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ESTABLISHMENT OF A DEVELOPMENT PLAN

FOR THE PHARMACEUTICAL INDUSTRY

UC/ALG/85/062

ALGERIA

Technical report: Establishment of facilities and Transfer of Technology for the Production of Intravenous Fluids *

Prepared for the Government of the Democratic and People's Republic of Algeria by the United Nations Industrial Development Organization

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I. SUMMARY

1. The production of intravenous fluids in Algeria is confined to Biotic. The current production is around 1,300,000 units of 500 ml each per year.

2. Based on the development plan for the Pharmaceutical Industry prepared in 1985, the consumption of intravenous fluids is expected to go up to 7.6 million units by 1990. A rehabilitation and rationalization programme for Biotic is recommended to start in 1986. If this recommendation is implemented, the production of intravenous fluids at Biotic is expected to increase to about 3,000,000 units of 500 ml per year. This will still leave a shortfall of 4.6 million units by 1990.

3. Taking into account the projected domestic demand by the year 1990, infrastructure facilities and skilled manpower available at Biotic, the establishment of a plant for the production of 4 million units of 500 ml of intravenous fluids is recommended. With the completion of the new project, the country will achieve near self sufficiency in intravenous fluids.

4. An important feature of the proposed plant is the transfer of technology involving polypropylene containers and a continuous process with integrated blow-moulding and filling operation. Polypropylene containers have definite advantages over the glass containers presently used. Further polypropylene containers can be sterilized at higher temperatures than other plastics.

5. Equipment is also provided for blow-moulding containers at site and training will be imparted in handling the sophisticated machines. This will avoid importation of empty containers.

6. The selection of equipment is such that latest trends in production and requirements of Good Manufacturing Practices are taken into account.

7. Training is an important feature of the proposed plant. Algerian pharmacists and engineers will be trained abroad in production, quality control and maintenance.

8. Investment parameters have been worked out. The proposed plant will entail an investment of US$ 8 million out of which 60 percent is the cost of equipment and know-how and the balance cost of civil construction.

II. INTRODUCTION

Diarrhoeal diseases could cause severe dehydration, which is one of the primary causes of a high child mortality role in Algeria. Dehydration can be rectified thorugh the administration of solutions correcting fluid and electrolyte deficits orally by rehydration salts (ORS) or parenterally by intravenous fluids (I.V. fluids).

The solutions intended to be administered by intravenous infusions are commonly called I.V. fluids and are included in the group of sterile products referred to as large volume parenterals. Intravenous fluids are commonly used for a number of clinical conditions. These include (i) correction of disturbance in electrolyte balance as well as body fluids (fluid replacement), for example, in acute cases of diarrhoea (ii) the means of providing basic nutrition, for example, post-surgery condition (iii) the basis for the practice of providing total parenteral nutrition (TPN) or parenteral hyper-alimentation and (iv) use of vehicles for other drug substances. Using I.V. fluids as vehicle offers the advantage of convenience, the means of reducing the irritation potential of the drug and provides a method for continuous drug therapy I.V. fluids are sterile solutions of simple chemicals such as sugar, aminoacids or electrolytes - materials which can easily be carried by the circulatory system and assimilated. These are packed in glass or plastic containers of 150-1000 ml capacity.

It has been estimated that 40 percent of all drugs administered in hospitals are given in the form of injections and their use is increasing, part of this increase due to the wider use of I.V. fluids.

In the light of above, it is obvious that both ORS and I.V. fluids are essential for reducing diarrhoeal disease related mortality. Further, I.V. fluids are indispensable for any hospital for a number of clinical conditions.

The consumption of pharmaceuticals in Algeria was about 273 million sales units in 1982 and is expected to increase to 481 million sales units in 1990 and 1,355 million sales units by the year 2005. However, the domestic production which is in the form of pharmaceuticals in dosage form during the year 1983 amounted to about 8 percent in terms of value, that is 144.1 millions of Algerian Dinars out of a total consumption equivalent to 1,803.7 millions of Algerian Dinars. The balance constituted imports.

The National Enterprise for the Production of Pharmaceuticals "SAIDAL" has a monopoly on the imports of raw materials, excipients and packaging materials and the production of pharmaceutical products. The production activity of SAIDAL is supervised by the Ministry of Energy and Chemical and Petrochemical Industries, while the importation and distribution of drugs by ENAPHARM, ENOPHARM and ENCOPHARM are in the domain of the Ministry of Public Health. SAIDAL operates three production facilities; namely, Biotic, El Harrach and Pharmal. Biotic and the National Quality Control Laboratory for pharmaceuticals share a common facility. The Research and Development Laboratory of SAIDAL shares a facility with El Harrach production unit. (Pharmal has the biggest capacity out of the three units and has some modern machines for formulation of dosage forms.)

The most important project of the Algerian Pharmaceutical industry is the Antibiotic fermentation complex in Médéa. This project with an initial investment of approx. US$ 200 million was designed by the Societé Nationale des Industries Chimiques (SNIC) and CTIP of Italy, which also takes part in the execution of the project. The capacity of this plant will be 200 tons of antibiotics per year. The technologies were provided by Squibb and Co. of USA and IBI of Italy. The project includes facilities for fermentation, chemical synthesis, extraction quality control, recuperation of solvents, etc. According to the revised work plan, the formulation and packaging unit of this project could commence its operation in early 1986 and the fermentation unit in 1987.

The production of I.V. fluids in Algeria is confined to Biotic. The current production is around 1,300,000 units of 500 ml each per year. The present production range of I.V. fluids is indicated in Annex I. I.V. fluids are filled in glass containers. The list of major equipment currently in use at Biotic is shown in Annex II.

Pursuant to the request of the Government of the Democratic People's Republic of Algeria, UNIDO fielded 16 international experts in various disciplines of the pharmaceutical industry in Algeria during 1985 on the basis of which a development plan for the pharmaceutical industry was prepared. In Phase I of the Plan, the existing production units will be rehabilitated and rationalized. Based on this at the end of Phase I, in 1988, annual production of I.V. fluids at Biotic is expected to be about 3,000,000 units of 500 ml. As against this, the present consumption of I.V. fluids is 6 million units and this is expected to increase to 7.6 million units in 1990 and to 16.4 million units in the year 2000 as shown in Annex III.

Even after the completion of the rehabilitation and rationalization, it is expected that there will be a shortfall of 4.6 million units between production and demand by the year 1990. In the light of above, a project for the establishment of 4 million units of I.V. fluids capacity when completed will enable Algeria to attain near self-sufficiency with regard to I.V. fluids. Further, the country depends totally on the import of empty glass containers for the production of I.V. fluids . Apart from a recurring import bill and high cost of production, the recycling of glass containers has certain obvious disadvantages. In view of this it is desirable to use polypropylene containers and provide equipment for the production of polypropylene containers at site. Apart from these being disposable containers, they can be sterilized at a higher temperature, thus ensuring safety. An important element of the project will be the transfer of technology for the production of empty polypropylene containers as well as production of I.V. fluids in such containers.

III. ESTABLISHMENT OF A PLANT FOR THE PRODUCTION OF INTRAVENOUS FLUIDS IN ALGERIA

Taking into account the domestic demand and prospects for the year 1990, infrastructure facilities and skilled manpower available at Biotic and in the country, the establishment of a plant for the production of 4 million units of 500 ml of intravenous fluids is recommended. The type of intravenous fluids and the production level proposed in each case are indicated in Annex IV.

A. BASIS FOR SELECTION OF INTRAVENOUS FLUIDS

The anticipated consumption figures for intravenous fluids for the years 1990 and 2000 are given. The production level proposed in the case of each product is the anticipated shortfall between projected demand and local production (after completion of rationalization and rehabilitation).

B. SELECTION OF CONTAINER

Different types of containers are used for intravenous fluids including glass, P.V.C. polyethylene (low density) and polypropylene. The selction of the container depends on many factors such as the traditional use of a particular type of container, to which the medical profession and the public are accustomed, availability of containers, availability of raw materials for the production of containers and facilities for their production, local cost, etc. By and large P.V.C. containers are popular in the U.S.A. and some European countries (as can be seen from Annex V). P.V.C. is transparent and the presence of foreign particles can be easily detected. However, there is a virtual monopoly over production of P.V.C. sheets of pharmaceutical grade and limited sources for P.V.C. bags and this increases the cost of the containers.

All plastic containers for intravenous fluids should conform to WHO specifications (WHO Technical Report Series 614, 1977, pages 25-53). With P.V.C. containers there is also possibility of additives used in the production of P.V.C. sheet contaminating the intravenous fluids in the P.V.C. container. The sterilization of the solutions has to be carried out at 115°C for a longer time. The other plastic containers are of polyethylene and polypropylene. These are widely used in some of the European countries. For example polypropylene is used widely in Denmark. Polypropylene has the advantage that the containers can be sterilized at higher temperature, that is, at 121°C for a shorter time than in the case of other plastic containers and this ensures sterility and quality of product. The containers can be produced at site by blow moulding and this saves expenditure on importing empty containers. However, polypropylene is not as transparent as P.V.C. and is more brittle. Polyethylene is transparent, can be blow-moulded at site but has to be sterilized at a temperature lower than that of polypropylene and this is a disadvantage. Considering all the above factors, polypropylene has certain advantages and that is the reason why it has been selected for the project.

Glass containers have been in use over the years. These containers are transparent, can be sterilized at a higher temperature and can be recycled. However, they are liable to break during transport and the freight costs are high in case there are to be imported. Recycling can be hazardous if the containers are not handled carefully after use and returned to the factroy. This is not easy in some of the developing countries. Further the quality of glass required for intravenous fluids is rather expensive. This is the reason why glass containers are widely used in developed countries such as France, Italy and Japan where there is a well established glass industry.

C. TECHNOLOGY

Technology is an impotant element in the production of intravenous fluids. At present technology based on glass containers is available in the country. In the propoposed plant, technology based on the use of polypropylene containers will be introduced. A special feature is the technology for the production of empty containers at site. Another innovation in technology is the introduction of a continuous process, that is integrated operation involving blow-moulding and filling in the same machine. This will avoid handling of empty containers , separately storing, opening in sterile area and filling. The containers are produced in one section of the machine through blow-moulding and filled instantaneously in the other section of the machine without exposing the container to outside environment. This reduces the risk of contamination. Further the containers are blow-moulded at a temperature above 200°C and hence they are sterile prior to filling. The integrated machine is rather sophisticated and the Algerian engineers will be trained in the operation and maintenance of this machine.

D. SELECTION OF EQUIPMENT

Equipment selection is based on the use of technology involving polypropylene containers and integrated blow-moulding and filling under asceptic conditions. Two door autocalves are provided to ensure sterile handling. Equipment selection is based on conforming to GMP requirements and the latest practices adopted in developed countries. Proposed list of equipment is given in Annex VI.

E. TRAINING

Training assumes great importance while planning the establishment of a unit for the production of intravenous fluids. In view of this, training is an integral part of the intravenous fluids plant right from the design stage through installation and operation. The personnel requirements are shown in Annex VII. Out of these, supervisory personnel in production, quality control, maintenance and blow-moulding technology will be trained abroad. The number of persons and the length of training will have to be decided after detailed assessment of local skills, therefore costs of training in Algeria and abroad are not included.

F. INVESTMENT PARAMETERS

The cost of civil construction is indicated in Annex VIII. The cost of installed equipment is given in Annex IX. The estimated cost of the project is given in Annex X . As can be seen from the latter annex, the project is estimated to cost US$ 8 million out of which 60 percent is the cost of equipment and technical know-how and 40 percent is that of civil construction. The flow-sheet is given in Annex XI.

Present Production Range of Intravenous Fluids at BIOTIC

Glucose, isotonic	5 %	500 ml
Glucose, hypertonic	10 %	500 ml
Glucose, hypertonic	15 %	500 ml
Sodium bicarbonate	1.4 %	500 ml
Levulose, isotonic	4,82 %	500 ml
Mannitol	10 %	500 ml
Peritoneal Solution for Hemodialysis		
Sodium acetate	166 g/l	
NaCl	204 g/l	
KCl	3 g/l	
CaCl2	7 g/l	
MgCl2	5 g/l	
Sodium bicarbonate	1.4 %	250 ml

Annex II

List of Equipment in use at BIOTIC for Intravenous Fluids Production

Serial No.	Item	Capacity	Number
1	Distillator	800 l/hr	1
2	Tanks with agitation	4000 l	2
3	Washing machine of flasks, PROT	30-35.000 flasks per 8 hours	1
4	Filling machine, PKB	20.000 flasks per 8 hours	1
5	Closing machine	25.000 flasks per hours	1
6	Capsulating machine	25-30.000 per 8 hours	1
7	Autoclaves	800 flasks each	5

Projection of IV fluids to be Manufactured

Annex III

	Unit Volume	Proportion of Consumption	Projection of Requirement in million units 1990	2000
Glucose, isotonic, 5 %	500 ml	1.000.000	3,5	8,0
Glucose, hypertonic, 10 %	500 ml	50.000	0,2	0,4
Glucose, hypertonic, 15 %	500 ml	50.000	0,2	0,4
Na bicarbonate, 1.4%	500 ml	16.000	0,06	0,1
Na bicarbonate, 1.4%	250 ml	50.000	0,2	0,4
Levulose, isotonic, 4,82 %	500 ml	30.000	0,14	0,3
Mannitol, 10 %	500 ml	7.000		
Mannitol, 20 %	250 ml	1.000		
Peritoneal Solution for Hemodialysis	500 ml	200.000	0,7	1,5
NaCl, isotonic	500 ml	500.000	2,0	4,0
NaCl, isotonic	250 ml	80.000	0,3	0,7
NaCl, hypertonic	250 ml	70.000	0,3	0,6
		Total	7,6	16,4

PROPOSED LEVEL OF PRODUCTION IN 1990

(Units of 500 ml each)

Quality: French Pharmacopoeia

Item	Quantity
Glucose, isotonic, 5 %	1,800,000
Glucose, hypertonic, 10 %	105,000
Glucose, hypertonic, 15 %	105,000
Na bicarbonate, 1.4%	140,000
Levulose isotonic 4,82 %	75,000
Peritoneal Solution for Hemodialysis	370,000
NaCl, isotonic	1,255,000
NaCl, hypertonic	150,000
	4,000,000

BASIS OF CALCULATION

- Yearly production : 4,000,000 containers x 500 ml
- Yearly working days : 250 days
- Number of shifts per day : 2 shifts (1st.shift =9,600 bottles, 2nd.shift =6,400 bottles)
- Working hours per shift : 8 hours
- Daily production : 16,000 containers of 500 ml

Annex V

CONTAINERS FOR INFUSIONS

COUNTRY	PVC	POLYETHYLENE/ POLY PROPYLENE	GLASS
U.S.A. and Canada	60%	20%	20%
U.K	85	10	5
W.G.	0	60	40
Switzerland	18	75	7
Italy			100
Syria	100		
Jordan	100		
Lebanon	80	10	10
Saudi Arabia	20		80
Kuwait	100		
UAE	80	20	
Yemen	100		
Iran	50	50	
Iraq	20		80
Pakistan	95	5	
Afghanistan	60		40
Bangladesh	80	20	
Thailand	15	25	60
Japan	5		95

PROPOSED LIST OF EQUIPMENT

Serial No.	Equipment	Quantity
1	Thermocompression water distillation unit, output 800 l|h, water-still made out of stainless steel AISI 316, compressor made out of stainless steel, machine completely protected with metallic panels. Heating system by steam and or electricity. Complete with built-in safety device, resistivity cell for automatic control of water quality, automatic signal of failures and electronic switch for automatic running.	1
2	Water softening columns for alternative operation provided with full load of softening resin. Max. output 9 m^3|h.	2
3	Double column deionizer plant - mixed bed type provided with full load of deionizing resin. Nominal output 6-12 m^3|h.	1
4	Neutralizer of 600 l capacity made out of strong PVC.	1
5	Storage tanks for deionized water 5000 l capacity stainless steel, with a coarse filter between tank and distillation unit.	2
6	Storage tanks for distilled water 5000 l capacity made out of 18|8 stainless steel polished fitted with air filter 0.8 - 1.0 microns and arrangement to heat to 85°.	2
7	Stainless steel vats for solution preparation (ss 18|8) capacity 2000 l. Inner surface highly polished with jacket for heating and cooling. Stainless steel lid, equipped with graduation device with sterile air filter.	3
8	Stirrers for the mixing vats for wall fixation. Axle and propeller of stainless steel 18|8| complete with driven motor of 1,1 KW and holder.	3
9	Filtering units for the solution. Output 50l|min; complete with stainless steel centrifugal pump and motor of 2,2 KW. Built-on filter holder in stainless steel for membrane filter 0.44 mμ and 0.22 mμ filters.	2
10	Sets of pre-filters and filters membrane for the filtering unit (including 500 pre-filters and 500 filter membranes).	2

Serial No.	Equipment	Quantity
11	Bottle pack type 302 - 5 cavity mould integrated blow moulding and filling machines for polypropylene - capacity 1200 bottles|h of 500 ml with ancillary equipments including two moulds, regranulator, sterile air compressor, filters, etc.	2
12	Autoclaves for sterilization: double door, horizontal type. Minimum capacity - 3 cubic meters designed for polypropylene bottles with automatic counter pressure adjustment. Inner chamber made out of stainless steel AISI 316 jacketed. Insulated with mineral wool. Doors equipped with automatic locking and safety device provided with ancillary equipment and controls for automatic steam sterilization. Standard sampler made of stainless steel AISI 316 with immersion probe showing temperature inside the bottles. Possibility of ventilating chamber.	2
13	Sets of carriages and stainless steel trolleys and baskets for sterilization of filled bottles, adopted to the autoclave.	12
14	Labelling machines 1000 bottles|h	2
15	Polarimeter for dextrose determination complete with sodium lamp and observation tubes of 100 and 200 mm.	1
16	Flame photometer for sodium and potassium determination complete with air compressor.	1
17	Laminar flow bench for bacteriological laboratory 80 x 50 cm, complete with illumination tubes and filter holder.	1
18	Bacteriological stove for incubation inner volume 36 l. Temperature range up to 70° C, power 0,2 KW regulation by thermostat.	1
19	Electric stove for instrument sterilization inner volume 55 l, temperature range 40 - 240°C, power: 1,2 KW, equipped with thermostat.	1
20	Sets of rabbits' cages (for 48 rabbits). Cages mounted on metallic racks and equipped with feeding and drinking devices. Automatic washing by periodic water flow. Automatically regulated supplied with 6 retention boxes for rabbits.	One set
21	Temperature measuring device for rabbits. Direct reading on scale. Complete with connecting box and 9 temperature probes.	1

Serial No.	Equipment	Quantity
22	Air compressor with compressed air tank of 3200 l. Output: 360 m^3|h Working pressure: 7 kg|cm^2 Complete with automatic regulation and noise protective case. Water lubricated type; oil lubricated type not suitable.	1
23	One steam boiler, complete with water feeding tank and switch panel for automatic regulation. Output: 1t|h. Equipped with particle retaining filter or a sterile filter and stainless steel exchanger.	2
24	Standby Diesel generator 200 KVA with switch-board for automatic switch on in case of power failure equipped with accessories.	1
25	0.8m^3 autoclaves for sterilizing filters and small parts.	2
26	Equipment for thin layer chromatography .	1
27	U.V. spectrograph .	1
28	Analytical balances .	3
29	Automatic particle counter .	1
30	Slit sampler for the microbiological environmental control in clean rooms .	1
31	Microscope for microbiological work .	1
32	Equipment for sterility tests .	One set
33	Bacteria counter.	1
34	Turbidimeter and the necessary equipment to carry out Limulus Amebocyte Lysate Test for routine controls.	1
35	Shelves and cupboards in sterile area for men and women.	As required
36	Stainless steel tables with sink, shelves.	As required
37	Weighingscales, different denominations for raw materials.	3
38	Stainless steel loading cars and under cars.	4 sets

Series No.	Equipment	Quantity
39	Stainless steel unloading cars with unloading cars for cooling period, labelling.	4 sets
40	Tables and shelves.	As required
41	Storage shelves for control bottles.	As required
42	Storage shelves for raw materials.	As required
43	Raw materials for commissioning and testing.	As required
44	Air conditioning and ventilation plant; clean areas should have a separate air conditioning system provided with disinfection dampers. Mixing room with cleanliness class B or class A.	1 unit
45	Other equipment required for complete analysis including chemical analysis, sterility and pyrogen testing.	As required
46	Equipping animal house for pharmacological tests.	As required

Annex VII

PERSONNEL REQUIREMENT *

Serial No.		Production	Laboratory	Maintenance	Administration
1	Pharmacist/chemical engineer	1	1		
2	Supervisor	3			1
3	Mechanical/electrical engineer			3	
4	Operators/technicians	6	3		
5	Skilled workers	30		3	
6	Unskilled workers	5			
		40	4	6	6
	Grand Total	56			

* Secretaries, drivers, cleaners, and watchmen are not included.

Annex VIII

COST OF CIVIL CONSTRUCTION

Particulars		US $
Production building 825 sq.m. ($1,620|sq.m.)		1,336,500
Laboratory 300 sq.m. ($ 1,620|sq.m.)		486,000
Office accommodation 50 sq.m. ($1,080|sq|m.)		54,000
Warehouse for raw materials 500 sq.m. ($1,080|sq.m.)		540,000
Warehouse for finished products 250 sq.m. ($1,080|sq.m)		270,000
Building for utilities 200 sq.m. ($ 960|sq.m)		192,000
Workshop, cafeteria, time office, etc. 200 sq.m. ($1,080|sq.m.)		216,000
Animal house for rabbits 100 sq.m. ($1,080|sq.m.)		108,000
	Total cost of buildings	3,205,500
	say	3,200,000

Annex IX

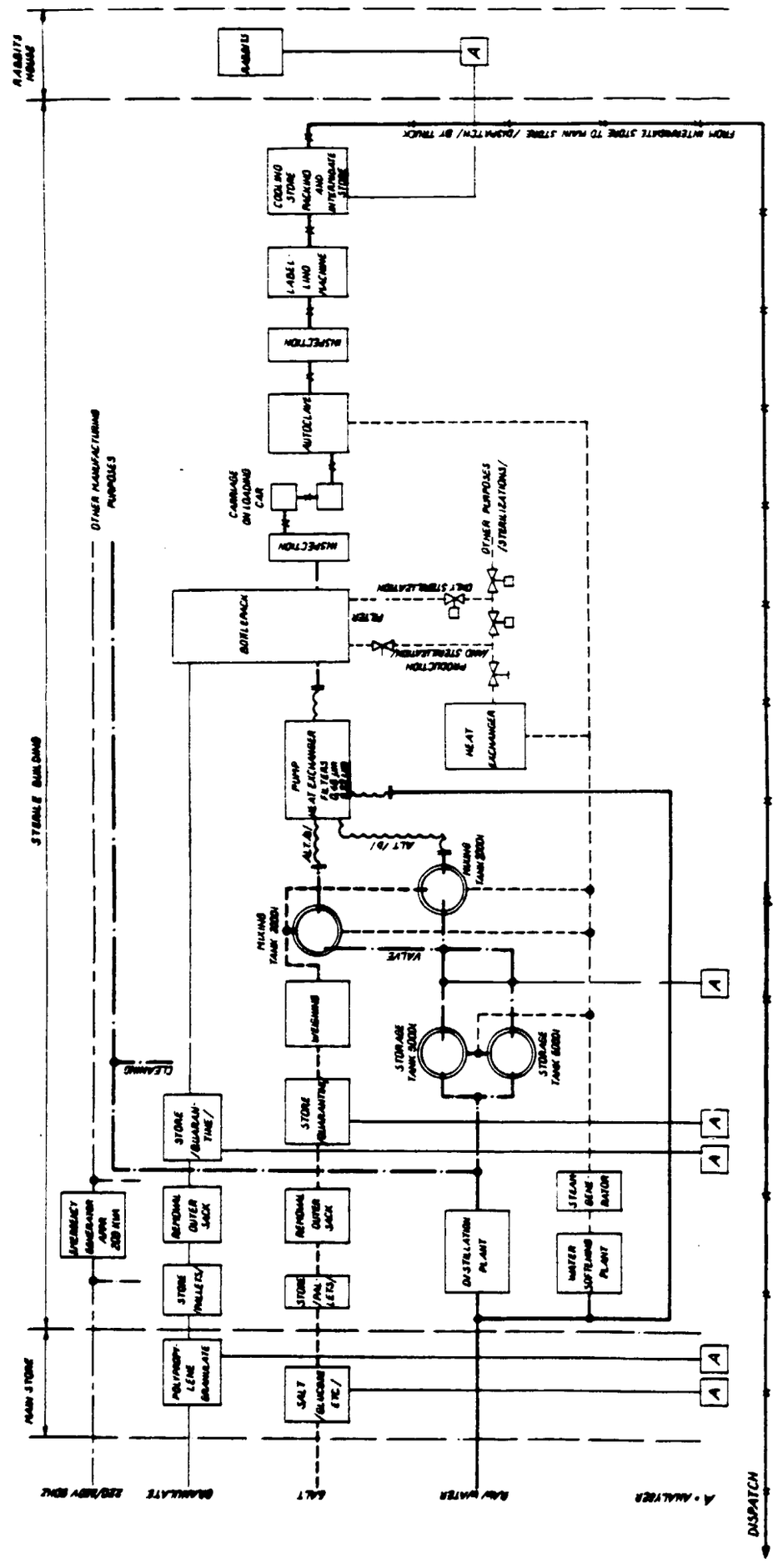
COST OF INSTALLED EQUIPMENT

	US $
Equipment for process and utilities	3,090,000
Laboratory equipment	150,000
Reserve for spareparts and installation materials and technical know-how	400,000
Cost of equipment F.O.B.	3,640,000
Cost of equipment (C.I.F. 25 percent of F.O.B. cost)	4,550,000
Handling charges in Algeria	100,000
Installation charges	150,000
Total installed cost of equipment	4,800,000

Annex X

ESTIMATED COST OF THE PROJECT

Particulars	US $
Cost of installed equipment including technical know-how	4,800,000
Cost of civil construction	3,200,000
Total	8,000,000


RABBITS
RABBIT HOUSE
FROM INTERMEDIATE STORE TO MAIN STORE /DESPATCH/ BY TRUCK
COOLING STORE PACKING AND INTERMEDIATE STORE
LABEL LINO MACHINE
INSPECTION
AUTOCLAVE
CARRIAGE ON LOADING CAR
INSPECTION
OTHER PURPOSES /STERILIZATIONS/
DILT STERILIZATION
FILTER
INJECTION AND STERILIZATION
BOILERPACK
HEAT EXCHANGER
PUMP HEAT EXCHANGER FILTERS
ALT /B/
MIXING TANK 3000l
VALVE
MIXING TANK 3000l
WEIGHING
STORAGE TANK 3000l
STORAGE TANK 6000l
STORE /QUARANTINE/
STORE QUARANTINE
CLEANING
STERILE BARRIERS
OTHER MANUFACTURING PURPOSES
EMERGENCY GENERATOR APPR. 200 KVA
REMOVAL OUTER JACK
REMOVAL OUTER JACK
STORE PALLETS
STORE PALLETS
DISTILLATION PLANT
STEAM GENERATOR
WATER SOFTENING PLANT
POLYPROPYLENE GRANULATE
SALT /GLUCOSE ETC./
MAIN STORE
ESS/BEV BOAT
GRANULATE
SALT
RAW WATER
A = ANALYZER
DISPATCH
NOTE MAIN BRANCHES ONLY - NO DETAILS E.G. VALVES, ELECTRIC WIRING