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ESTABLISHMENT OF A DEVELOPMENT PLAN FOR THE PHARMACEUTICAL INDSUSTRY

DP/ALG/86/010

ALGERIA

Technical report: The Medea Antibiotic Complex *

Prepared for the Government of the People's Democratic Republic of Algeria
by the United Nations Industrial Development Organization
acting as executing agency for the United Nations Development Programme

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C O N T E N T S

1. TECHNICAL SURVEY

The latest reports about the production output of the Algerian Pharmaceutical Industry indicate that the consistent support by the Government properly served the purpose: the local production - both of bulk products and formulated specialities - is increasing. In 1984 according to SCRIP reports, the demand of formulated products and raw materials has been covered by algerian factories at a rate of 12 % and 26 % respectively /SCRIP No 985; 27, March 1985/.

1.1. Project Scope

The new Medea Antibiotic Complex which is near completion, will have an important role in this long-term development program. According a turn-key contract, which has been signed in 1977 by the Algerian Government with the Italian Agency CTIP, in Medea area an antibiotic factory will start the production of bulk antibiotics and their formulation. The task of the new factory is to cover the demand of the country of today and of the coming years. Last year a technical report has been prepared by UNIDO experts on the Medea project. The present mission has been focused - as expressed by Mr. Belkebir, general manager of SAIDAL - to special technical aspects of the new plant.

The technical specifications for the Medea plant were given 10-12 years ago regarding the selection of expedted products, technical level, etc. In the last decade there were substantial changes in the antibiotic market.New semisynthetic products of penicillin and cephalosporin were developed. Some antibiotics are no longer in demand. New forms of formulations are introduced. The general use of antibiotics is increasing in tendency. The algerian population is increasing substantially. This fact also was to be taken into consideration.

So the aim of our present mission was to investigate the real production capacity of Medea Antibiotic Complex to establish reasonable analysis how the production and formulation of antibiotics can cover the present and projected demand both in quantity and selection. It was a special request to see and propose how to make the operations in Medea Complex as economic as possible. Different options were to be presented to the management of SAIDAL to enable them to select and adapt the best scenario to different demands and conditions. Present survey is dealing with the bulk production of antibiotics and semisynthetics only.

1.2. Site plan description

The size of the lot of Medea Antibiotic Complex is appr.

12 hectares. The location is about 10 km from Medea-city. The city itself is roughly 100 km from Alger. The site of factory is accessible only on the connecting road No. 18 to KHEMIS MILIANA south-west from Medea. There is no railway connection to the factory. The actual altitude of the site is about 800 m above see level - among still higher mountains around - on a plateau levelled with great efforts. The air is very dry. The climate in general is very hot, but in winter there is snow around the mountains. In the winter rain is usual. The general orientation of the site is providing a slope to the south-east corner. This slope is used to collect the rain water also. The compound has practically a square-form and the axes of the compound lay to the 4 cardinal points. The gate is on the southern side /Figure 1/. The buildings and the different units in four rows are arranged according to their functions. In the western higher level are situated the energy receiving units: gas, water, electricity. Here are settled the boilerhouse, cooling towers, cooling compressors, air-compressors, water tanks, water treating units, electrical mains, transformers. On the eastern side of this strip are erected the solvent store tanks and regenerating units.

In the second row are the five production workshops and central maintenance building. In the third row are put

the canteen, administration, central store and central laboratory buildings and one of the formulation units. The fourth line is for the effluent purification unit, incinerator and animal-houses. At the end is the second formulation building parallel with the first similar one.

Broad service and circular road-system is constructed in the compound.

1.3. Energy supply

Gas is used for heating of boilers and incinerator. For the boilers oil supply is provided also. Gas is used for the operation of the turbo-generator for electricity. There is a special gas-pipe connection from the main-line for the Complex. Water is supplied from a water-reservoir, what is some 30 km away through a pipe-line specially constructed for the Complex. The receiving station, store tank for the estimated daily use /6.000 m^3/, pretreatment operations /reverse osmosis/ are set in a unit on the western side.

Electricity is provided in some extent by an own turbo-generator operated by gas. It is in permanent operation and able to provide electricity to the main units for the fermentation workshop stirrers, air compressors, cooling

machines, etc. There are also two independent high voltage cable connections coming from two grids to provide undisturbed supply. Steam is produced in two steam-boilers. Their capacity is 32 tonnes/h /2 x 16 to / on 10 bar pressure.

The main steam consumers are the fermentors, solvent recovery unit and some evaporation.

Compressed air is supplied from a central compressed air-station, also in the western side of the plant. Three independent centrifugal compressors are installed in the station. It is so calculated that two of them are for continuous use and the third is for reserve. Compressed air temperature is 230°C at outlet. This temperature is cooled to 30-35 C° before use in fermentors.

Cooling towers and cooling compressors provide proper facility to maintain the temperature in fermentation. Their use is designed for the special climate. The fermentors are cooled with 5 C° cold water. From the cooling coils the water is transferred to the cooling unit and ultimately the accumulated heat is removed by the evaporation through forced ventillation in cooling towers. There are 32 cooling fans in two rows.

Water purification is installed for the sanitary units and technological effluents. The mycelial by-products are incinerated in a special unit. There is an aerobic biological purification unit used with proper settling tanks.

Cooling and ventillation of the buildings is solved individually. For production halls cooled fresh air intake is usual, but a surprisingly great number of operational and store places are centrally air conditioned by locally operated units.

1.4 Design work, execution

The overall look of the Complex is impressive. The settling of different buildings and auxiliary units, the system of building construction, the road connections, the pipe-arbors provide good orientation. The different units are settled according to their funcitons and good interconnections with other coupling units. The finishing of the building, the coating of machines, supports and steel structures are according to good standards. Heat insulation, air-ventillation and conditioning fit the tropical hot and dry air conditions. Environmental protection is calculated: effluent air and gases are washed in towers, mycelial by-products are incinerated, effluent water, sanitary and technological, is

treated in an aerobic purification and settling unit. Fire protection is calculated and a proper main water supply pipe-system is constructed, on sensitive places water-guns mounted. Laboratories, changing rooms, canteen are provided for the workers.

1.4.1. Buildings

The majority of the buildings are constructed as steel-structures covered inside-outside with metal plates with inlet insulation /Sandwich system/. Exceptions are the office, the labor buildings which are of traditional block-mason type and the headpieces to the process-buildings. They are of concrete constructions. As rough measure the buildings are.

Store building for fermentation: 26 m x 96 m, one floor, inside hight 5 m; in its western end is installed the medium preparation system.

Fermentation workshop: 26 m x 54 m. Three main floors. In longitudinal axis 5 m wide passages. Main stair in one side, steel grate stair on the opposite side.

Penicillin recovery unit: with sterile-processing head-piece. Two main floors.	26 m x 84 m,
Tetracyclin, OTC and Streptomycin recovery unit: Similar to penicillin unit.	26 m x 78 m.
Tetraciyclin purification building: Like penicillin unit.	26 m x 54 m.
Maintenance:	60 m x 70 m.
Offices, stores and two workshops: each, 8 m inside hight, with cranes.	20 m x 40 m
Office building: tow stories.	15 m x 40 m,
Laboratory building: three stories.	15 m x 50 m,
Central store: one floor.	30 m x 50 m,

Formulation building: 2 x 6.500 m^2
/65 m x 100 m/,

one floor.

Canteen and social services: 20 m x 50 m,

one floor.

1.4.2. Machinery

The installed machines and equippments are selected for the purpose uf use. The fabrication is of good quality. Mostly stainless steel was used for fabrication of machines, tanks, pipelines. The majority of valves and other fittings also are from stainless steel. The welding is of good quality. Pipe-arbors are properly installed. Foundations and mounting are made according to good standards. For cooling and heating an externally welded spiral-coil system is used in general. For stirrers flat blades are used mostly. In bigger units breaking blades are fixed. The arrangement of equippments and machines are spacious. Access to valves, fittings, instruments is provided.

Characteristic main units are:

Fermentors

9 x 130 m^3 total capacity, stainless steel tanks, with out-side-welded spiral-coil jacket for cooling and heating.

Measurements: hight: 11,4 m

diameter: 3,8 m

their ratio is: 3:1.

Inside there are 8 breaking blades fixed. They are hollow and used for cooling purpose also. On the stirrer shaft in 4 level 8 flat-blades stirring units are fixed. For stirring 375 kw electrical energy is provided. Tiristor operated continuous speed regulation /90-140 rpm/ is used. Monel-teflon shaft sealing. Bottom discharge valve pneumatically operated. Access pipe connections with ball valves and three-valve steam sterility system. Sterile air with Pall double filtering system. Dry air is provided from centrifugal compressors /heated upto 230°C and cooled back to 30°C/. Air intake from bottom through spargers. Instruments: t°C, pH, air pressure, shaft rotation, anti-foam control. End air pressure and temperature are controlled automatically. Batch sterilization. Inoculum fermentors for 6 % inoculation.

Drum filters

Vacuum rotating drum filters with water-ring vacuum pumps. Stainless steel machines with store tanks.

2 x 24 m^2 for penicillin production

2 x 20 m^2 for TC, OTC, SM production.

Extraction

3 pcs Podbielniak countercurrent continuous liquid-liquid extractors for penicillin production

1 pc Alfa-Laval countercurrent liquid-liquid centrifugal extractor /with solid removal/ for penicillin production

Ion exchange columns

8 x Ø 0.8 m x 6 m /cc.3 m^3/ IRC-50 columns

8 x Ø 0.6 m x 4 m /cc.1 m^3/ IRC-120 columns

for SM recovery technology. Stainless steel.

Vacuum evaporator /Concentrator/

Stainless steel construction. Vertical recirculating vacuum destillator; estimated capacity 2.000 l/h.

Precipitating vessels

4 x 25 m^3 stainless steel tanks with stirrers for TC production through quaternar-complex precipitation.

Lyophilization unit

4 chambers deep-freezing and evaporating unit fully automated for SM fine processing.

6-APA unit

2 reactors, stainless steel, 8 m^3 capacity with stirrer

1 cooling tank, stainless steel, 3 m^3 capacity with stirrer

2 centrifuges Ø 1,5 m.

Semi-synthetic unit

10 pcs different reactors, vessels, store tanks, centrifuges /3-6 m^3 capacity units/.

Sterile processing units

Adjoining sterile building connections to Penicillin, TC-OTC and SM processing buildings with stainless steel reactors, vessels, dryers, homogenization mixers, sterilizers, etc.

1.4.3. Instrumentation

The majority of instruments are mounted on the equipments for local reading. The main parameters, like temperature, pressure, volume are indicated in all cases, in few cases registered. Some operations are controlled from a local panel. Two central instrumentation centers are installed /fermentation workshop and solvent recovery plant/.

1.4.4. Solvents store and recovery department

This department is responsible for storing and recovery of all the solvents and liquid chemicals used in the factory. The solvents are imported except methanol. All the solvents are to be transported in drums, out of which the solvents

are pumped by special pumps to respecitve store tanks. The department compound is devided into four areas:

1./ To receive and store fresh solvents
/purchased or recovered/

Solvents are:	Ethyl-acetate
	Buthyl-acetate
	Isopropanol
	Kloroform
	Methyl-isopropyl-acetate
Here is stored	Ethyl-cellosolve also
Facilities:	20 store tanks 20-40 m^3 each
	transfer pumps

2./ Solvents and chemicals stored in drums
This area is protected from direct sunshine by a corrugated metal roof.

3./ Liquid chemicals and solutions

NH_3 gas	Liquid ammonia is transported in tankers. Special pumps to transfer into store tanks.
	2 x 45 m^3 tanks.
26 % - NH_3	solution is prepared by evaporation and absorbtion
	200 m^3 store tank

NaOH 50 %	transport in tankers. Store in heatable plastic coated iron tank /200 m^3/
NaOH 25 %	is prepared for the technologies /200 m^3/
Sulfuric acid 98 %	2 x 70 m^3 tanks
HCl 40 %	25 m^3 tank
Antifoams	4 x 40 m^3 tanks
K-phenyl-acetic acid	25 m^3

4./ Solvent recovery

a./ 7 different solvents /mixtures/ from semisynthetic department	8 x 20 m^3 tanks
b./ penicillin department	
extracted ferm. broth 3 %	250 m^3 tank
buthyl-acetate	50 m^3 tank
buthanol	30 m^3 tank
c./ mixed solvents TC.OTC-SM	
water aceton	20 m^3
water-methanol	15 m^3
Buthanol-ethyl-cellosolve	20 m^3
solvents residue /incineration/	20 m^3

Recovery units

1./ For solvents from semisynthetic department

25 m^3 destillation tank + perforated plate column

25 m^3 destillation tank + bubble cup tower

2./ for recovery of buthanol

25 m^3 destillation tank + bubble cup tower

3./ for recovery of buthyl-acetate

continues system with preconcentrating column

4./ washing tower for columns-aeration

5./ store tanks for solvents till analysis received

8 x 25 m^3 tanks

Capacity /M. Taleb's data-sheet info/:

1.	CH_3Cl /buthanol/water	3.2 m^3/h	3.8 to/h
2.	Buthyl-acetate/water	2.48	2.18
3.	Effluent /3 % buthyl-acetate in broth/	10.0	10.0
4.	TC OTC solvents	1.64	
		0.84	

Environment protection

1. Residue from concentrators transferred into small hand-operated transport tank carriages for incineration
2. Broth /penicillin/ residue from column continuously neutralized and transferred to water purification unit
3. aeration vents of columns are connected to a special air-washing tower
4. store tanks are set with safety distance.

Instrumentation is adequate.

Local indicators on all tanks
pH control /automatic process/
temperature control
operation of regenerating columns controlled in spacious central instrument room,
the data are registered an monitored
/FFY, FY, LIC, FIC, PDI instruments/.

1.4.5. Maintenance

For preventive maintenance, repair and new fabrication purposes there is the central maintenance workshop. The building itself is 60 x 70 m. It contains offices, special workshops for instrumentation, electrical,

mechanical etc. type of work. There are special store facilities also in this department.

For big repair-work there are included two 20 x 40 m 8 m height workshops with heavy duty cranes. For repair of machines and equipments adequate tools and small machines are available in the workshops.

The size of the complex is two to three times as big as any of the production workshops. This ratio is higher then usual. But for a secluded unit like the antibiotic-factory there is no other choice, but be independent. In 100 km distance there is no other facility.

The complexicity of operations, the number of huge machines /air compressors, cooling compressors, water cooling towers, gear-boxes for fermentors and other big units/, the instrumentation, the electrical supply system, the piping /valves, fittings/, ventillation, air-conditioning, etc, etc. is an enormous task for the maintenance. The chief in charge, the special experts in different fields, the trained maintenance men are in a key position to provide undisturbed and excellent service to each of the machines, instruments, etc. in the plant. They have to have proper supply of spare parts and other staff for maintenance and repair.

I dare to state that this department is running the complex-machinery of the production units. The micro-biologists and chemists are using only - on their special way - the production facilities. The antibiotic production is a year-to-year, day and night continuous operation. The yield, the production, quality and economy depend not only from the expert work of microbiologists and chemists, but in great extent from the proper maintenance.

It was not possible to study the activity and organization and quality of the work in the maintenance department, because the factory is not commissioned, but had to emphasize here also in advance the importance of it.

1.5. Technologies

Six technologies are available presently:

Product	Technology supplied by
Penicillin G or V K-salt	Squibb, Italia
6-APA	I B I
Semisynthetics /Ampi-Oxa/	I B I
Tetracyclin HCl	I B I
Oxitetracyclin HCl	I B I
Streptomycin	Squibb, Italia

Penicillin GK

200 hours fed batch technology for fermentation. Main carbon source in glucose-solution. Total penicillin activity in broth 1.698 kg per batch.

This is 28.800 U/ml /X kg/m^3 x 1.7 = y U/ml/.

Product recovery after filtration by solvent extraction with buthylacetate, K-salt formation, crystallization.

Product 1.250 kg	Pen GK	Yield:	73.6 %
Yield stepwise:		filtration	93 %
		extraction	81 %
		crystallization	85 %

Pen G Pen GK factor = 1.113

Overall yield: 93 x 81 x 85 x 1.113 = 72.3 %

6-APA production

Chemical conversion of Pen GK to 6-APA. Selective cleavage of the amide bond is accomplished by treating the silyl ester of Pen GK consecutively with PCl_5, n-buthanol and water at low temperatures.

Batch size 374 kg Pen GK to produce 170 kg 6-APA /theoretical 291.7 kg/.

Yield on theoretical basis: 58 %.

Semisynthetics

Ampicillin.$3H_2O$ prepared by the Dane method using

6-APA and alfa-amino-phenylacetic acid.

Batch size: 110 kg 6-APA

Product 135 kg Ampi.$3H_2O$ /theoretical 205.4 kg/

Yield on theoretical basis: 65 %

OxacillinNa.H_2O prepared by the same method coupling 6-APA with methyl-5-phenyl-3-isoxazolyl group.

Batch size: 70 kg 6-APA

Product 80 kg oxacillinNa.H_2O /theoretical 142 kg/

Yield on theoretical basis: 56 %.

Tetracyclin.HCl

Fermantation time 160 hours, on starch basis, fed batch system. Broth activity on total volume about 10.000 micrograms per ml; in TC expressed about 1.230 kg product.

Activity after filtration 1.045 kg /85 %/.

Recovery of the product by quaternary ammonium complex compound, precipitation in Tetracyclin.HCl salt form.

Final product 845 kg, yield 80 %

Allover yield around 68 %.

Oxytetracyclin.HCl

Fermentation, recovery processing the same, but the activity - 10 % less. Product in broth 1.100 kg, end product in OTC.HCl form 700 kg.

Allover yield about 64 %.

Streptomycin.SO_4

200 hours fermentation time, fed batch technology on starch basis. Broth activity 6.000 micrograms per ml.

Product in broth 750 - 780 kg.

Recovery process on ion-exchange columns. Eluate is concentrated in vacuum evaporation. Product isolation by lyophyllization.

SM.SO_4 product is 450 - 460 kg

Overall yield is 60 %.

Note:

Data and details about the above technologies are based from information of technicians in Medea and in some extent from technological description provided by IBI and Squibb. There was no possibility to study in details the official documentation. The referred data are therefore only approximately correct. So are the data and informations provided in the attached sheets and drawings. They are to support the estimation of facts. /Figures 2-14./

1.6. Start-up

The installation work is practically completed by CTIP. All the important units are ready to start.Some of the services are already in operation. Minor installation is

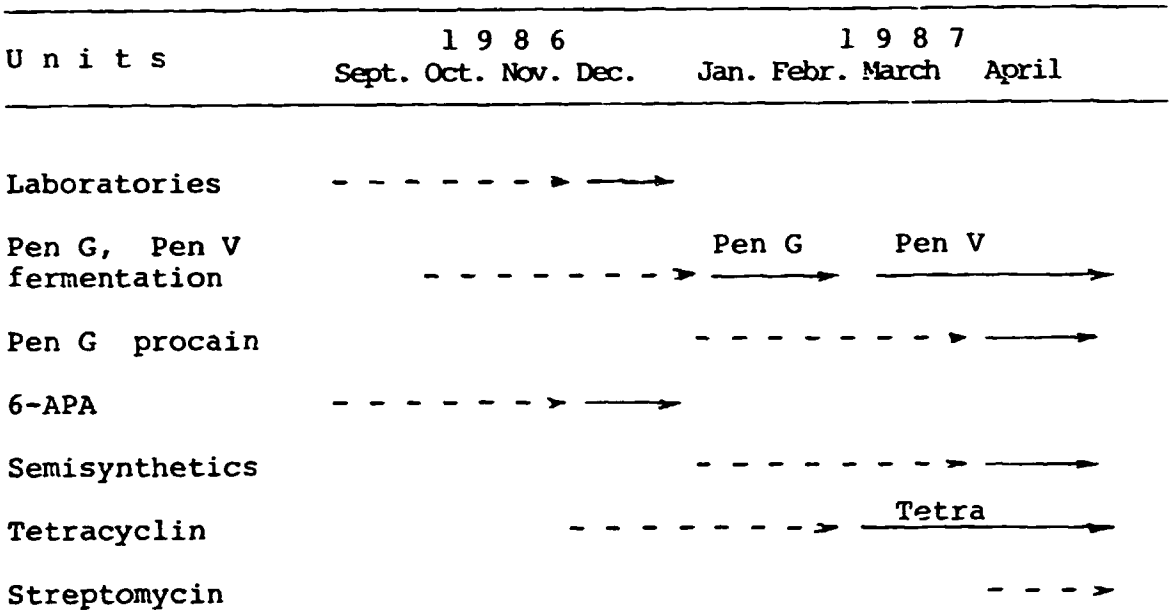
going on mostly in the penicillin processing unit, like plate-cover and exhausting conducts, etc.

The run-up and trial work really has not yet been started at Medea.

According to management information the start-up and support test production for guarantees fixed in the agreement is the following:
the CTIP will provide the precommissioning test and
4 batch production period in the different departments
to demonstrate their guarantees.

Start-up scheme

/according to the modified contract's provision/



During the so called _____> precommissioning period the tests will be made in laboratories and in production areas. In the _____> demosntration period the production, like normal batch-size operation, will start.

There is no information available that how shall be organized the start-up which is very complex and extremely important regarding the proper use of installed production capacity. Presently even the skeleton staff is missing. The department leaders themselves are not yet properly trained.

Some scheme is on move by SAIDAL to provide the staff and the workers.

1.7. Expected cpacity

Expected production in bulk antibiotics
/in tonnes per year/

	Pen G	Pen V	S.Synthetic	TC	OTC	SM
SAIDAL[1.]	61		51	64		33
UNIDO report[2.]	32	29	51	49	15	33

1. M. Belkebir's report

2. UNIDO/IO/R. 177. - 16. September, 1985

The data are the same, though SAIDAL' figures contain the summary of Pen G and Pen V, respectively TC and OTC. Both of the informations refer to 51 tonnes of different semi-synthetics without specification. From the prepared production plan of the semisynthetic department this seems to be as follows:

Ampicillin.$3H_2O$	22.7 tonnes
OxacillinNa.H_2O	21.3 tonnes
Apmicillin.anhydr.	5.9 tonnes
AmpicillinNa.sterile	4.4 tonnes
Oxacillin sterile	2.6 tonnes
Total:	56.9 tonnes

One has to consider that for conservative considerations, the department has calculated lower yield conversion rates. For details see Figures 15-16. For the prepared 51/56.9 tonnes of semisynthetics 106 tonnes of Pen GK is necessary.
So the expected bulk anticiotic production capacity is:

Penicillin V	29 tonnes
Penicillin G	138 tonnes
Tetracyclin HCl	49 tonnes
Oxitetracyclin HCl	15 tonnes
Streptomycin SO_4	33 tonnes
Semisynthetics	51/56.9 tonnes

While discussing the capacity figures we came to know that technologies are available for different other salts of

ampicillin and oxacillin and for production of penicillin G, benzothin salt also. Production of these other compounds is planned in the sterile building-section of penicillin processing unit.

2. ESTIMATION OF FACTS

2.1. Site evaluation

The factory looks attractive, the size is impressive, well situated in the surrounding. By settling the complex wind direction, proper sloping were taken into consideration.

The site is 10 km from Medea city ant the access to the complex is only by road. Substantial quantity of raw materials is to be transported from about 600 km distance on road. Total number of workers expected is about 1.200-1.300 people. Their transport to and from is a major problem of logistic, taking into consideration the shift patterns.

The antibiotic fermentation is a highly sophisticated technology executed with sensitive machines and extremly strict demand to maintain the technological instruction. Devoted and well trained technicians with high qualification and long practice are necessary to run the production

and machines. Trained workers with special skills should follow without any deviation the technological instructions. This is a very basic question everywhere. The staff and workers are trained usually step-by-step with the machines and technology. It is not an exaggeration if some expert opinion claims 2-3 years are necessary to establish this type of standards, which on the other side is a guarantee of quality and reliable production. These are the very important human factors of the economic production.

One has to consider the site as a far-from-city working place with special demands and tiresome working-patterns.

In Medea city itself some other factories are now in operation and it is a growing industrial center. If other choise is available people will select the nearest and more simple job offer. So this question is very decisive.

For staff procurement seemingly SAIDAL has to transfer experts from other places. To provide them housing and attractive living conditions is not yet solved. Presently even the basic skeleton of staff is incomplete. Missing is the most important industrial microbiologist for the laboratory.

2.2. Energy

There is no experience for the actual use. If the complex will run with full capacity, the reliability of supply is the main criterion. In the gas supply the continuity is reasonable, so is it for the electric power. Regarding water supply we miss such informations like how safe is the water-level at the end of the dry-season in the water-reservoir, in what extent the hardness of water is concentrated due to evaporation, how frequently cleaning and fleshing the long pipe-line system is necessary. In other respects, the complex is self-supplying, which seems to be reliable. A special reference is necessary for the maintenance. The energy-center is quite a size with different machines, compressors, boilers, coolers, etc. Undisturbed supply of energy is depending in a great extent from the maintenance.

2.3. Buildings

Building design and construction is good. The dimensions are spacious. They used international standards in hight, span of support columns, etc. Though there is harmony in arrangement, one has an impression that the measurements are in some extent exceeding the necessary ones. The doors, windows, stairs, ventillation, air conditioning are well provided. Safety

regulations seemingly are kept as necessary. Good rust protection, final painting and finishing is applied. The sterile sections of the buildings are prepared with care. Sanitary facilities are adequate.

2.4. Machinery

The design work in general is good. The welded outside heating-cooling spiral coil system is in some respect uncommon. Very much welding is done on the sensitive surface of tanks and reacting vessels. Usually the welding is the starting point of corrosion. From other aspects the welding is of very good quality.

The flame-proof electrical installation is provided with care. The centrifuges are rotated by hydro-motors with oil, power provided by individual srew-pump generators. The installed ball-valves and other valves and fittings are of good quality. The piping is properly connected, their line is clear and diameters are proper to the transfer task. To remove and reinstall machines is made possible.

The fermentors, the drum-filters are huge machines. Their installation is properly done. Some minor observation. The dynamic balancing couplers for fermentor shafts were not

yet fixed into position though shaft and gear systems are mounted. Seemingly by design mistake there is no space to fix them. To make it possible they have cut out a section from the motor support steel construction which is fixed back by screw coupling. Better to ask for the checking of statical calculations.

Similar comment, that in some pipeline section ther is not clear how the content of "bags" is handled. In pipes of 150-180 mm diameter the residual liquid is substantial and if contaminated, dangerous. If washing water remains trapped in, the situation is similar. The bottom discharge valves are already fixed on the fermentors, but it is not clear by what means they are operated.

2.5. Instrumentation

My comments refer to the instrumentation of the fermentors. The present level of instrumentation is 10-15 years old. No doubt good operations can be run with them, but in this period great steps were taken in understanding the fermentation processes. The sensors, the instruments are nowadays so developed that by establishing the basic pattern of a good fermentation, the data are fed into computers and the processes are run on a present program by the computers.

Even the so-called on-line process control is introduced to the big industrial fermentors also. In this respect in the coming years the instrumentation of fermentors is to be improved. That is quite possible, because there is a spacious central instrument room provided for the fermentors.

2.6. Technologies

One has to know that the technologies provided by CTIP are not the peak ones of today. The agreement has been signed 10 years ago. So is the level of provided technologies.

We can estimate a technology by the level of the active content of the broth, by the composition of the medium, by the energy consumption and by the recovery yield of the active content. /Figure 17/. For the economic considerations later more will follow.

To define the CTIP technologies, one shoned compare the active content of the broth and the yield of the recovery of different antibiotics with similar values of technologies acceptable today.

	CTIP activity	yield %	Today activity	yield %
Penicillin	28800 u/ml	72.3	40-60000 U/ml	85
Tetracyclin HCl	10000 /ml	68	14-16000 /ml	80
Oxytetracyclin HCl	9000 /ml	64	14-16000 /ml	80
Streptomycin SO_4	6000 /ml	60	7- 9000 /ml	80
6-APA		58		70
Ampicillin.$3H_2O$		65		75
OxacillinNa.H_2O		56		75

Penicillin fermentation level is roughly 50 % of the good international one. This is only due to the lower production capacity of the strain beeing supplied by CTIP. No one was able to define in what way the strain will be provided. It is clarified that for the maintenance of the production strain there have been made provisions. No information wheather the strain has been deposited when the contract was signed.

The fermentation technology in general is according to the usual demand. With better strain proportionally better yield will be available. The processing is 15 % less efficient than the international level. There is no reason, that this gap could not be eliminated. The extraction section of the processing is very good.

Tetracyclin, Oxytetracyclin, Streptomycin fermentation levels are 30-40 % lower than the present good average. The recovery yields are lower with 15-20 %. With better strains the level could be increased. As the yield of recovery should not be so much lower. The machinery, the process is good. It is sure that the recovery yield is improved a lot in the last decade. After the regular production has established in the frame of a technical brush-up program, this substantial difference can be reduced to a great extent.

The technology of 6-APA from Pen GK is a chemical method. This process has been developed at the end of the sixties for producing 7 ACA from cephalosporin C. Later when the research laboratory in Delft established some facts regarding the temperature influence on the yield if the method is applied for penicillin conversion, the yield has been improved substantially. In the last decade a new, enzymatic method was also introduced for producing 6-APA. It is very simple to operate, no special demand in respect of machinery and the yield is very high. In the chemical method extremely law temperature is used /- 70°C/ and special organic solvents in big quantity. In those years the penicillin semisynthetic compounds were in the focus.

Today mostly the enzymatic methods are used. This is a special cleavage by fixed form of E. Coli penicillin-acylase packed in a column and the penicillion solution is circulated through the column on fix pH and temperature value. Though the method is simple, still it is not so cheap. After certain number of use the fixed enzyme filling of the system is to be changed and the enzyme price is expensive.

It has been established as fact that the similar cleavage on cephalosporin C is not possible by the enzymatic method. It is also to be stated that the cephalosporin semisynthetic compounds are nowadays more and more in use due to their very broad spectrum effects agains most pathogenic strains. Today their use is surpassing the use of penicillin semi-synthetic compounds in most of the countries. For cephalo-sporin semisynthetics, the chemical method is used to produce 7 ACA. The 6-APA technology in Medea Antibiotic Complex is very similar to the method, reported by H. W. O. Weissenburger and M. G. Van Der Hoeven in 1970.[1] In the antibiotic literature there are references to this method under granted

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1. An efficient non-enzymatic conversion of benzyl-penicillin to 6-aminopenicillanic acid.
   89 /1970/ RECUEIL 1081-84.

patents of the same Delft research institute /Belg. Pat. 718.824, 719.712, US Pat. 3,499.909/.It is advisable to confirm the patent right situation for Medea Antibiotic Complex, though mostly the patents expire in these years.

In the Medea semisynthetic department 7 ACA can be produced without any change in technology and machinery, though some chemical calculations are to be verified. There is an observation regarding the size of reacting vessels used in 6-APA department. The 8 m^3 vessels with 374 kg PenG batch size are very big. According to available information, in good producing factories, only half of this size is used due to the very strict technological conditions. The bigger the size, bigger the risk and expense.

The technology for semisynthetics include the method of producing Ampicillin.$3H_2O$ and OxacillinNa.H_2O as starting compounds for similar formulation forms. The technology is well known /Dane method/ and the level is up-to-date. Regarding conversions of the basic salts to other formulation compounds in Medea, data were not available, but seemingly this is a simple problem.

2.7. Start-up

The Medea Antibiotic Complex is a turn-key project. We have no information what arrangements are, if any included in this respect. Few Algerian experts have already spent some time in Italy for training purpose. This should be sufficient for experts, who have already longer own practice and experience on the same or similar line. To my best knowledge none of the trainees had such experience. This training has been commenced some time ago.

No doubt about the machinery. As I have visited all the places, I am convinced that the production capacity in this respect will be ready to start in short time.

From the view of supply, and I mean established continuous supply of raw materials with approved specification of quality, I see problems. I have inspected corn steep liquor and glucose samples. Without analytical certificate and tests according to my practice they were not matching the standards /too diluted/. These samples were just now sent to Italy for testing before establishing the start-up fermentation technology. This is very surprising. One expected preliminary tests of raw materials both analytically and in pilot-plant fermentation. Usually before planning one

establishes the raw material supply position. Proper quality CSL and glucose is available from import, but this is expensive and makes the operations dependent. On the other side, in Oran there is a starch factory, it is to be noted that close cooperation is necessary to provide good quality CSL, what is one of the most important factors for good yield and undisturbed production.

As energy supply I accept that the arrangements are sufficient with comment made for regular water supply.

Returning to the fact that is a start-up of a huge project where the most different operations are to be started practically parallel in short period, I see also problems. Very simply presently there is no way for a quick and smooth start-up. Missing are the trained workers with sufficient skill, missing are the key experts from many sections. Most disturbing is that neither the microbiological laboratory, nor the so called "training fermentation group" are yet in operation. Even the industrial microbiologists for the laboratory are not yet in Medea. The Medea Antibiotic Complex is much more sophisticated than the usual pharmaceutical units for basics or for formulation. This size of production is very expensive. Raw material costs for one PenG batch is 20-22.000 US$. If the proper yield is not achieved, the losses are accumulating very quickly.

This is a consideration for the case CTIP will provide the demonstratior. Even if they have to bring raw materials and transfer a "special team" for the production. There is a possibility for CTIP to prove the guaranteed parameters. After that a serious break-down could be expected. As of now I can estimate a quick, unproperly prepared start-up, which could be desastrous as such in itself and could be setting-back the beginning of regular production.

2.9. Projected demand of antibiotics

UNIDO experts prepared a summary of the actual use of different antibiotics in 1982 and 1985 in Algeria. From the formulated specifications the bulk quantity is calculated in tonnes. Using different considerations, like new forms of formulations, trends in use of different antibiotics, groth of the Algerian population, etc. they prepared the projected demand of antibiotics. This summary has not taken into consideration whether the product produced locally or not, whether funds are available from import or not, whether in Medea Antibiotic Complex there is provision for the production of all of them, or not. For 1985 and 2000 two forcasts are given, for lower and higher estimations. /Figures 18, 19./ The summary is important and basically the capacity calculations in the next chapter are compared to its indications. In the final conclu-

sions for the bulk production in Medea Antibiotic Complex, the projections were taken into consideration.

We can assume this summary as a basic trend as we see today. One has to keep in mind that big changes happened in the last decade in the research and development of new antibiotics and their compounds. We can observe a similar new trend regarding cephalosporins which are not yet in common use in Algeria.

2.9. Capacity calculations

2.9.1. Expected /contractual/ capacity /1.7./

Penicillin	167	tonnes
Tetracyclin	49	tonnes
Oxytetracyclin	15	tonnes
Streptomycin	33	tonnes
Semisynthetics	51/56.9	tonnes

2.3.2. Installed capacity

/present technologies and machinery/

<u>Penicillin</u>	5 x 130 m^3 fermentors,
	200 hours cycles,
	1.250 kg PenG or PenV per batch,
	11 months
	- 130-133 batches per year /CTIP program/:
production	162.5 - 166.2 tonnes
	- 180 batches per month /according to good practice/
production	225 tonnes
<u>Tetracyclin</u>	4 x 130 m^3 fermentors,
	160 hours cycles
	845 kg product per batch
	- 12 batches per monts /CTIP program/
production	10.1 tonnes
5 months production	50.5 tonnes
	- 16 batches per month /according to good practice/
production	13.6 tonnes
4 months production	54.4 tonnes

Oxytetracyclin	4 x 130 m^3 fermentors,
	160 hours cycles
	700 kg production per batch
	- 12 batches per month /CTIP program/
production	8.4 tonnes
2 months production	16.8 tonnes
	- 16 batches per month /good industrial practice/
production	13.4 tonnes
1 month production	13.4 tonnes
Streptomycin	4 x 130 m^3 fermentors,
	200 hours cycles,
	750 kg production per batch
	- 12 batches per month /CTIP program/
production	9.0 tonnes
4 months production	36 tonnes
	- 13 batches per month /good industrial practice/
production	9.75 tonnes
4 months production	38 tonnes
Semisynthetics	the basic compound for this group is the 6-APA. For the 51/56.8 tonnes quantity 37.1 tonnes of 6-APA is necessary. This is 218 batches per year. The installed capacity makes possible to run

250 batches per year. So the capacity of producing semisynthetics is satisfying.

Production of the penicillin semisynthetics, like
22.75 tonnes of Ampicillin and
21.27 tonnes of Oxacillin is possible with the two batches per day pattern, as programmed by the technicians in Medea.
CTIP schedule is 2 x 250 = 500 batches per year.
33.75 tonnes of Ampicillin plus
20.0 tonnes of Oxacillin production is realistic.

For the expected /contractual/ quantities only 169 + 266 batches are necessary, respectively. With a modified program the production capacity could be increased. Details in 3.2. Chapter.

Summarizing the figures we can conclude that the expected bulk antibiotics in 11 months production period could be produced according to CTIP schedule. The 6-APA production capacity is also well supported.

The semisynthetic production capacity well satisfy the expected /contractual/ demand, but a modified production program is necessary for the projected demand. Further study seems necessary for calculations how to satisfy the projected quantities.

For the future production program of the Medea Antibiotic Complex further considerations are to be taken into calculation.

2.9.3. Comparison the production capacity and projected demand

A quantitywise comparison shows very substantial difference:

- the Tetracyclines consumption in 1985 represented only 14.5 % of the installed capacity and this remains the same in the projection, too

- the Streptomycin consumption is very negligable - in 1985 only 4.2 % of the installed capacity. In the future even smaller consumption could be expected

- the use of Semisynthetics in 1985 was already near to the expected 51/56.9 tonnes

- the Macrolides are in substantial use /oleandomycin and spiramycin/. In 1985 their consumption was of 30.2 tonnes, what is not at all included to the Medea-program. At the same time the Erithromycin consumption is very low, though it is a new renaissance of its use everywhere

- surprisingly, there is no reference in the projection to the use of cephalosporin compounds which are now in leading position in the use of antibiotics. Their use is surpassed the use of penicillin semisynthetics and other antibiotics in Japan and USA in the following ratio 20:6:1. Without question, the much higher price itself is some kind of explanation of the use of other antibiotics, since presently all the antibiotics are imported in Algeria. At the same time, new treatment possibilities are provided to the phisicians, which should not be limited only by the price-factor.

2.9.4. Penicillin production /expected/ and projected demand

If the projected demand of the different antibiotics is summarized in a table form, the previous comments are well supported:

to/year	1985	1990	1995	1995	2000	2000
Semisynthetics	41.2	56.3	76.0	70.3	104.1	87.4
6-APA	34.6	47.3	63.9	59.0	87.5	73.4
PenGK	76.1	104.1	140.6	129.8	192.5	161.5
Penicillin additional	60.0	80.0	100.0	100.0	120.0	120.0
Penicillin total	136.1	184.1	240.6	229.8	321.5	281.5
TC OTC + 10 % others	9.5	13.6	19.0	17.5	25.0	20.0
Macrolides + 10 % Erithro 3 % others	30.3	45.0	65.9	59.6	94.9	69.8
Streptomycin	1.4	1.8	2.2	2.1	2.7	2.3
other aminoglycosides	0.9	2.0	2.8	2.6	3.8	2.9
Other antibiotics	4.8	6.5	8.7	8.1	11.1	9.0

It is clear the vast majority of penicillin demand is due to the very high semisynthetics consumption. The projected consumption of the macrolides is practically the same as the one of penicillin semisynthetics. There is no provision presently for the production of macrolides, so I focused with a special penicillin comparison, i.e. expected production and projected demend /see Figure 20/. This is indicating that the CTIP technology and production program with the installed machinery will ensure the national demand of Algeria upto 1988.

With modified production patterns, the demand could be covered till 1994. For the near future SAIDAL has to plan necessary modifications of the penicillin production.

3. CONCLUSIONS

3.1. Considerations of economy in general

The fermentation of antibiotics is a compex operation. As discipline, it contains special principles outlined under biochemistry, microbiology and chemical engineering, as excercise puts all the knowledge into commercial practice. Apart from the technical side the fermentation production processes are strictly controlled by the concern over manufacturing productivity and cost. Antibiotic production processes share certain basic features. The essential ones are raw-material storage and batching, sterilization, reactor-vessel construction, culture maintenance, seed-culture production, monitoring of feeds, temperature, pH-value, foam control, cell separation and disposal of gaseous, liquid and solid effluents. Special features of antibiotic fermentation include the use of complex slow-releasing particulate nutrients for carbon and nitrogen /CSL, starch/, kinetics of product accumulation, filamentous type of cell growth at the fermentation stage, and costly product extraction and purification at the recovery stage.

Because of the relatively easier success with strain improvement, much effort is usually devoted to the fermentation process development and little is directed to study of product recovery. After all, the recovery efficiency can go no higher than 100 %, where as the fermentation yeld improvements of tens or higher of that are not unusual. While there is a steady improvement of increasing the yield of production in the last 30 years, the recovery steps remained practically the same, though, with some improvement of the technical-mechanical solutions.

Fleming's original strain of Penicillium notatum produced only a few milligrams of penicillin per litre, but today's production strains approach broth potencies of penicillin GK close to 30 g/litre, i.e. 50.000 Oxford units/ml. The present peak penicillin fermentation level has been estimated at about 40-50 g pen GK per litre /or 67.000-83.000 Oxford units of pen GK per milliliter of broth or 112-140 gram-mol of penicillin GK per litre of broth by Bérdy - 1984/.

Penicillin production is fermentation cost intensive, representing about 80 % of total manufacturing cost of Pen GK.

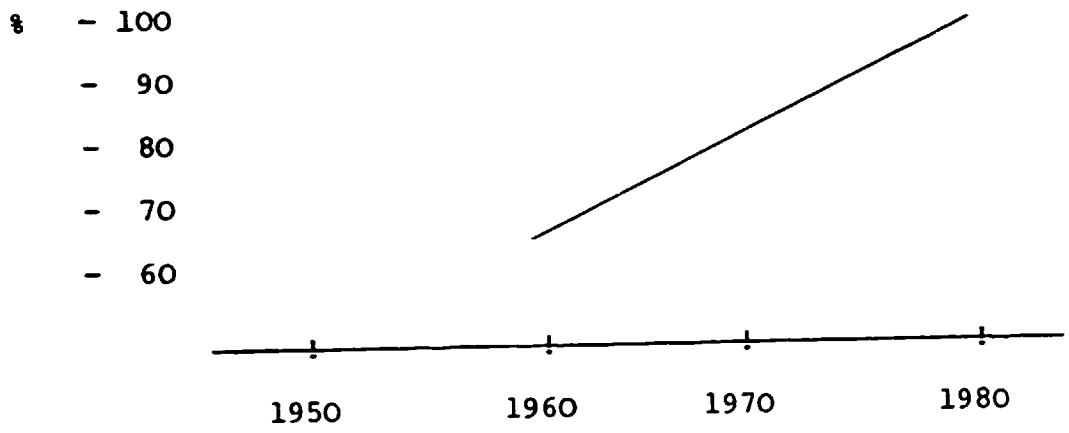
Schwartz's analysis of penicillin manufacturing cost is:

/Eli-Lilly, US prices/	% of total	/The same split in European prices/	
Fermentation cost			
Raw materials			
Glucose	12		
Precursor	11		
Others	5		
		28	44
Utility	12		
Labour-supervision	3		
Maintenance/laboratory	9		
		24	8
Fixed charges	21		
Plant overhead	6		
		27	26
Purification cost			
Direct production cost	13		
Fixed charges/pland overhead	8		
		21	22
	100	100	100

Fermentation production increase can be obtained the easiest way by an increase in the penicillin production rate. To

support the flexibility of this demand, I refer only to the glucose utilisation. Hardly 10 % of the glucose is utilized direct for penicillin conversion. The rest is used for growth and maintenance of the culture during the run-period. As model, the same is valid for the other fermentation processes, too.

Though basically the recovery process remained unchanged - technically - the penicillin recovery yield is improving steadily /Gist - Brocades/



3.2. Economy considerations of Medea Antibiotic Complex

There are 9 production fermentors installed, 5 of them for penicillin production. As calculations show their use is necessary from the very beginning. 4 fermentors are planed for TC-OTC-SM production. As SM it is very advisable not at

all to start the production of it. Its use will be still more reduced. Presently 1 month production cycle is enough to cover the TC-OTC demand. In 2000 with higher estimation 2 months time will be necessary for the same. So from the total number of fermentors 4 will remain practically without use. That involves also the idle position of two processing work-shops.

For any production capacity it is the more economic use if it is used for production to the maximum. Technically the free fermentors could be used for penicillin fermentation, product is growing demand. According to this concept, the penicillin production capacity could be as follows:

5 fermentors	11 months	225 tonnes
4 fermentors	10 months	165 tonnes
	Total	390 tonnes

As the previous estimations show, the extraction and purification capacity of the penicillin processing is so loose that the additional broth processing is possible. The solvents recovery is to be reviewed accordingly. This new program involves no new installation and no substantial changes.

From the capacity calculations, it is clear that the semi-synthetic production is limited if we consider the actual

and projected consumption figures. This is so first for Ampicillin, Oxacillin. In some respect 6-APA production is limited for the coming years. It is imperative from a capacity and an economic point of view that the semisynthetic production should be increased. From the attached papers, Figure 14 and its calculations it is evident that a certain portion of the Penicillin processing unit is used to install a given size for 6-APA and semisynthetic products. And this portion is very well packed with machinery. There is no way to put additional equipments to the present ones. Definitely not to the 6-APA unit. There is some possibility to reorganize the semi-synthetic part of machines, but not at the beginning. Therefore one has to consider how to use the present capacity either by modifying the technology itself, or by a better organization of the operations, that means to use better the time available with the machines available. I do not propose any change in the technologies, but firmly support the latter. Instead of that, I propose to establish the conditions for 6 days per week operations for both of semisynthetics and 6-APA productions. For 6-APA one can apply the 3-batches-in two days process, meaning 18 batches per week. This capacity is for more than the projected demand.

So the expected production will be as follows:

1. 50 weeks per year, 12 batches per week,
2 x 300 batches per year, which means
24.0 tonnes of oxacillin and
40.5 tonnes of ampicillin production
or their combination

2. 50 weeks per year, 18 batches per week,
2 x 450 batches per year, which means
36.0 tonnes of oxacillin and
60.7 tonnes of ampicillin production
or their combination

1. 50 weeks per year, 12 batches per week,
600 batches per year, which means
102 tonnes of 6-APA production

2. 50 weeks per year, 18 batches per week,
900 batches per year, which means
153 tonnes of 6-APA production.
/Figure 21,22./

That all means that 6-APA is more than the production capacity of semisynthetics can process:

22.7 to Ampicillin + 21.3 to Oxacillin = 35 to 6-APA

40.5 to Ampicillin + 24.0 to Oxacillin = 52 to 6-APA

60.7 to Ampicillin + 36.0 to Oxacillin = 170.3 to Penicillin GK

Penicillin GK consumption for 6-APA:

35 x 2.29 = 77 tonnes penicillin GK

52 x 2.29 = 114 tonnes penicillin GK

So to make the production more economic we could increase the output of 6-APA and semisynthetics substantially without further installation. To increase still further the semi-synthetic production capacity one could consider some installation to reorganize the present set of machinery to enable parallel capacity operations. To verify the proposed capacity calculations I propose SAIDAL a special study, when the production of amoxicillin could be investigated. I will make further suggestions in the 4. Chapter.

3.3. Revision of production program

The first task for Medea Antibiotic Complex is to start the production with the available technologies and establish the production of the products on the guaranteed level of yields. Exception seems to be the Streptomycin. The national demand is negligable. To keep packed the ion-exchange resin

columns for 1 week production in a year is very uneconomic, unless other technology is available involving resin-extraction technology.

But soon it is advisable to review the production program. There is no reason to question the reality of the production of the penicillin and its semisynthetics. Even the production of TC and OTC should be accepted though 1 month production per year is not well supported. They are the so called cheap products and very competitive offers are available on the world-market. As previously calculated parallel production of penicillin with one month per year TC-OTC production means 390 tonnes penicillin. This is more than the installed 6-APA and penicillin semisynthetic capacity could process. It is not clear for what other use could be utilized the 100-170 tonnes extra penicillin. And still there is the fact that two prccessing workshops will remain unused 11 months a year. It is unavoidable to come out soon with a new production program what will include better technologies to swich over when the initial production is established with the present technologies. I mean it in full extent: training the technicians, the workers, organizing the raw material supply, providing the undisturbed energy, maintenance and formulation of the produced bulk antibiotics. Here I suppose that the run-up is made, the guaranteed yield is

proved both in the activity-level in broth and in the yield of recovery and the quality of the end products is accepted.

This task is the first and its beginning is urgent, otherwise the whole investment is depreciated without return. With conservative estimation one can expect 18-24 months will be necessary to accomplish all that.

In this period a systematic review is imperative. For this work experts opinion and detailed study and propositions are necessary to update the production program.

One has to keep in mind that the Medea Antibiotic Complex is a very significant antibiotic fermentation unit in its class, with very expensive execution. The technologies are obsolete today. Therefore the production with low-level yields are also expensive. It is to be understood that by all possibilities the production output is today and will remain so in the future - even with projected consumtion figures - higher than the strict Algerian demand, if up-to-date products and technologies are used in the Complex, using the installed buildings and machinery. They were seemingly very expensive but very good quality and with surplus capacity for certain operations.

As soon as teasible, it is to be calculated that the production program is to be reformed in this sense, i.e. expensive products should be introduced, today's peak yield processes are to be acquired and this production program should utilize the installed capacity fully. The new products should be selected taking into consideration the marketing possibilities. It is clear that the most economic operation will be in Medea Antibiotic Complex what is satisfying the maximum national demand and the same time the most economic export potential is utilized. Here I advise very coutious entry to the world-market. The big producers can create an enbarassing situation to a newcomer with price and quality claims.

It is pertinent to mention also that the present use of macrolides is very unusual /TAO and spiramycin in local specialities./ I am not convinced that such high use is necessary. The same time the use of erithromycin is limited. Some solution is to be included in this respect, too.

3.4. New technologies

We have to consider new technologies which support the previous demands: higher yield and higher price products for the local and export markets.

First I propose to acquire an up-to-date penicillin fermentation technology. The present process has a 25-26.000 U/ml penicillin activity in the broth after 200 hours fermentation. This means 14.7-16.5 gram/litre penicillin activity. This is an expensive operation: the long period involves high glucose consumption and very moderate production. Today it is obsolete.

There are technologies providing the same activity in 140-150 hours, or 50-50.000 U/ml penicillin activity in the broth in 200 hours, i.e. 29.4-32.3 gram/litre penicillin in broth. I refer here also the considerations given in 3.1. chapter with special emphasis of the improvements of the processing yield. Without changing anything else in the same building, on the same machinery we can produce the double quantity of penicillin or, roughly 800 tonnes. This is a very sizable production.

We have to consider the change of the present chemical method to produce 6-APA by the enzymatic cleavage. Sooner or later this will be a limiting capacity. In the present workshop there is no possibility to enlarge the capacity with new equipments. The installation of present liquid store tanks makes impossible, or better to say very expensive to shift the whole unit somewhere else. Therefore, this 6-APA capacity

should be kept where it is and a new technology introduced for which very simple vessels are applicable and no chemical supply lines are necessary. For example, in the TC-OTC purifying workshop. For the chemical process I have other ideas.

With these two new technologies, maintaining the wish to produce TC-OTC also, in Medea substantial improvement of penicillin production, both in quantity and economy could be achieved.

3.5. New products

I consider in this respect three main products, though not exclusiverly. First the cephalosporin C fermentation. It is absolutely impossible that today with such excellent technical possibilities in Medea, cephalosporin C fermentation is not used. This β-lactam antibiotic is the successor of the penicillin throughout the world. Its semisynthetic compounds are now very much used. Their specialities surpass the use of penicillin semisynthetics three-times. Today, the third generation of cephalosporin semisynthetics are the most powerful products in this line. There are two very lucky situations in Medea Antibiotic Complex which makes it easy to introduce the fermentation of cephalosporin C and its

conversion to 7 ACA. Firstly, the cephalosporin C fermentation is very similar to that of penicillin. The main nutrients are the same, technology is the same, processing is the same. With a new cephalosporin C strain culture, the production can be introduced on the penicillin-line. Today strains are available with 20-30 g/litre cephalosporin C activity in 150-200 hours. Practically the same yield could be expected for the processing, too. To what extent to produce penicillin, or cephalosporin, is for a later decision.

Secondly, the 7 ACA production is possible only with the same chemical method installed in the Medea Complex for 6-APA. Actually the process has been developed for 7-ACA. Very probably, the CTIP technology could be adopted with some consultation. Lately a so called ring-enlarging technology has been introduced to produce 7 ADCA, a new basic compound for cephalosporin semisynthetics, from penicillin G. This is also a very expensive product. New technology is necessary for the production of semisynthetics from 6-APA. It is to be considered what compound is necessary for the present and coming demand. After having established a scheme for it, technologies are to be acquired. Depending from the compound selected, the machinery for production is to be selected and installed. Here I keep in mind that in the Complex itself this type of machines and vessels will be available, if careful

screening will follow the need of already installed equippments. For placing this new capacity I propose also using the TC-OTC fine processing workshop.

Regarding macrolides, I propose a broad survey determining to what extent the use of TAO and spiramycin are justified. We can consider updating this type of use and transfer their use for erithromycin, claimed to be as efficient as TAO or spiramycin. No doubt, erithromycin had negative side effect on the stomach and on the intestinal flora. But today the so-called Eric-capsules are introduced and the use of erithromycin is increasing. Erithromycin also can be fermented in the installed fermentors and processed with extraction. It is also confirmed that the new semisynthetic penicillins and modern cephalosporins could replace TAO and spiramycin.

4. SUMMARY, PROPOSITIONS

The aim of the present mission was to analyze the real production capacity of bulk antibiotics in the Medea Antibiotic Complex to verify to what extent the present and projected demand of antibiotics of Algeria could be covered by its own production. SAIDAL will run the operations in the most economic way. They wanted different scenarii presented about the proposed options.

Summarizing the results of my calculations I can conclude:

- the installed machinery and production provisions in the Complex enable the production of the expected /contractual/ quantities of different antibiotics,

- there is a substantial difference between the aimed production and the present actual consumption. Some products are used to a great extent more, than the Complex's capacity, some are used in substantial quantity, but there is no provision for their production,

- this gap is increasing in the projected future consumption,

- neither in the production program, nor in the actual use did we find the use of cephalosporin-compounds, which are now in a leading position of the antibiotic consumption and marketing,

- the present technologies are studied only by "hearing", because the actual production has not been started. But it is evident that the activity level in broth and the yield of processing is 10-12 years old and in less than the expected levels today /in general 15-20 % lower in activity and yield/. Regarding penicillin the activity

is only 50 % of the accepted activity level of today's producers,

- the economy would be unacceptable calculating with up-to-date norms,

- the installed machinery and production facilities can be estimated as good both in quality and execution. Sustantial "built-in" extra capacities are available. The investment seems to be very high.

- with a modified production scheme, the production of antibiotics could be increased,

- the economy of operations could be improved to a great extent with a new production program. I do not propose at all the regular production of streptomycin due to its negligable demand. So is the consideration of the economic reality of producing TC-OTC, if a new production program with more efficient technologies and more expensive products is introduced.

- I propose to start fermentation of cephalosporin C and production of its semisynthetic compounds, propose to acquire new penicillin strains and new enzymatic cleavage

technology for 6-APA, propose to consider the justification of using some macrolides presently, propose to acquire erithromycin fermentation technology and the new formulation form for it,

- I propose to study what new fermentation processes could be introduced with ion-exchange resin-processing technology, such as gentamycin, for example.

Proposed options to operate Medea Antibiotic Complex:

The above propositions suppose that the start-up is well made and some regular fermentation operation is established on an acceptable level. I have expressed my concerns in this respect. So to fulfill the propositions and make the Medea Antibiotic Complex economic in operations and provide the demanded products the following options are available:

1./ SAIDAL will organize the start-up, the establishment of regular production and will introduce modifications of any kind. It involves the marketing of bulk surplus antibiotics and formulated products. I do not propose this way. To train people parallelly to definitely forced /by economy/ production is most inadvisable. To buy new technologies, to introduce their production is very

complex and risky affair. The marketing of a new-comer to the international "club" of producers involves a lot of hard rocks. I am convinced that this complex task does need assistance from outside.

2./ It is evident that if operation will run only on present proposed CTIP level, excess fermentation capacity will remain. It is a possibility to utilize this excess capacity by leasing it to a foreign company. This could bring some income instead keeping the capacity unutilized. Many aspects seem against such agreement.

3./ There also is the possibility that a foreign firm will accept in a contract to guide the run-up and provide new technologies, etc. This would be very expensive and after a contractual period the continuous efforts to support the new developments will remain for the Algerians and so will be the marketing of the excess products. Ultimately, the aim is to produce as much extra quantities after the local demand has been taken care of. Small quantities are better to be imported, if substantial export is generated.

4./ My proposition is that SAIDAL has to enter into a package-deal agreement with an internationally accepted

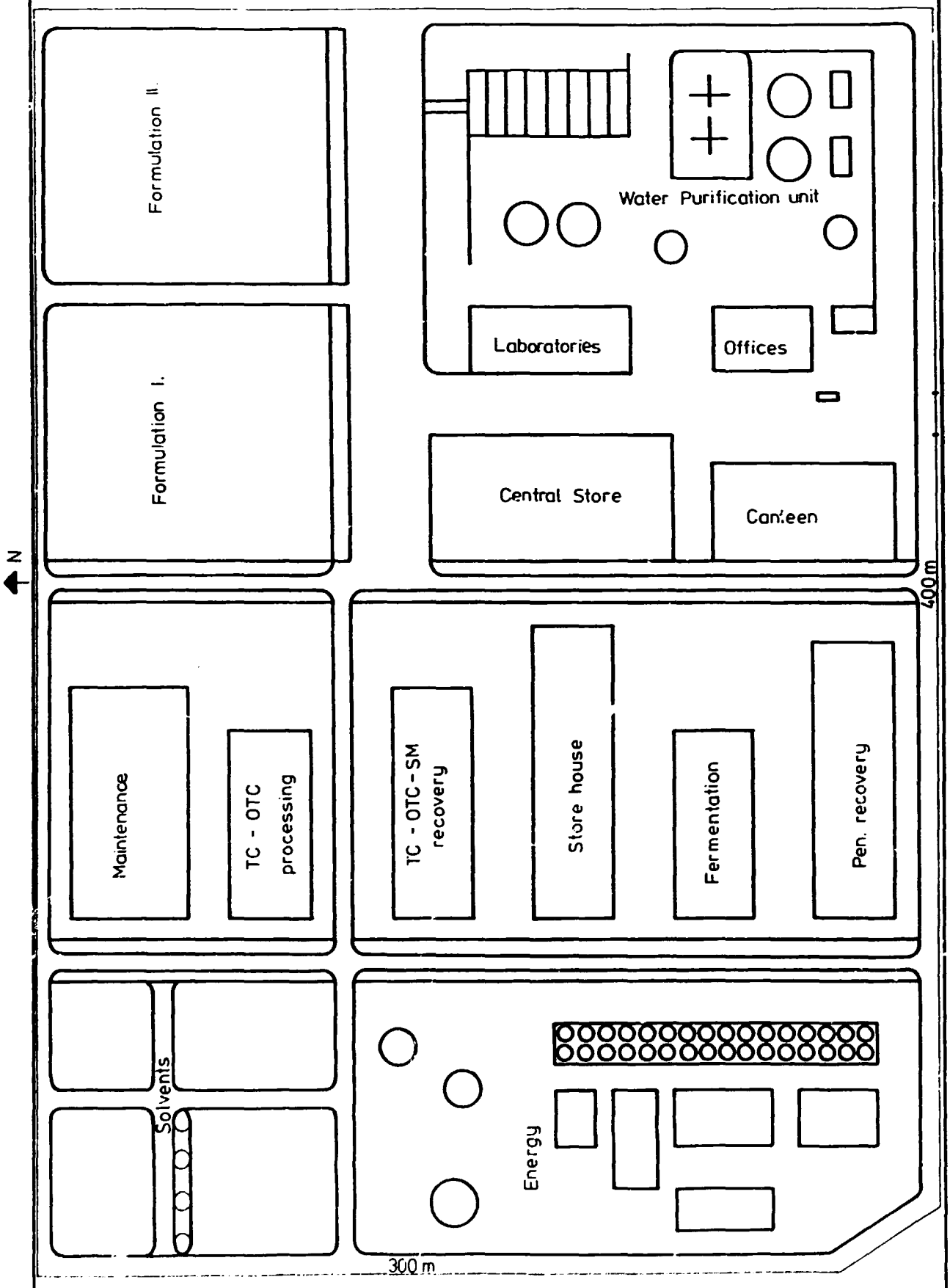
company, having technologies, expertize, providing the training, assisting in the run-up, establishing the initial production program and introducing the new processes, helping the necessary reshuffling of production lines and machinery. This cooperation could involve eventually join production and marketing. This package-deal could enable SAIDAL to get assistance and to pay for it with products produced in the Complex to a substantial degree.

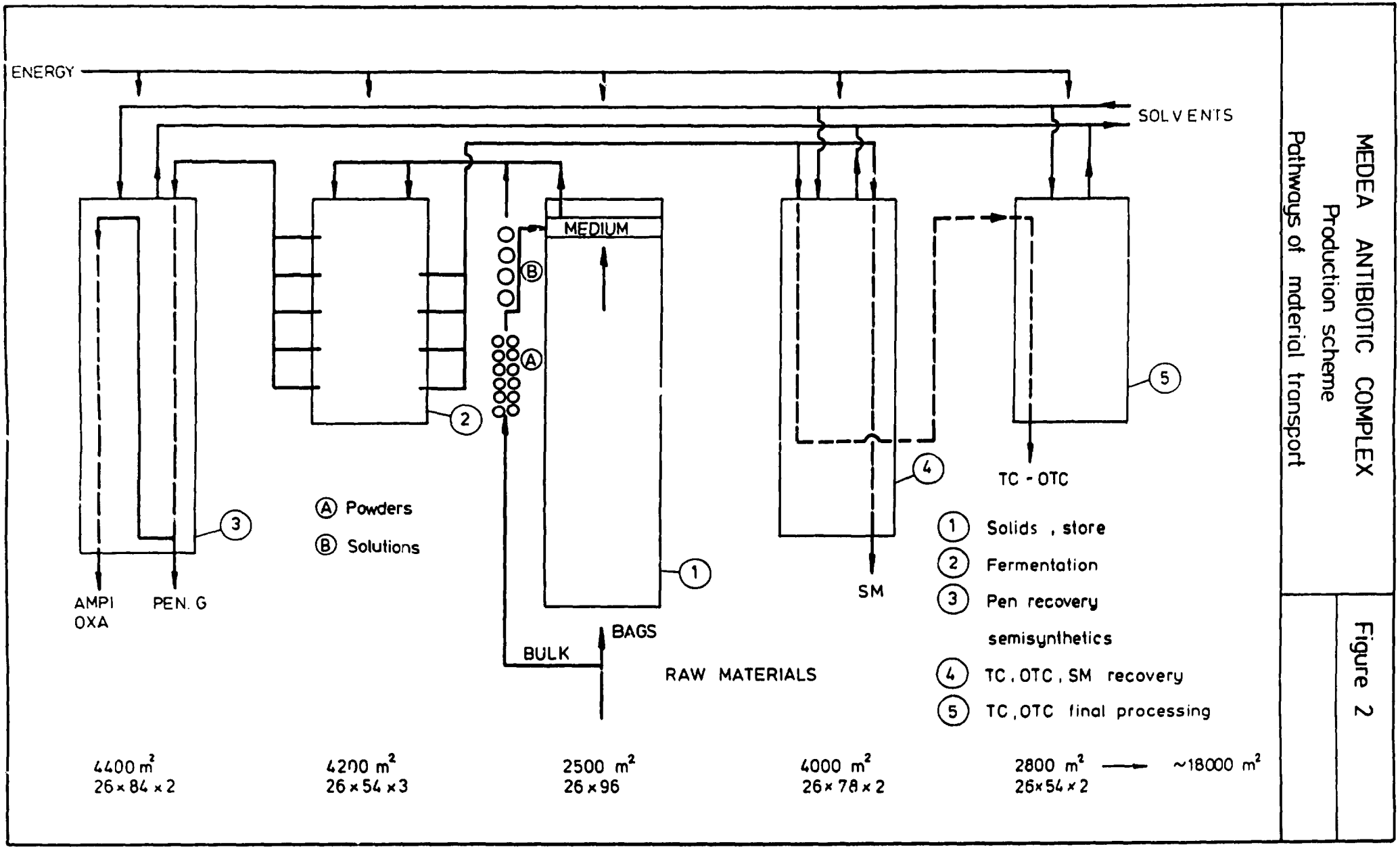
dr. János Fári

5. ANNEXES

MEDEA ANTIBIOTIC COMPLEX
Building arrangement
Lay-out

Figure 1





MEDEA ANTIBIOTIC COMPLEX
Production scheme
Pathways of material transport

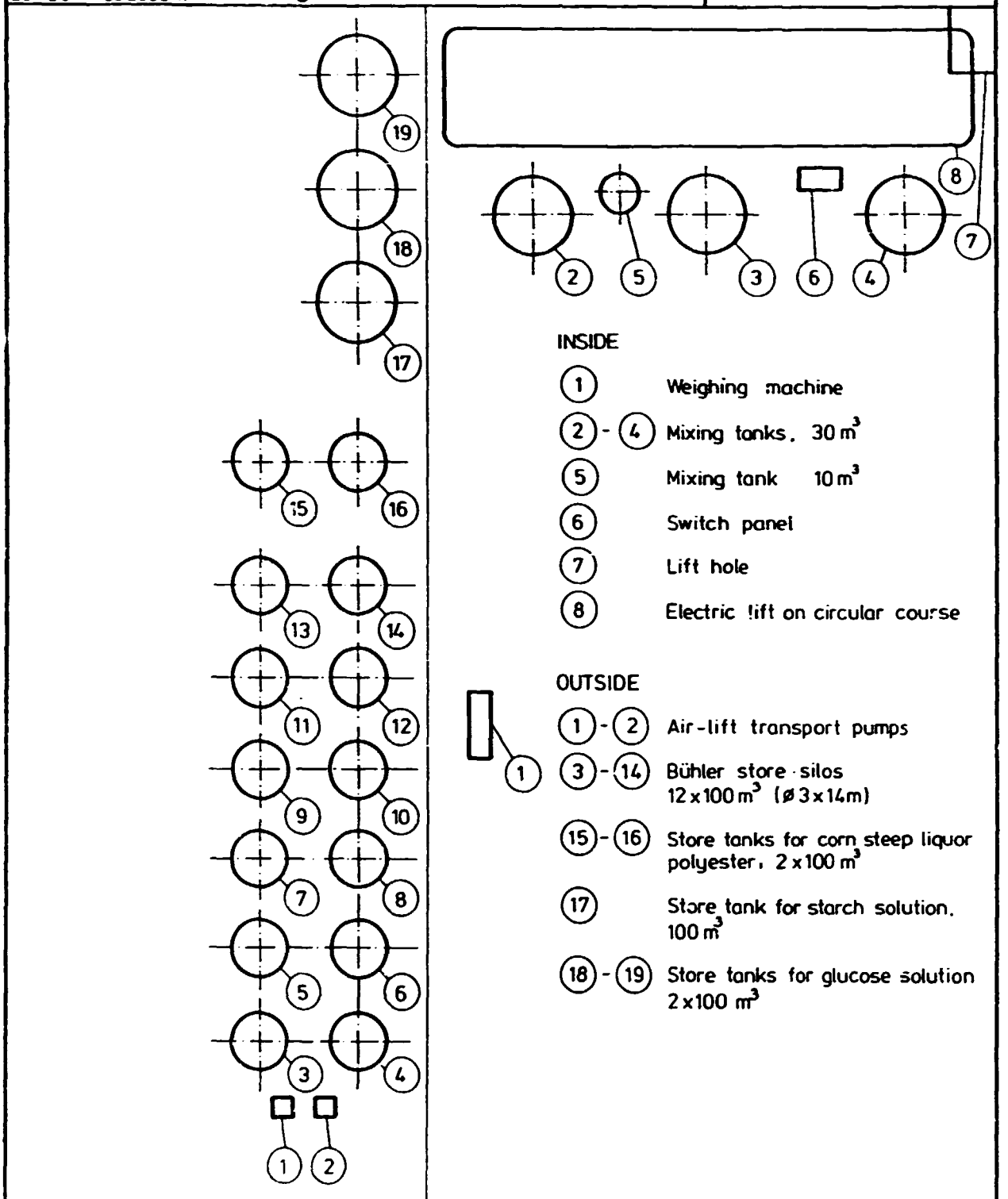
Figure 2

MEDEA ANTIBIOTIC COMPLEX

Storehouse for raw materials, medium preparation

26 x 96m = cc 2500m2 Lay-out

Figure 3



INSIDE

(1) Weighing machine

(2) - (4) Mixing tanks, 30 m^3

(5) Mixing tank 10 m^3

(6) Switch panel

(7) Lift hole

(8) Electric lift on circular course

OUTSIDE

(1) - (2) Air-lift transport pumps

(3) - (14) Bühler store-silos 12 x 100 m^3 (ø 3 x 14m)

(15) - (16) Store tanks for corn steep liquor polyester, 2 x 100 m^3

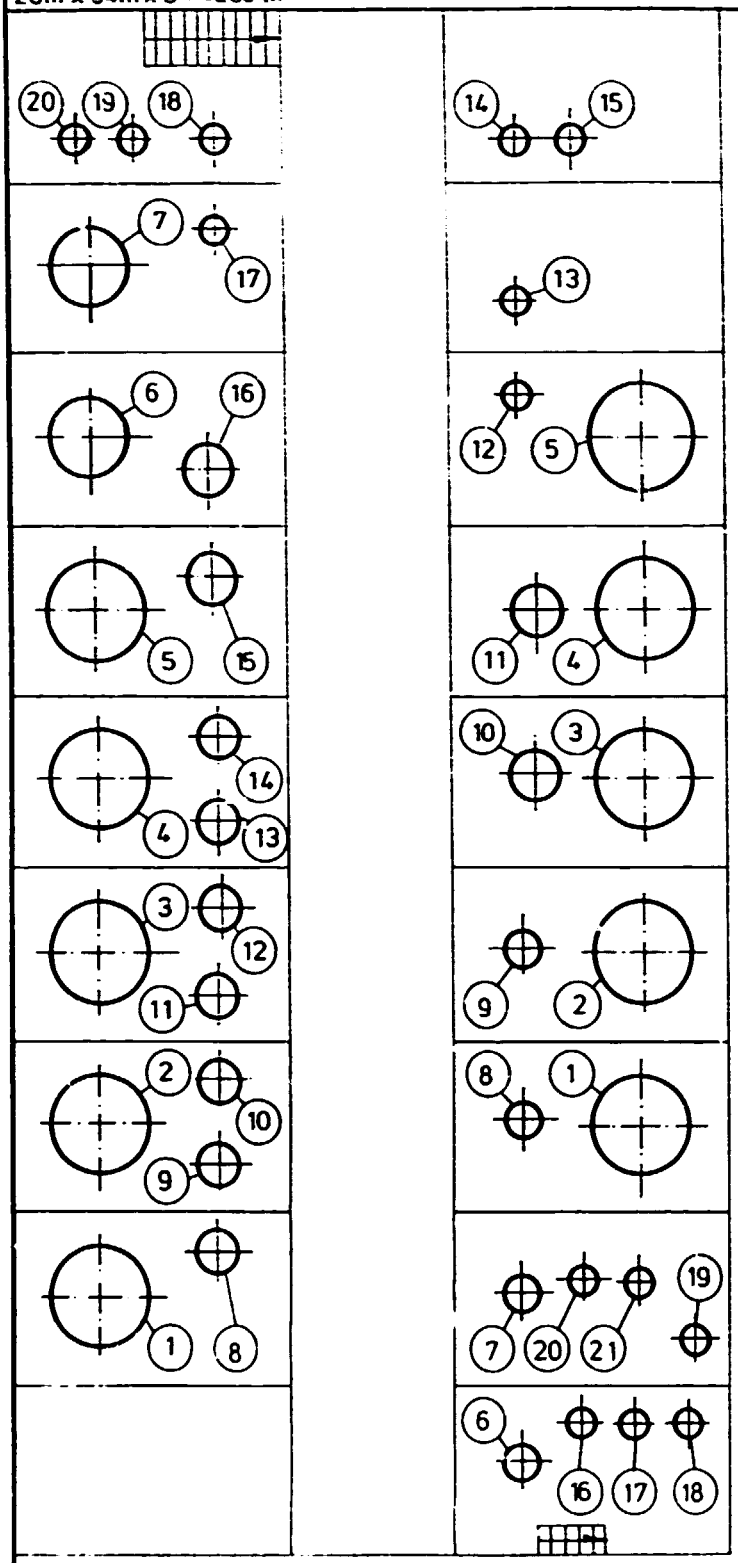
(17) Store tank for starch solution, 100 m^3

(18) - (19) Store tanks for glucose solution 2 x 100 m^3

MEDEA ANTIBIOTIC COMPLEX
Fermentation workshop
Lay - out

Figure 4

26m x 54m x 3 = 4200 m²



PEN - line

(1) - (5) Fermentors, 5 x 130 m³

(6) - (7) Processing tanks, 2 x 60 m³

(8) - (10) Inoculum fermentors, 3 x 10 m³

(11) - (12) Transfer tanks for CSL, 2 x 10 m³

(13) - (14) Transfer tanks for amm. sulfate sol. 2 x 10 m³

(15) - (16) Transfer tanks for glucose sol 2 x 30 m³

(17) Precursor tank for PEN G, 2 m³

(18) Precursor tank for PEN V, 2 m³

(19) Store tank for NAOH sol., 1 m³

(20) Store tank for antifoam, 1.4 m³

TC - OTC - SM line

(1) - (4) Fermentors, 4 x 130 m³

(5) Processing tank 150 m³

(6) - (7) Fermentors, 2 x 10 m³

(8) - (9) Inoculation fermentors, 2 x 10 m³

(10) - (11) Transfer tanks for strech sol., 2 x 30 m³

(12) - (13) Transfer tanks for antifoam, 2 x 7.2 m³

(14) Transfer tank for amm. hydr. sol., 3.2 m³

(15) Transfer tank for sulfuricacid 0.3 m³

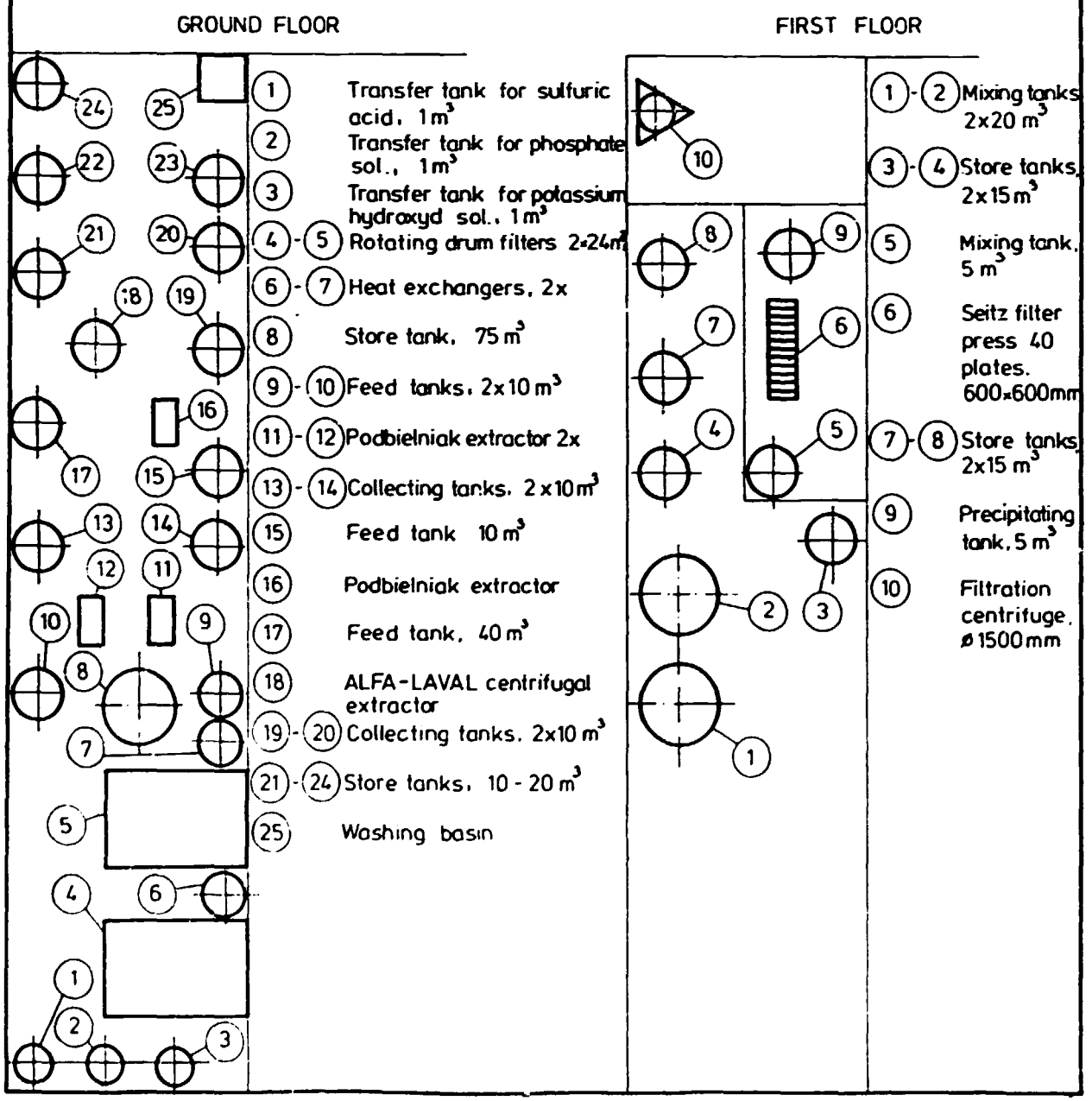
(16) Fermentor, 0.9 m³

(17) - (19) Fermentors, 3 x 140 liters

(20) - (21) Sterilizing tanks, 3 x 140 liters

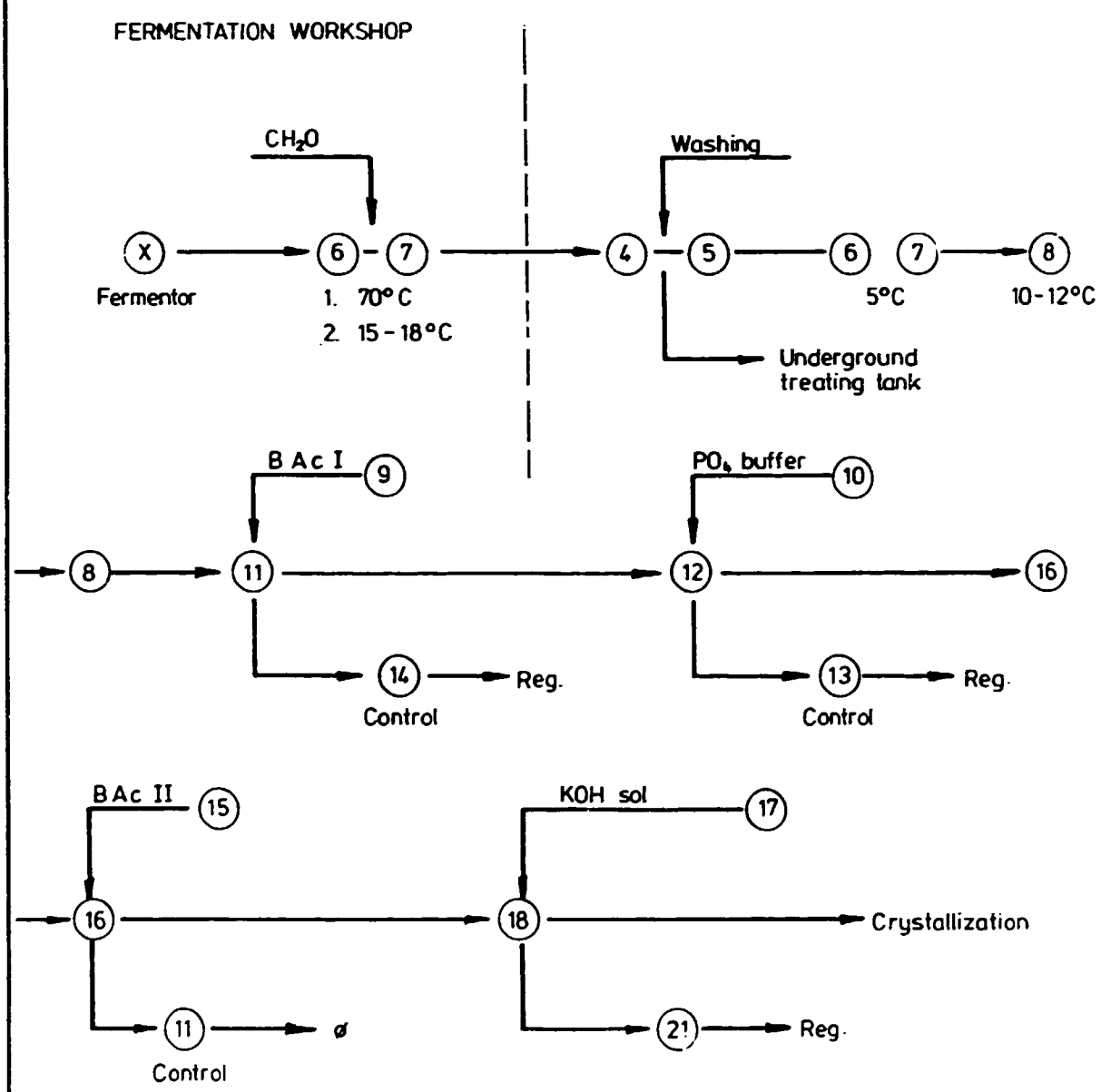
MEDEA ANTIBIOTIC COMPLEX
Penicillin recovery
(filtration – extraction)
26x84m. two floors = cc. 4400 m² Lay-out

Figure 5



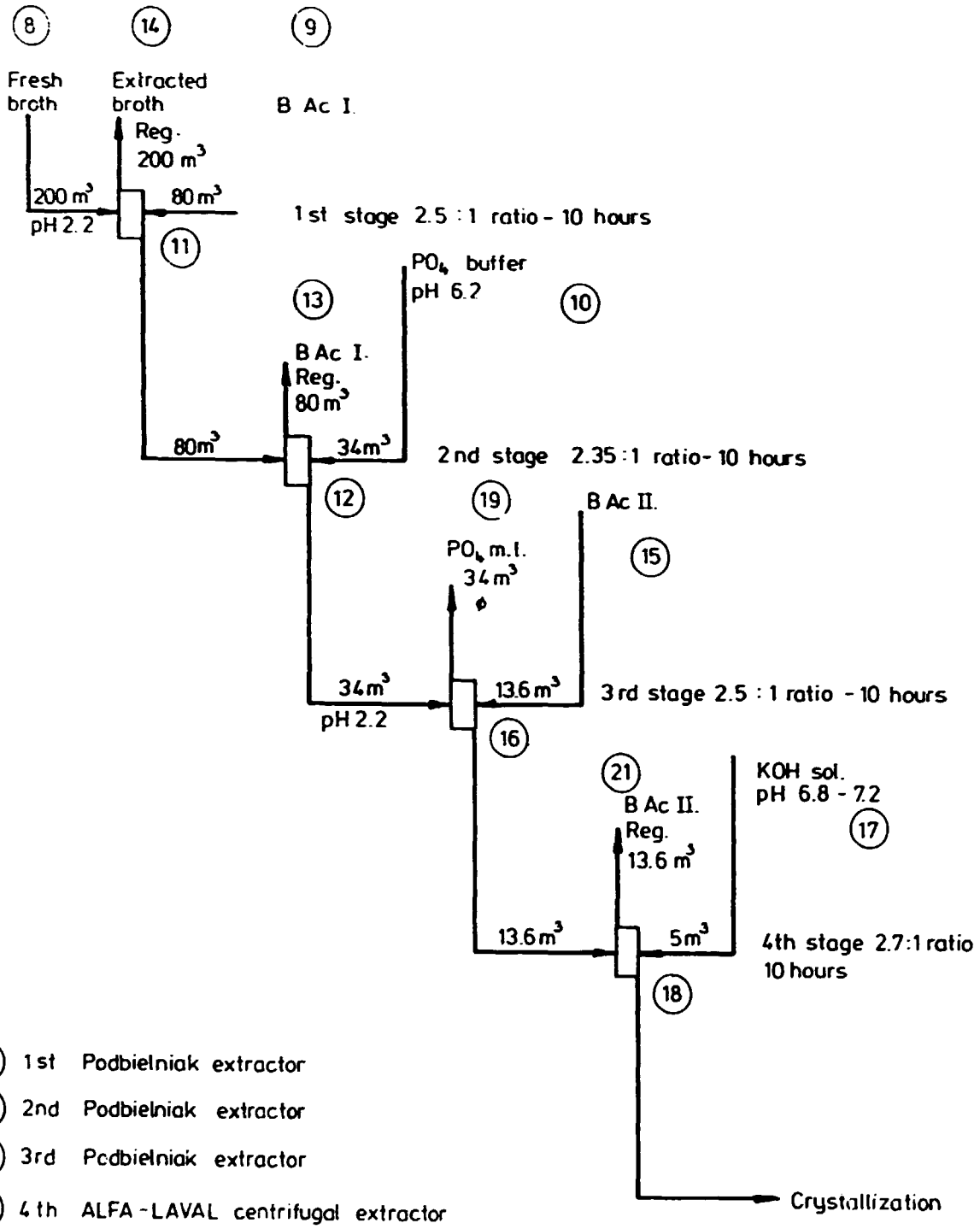
MEDEA ANTIBIOTIC COMPLEX
Penicillin recovery
Technological flow-sheet

Figure 6



MEDEA ANTIBIOTIC COMPLEX
Penicillin extraction
Coupling - loading

Figure 7



(11) 1st Podbielniak extractor
(12) 2nd Podbielniak extractor
(16) 3rd Podbielniak extractor
(18) 4th ALFA-LAVAL centrifugal extractor

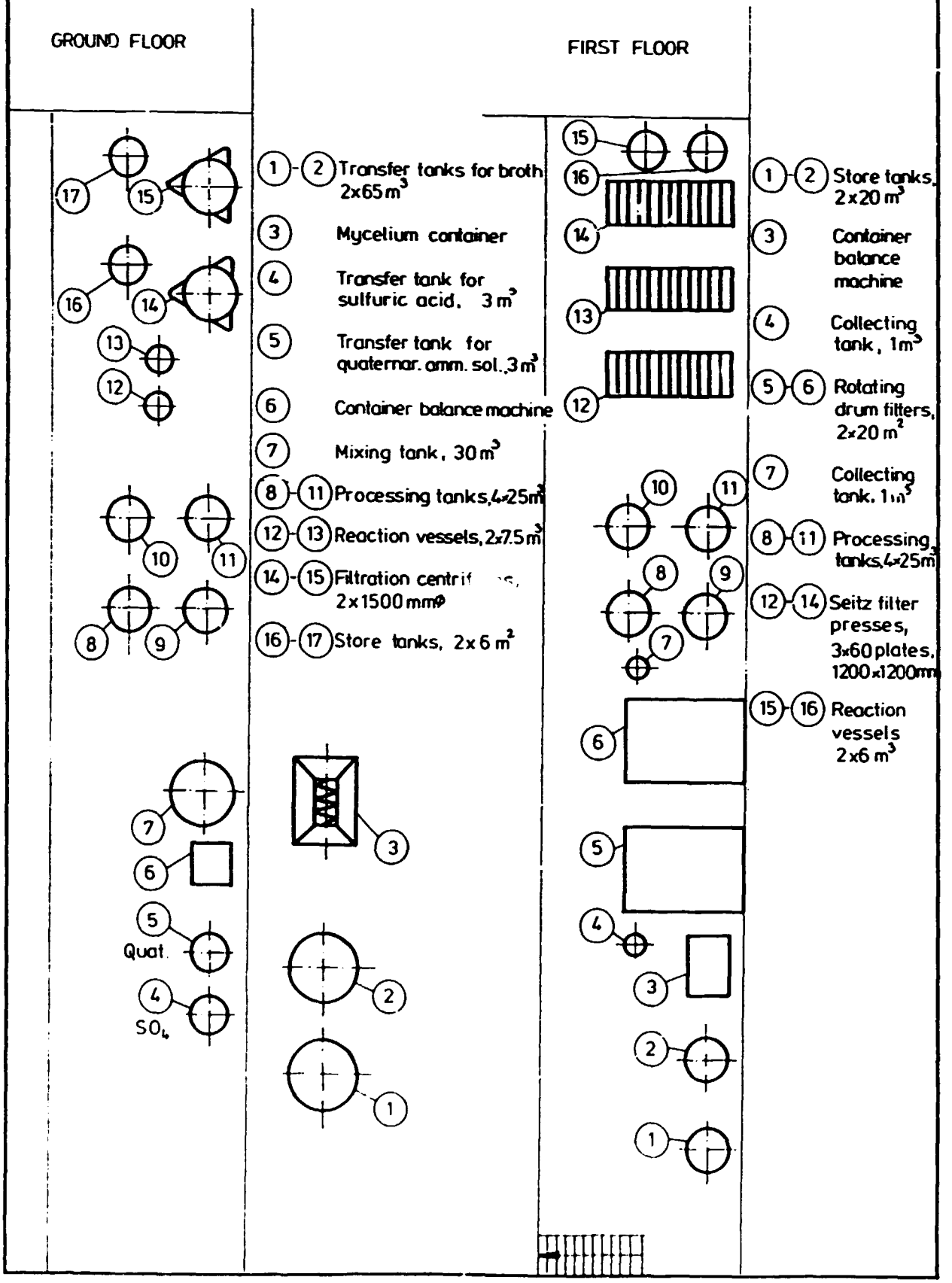
MEDEA ANTIBIOTIC COMPLEX

TC - OTC recovery (filtration, complex)

Lay - out

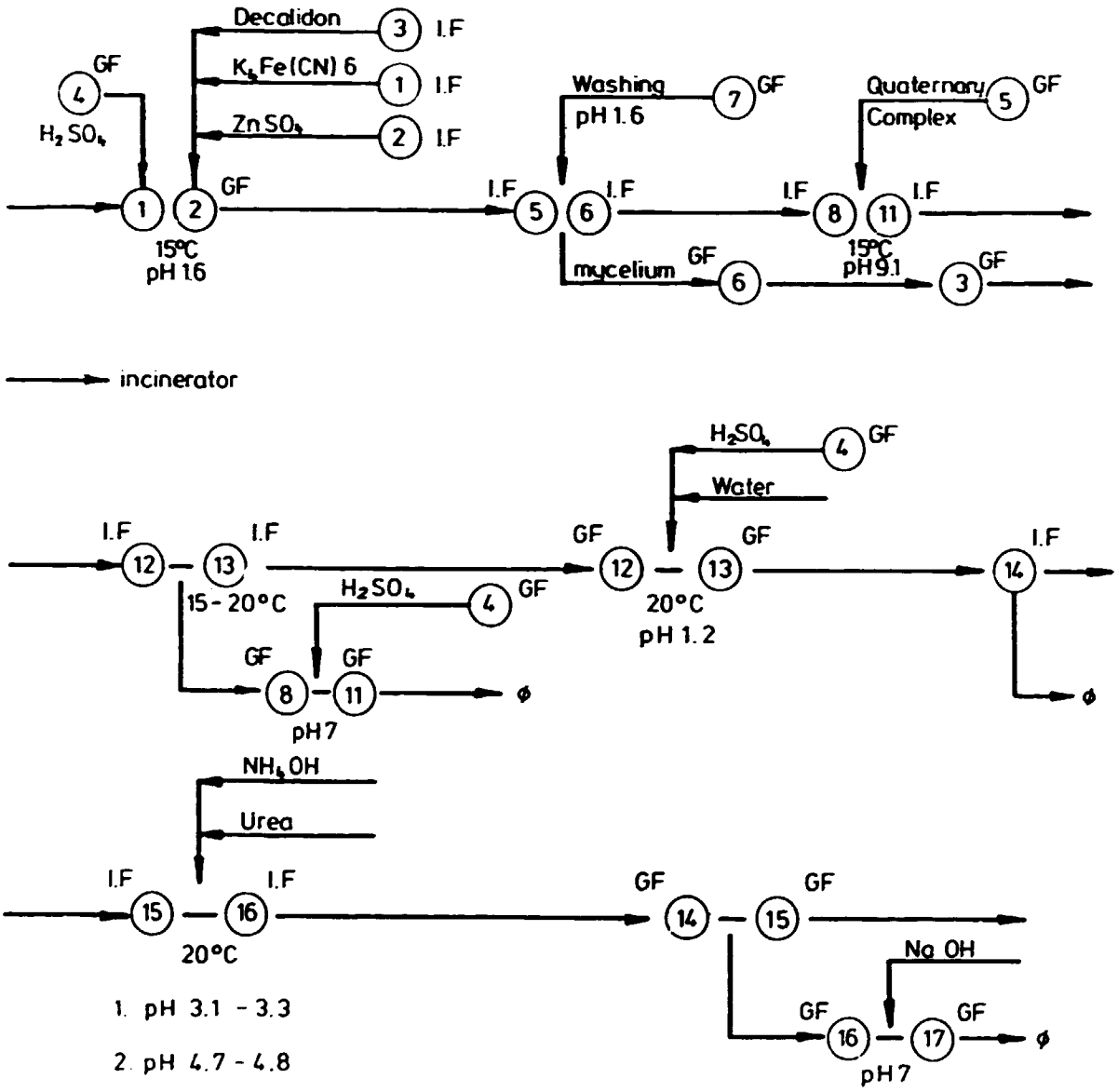
26m x 78m x 2 ~ 4000m²

Figure 8



MEDEA ANTIBIOTIC COMPLEX
TC-OTC recovery
Technological flow-sheet

Figure 9



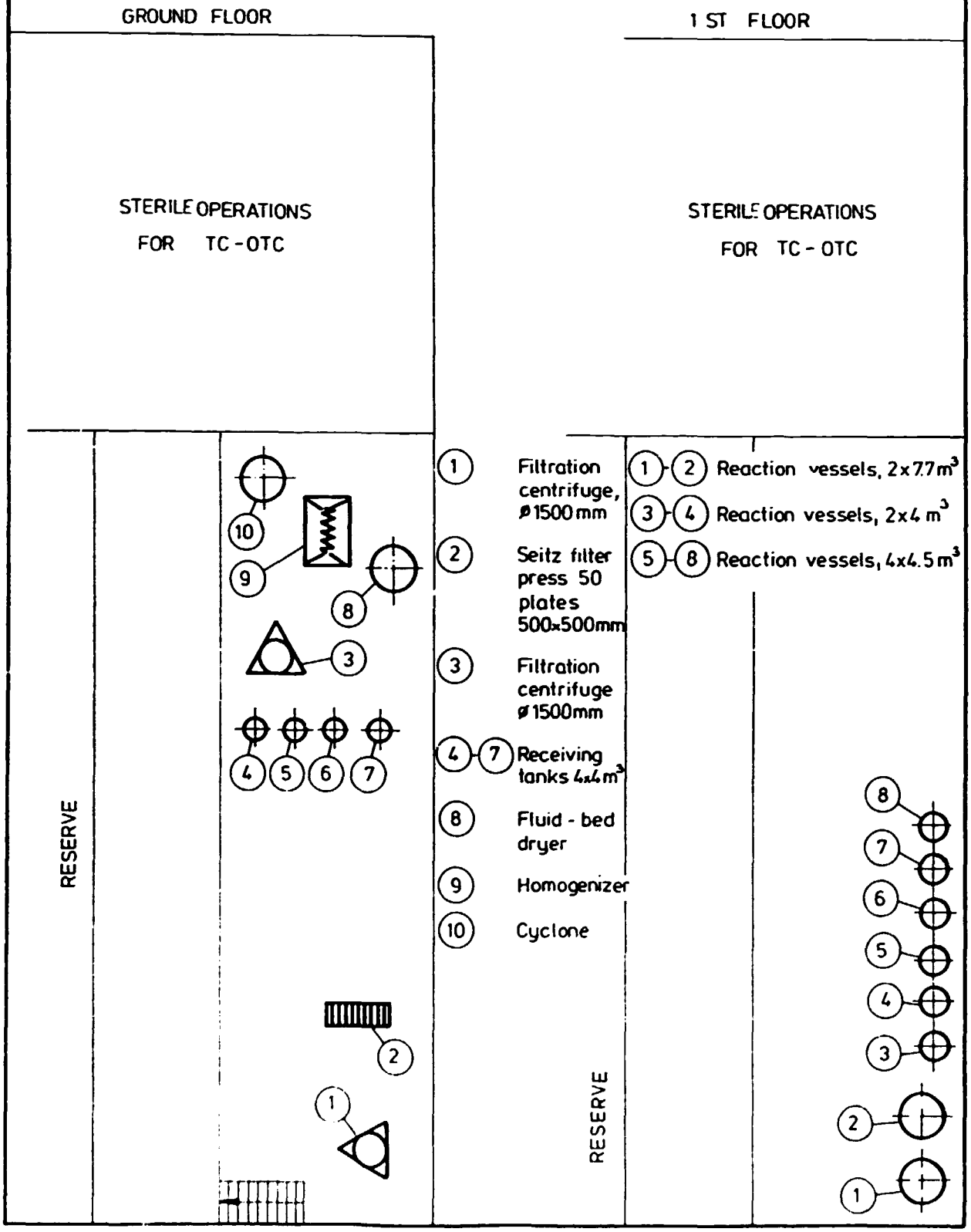
MEDEA ANTIBIOTIC COMPLEX

TC - OTC processing (HCl - salt formation)

Lay - out

26x54m two floors = cc 2800m²

Figure 10

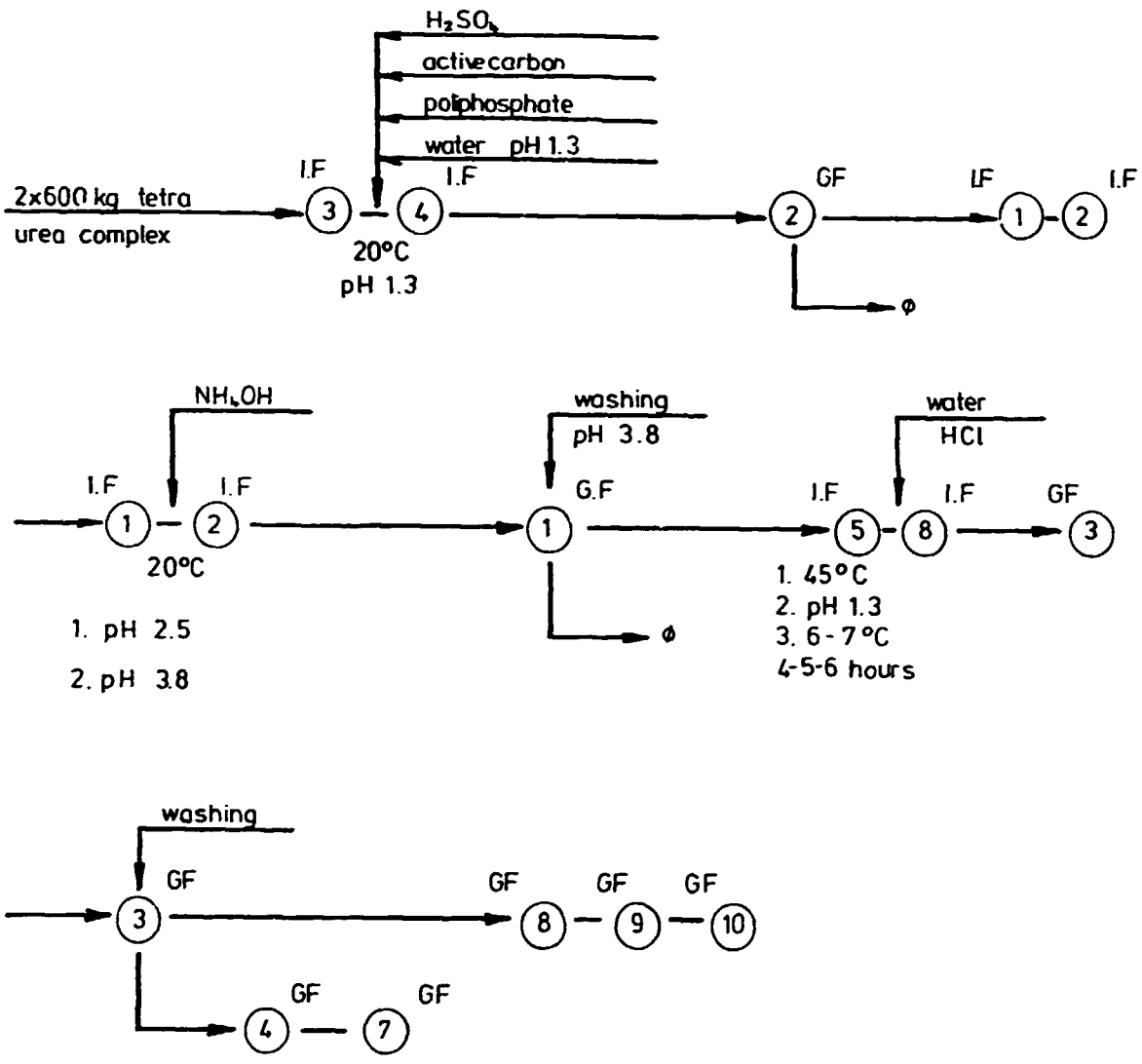


MEDEA ANTIBIOTIC COMPLEX

TC - OTC processing (HCl-salt formation)

Technological flow - sheet

Figure 1!



GF = ground floor

I.F = 1st floor

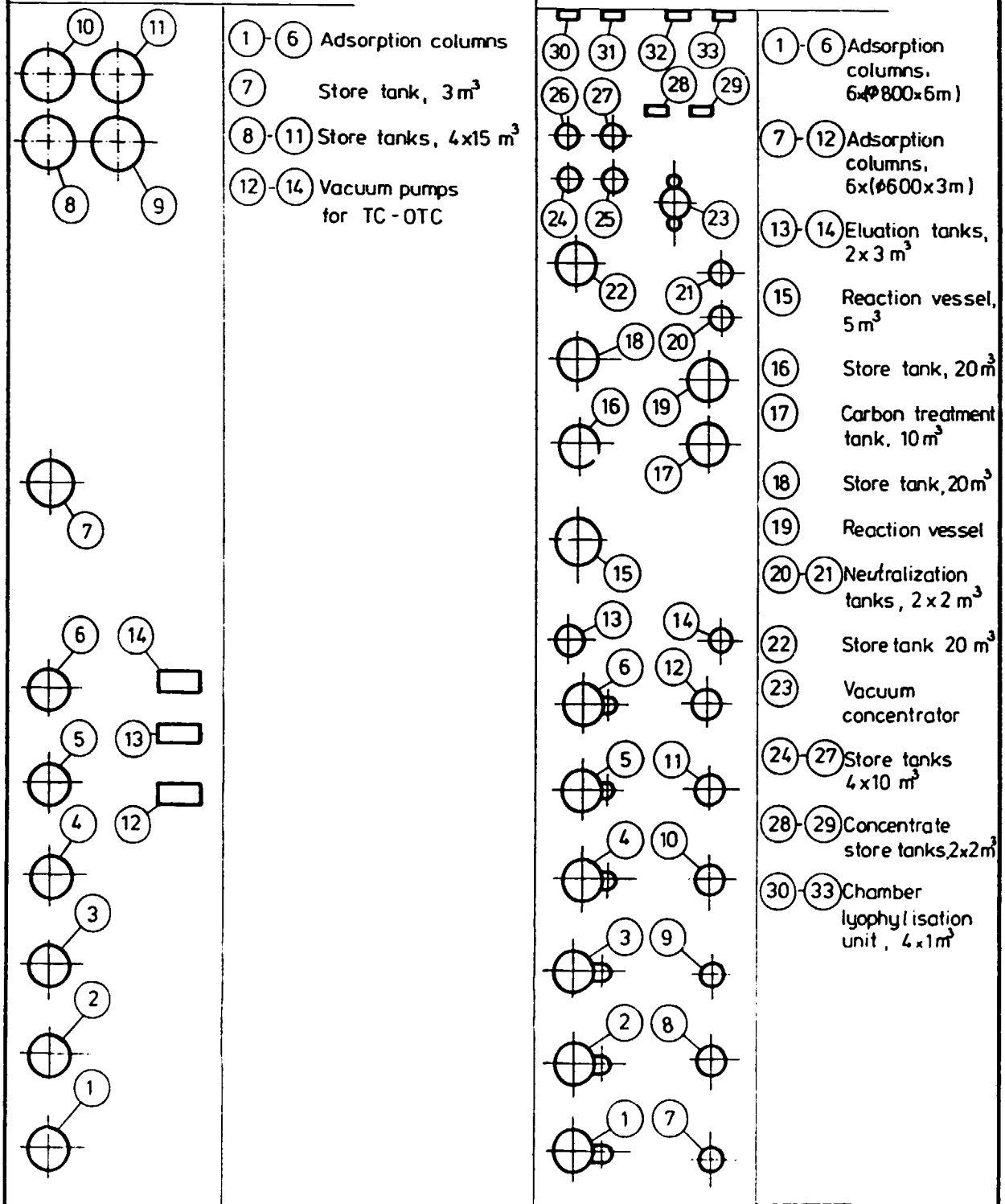
MEDEA ANTIBIOTIC COMPLEX

SM recovery line (together with TC-OTC recovery line)

Lay-out

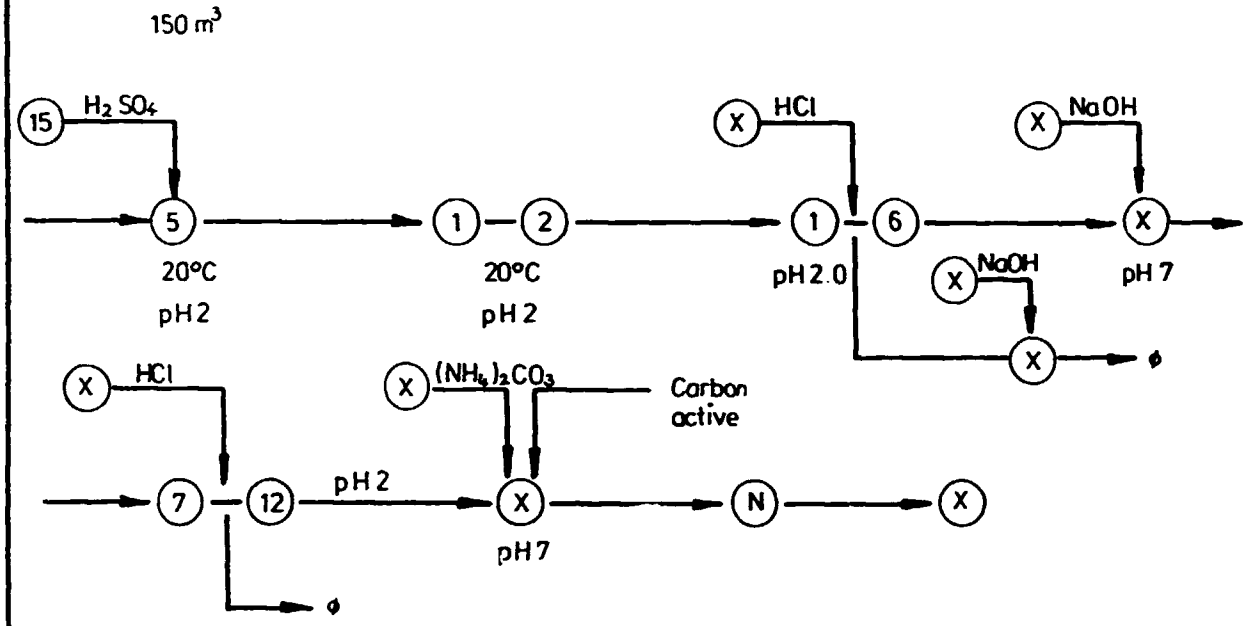
26m x 78m two floors = cc. 4000 m²

Figure 12



MEDEA ANTIBIOTIC COMPLEX
Streptomycin recovery line
Technological flow - sheet

Figure 13



MEDEA ANTIBIOTIC COMPLEX
6-APA, semisynthetics
Lay-out and maschines flow-sheet
Penicillin workshop

Figure 14

6 - APA

(1) Cooling tank for butanol. 3 m³

(2)-(3) Reaction vessels. 2 × 8 m³

(4)-(5) Filtration centrifuges, 2 × ϕ 1500 mm

(6)-(7) Receiving tanks, 2x600 liters

AMPI - OXA

(1) Reaction vessel, 1m³

(2)-(3) Reaction vessel, 2 x 3 m³

(4) Precipitation tank, 6m³

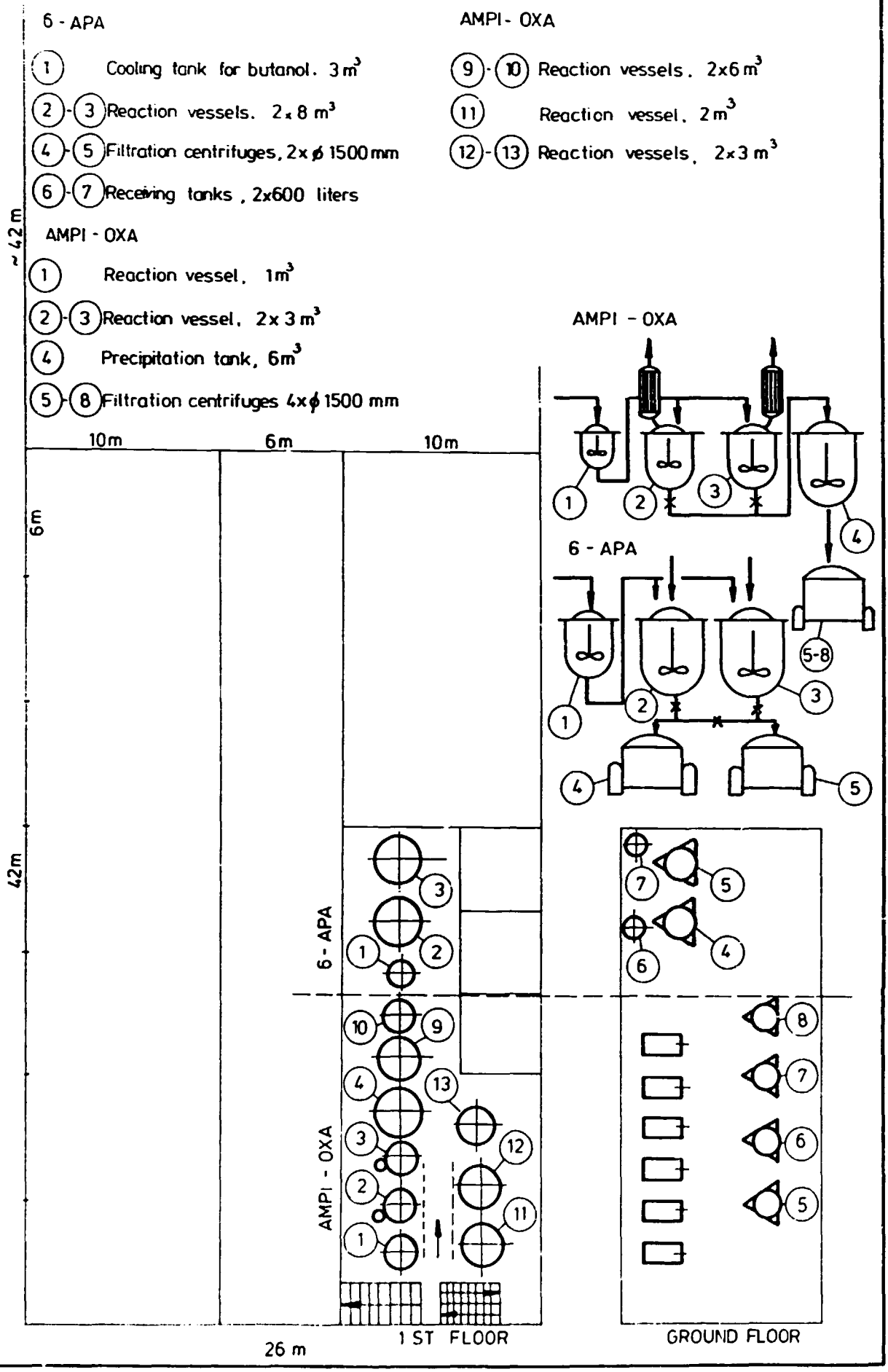
(5)-(8) Filtration centrifuges 4 x ϕ 1500 mm

AMPI - OXA

(9)-(10) Reaction vessels. 2x6 m³

(11) Reaction vessel. 2 m³

(12)-(13) Reaction vessels, 2×3 m³



MEDEA ANTIBIOTIC COMPLEX
Production program for bulk antibiotics
in medea complex (CTIP)

Figure 15

Pen. GK	374 kg	⟶	6 - APA	170 kg	⟶	275 batches	= 46.7	to
6 - APA	110 kg	⟶	AMPI. $3H_2O$	135 kg	⟶	169 batches	= 22.8	to
AMPI.3H 0	200 kg	⟶	AMPI. ANH	160 kg	⟶	37 batches	= 5.9	to
6 - APA	70 kg	⟶	OXA .Na	80kg	⟶	266 batches	= 21.3	to
AMPI. ANH	48 kg	⟶	AMPI. Na steril	36 kg	⟶	123 batches	= 4.4	to
OXA. Na	92 kg	⟶	OXA. steril	60 kg	⟶	44 batches	= 2.6	to
Pen GK	43 kg	⟶	Pen. benz. steril	40kg	⟶	75 batches	= 3.0	to

MEDEA ANTIBIOTIC COMPLEX Actnal consumption of semisynthetics production	Figure 16

167 to Pen G + Pen V ⟶ 32 to Pen G
29 to Pen V
3,2 to for 3 tonnes Pen. benzath.
102.6 to for 46.7 to 6-APA

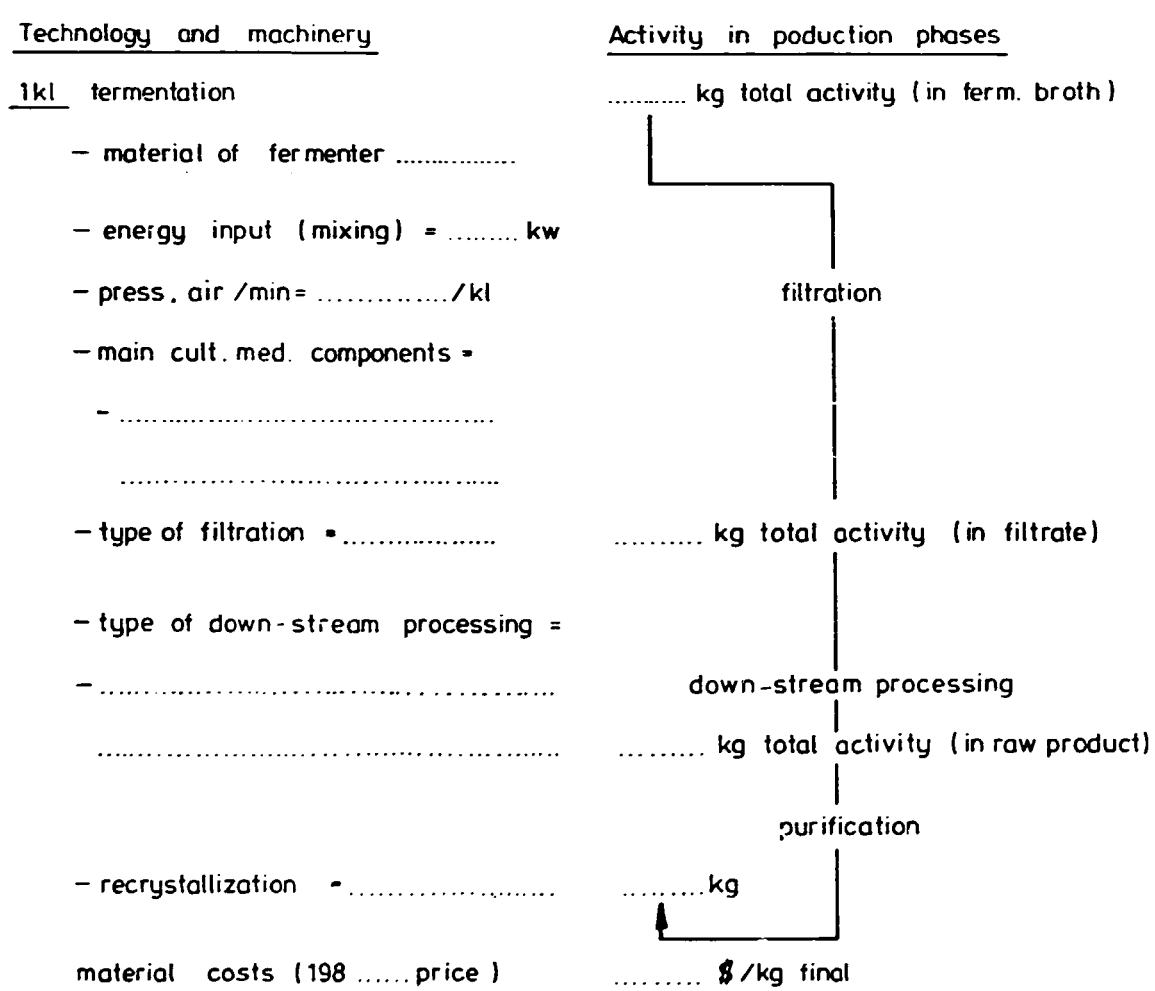
46.7 to 6-APA ⟶ 18,5 to for 22,7 to AMP. $3H_2O$
18,6 to for 21,3 to OXA.Na
9,5 to for Extra

22,7 to AMP.$3H_2O$ ⟶ 7,4 to for 5,9 to AMP. ANH
15,3 to for Extra

21,3 to OXA.Na ⟶ 4,1 to for 2,6 to OXA.Sterile
17,2 to for Extra

5,9 to AMP. ANH. ⟶ 4,4 to for AMP. Na Sterile

MEDEA ANTIBIOTIC COMPLEX Characterisation of an antibiotic producing fermentation technology	Figure 17



Basic guaranteed values :

output from 1kl ferm. broth = ... kg of ..... quality

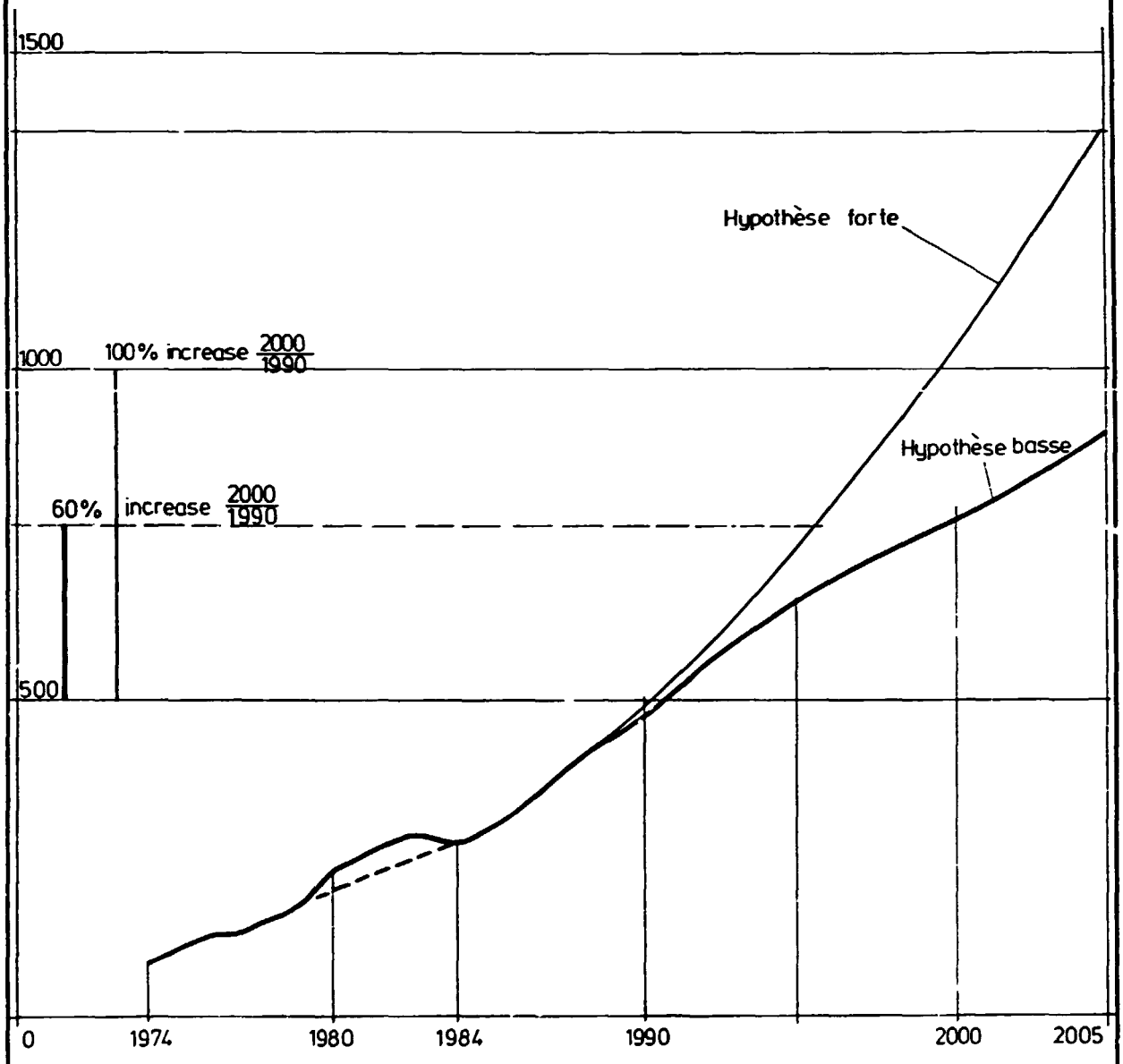
material costs (198 ..... price *) 1 kg final product = $ .....

* before final agreement a price list is necessary

MEDEA ANTIBIOTIC COMPLEX
Algerie
Projection de la consommation (1984 - 2005)
(millions d'unités de vente)

Figure 18

UC/ALG/85/062



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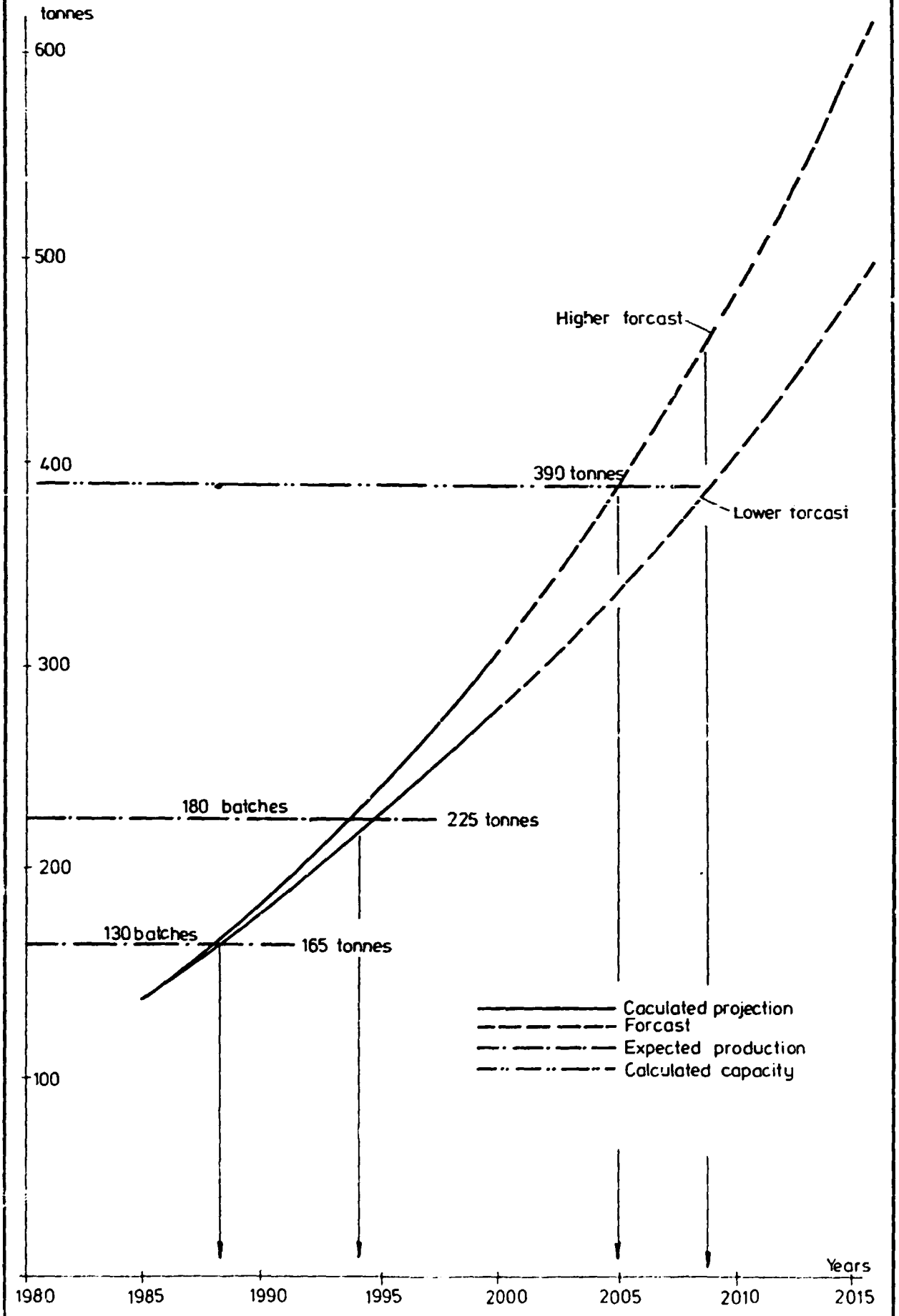
MEDEA ANTIBIOTIC COMPLEX
Projected demand of antibiotics in Algeria

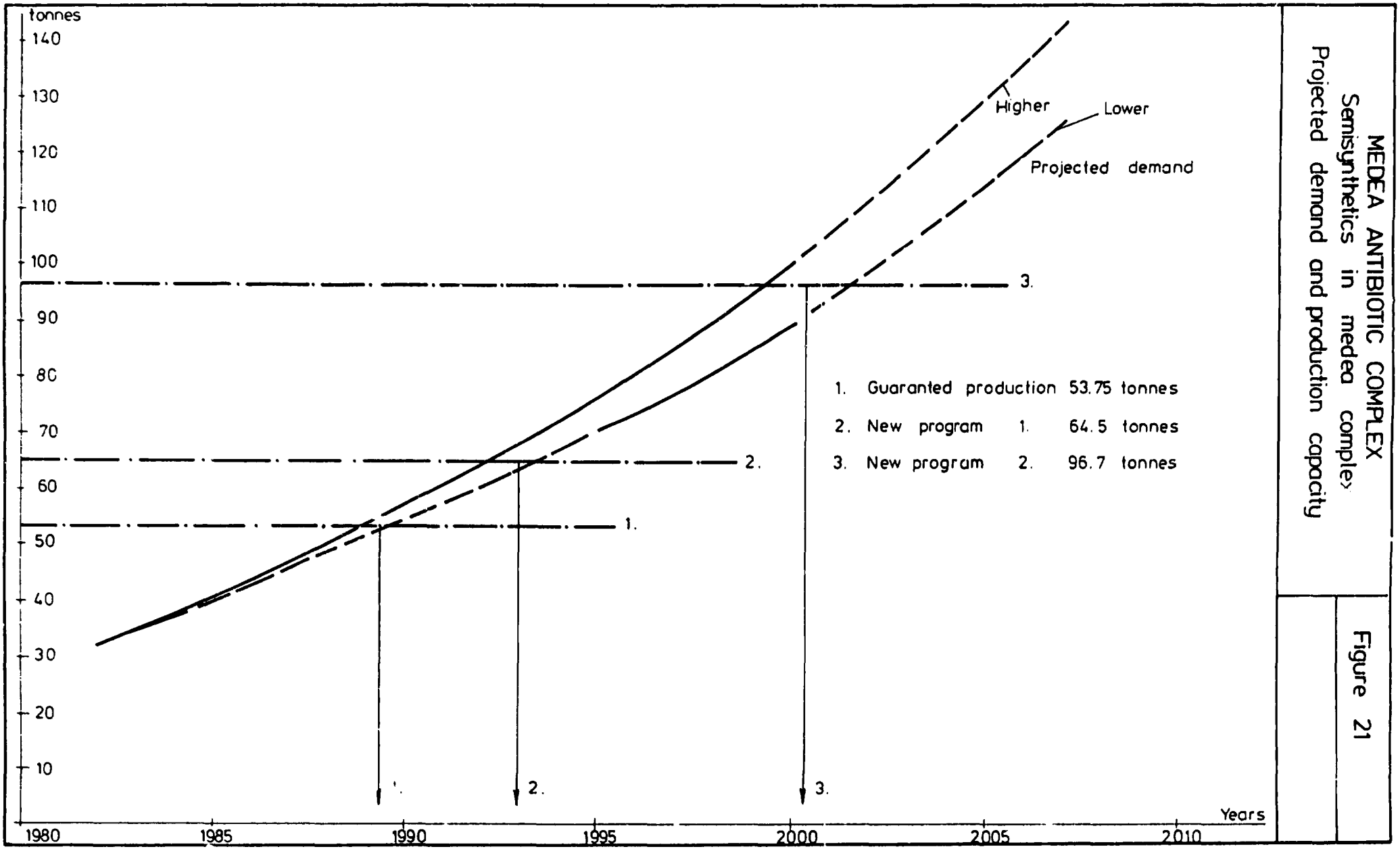
Figure 19

ANTIBIOTICS IN TONNES	1982	1985	1990	1995	1995	2000	2000
Penicillins							
Pen GK	11.7	13.6	17.3	21.6	20.4	25.9	22.3
Pen GV	9.1	11.6	11.4	25.8	23.3	35.7	27.4
Amoxicillin	5.5	6.8	9.5	13.1	12.0	16.8	13.6
Ampicillin	19.5	24.0	33.1	45.2	41.7	63.5	52.3
Oxacillin	6.2	7.4	9.6	12.2	11.5	17.0	15.7
Metampicillin	1.8	2.1	2.8	3.7	3.5	4.7	3.9
Hetacillin	0.8	0.9	1.3	1.8	1.6	2.3	1.9
Pen G. benzath.		2.0	2.6	3.3	3.1	3.9	3.4
Pen. G. procain		3.5	4.4	5.5	5.2	6.6	5.7
Tetracyclines							
Tetracycline	2.0	2.7	4.2	6.2	5.6	8.5	6.6
Oxitetracycline	5.4	6.8	9.4	12.8	11.9	16.5	13.4
Clortetracycline	0.3	0.4	0.6	0.9	0.8	1.1	0.9
Doxycycline	0.3	0.4	0.6	1.0	0.9	1.4	1.0
Macrolides							
Oleandomycin	9.2	12.3	19.8	31.2	27.7	45.4	33.5
Erithromycin	2.6	3.2	4.6	6.4	5.9	8.3	6.7
Pristinamycin	0.7	0.9	1.3	1.8	1.7	2.4	1.9
Virginiamycin	0.4	0.5	0.7	0.9	0.9	1.2	1.0
Spiramycin	14.4	17.9	25.2	34.7	31.9	49.0	36.3
Aminoglycosides							
Streptomycin	1.2	1.4	1.8	2.2	2.1	2.7	2.3
Gentamycin	0.2	0.3	0.4	0.5	0.5	0.6	0.5
Neomycin	0.3	0.5	0.9	1.3	1.2	1.9	1.4
Paramomycin	0.4	0.5	0.7	1.0	0.9	1.3	1.0
Other antibiotics							
Lyncomycin	0.8	1.0	1.2	1.5	1.4	1.9	1.6
Colimycin	0.1	0.2	0.3	0.4	0.4	0.6	0.4
Rifampycin	0.4	0.5	0.8	1.2	1.1	1.6	1.2
Thiamphenicol	2.6	3.1	4.2	5.6	5.2	7.0	5.8

MEDEA ANTIBIOTIC COMPLEX
Penicillin
Projected demand and production capacity

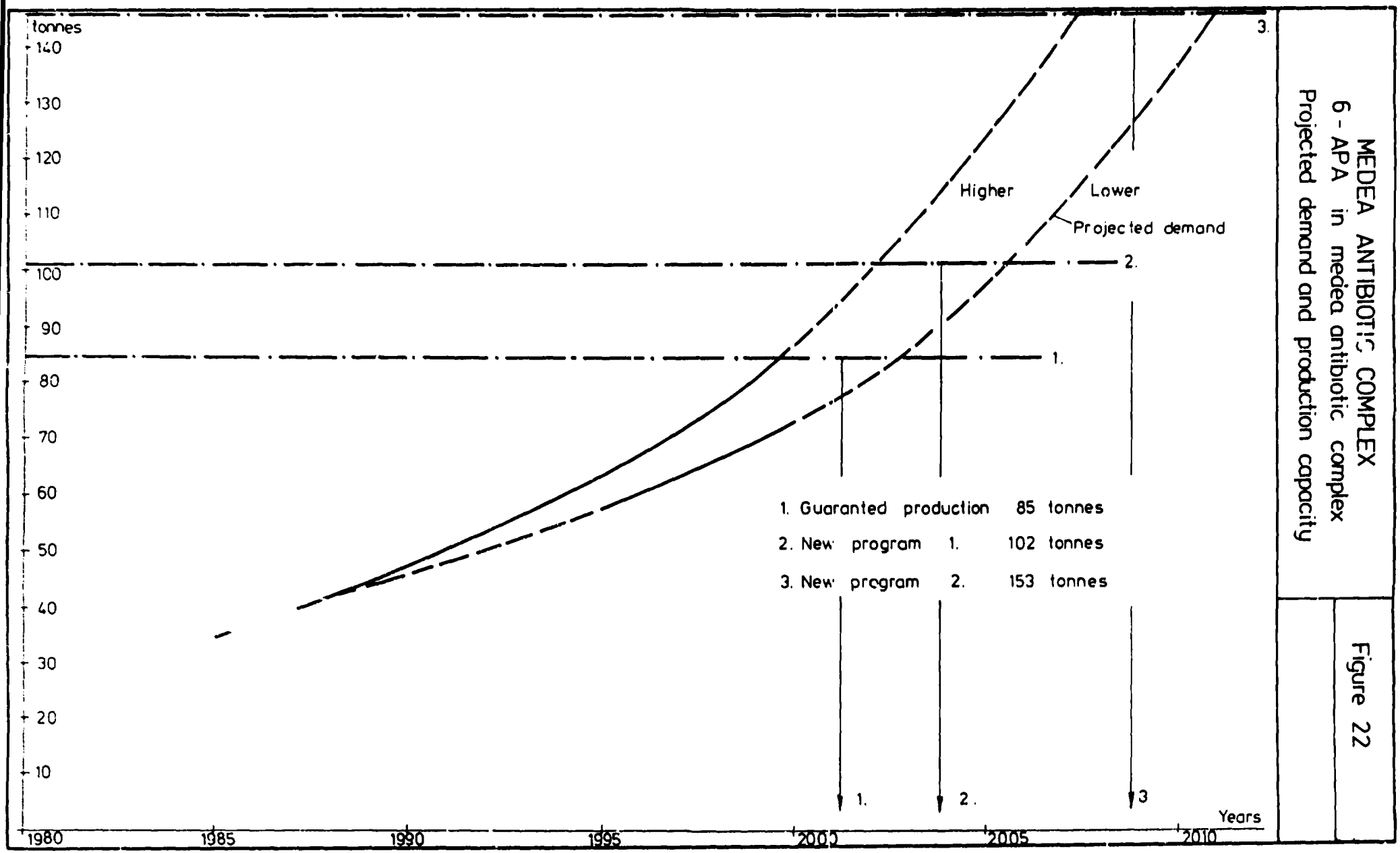
Figure 20





MEDEA ANTIBIOTIC COMPLEX
Semisynthetics in medea complex
Projected demand and production capacity

Figure 21



MEDEA ANTIBIOTIC COMPLEX
6 - APA in medea antibiotic complex
Projected demand and production capacity

Figure 22