium boxes)
Machines proposed to be purchased
1978 one automatic line
1979 one automatic line
1980 one automatic line

IV: Distribution of products
Limited quantities have been exported during the last two years, nevertheless the estimated output for 1977 is supposed to be consumed by the local industries. The needs of the local market are still higher than the actual production capacity.

C. Plastic tubes

a) Present:

The Medical Packaging Company has facilities for the manufacture of plastic vials (called plastic tubes) and closures for vials and tubes. Most of their machines have been imported from German Democratic Republic and some old "Battenfeld" machines from Federal Republic of Germany. Each machine is a separate unit producing the finished article. Practically all molds used on these machines are produced in the tool room of the plant. AS the precision on the tools is poor, the quality of some products was found to be deficient. Burrs were observed on the caps as well as vials. 23 individually controlled machines are producing polystyrene vials. An additional 20 machines can produce closures for metal tubes and vials. These machines are equipped with unscrewing devices in order to guarantee good quality of the thread. The outside of the cap is substandard due to lack of precision in the finishing molds. Some machines have been acquired recently for producing buckets and crates and their performance has been found to be satisfactory. Raw materials are imported from France, Italy and the Federal Republic of Germany. The storage facilities are adequate.

According to the information received from the Pharmaceutical Companies, the consumption of plastic vials or tubes is on the decline as the blister packaging covered by aluminium foil is becoming more popular on account of certain advantageous features in the case of the latter such as the pills or capsules are individually protected, prevention of contamination and these machines are easy to set up and operate.

However, child proof closures for vials are not produced at present. These closures are required according to the Food and Drug Regulations in North America. Production of such vials and closures requires high precision tools.

D. Metal tubes

a) Present:

The facilities for the manufacture of metal tubes are located on the ground floor of a six storey building under construction. This section has three impact extrusion presses working independently and producing a fair quantity of aluminium and tin tubes. As in the case of the presses, the threaders for cutting to length and forming the thread are performing independently.

90% of the tubes produced have to be lacquered inside to protect against contamination. MPC has two hand operated inside lacquering machines, and annealing ovens. All these equipments are outdated and need early replacement, as they are not equipped with proper exhaust systems for removing the solvents contained in the lacquer. Two separate decorating lines comprising a base coating machine, drying oven and a printing line with a second drying oven are also hand operated. They produce 1-2 colour printings. However, the quality is poor. All the tubes produced on these old lines are capped (putting closures on) manually on a table located away from the printing machines. This can result in the mix up of tubes. The boxes are made by MPC and repaired by the people capping the tubes.

The boxes have to be inspected and vacuum cleaned. Similarly there has to be control over the tubes left over.

Recently MPC installed an automatic line from Federal Republic of Germany and this unit can produce Aluminium tubes in an uninterrupted cycle. However, it is necessary to pay immediate attention to the following points to obtain the optimum output from this unit:

1) Provision of all the necessary components.
2) Supply of adequate spare parts and chests for spare parts.
3) Written instructions in English as well as Arabic for operation and maintenance.
4) Planned preventive maintenance programme.
5) Special tools for interchange of sizes, shafts and printing plates and toolboxes.
6) Avoiding the influx of sand into the area.
7) Submission of closures to the manufacturer of capping machines to facilitate the adjustment of the automatic capping machine.
8) Testing of different latex materials to find out the one suitable for the latex machine.
9) To rectify the supply of compressed air by providing suitable cylindrical containers to absorb the condensed water to avoid interruptions in production.
10) Establishment of a testing station close to the lines(Test with mercuric chloride, copper sulphate or electronic test). Hourly test recommended.
11) Statistical quality control.
12) Daily production reports enumerating causes for shutdowns.
13) Accurate application of lubrication of raw materials (slugs) to facilitate complete removal during the annealing process.

14) Accurate set up on the threader.

15) Proper air installation on the inside lacquering machine.

16) Correct set up on base coaters and printing machines.

17) Good housekeeping.

18) Location of the ovens outside the working area possibly on another floor to avoid the heat on the lines.

In the absence of action on the above, the line has not worked to capacity. To rectify the factors referred to, it is recommended that advice from the manufacturer should be sought. Only specialists with experience could remedy some of the problems encountered as e.g. in the case of the inside lacquering, the capping and the latex machine. Remedial of these problems is not only necessary to give optimum production without interruption but to meet the quality standards required by the pharmaceutical units. This would obviate the import of metal tubes, which has now become necessary due to the poor quality of the tubes produced at present.

Latexing has been recognized as efficient protection against leakage from the fold of the tube. This also will be impervious during hot climate. This will further avoid the current practice of wrapping the ointment tubes in a plastic folder on account of leakage.

It is also recommended that the machine operators should get the necessary know-how by visits and working in modern tube plants abroad. It is necessary to introduce in-plant training for housekeeping, cleanliness and safety.

b) Future:

According to MPC, the requirements of the local market are higher than the existing capacities. MPC has two hand-operated lines which together can produce 40 million tubes per year. One automatic line produces 38 million per year. In all, therefore, the output should be 78 million per year. However MPC expects to produce 36 million tubes in 1977. Even granting that the new automatic line has been recently installed and has yet to attain optimum production, the output is still far below what it should be on account of reasons enumerated above. MPC therefore, proposes to install one new automatic line every year starting from 1978 to 1980. Each such line will entail an investment of about US$250,000. In view of this, it is recommended that the existing facilities should be improved on the lines referred to above to obtain the optimum capacity with the

required quality standards. After achieving this, it is recommended that ACDIMA may plan for the erection of a new tube plant outside of Egypt. It is also necessary to carry out market research to find out the requirements of tubes in other areas such as toothpaste, shaving cream, skin cream, etc. The combined requirements of the pharmaceutical, cosmetic and other industries may justify the big investment needed. The following guidelines may be taken into consideration prior to the establishment of new manufacturing facilities for metal tubes.

1) The decision on the site may be based on the findings of the pharmaceutical experts.

2) The site chosen should be close enough to the pharmaceutical plants to ensure close liaison between the producers and users and to avoid long and costly transportation.

3) The site should be in a dust and pollution free surroundings to obviate contamination of raw materials.

4) The new plant may preferably consist of one floor with facilities to install the ovens on the roof. Transfer conveyors and chains could be extended, to improve cooling before the tubes reach the next stage of operation.

5) The layout of the proposed plant as submitted by the construction firm should be cleared by an experienced tube manufacturer.

6) Training of personnel of the following categories:-

i) Pressman, also should be able to train helpers and setup men for threaders, conveyors, etc.

ii) Offset printers for multicolour printing and also should be able to train assistant.

iii) Training in the set up of inside lacquering machine and capping machine and eventually being able to handle the latexing.

The North American Tube Council in co-operation with the tube manufacturers established an educational programme for setting up Herlan extrusion presses comprising audio-visual techniques.

7) The lay out of the new building may include the following:-

i) A secluded area for tool room and ample space.

ii) Adequate facilities for the storage of raw materials.

iii) Room for packing material and cleaning facilities.

iv) Production area.

8) Tooling:

The backbone of good tube production is a well equipped tool room. Equipment should consist of different types of lathes, milling machines, surface and cylindrical grinders and heat treatment facilities with hardness testers. The manufacturers of presses will supply the required tool sets. The wear out of tools on impact extrusion presses is high due to accumulated heat and high pressure. The extrusion tools (die and puncher) lose accuracy after extrusion of approximately 150,000 pieces. Wallram, Essen, Federal Republic of Germany, General Electric United States produce tools with cabrde inserts. This tool room can also be used for making molds for plastic componrntssuch as closurers for tubes, plastic vials, etc. The use of prefabricated units is recommended to ensure proper and timely commissioning of the new plant.

c) Suppliers of Equipment:

The most well known producers of machineries for the metal tubes and cans are:-

i) M/S Herlan, Karlsruhe, Federal Republic of Germany. This firm assembles complete production lines, manufactures different types of presses, threaders, coaters, printing machines, cappers and ovens. The inside lacquering machines and latexing machines supplied by M/S Sprimag, Kirchheim, Federal Republic of Germany are incorporated in the lines assembled by Herlans. ii) M/S Alpons Mall, Berghause, Federal Republic of Germany. This company produces only threaders, coaters, printing machines, ovens and coppers. They also assemble complete lines, using presses made by M/S Schuler, Goeppinger, Federal Republic of Germany and inside lacquering and latex machines supplied by Spriman.

iii) Polytype SA, Fribourg, Switzerland.

This firm produces only threaders, coaters, printing machines, cappers and ovens. They also assemble complete lines, using presses from a Swiss manufacturer. Inside lacquering and latexing machines are provided by a Swiss subsidiary of Sprimag. The polytype printing machines are accurate and easy to set up.

iv) Joseph Rhodes and Sons Ltd, Bellevue, United Kingdom. This company manufactures presses.