OCCASION

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

DISCLAIMER

FAIR USE POLICY

CONTACT

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

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

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

15004

Distr.
RESTRICTED

UNIDO/IO/R.180
16 September 1985

ENGLISH

UNITED NATIONS
INDUSTRIAL DEVELOPMENT ORGANIZATION

ESTABLISHMENT OF A DEVELOPMENT PLAN
FOR THE PHARMACEUTICAL INDUSTRY

UC/ALG/85/062

ALGERIA

Technical report: Production of
bulk antibiotics*

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

Based on the work of Mr. P. Sensi,
expert in fermentation

---

* This document has been reproduced without formal editing.

V.85-30904 (EX)

TABLE OF CONTENTS

I. SUMMARY

The establishment of an industry for the production of antibiotics in Algeria is very important for the needs of the country and for entering in the developing area of biotechnology.

The market data on antibiotics in Algeria reveal certain peculiarities. It is advisable to establish a program for monitoring the use of antibiotics.

Status of the Medea plant for the future production of antibiotics:

- Size of operation (volume and number of fermenters), quality of engineering and equipment in fermentation, recovery, purification and semisynthesis, facilities: adequate to a modern plant for antibiotics production.
- Analytical and control laboratories: well designed and well equipped.
- Levels of contractual fermentation technology in comparison with the current competition levels: penicillins ~36%; tetracyclines ~50-60%; streptomycin, not evaluable.
- Levels of contractual technology in recovery, purification, chemical transformation into semisynthetic penicillins: acceptable.
- Personnel for the plant and laboratories: trained mainly for running the chemical and analytical processes; severe shortage of experts in industrial microbiology.
- Department for development of chemical process: adequate.
- Department for development of fermentation process: adequate for the current assistance to production, but inadequate for the necessary improvements.

. Production program of bulk antibiotics (contractual): superior to the needs of the country particularly for streptomycin and tetracycline; inferior to the potential capacity of the plant at current international levels. Therefore either a part of bulk antibiotics will be sold on the international market (after carefully checking the production costs) or a part of fermentation capacity will not be utilized.

Recommendations:

. Personnel: intensify the training or retraining program particularly on industrial microbiology. Establish post-graduate courses in industrial microbiology at Institut Pasteur in Algiers and special courses on biotechnology at the Universities of Algiers and Blida.

. Consider the establishment of a research unit on biotechnology, connected with the Medea programs, in an implemented cultural environment.

. Timing of start-up production:

1986 - Semisynthetic penicillins: confirmation of contractual yields.

1987-1988 - Tetracyclines by fermentation: confirmation of contractual yields

1988-1989 - Penicillins by fermentation: confirmation of contractual yields

Streptomycin production to be reconsidered.

. After the start-up of production and confirmation of yields, check the availability of a better know-how on penicillins and tetracyclines. Consider other fermentation products, particularly cephalosporins.

II. INTRODUCTION: DEVELOPMENT OF ANTIBIOTICS AND RECENT TRENDS

Since the discovery of penicillins in the 1940s, extensive research programs led to the identification of a great number of microbial metabolites with antibiotic properties. Only a small percentage of them had the necessary characteristics for the human therapeutic use. Most of the antibiotics which are now used for the therapy of bacterial infections belong to chemical families discovered in the period 1940-60, while the period 1960-85 is characterized by the identification of new members of the same families, plus a proliferation of derivatives of the original natural antibiotics obtained by semisynthesis.

In spite of the number and quality of antibiotics, bacterial infectious diseases continue to be a major cause of morbidity, and although much less than in the past, of mortality. For this reason the research on antibacterial antibiotics (by fermentation or semisynthesis or total synthesis) is very active in many laboratories in the world with the objective of improving efficacy and decreasing untoward effects.

Among the most important new products recently introduced in therapy it is to mention: new generations of cephalosporins, effective against gram-negative bacteria or with improved pharmacokinetics, the monobactams like azthreonam, produced by total synthesis, some penems also produced by total synthesis, some semisynthetic derivatives of aminoglycosides and macrolides, and some betalactamase blocking agents (clavulanic acid, sulbactam). There are also new members of synthetic chemotherapeutic agents called quinolones, which include from nalidixic acid to oxolinic and pipemidic acids and more recently ofloxacin, nofloxacin, enoxacin, perfloxacin, ciprofloxacin; the last ones have a very broad spectrum of action and low toxicity.

Considering that in the future totally synthetic products (monobactams, penems, quinolones) could conquer a substantial role in the treatment of infectious diseases, this fact together with the continuous improvements of productivity of fermentation yields could lead to a surplus of fermentation

capacity for production of antibiotics. This does not mean that a fermentation plant will be less valuable, because there is an increasing interest in the biotechnology as a tool for producing products useful to the man, through the use of microorganisms or part of them (e.g. enzymes). These products include antitumors, antivirals, antiprotozoals, products useful in veterinary and in agriculture, aminoacids, vitamins, etc. In the future many hormones and enzymes for therapeutic use will be produced by fermentation with strains obtained by genetic engineering. Only the countries which have fermentation capacity and people expert in industrial microbiology could have access to the new era of biotechnology.

III. THE USE OF ANTIBIOTICS IN ALGERIA

The chemotherapeutic agents represent a relatively high percentage of drugs used in therapy. Their market share ranges from 10-12% in developed countries to 30% or more in developing countries where adverse factors (malnutrition, hygienic conditions, etc.) favor a high incidence of bacterial infections.

From the data reported in two Algerian documents ((1) Antibiotherapie en Algerie, Congrés Médicale Magrebin 1983; (2) Etude de marché des médicaments en Algerie 1985, with market data of 1982) the market of anti-infectives in this country represents 23.7% of the total drug market. According to the document (1) the breakdown of the consumption of antibiotics in 1981 was the following:

	Hospitals	Pharmacies
Penicillins	37.8	36.0
Cephalosporins	0.2	0.0
Aminosides	6.1	9.3
Tetracyclines	15.1	14.4
Phenicols	4.8	6.9
Macrolides	14.1	19.5
Various	6.8	13.3
Antituberc. Ag.	15.1	0.6
	100.0	100.0

This subdivision in the use of antibiotics classes is not surprising. The small percentage of cephalosporins is evidently due to their high cost and their use has been reserved to special cases in the hospitals. The high share of antituberculous agents is probably related to a campaign for introducing the short course chemotherapy for eradication of tuberculosis.

A more detailed analysis of the antibiotics market in Algeria (document (2)) reveals some peculiarities. It should be clear that the following comments on the market data do not imply that the status of chemotherapeutic treatments in this country is not adequate.

In the field of macrolides, TAO and spiramycin have a great market share, both in value (TAO) and in volume (spiramycin). TAO is the drug with the highest share in Algeria in 1982. This does not correspond to the world-wide position of the two drugs in the frame of the macrolides. In the world the most used macrolide is erythromycin, which has a relatively low market share in Algeria. Another peculiarity is the high use of oxytetracycline (injectable and capsules) in comparison with tetracycline, which is the most used in the world among this family of antibiotics. Phenicols are rather largely used, probably in relation to a high incidence of intestinal infections, and thiamphenicol is the drug of preference over chloramphenicol. Among the aminoglycosides streptomycin appears to have a rather limited use and this is a common trend in the world because in the treatment of both tuberculosis and non-tuberculous infections streptomycin is nowadays overcome by other drugs. Gentamycin is very little used. In volume, paramomycin has a larger use probably due to the claimed antiamebic properties. Neomycin is as usual employed in various topical preparations. Penicillins have the largest market share both in volume and in value. Among the various broad spectrum semisynthetic penicillins, ampicillin is the most used one and in the pharmacies also metampicillin, a prodrug of ampicillin very little known in the world market. The market share in Algeria of two antibiotics, virginiamycin and pristinamycin, although rather limited is surprisingly superior to their international use. Pristinamycin is practically unknown in most countries and virginiamycin is largely used as feed addictive and not for human therapy.

In view of a long term planning of pharmaceutical production in the country, it is important to review carefully and monitor the use of the antibiotics registered on the "Liste des produits agree a la nomenclature". It is a problem different from that of the "Commission de la nomenclature" which has the responsability to introduce or eliminate drugs on the basis of the knowledge of their risks and benefits. The problem is to have a proper use of the registered antibiotics. It is a difficult task which includes actions at various levels from the Medical Schools, to the Hospitals, to refreshing courses for medical doctors with the objective to educate the health community on the efficacy, safety and cost of antibiotics. A program

of continuous education on the use of antibiotics will have various positive implications (on therapy, epidemiology, economy and management of drugs consumption and distribution in the country). For the purpose of planning an antibiotic industry for the next twenty years, it would be important to have such a program in order to rationalize the production of the antibiotics really needed by the country.

IV. THE ANTIBIOTICS INDUSTRY

The antibiotics industry is typically based on biotechnology, e.g. on the combined use of microbiology, chemistry, genetics and engineering for the production of useful substances through microbial processes. It is a rather sophisticated industry with some distinctive characteristics.

Personnel. It requires personnel with good competence in various fields and obviously a good interaction and collaboration among experts in different disciplines. The multidisciplinarity of a biotechnological industry requires a careful system of recruitment and management and a good program of training.

Technological levels and improvements. A fermentation process for antibiotics has potentially such a large possibility of improvements that any industry of antibiotics, also at a high technological level, run the risk to be overcome by a competitor who has developed a more advanced process. Although this is common for many technological processes, it is particularly relevant in the antibiotics industry as illustrated by the following data:

Penicillin G - Yields in	1946-48	200 u/ml
" "	1950-58	2000 "
" "	1958-68	4000-8000 "
" "	1972	16000 "
" "	1985	67000-83000 "

There is still room for improvements considering that, also for high producing strains, the conversion value of glucose into penicillin is still very low, of the order of 6-12%. The value of antibiotic yields is not the only parameter to be considered. The cost and availability of raw materials for fermentation, the duration of fermentation, the consumption of utilities are some examples of important parameters to be evaluated in the economics of the process. The operations following the fermentation (recovery, purification, transformation into semisynthetic derivatives) are also subject to potential improvements. But, generally speaking, the economy of the antibiotics production depends primarily from the fermentation yields.

Research and development. From the previous paragraph it is clear that the production of antibiotics on industrial scale cannot be maintained without continuous development work, which is in turn fed by scientific knowledge resulting from research. Departments of process development are often located in the production unit and provide technical assistance and process improvements through experiments at laboratory and pilot level. Research departments on industrial microbiology, chemistry, biochemistry and bio-engineering perform studies on the selection of new high producing strains, on media and fermentation conditions, on new improved recovery or chemical processes, on the evaluation of new projects and on selected new areas of biotechnology. The research departments are not necessarily located at the production site.

The performance of an antibiotic plant possessing a good process depends from the size of the operation (fermenters of capacity inferior to 100 m^3 are now obsolete) and from the equipment for control and adjustment of the process parameters and obviously from the general organization and planning of the operations.

V. THE PLANT FOR PRODUCTION OF ANTIBIOTICS IN MEDEA

On the basis of the previous general considerations on the antibiotics industry, a preliminary analysis of the Medea plant indicates the following strong and weak points:

a) From the engineering point of view the design and the installation of the plant can be judged rational and modern. The size and number of fermenters (9 fermenters of 130 m^3 total capacity each), although not as large as the recent trends suggest, seem adequate for a large production of antibiotics. The equipment for the control and adjustment of the fermentation parameters are among the best in the international market. Also the design and installation of the recovery and purification sector and of semisynthesis indicate a good competence of the responsible engineering company. Concerning the facilities, they seem adequate to the production needs, including the water whose supply and purification has been recently assured.
The performance of a plant is difficult to judge before operating; only the start-up will reveal possible weak points.

b) The analytical and control laboratories have been designed and equipped with accuracy and competence. Their size (more than 3000 m^2 + 1000 m^2 for pharmacotoxicology) is very large, although they will be involved mainly in the control of the production of pharmaceutical formulations. The list of the instruments indicates that they will be more than adequate for the needs. However some of these instruments (e.g. spectrophotometers) require a technical assistance, the organization of which is to be checked.

c) Level of available technology for production. The contractual commitments for the bulk production of antibiotics in the Medea plant are apparently the following: 5 fermenters, 130 m^3 total capacity each, ca. 90 m^3 effective capacity each, 450 m^3 effective fermentation capacity total, are supposed to produce 163 tons of penicillin G + penicillin V / year (31.8 penicillin G as sterile salts, 102.62 of penicillin G K for the production of 61.06 semisynthetic penicillins and 29.0 of penicillin V).

The fermentation yields of the competitors (possibly not at the highest levels) are reported to be of the order of 50.000 u/ml in a 200 hours cycle, corresponding to a potential production of the Medea plant of 450 ton/year. Therefore the penicillin fermentation plant is foreseen to start at yields which are about 36% the current levels of competition.

In the case of tetracyclines the contractual commitment is to produce ca. 64.3 ton of tetracycline (48.9) + oxytetracycline (15.36). In this case the committed productivity of the plant at start could be estimated (from some data on the Medea fermentation yields) to be between 50 and 60% of the competition levels. The potential production of 3 out of 4 fermenters at the current productivity level of 0.75 ton/m^3/year could arrive at about 200 ton per year.

The productivity level of streptomycin process cannot be estimated due to the unavailability of data, but the present (1982) low use of this antibiotic in Algeria (1.25 ton/year) and in the world suggests that the streptomycin project is nowadays questionable.

The technical level for the production of the semisynthetic betalactams is in a more favourable situation. According to the contractual commitment about 103 tons of pen. G K will be converted into 6-APA and from this intermediate into 61 tons of ampicillin + oxacillin/year. These conversion yields can be accepted as a starting point. However, it is to point out that the plant for the production of 6-APA installed in Medea is based on the classical chemical process, i.e. the chemical hydrolysis of penicillin involving rather drastic and toxic reagents. Many important companies have adopted the enzymatic process which is simpler, safer and cleaner than the chemical one, but requires the technology for the production of the enzyme (penicillin-amidase). There is the possibility that in the future more stringent specifications on the chemical impurities of the derivatives of 6-APA in the official Pharmacopeas could give serious problems to the products obtained by the chemical process.

d) Personnel. The recruitment of the personnel has been done mainly among chemical engineers and in general among people with a certain chemical background but very limited formation in microbiology. The training program

at IBI and, in minor extent, at SQUIBB has permitted technical people to acquire experience on the chemical and analytical aspects of the production but not on the fermentation process. This training was probably enough for running the chemical plant and the analytical laboratories on the basis of available specific procedures. Unfortunately, many persons have been inactive for months and years after their initial training. No refresher courses have been done and in Medea there is not a library. The Medea management should take initiative for further intensive training programs particularly in industrial microbiology as emphasized in the "Recommendations" paragraph.

e) Development of industrial processes. A department of chemical development has been designed in the analytical building. The equipment (among which 3 semi-industrial reactors and 1 glass reactor) and the space are more than adequate for working on the improvements of the chemical processes and also for studying new chemical alternatives.
A department of industrial microbiology development will be located in the industrial fermentation building. It is provided with 16 shakers, four 150 l fermenters and one 800 l fermenter, and other equipment. Strain lyophilization has not been foreseen. The location and the structure of this department of industrial microbiology is adequate mainly for the current assistance to the production plant, for a rather limited program of checking raw materials, strains and fermentation conditions and for training technical people for the plant. It is not adequate for an intensive program of genetic manipulation of strains (by screening of mutants or more recent sophisticated methods) in order to improve the yields of the produced antibiotics and for introducing technologies for producing other antibiotics or other products by fermentation. On the other hand the low level of contractual fermentation processes and the shortage in Medea of personnel trained in industrial microbiology indicate the urgent need of a particular attention to this problem.

VI. PROGRAM OF BULK ANTIBIOTICS PRODUCTION IN MEDEA AND ALGERIAN NEEDS OF ANTIBIOTICS

An analysis of the use of antibiotics in Algeria (1982) compared with the contractual bulk production of the Medea plant is reported in the following table where the last column indicates the potential productivity of the plant if running at the current international levels. The use of antibiotics will certainly increase in the next years in correspondence of a larger public health coverage and with the increase of the population and certainly some changes in the use of antibiotics could occur. Furthermore, the use of antibiotics in the veterinary field and as feed additive must be considered. Nevertheless, the size of the Medea plant is such that its contractual productivity largely exceeds the needs of the country particularly for tetracycline and streptomycin. This excess of production will become particularly relevant if the plant produces at the average international levels of fermentation yields, as indicated in the third column of the table.

Antibiotics	Evaluated use for human therapy (1982) (ton)	Contractual production of bulk (ton)	Potential productivity at international levels (ton)
Penicillin G	15.464	31.8	ca. 450 a part of which to be converted into semisynt. pen.
Penicillin V	8.688	29.0	
Semisynthetic penicillins	40.102	61.06 (from 102 ton pen. G K)	
Oxytetracycline	6.854	15.36	ca. 200
Tetracycline	1.950	48.9 (incl. vet.)	
Streptomycin	1.244	32.56	not considered
Spiramycin	13.00	——	
Oleandomycin	7.50	——	
Erythromycin	5.80	——	
Griseofulvin	2.88	——	
Rifamycins	2.00	——	
Amphothericin	2.00	——	
Neomycin	1.00	——	
All other antib. (no one exceed- 1 ton)	5.00	——	

This means that a part of the bulk production could be sold on the international market at competitive prices. It is important that the Medea management could make a careful evaluation of the production costs of penicillin, tetracyclines and streptomycin at the contractual productivity levels and at the average international levels potentially to be reached in the near future. In certain conditions it can be accepted a high industrial cost only for the antibiotics produced for captive use in consideration of the intangible benefits (employment, technological development, supply independence, etc.).

VII. RECOMMENDATIONS

From the reported analysis some recommendations can be made:

a) Personnel. It is of primary importance to intensify the training or retraining program particularly on industrial microbiology. Besides the training at the industries in Italy which are transferring the know-how in Medea it would be productive to send people to work in some public institutions in Algeria or abroad. A stage period at the Institut Pasteur in Algeria will be very useful for some selected persons. The installation of a library in Medea must be considered immediately.
For the future needs of an industry based on biotechnology, it is necessary to establish in the country post-graduate courses in industrial microbiology. The large experience of the Institut Pasteur in Algeria in organizing courses for specialization in certain biological fields indicates that this Institut could undertake the task of starting soon post-graduate courses in industrial microbiology and biotechnology. Also, the Faculty of the Algiers University should address some special teaching courses to the biotechnology of industrial antibiotics. A four year course on microbiology and its applications started two years ago at the Faculty of Science and Technology in Algiers. A similar course should be instituted at Blida University.

b) Research and development. The future of a biotechnology industry depends on the resources in research and development. This is particularly important for an industry starting at relatively low level as the Medea plant. It is advisable to increase step-wise the size and equipment of the development department of industrial microbiology in Medea, possibly in an area outside the industrial fermentation building. The responsibility of the development of industrial microbiology should be carefully selected among the most brilliant and well-prepared persons. In the meantime, it would be advisable to plan the institution of a modern research laboratory on microbiology, genetics and biochemistry of microorganisms, with the purpose of establishing intensive programs on improvement of productivity of the strains with advanced techniques, and of studying other alternatives of

production of new fermentation products of commercial interest. This research laboratory must be located in the best cultural environment.

c) Production program. Although the levels of the contractual fermentation processes are much below the international competition, it is advisable not to create panic or discouragement. It is important to start up with the contractual commitments in order to acquire most of the experience necessary to run a plant for industrial fermentation, recovery and semisynthesis. It must be recommended to start production in a step-wise program. A reasonable timing for the start-up of production could be the following:

1986 - Initiate with semisynthetic penicillins and confirm contractual yields and quality, so that start-up problems are identified and solved. Start a program of process improvement in the development laboratory.

1987-88 - Start production of tetracyclines by fermentation. This production is technologically easier than that of penicillins. Confirm the contractual yields and quality. The laboratory of industrial microbiological development will acquire experience in solving various problems concerning raw materials, strains, fermentation conditions, etc.

1988-89 - Penicillins by fermentation. Confirm contractual yields and quality, identify and solve all start-up problems.

----- Streptomycin has not been considered because its captive use is very limited and it is a product of decreasing therapeutic and commercial value.

d) Improvements and future new opportunities. While running the Medea plant at the contractual levels of production, it would be advisable to start negotiations for the acquisition of better technologies for penicillins and also for tetracyclines. The first option could be the two companies which have offered the present know-how. Furthermore, there are various other companies which could be interested either to sell an acceptable know-how or to utilize the Medea plant as a common source of bulk antibiotics produced with their own technology. There are also some non-producing companies which

however sell strains and know-hows of competitive levels (e.g. Panlabs, McKee, etc.).

In consideration of the high potential production volume of the plant, various other products have to be considered for their possible production in Medea, e.g. cephalosporin C appears one of the products of great commercial interest. However, a survey on the future opportunities should be done when the technical people at the research, development and production level in Medea have acquired a reasonable competence in the complex area of the bio-technology industry.