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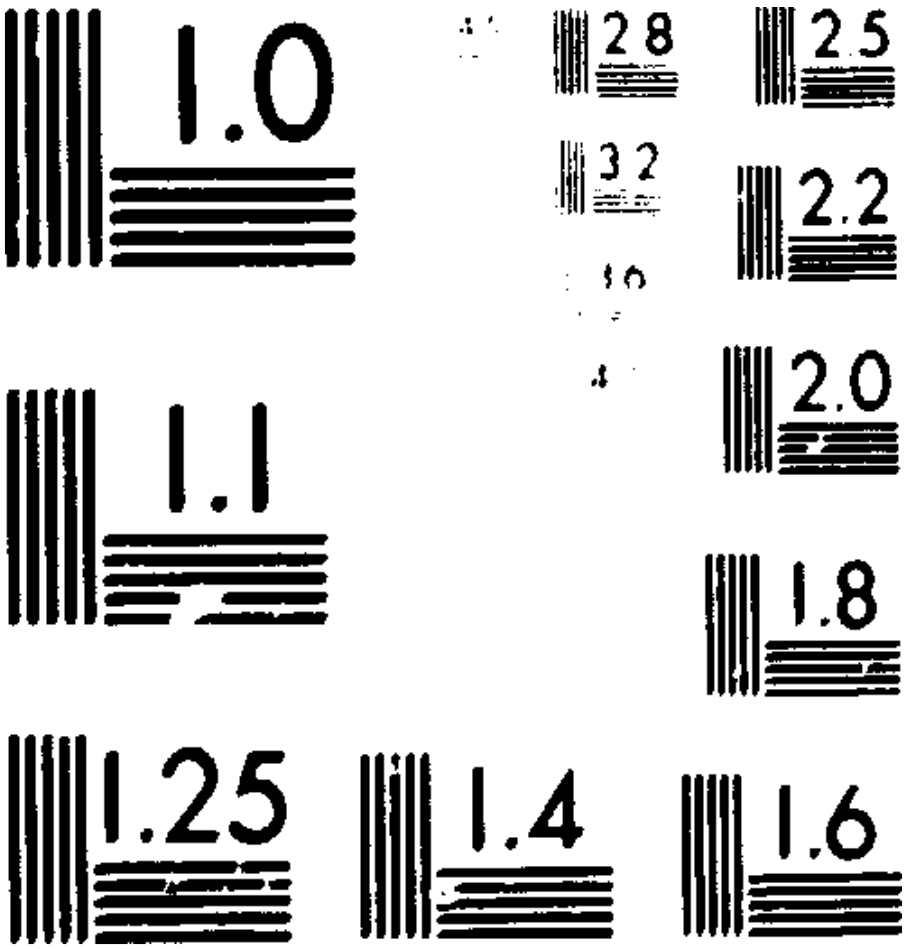
UNITED NATIONS INDUSTRIAL DEVELOPMENT ORGANIZATION
Vienna International Centre, P.O. Box 300, 1400 Vienna, Austria
Tel: (+43-1) 26026-0 · www.unido.org · unido@unido.org



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SUBREGIONAL CENTRE FOR RESEARCH AND DEVELOPMENT ON ANTIBIOTICS*

ST/RLA/81/002

MEXICO, CENTRAL AMERICA, PANAMA, THE CARIBBEAN and GUYANA

Report by the group of experts of the evaluation mission

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* This document has been translated from an unedited original.

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The present report has been prepared by way of continuation of the Latin-American Seminar on Applied Microbiology, DP/REL/77/023, held in Havana. The participants, recognizing the need to have available facilities for research and development work in the fields of fermentation and antibiotics in Latin America, recommended the creation of two sub-regional research centres, one for the central region and the Caribbean and the other for South America.

The Pharmaceutical Industries Unit of UNIDO organized an evaluation mission, financed by the Interim Fund for Science and Technology, which would visit various countries in Central America and the Caribbean in order to collect information relating to the antibiotics industry, and especially the existing research centres and institutions, and to evaluate their activities, work programmes and installations, and so recommend the most suitable location for such a Centre. The evaluation mission, consisting of Dr Meneses, Dr Rabassa and Dr Sensi, followed the norms and directives issued by the Advisory Group formed from official representatives of the Governments of the countries forming the subregion. The design of the Centre and its various activities and functions was developed at the UNIDO headquarters, based on the conclusions and recommendations of the experts R. Rabassa, P. Falini and C. Correa, with the fullest cooperation of Dr Tcheknavorian-Asenbauer, Head of the Pharmaceutical Industries Unit, and María Quintero de Herglotz.

The Pharmaceutical Industries Unit of UNIDO expresses its most sincere thanks to the Interim Fund for Science and Technology, and in particular to Mr Lees, its Director, Mr Lalkaka, Deputy Director, and Mr Brandt, and also to the Governments of the subregion, the members of the Advisory Group and the experts for their personal support for this project which is of such importance for Latin America.

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A C K N O W L E D G E M E N T S

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DR. RODRIGO JIMENEZ MONJE	Director General of Health COSTA RICA
DR. RAMON DIAZ VALLINA	Deputy Minister of Public Health CUBA
DR. GUSTAVO ADOLFO CORDERO	Deputy Minister of Health GUATEMALA
DR. RICHARD VAN WEST CHARLES	Minister of Health GUYANA
DR. JUAN ANDONIE FERNANDEZ	Minister of Health HONDURAS
SR. MARCOS WHEELOCK, Eng.	Deputy Minister of Health NICARAGUA
SR. LUIS FIALLOS, Eng.	Deputy Minister for Industry NICARAGUA

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NATIONAL COUNTERPARTS

COSTA RICA

SR. ROBERTO FRANCESCHI, Lic.

Technical Assistant at the Office of the Executive Secretary for Planning

CUBA

DR. RAMON DIAZ VALLINA

Deputy Minister for Public Health

GUATEMALA

SR. RAFAEL PINEDA REYES, Lic.

Adviser for the National Council for Economic Planning

GUYANA

DR. WILFRED AUGUSTUS LEE

Executive Director, Guyana Pharmaceutical Corp. Ltd.

HONDURAS

DR. ELVIRA GASTEJON DE DAVID GALEANO

Professor of the Faculty of Chemistry and Pharmacy

MEXICO

SR. FERMÍN FERNANDEZ-VIANA, Eng.

National Coordinator for the Pharmaceutical Industry,
Ministry of National Resources and Industrial Development

NICARAGUA

SR. J. GONZALO CALDERON, Lic.

Deputy Director of Technology,
Ministry for Industry

PANAMA

SR. JUAN ADOLFO ALVARADO, Eng.

General Deputy Director of Industry,
Ministry for Trade and Indus-

SUMMARY

1. The activities of the mission in the subregion were in accordance with the contents of the terms of reference approved at the Advisory Group Meeting which took place in Mexico City on 20 - 21 August 1981.

2. The countries visited by the mission were as follows: Costa Rica, Cuba, Guatemala, Guyana, Honduras, Mexico, Nicaragua and Panama. The visit to the Dominican Republic was postponed, as agreement to the mission's request was not received in time.

3. The current level of consumption of antibiotics in the subregion has been estimated at 1,770 tonnes of drugs in bulk, valued at US$ 95 million. It should be noted that consumption figures ascertained for Mexico, Cuba and Guyana represent absolute values, whilst those for the other countries were obtained by projection of available statistical data.

In general terms, the national markets can be subdivided into three well-defined areas.

- Ethicals sector, represented by drugs sold under prescription and, in the majority of cases, marketed under registered trade marks by large companies.
- Mass market, with products of a lower therapeutic level, sold without prescription.
- Public sector, covering the majority of therapeutic categories, which government health departments obtain by public tenders and which, in some cases, are also produced at formulating plants owned by the state. This sector permits

the participation of smaller local companies, which have no means of direct promotion to doctors.

It is interesting to note that stricter quality control procedures in respect of drugs purchased are being implemented in all the countries visited, in order to ensure that contracts awarded on the basis of price do not result in the purchase of products of inferior quality. National companies have also been improving their industrial installations to comply with specifications.

4. The antibiotics market shows an increase in value of 16% per annum, compared with an increase in weight of 7% per annum.

There is a very marked shortfall in the production of penicillin at subregional level. This applies to both pharmaceutical and technical grades of 6-APA. On the basic of current production capacity the shorfall of penicillin for 1986 would be:

Sterile Grade:	996 tonnes
Technical Grade:	165 tonnes
Total:	1,161 tonnes, or about 1,200 m^3 of fermentation capacity

At national level the subregion can be divided into two distinct sectors. Mexico, for example, produces sufficient antibiotics by the fermentation method, (with the exception of penicillin as mentioned above) and semi-synthetic penicillins to cover the country's needs, and has an equally self-sufficient pharmaceutical formulating industry. However, production costs of antibiotics in bulk do not allow for exports to other countries:

this could be solved by increasing efficiency to international levels. Cuba produces its semi-synthetic penicillin requirements from imported penicillin and has export capacity. Its formulating industry is self-sufficient. The remainder do not produce any antibiotics in bulk and, although Guatemala and Costa Rica export finished products to other countries in the subregion, their contribution in respect of products based on antibiotics is not significant. The subregion is devoting a great deal of effort to the production of speciality products based on antibiotics. Honduras, Guyana and Panama have achieved positive levels of operation of their pharmaceutical plants within a relatively short time.

5. The main difficulty with regard to self-sufficiency in the production of antibiotics in bulk has been identified as access to suitable technology for the production of drugs which can compete, in price and quality, with traditional markets.

Knowledge is not considered to be extensive nor comprehensive, except in a very few cases in the actual antibiotics market in the subregion, and there is a growing need for local production to prevent a further increase in the present shortfall. It can be argued that this may be due to the fact that the greatest shortfall is to be found in the penicillin sector, despite the existing plant in Mexico, but which does not offer any hopes of an increase in productivity from the technical or economic standpoint. The other countries, with the exception of Cuba, which is about to start production of antibiotics by fermentation, seem to be mainly concerned with resolving pharmacotechnical and basic production problems. It should also be stressed that the smallness of these markets would not justify the prima facie installation of a plant

solely to meet national needs. The various countries would have to combine their requirements to justify a plant of suitable size. Only Caricom currently combines its members' requirements, so that sufficiently large orders for drugs can be placed to achieve better prices.

6. The mission also evaluated professional training and research activities in the subregion. This is relevant in view of the indisputable need for new technologies. Technologies are derived from the results of research based on very clear objectives, in this case the efficient production of antibiotics. The mission therefore thoroughly investigated this aspect during the many meetings and visits to laboratories at the research centres in the subregion where these activities are carried out. Intensive research of a highly scientific nature is being conducted in the area of industrial microbiology at higher education and research centres in all countries in the subregion. This confirms the fact that the subregion has the necessary human resources in this discipline to plan research programmes specifically designed to improve technologies for the production of antibiotics.

Work of very high quality has been carried out on biomass production, the degradation of polysaccharides, amino-acids, solid fermentation of fodder, etc. It should however be mentioned that only one case of locally developed technology associated with the purposes of this mission was found, namely, the production of 6-aminopenicillanic acid from penicillin by enzymatic means. This finding should not be interpreted as

lack of scientific skills for the development of technologies for the manufacture of antibiotics by fermentation, but rather as a possible lack of integration between research and industry.

7. As a result of these findings a plan was submitted to the countries in the subregion dealing with the acquisition of technology, training of personnel, access to local sources of raw materials and permanent technical assistance in order to resolve production problems, and also to ensure that such technologies continue to remain as competitive as at the time of their introduction.

8. On one occasion during the visit to Guyana, the mission had the unexpected opportunity of attending a meeting of Caricom (Caribbean Community on Pharmaceuticals) as special guest of this organization, and was also able to report on the basic contents of this plan.

   It was ascertained that Caricom also favours an increase in its pharmaceutical industry and is setting an example of cooperation between the member countries.

9. The plan was discussed in general terms with high-level government officials in the countries visited. Reaction to the plan was enthusiastic and it was ratified by ministers and deputy ministers of health and industry. A similar reaction was observed in the areas of industrial and academic activity.

   The need was also expressed for further assistance in the

pharmaceutical industry sector for the formulating of antibiotics, especially outside Mexico and Cuba. The mission felt that this concern is indeed justified, since intensive efforts are being made everywhere to increase production of pharmaceutical products.

Public and private officials interviewed also considered that the Centre had an important function in the development of the necessary human resources for the operation of industrial plant for the production of antibiotics by fermentation and semi-synthesis. The same positive comment also applied to the technical services which the centre could offer to the industry. The persons interviewed also showed an interest in the standards proposed by the centre to ensure proper functioning of the subregional plan, both at technical level and also as regards investments and expenditure.

10. In order to obtain information on which to base its recommendations the mission not only evaluated the academic and technological infrastructure, but also access to local raw materials, the necessary personnel for the centre and the financial backing which each country could provide. The willingness of each country to cooperate was also evaluated for the purpose of providing the centre with an accurate assessment of the subregion. It was also indicated that the Centre's operations would be controlled by statutes which would ensure the availability of its services to all member countries.

11. All aspects of the manufacture of antibiotics by fermentation were studied, although in those countries with no antibiotics industry under way it was the only method which could be evaluated.

Practically all the production facilities were evaluated in the specific cases of Cuba and Mexico, and the conclusion reached that, in qualitative terms, these manufacturing centres fulfil their function correctly, although, as has already been stated, output does not fully cover these countries' needs from the quantitative aspect.

12. The activities of the production centres face certain obstacles, which are being overcome with an obvious desire for improvement, but which are nevertheless reflected in productivity, quality and price. We would mention only the lack of some local raw materials of suitable quality, which therefore have to be imported, resulting in higher costs (freight alone may raise the price of a particular raw material by 100%), inadequate supply of electrical energy, lack of skilled labour, etc.

13. The availability of raw materials was thoroughly investigated in each country, not because this information is required by the Research and Development Centre, but because these raw materials are essential to the production centres. As many are produced locally, it was determined that the future Centre should include, in its work programmes, measures for the improvement of their quality and suitable technologies, and also that recommendations be made to producers of these raw materials, so that quality may be standardized and the required specifications met for industrial applications based on high productivity technologies.

14. Another aspect which the mission evaluated with regard to the future installation of new industrial plant was the existence in the subregion of an industrial infrastructure capable of undertaking the construction of industrial production units, covering the supply of equipment and civil engineering, installations and other relevant aspects of the activities in question.

One country in the subregion possesses practically all the components of the infrastructure mentioned, including the manufacture of reactors, fermenters, centrifuges, rotary vacuum filters, boilers, etc. It also has engineering teams capable of developing the basic engineering requirements of a plan and then putting it into operation.

Moreover, this country, Mexico, has all the necessary servicing and maintenance facilities for the control elements of industrial operations.

Cuba's industrial infrastructure is less complete, since it only manufactures auxiliary items of equipment, storage tanks and low pressure containers, but it everything pertaining to civil engineering, installations and design.

The remaining countries have the necessary civil engineering and installation services and can also provide certain less important elements.

15. Patent legislation in the subregion was examined with the main objective of determining the limitations which might apply to the Centre's activities if these rights were applicable. Only one country - Mexico - does not grant patents either for

products or for pharmaceutical processes, although certificates of invention are issued in the latter case. Costa Rica accepts patents for products and processes, but only for a period of one year, provided they are actually used in the country. The legislative solution imposed by this country is almost tantamount to absence of any patent system. In Honduras and Guyana protection is only recognized for pharmaceutical processes, whilst in Cuba, Guatemala, Nicaragua and Panama this applies to products as well.

The effect of the recognition of patents will depend on the extent of legal protection, the type of activities carried out, the type of processes used and products manufactured. The Centre would not encounter any barriers in principle if it were to confine its activities to research and development or, if it undertook other activities, it became established in a country without patent protection or where patents for products manufactured or processes used had already expired.

16. Requirements for antibiotics both for veterinary and medical use were not fulfilled, with the exception of Cuba.

17. Statistics relating to consumption and production capacity obtained by the mission were tabulated on its return and produced some interesting findings:

- The subregion could expect an increase in its production shortfall of antibiotics in bulk, especially insofar as penicillin is concerned.

- The projected shortfall for 1986 can be expressed in various units:

  Tonnes: 1,707 per annum
  FOB value at European prices: US$ 65 million
  C&F value at European prices: US$ 72 million
  Cubic metres of fermented product: 1,926
  Possible investment value: US$ 60 to 80 million

18. This figure for the increase in value of the shortfall of the order of some $70 million is a factor to be taken into account by the subregional centre. It should be noted that a comprehensive infrastructure will be necessary to achieve additional output of 1,700 tonnes by efficient and economic means, using a high proportion of local raw materials, labour and services, and this can only be provided by a well designed, programmed and managed centre.

19. National companies, one of which is a public company, own 59% of the fermentation capacity and 60% of the production capacity for semi-synthetic penicillins. This national group is of course one which is in a position to freely decide on the acquisition of technology, technical assistance and training. Nor is there any doubt that the most appealing, if not the only, way of obtaining these needs is via the Centre. The above is applicable to Mexico and Cuba.

20. A firm indication of the size of the market which the centre could expect to satisfy through its technologies and other services can be obtained by totalling the existing output by national companies and the figure already quoted for the additional production capacity required.

21. If, due to the existence of the Centre, expansion mainly involved national capital, the overall picture would indicate

a level of activity of local origin unequalled in any other developing area of the world.

22. Mexico, with a total pharmaceutical market worth about $1,120 million for the current year and a population of 67.3 million, invests US$ 16.6 per capita/per annum in drugs, of which antibiotics represent 16%.

Consumption of antibiotics in Mexico is 87% of the total for the subregion, and this must be taken into consideration when carrying out pilot economic studies, since although the remaining 13% might be within the minimum limit for a fermentation plant, it must not be forgotten that this figure covers seven countries.

23. The existence of very different factors in the respective countries concerning legal aspects of patents, freedom of transfer and size of operation calls for a careful study of these countries and the need for subregional cooperation to minimize the economic and political differences between the member countries and differences in the level of development achieved in the pharmaceutical area, which is reflected by widely fluctuating prospects.

24. Conclusions and recommendations and the proposed plan of action were based on the following premises:

- Many universities exist in the subregion, offering courses which wholly or partly cover the disciplines closely associated with the research, development and/or production of antibiotics.
- Although there are no research groups working specifically on topics relating to antibiotics, some are carrying out studies based on similar scientific processes.

- National industry devotes part of its technical resources to maintaining the productivity of processes, but in practice it does not carry out improvements, except those derived from improvements of the strains used.

- Multinational industry has its research centres outside the region. From the age of the plants and absence of any recent changes in instrumentation and equipment, it may be inferred that its technology is not being significantly improved on an ongoing and planned basis.

- The above two points indicate that the need for technological improvements in respect of processes applies to the entire industry.

- There is a considerable production shortfall for antibiotics in bulk, and this applies especially to penicillin, due to the fact that this is the antibiotic with the largest requirements whilst current capacity is insufficient and productivity the lowest of all sectors.

- If the Centre should become operational in one phase only, estimated investment expenditure would be of the order of $6 million and running costs would be $3.5 million per annum for any concept, including amortizing the investment costs.

- The country in which the Centre is located should ensure that experts from another or other countries are employed, and that technology and other information is passed on to the other member countries.

- The country in question must demonstrate a real interest in contributing in the appropriate manner towards financing of investment and running costs.

- The Centre's plan of action should be in the form of a programme which conforms with current priorities but which is sufficiently flexible to allow for future alternatives.

- The existence of other areas must not be overlooked by the Centre, probably consultancy and advisory services not directly associated with the basic plan, such as:

  Pharmacotechnical back up
  Manufacturing standards
  Concepts of design
  Quality control.

These services may be well received by those countries whose main current priority is the expansion of production capacity for finished pharmaceutical products and, of course, future industrial integration.

25. An analysis of the situation in each country by this mission, on the basis of the above premises, leads to the conclusion that the country which could fulfil the greatest number, although not all, of these requirements is Mexico.

CONCLUSIONS

The following conclusions may be drawn from the general recommendations analysing the varying levels of integration of the pharmaceutical industry in the subregion, information obtained by the mission on the usage of antibiotics, the state of technological advancement, human resources and experience in the field of antibiotics:

A) MARKET

The needs of the subregion constitute a market which, even considered over the short term for the most common antibiotics (tetracyclines, erythromycin, various penicillin salts and semi-synthetic penicillins), must be defined as significant.

If other, less widely used, antibiotics are added the figure for projected requirements is of even greater interest.

A simple mathematical calculation of the projected increase up to the end of the century gives a figure of over 7,000 tonnes for the above antibiotics.

The fact that requirements will have almost quadrupled over the medium term is not, however, a primary consideration, since figures for other antibiotics, the cephalosporins being the best example, will also reach significant levels during the same period, calling for local production.

B) TECHNOLOGY

The fact that antibiotics are obtained by fermentation and synthesis in one of two countries in the subregion and by synthesis in the other should not be interpreted as implying that the subregion is self-sufficient in this respect, since about 40% of the production is attributable to multinational companies, whilst yields by local firms are slightly lower than those of the multinationals, and none of them achieve the higher yields found in other countries of the world.

Improvements and innovations are, in fact, essential if the subregion wishes to be fully self-sufficient and competitive in the short term, not only in order to prevent the importing of drugs from abroad, but also to ensure trading between the countries which, in some cases, currently purchase their stocks outside the area at lower prices.

Finally access to up to date technologies, to generate products which are competitive in price and quality, is an irrefutable requirement.

C) HUMAN RESOURCES

The mission found the doors of all study and research centres open, and found the scientific content of their activities to be of high quality. It may be concluded that all the countries have an adequate number of researchers on the one hand, and undergraduate students on the other, in disciplines relating to research into fermentation technologies. Research is also being conducted in pharmacotechnical, pharmacological and chemical areas, based on synthesis and natural products, and in the quality control area.

This is a highly favourable finding, since the subregion has skilled human resources for both research and industrial operations.

The mission should, however, point out that it was unable to find evidence of integrated research activities directed towards problems connected with the production of antibiotics.

D) RAW MATERIALS

The subregion has a potential wealth of natural raw materials which, if integrated in production operations by suitably adapting technological processes, would represent, together with human resources and technology, a significant contribution towards self-sufficiency.

The proposed use of these raw materials will however call for a study by the Centre to determine whether improved yields can in fact be obtained if these are to replace traditional raw materials.

E) SUBREGIONAL INTEGRATION

Only one country, Mexico, has a market which justifies the existence of several plants. The others have needs which, considered individually over the short term, are still very close to the lower size limit for a plant designed solely for the production of antibiotics by fermentation, although multipurpose plants could be used to absorb fixed costs. In some countries expansion of the market and increased expenditure on health programmes could justify the installation of a plant over the medium term.

However, emphasis must be placed on the integration of various countries in order to obtain a market which justifies the economic operation of a plant. Cooperation may take various forms and interchange sought which does not lead to problems regarding the balance of payments.

F) LEVEL OF INTEGRATION OF THE PHARMACEUTICAL INDUSTRY

There is no uniform pattern of integration of the pharmaceutical industry in the subregion, the final stage of which is formulation of the finished product, the middle phase the production of semi-finished products and the initial operation the production of drugs in bulk, whether obtained by synthesis, by extraction from natural sources or by biological processes such as fermentation.

The three stages exist at subregional level, but there are marked differences between countries. It is concluded that the Centre should not ignore these differences but make provision for special aid to all countries in search of advice and solutions to problems.

G) GOVERNMENT HEALTH PLANS

It may generally be concluded that countries in the subregion have a large number of drugs available to patients under state health programmes. There is no doubt that this activity is being promoted by way of campaigns advertising more sophisticated drugs, such as antibiotics.

This fact must be considered from two equally positive approaches: higher demand will create more interest in the

production of antibiotics, and will call for larger plants. On the other hand, and as drugs are supplied under contract to hospital services, plant for the production of antibiotics in bulk could be integrated so as to provide pharmaceutical goods in the form of capsules, vials containing sterile products, etc. of much greater overall value, and therefore more profitable, thereby justifying a smaller fermentation plant since the higher cost of the antibiotic in bulk form would be offset by better absorption of fixed costs.

H) LOCATION

The mission evaluated the various determinant factors and was able to note with satisfaction that, as stated in section C, human resources in the subregion do not present any qualitative differences in respect of ability. This aspect could not therefore be taken as a determinant factor.

However it was concluded, from an objective evaluation of other aspects, that the country to be selected must be one which possesses the greatest number of positive factors, that is to say:

1. It has a high consumption of antibiotics, from which it may be concluded that it has, at least theoretically, a real interest in carrying out investment and development activities.

2. Its current output of antibiotics in bulk is sufficiently high to permit absorption of a considerable proportion of the running costs of the Centre and its current needs, together with projected requirements, which by the time the Centre would be providing valuable information, would be significant.

3. It does not have patents in this industrial sector.

4. No immigration laws exist preventing entry into the country of nationals from other member countries to work at the Centre, nor any advisors which the Centre may require. Nor should there be problems regarding the transfer of convertible currency.

5. Maintenance and spares services, sale of accessories and other aspects following the setting up of the Centre should not differ greatly from those in a developed country.

6. There should be political and economic stability, and there should be no problems in regard to other countries in the subregion.

7. Industrialists, members of the government and academics should have knowledge and experience in the production of antibiotics by fermentation.

8. It should have given its official decision to provide substantial economic and financial backing to defray the Centre's running costs and initial investment requirements.

The above conclusions are only valid if the following are applicable:

1. That the country where the Centre has its headquarters is able to place subregional objectives above its own interests.

2. That it acknowledges and observes the subregional nature of scientific and economic programmes and use of human resources.

3. That it explicitly acknowledges the Centre as an internationally recognized legal body.

4. The Centre should be both legally and economically independent of any national organization, if not self-sufficient.

It was concluded from a thorough analysis of the factors listed that the country which met the greatest number of criteria, if not all of them, is Mexico. It is understood that Mexico would undertake to fulfil the four points listed above.

RECOMMENDATIONS

The subregion has distinctive characteristics, which are derived from the different degrees of integration of the pharmaceutical industry. The priorities of the respective national programmes may therefore differ at any given time, although it may be concluded that all are aimed at achieving self-sufficiency in terms of quantity and quality of products at competitive prices.

In general the stages of drugs policy and the development of the pharmaceutical industry should follow a certain sequential order, as indicated below:

1. Establishment of a programme of priorities for the authorization and acquisition of drugs. These programmes form a suitable framework on which to base selection of the pharmaceutical products designed to satisfy the medical needs and the economy of the country.

2. Establishment of an information centre on the prices of pharmaceutical products, and a general quality control centre. This would lead to the purchase of higher quality drugs at lower prices.

3. Promotion of the installation of production plants for formulating drugs in the public or private sector. The priorities of formulating programmes depend on volumes and values. They also depend on local needs, available technologies and the combined value of the respective formulated products.

   Pharmaceutical plants should be designed along the most up-to-date lines, in accordance with manufacturing standards, and suitable and well-equipped analytical laboratories should be available.

4. Promotion of the installation of plant for the production of drugs of natural origin from local raw materials.

   This plan should permit greater use of local resources. An investment programme for natural medicinal products should not only help to establish suitable technologies for the extraction and purification of products with known therapeutic applications, but also contribute to the discovery of new active substances.

5. Promotion of the installation of plants for the production of bulk synthetic pharmaceutical products. The priorities of production programmes for synthetic pharmaceutical products in bulk should be based on the volume and value of the products to be produced, their medical relevance, the economic aspects of their production, and the technologies available. UNIDO has prepared a list of essential drugs to be produced in developing countries, and this list should be considered for these programmes.

6. Promotion of the installation of plants for the manufacture of drugs in bulk by means of more sophisticated processes. Antibiotics may be classified under this heading. The production of antibiotics by fermentation calls for the technological integration of knowledge and experience in various fields (industrial microbiology, genetics, biochemistry, organic chemistry, analytical chemistry and bio-engineering). Moreover, continuous and consistent studies relating to the improvement of yields are much more important than in the above mentioned fields.

The following recommendations may be made on the basis of this grouping of possibilities for the drugs industry and taking into account the different levels of integration in the subregion:

a. At individual country level

Support of private or public initiatives for the realization of the above mentioned requirements, with the emphasis on priorities. The priorities cannot be listed arbitrarily, since they are the result of the specific problems of each country but, in general terms, they should be fulfilled in the order in which they have previously been listed.

It should also be explained that the extent of subregional cooperation becomes more complex, but also more necessary, in respect of points 4 to 6 in the list. This is due to a fundamental factor, namely, the minimum size for a plant. Well established cooperation will assist the rational distribution of opportunities, avoiding duplication.

On the other hand many of these activities require the joint participation of various private or public bodies to deal with the risks encountered by any new operation. These risks should be covered by feasibility studies, specifying the incentives required for these projects, especially in the initial stages. Moreover countries should be aware of both the short and long-term growth prospects for the pharmaceutical market, which will eventually justify investments, producing in return not only the profits inherent in the operation, but also national benefits, basically less dependence on imports, resulting in the reduction in the use of hard currency.

In general terms governments should give full support to all projects connected with this activity in areas where their presence is specifically required. Laws promoting the installation of new plant or the expansion of existing equipment and economic and financial backing - which should not be mistaken for protection, since this regrettably only supports inefficient operations in some cases. Industrial operations should also produce up-to-date products of internationally acceptable quality and which are applicable to health programmes.

Aspects associated with patents should be reviewed to ensure that an operation is feasible and that no restrictions apply.

At university level graduates should be suitably trained to qualify them for the various disciplines which are needed.

The work of the research and development centre should be backed up by local measures, as this is the only way to ensure action at subregional level.

Recommendations for individual countries may be summarized as follows:

COSTA RICA

Retention of the quality control policy implemented by the central laboratory, with the necessary support for the increase of local production of pharmaceutical products, which only exists on a small scale, despite the motivation offered by state health programmes.

Planned research into local sources of drugs of natural origin and also research into industrial pharmaceutical technology.

CUBA

The mission noted that the pharmaceutical area was fully active, both in respect of the academic fields of research and development and also of industrial operations. Plant for the production of semi-synthetic penicillins, already in operation, and plant for multipurpose synthesis, in course of construction, will give the country the opportunity to meet product requirements at subregional level.

The current position of its pharmaceutical industry, with the certain possibility of total integration, is in contrast to most of the countries, suggesting suitable feasibility studies for the incorporation of a fermentation unit in its industrial synthesis centre. In view of the very special characteristics mentioned it is highly probable that a plant, smaller than that which is considered to be of minimum dimensions under other conditions, may be justified without detriment to achieving optimal production costs.

GUATEMALA

Despite a high level of local pharmaceutical production it is recommended that backing be given to the industries which, although they have reached a certain stage of advancement, have not started to manufacture pharmaceutical products based on antibiotics.

It is therefore considered that evaluation studies of the current pharmaceutical market should be carried out, and recommendations made.

The level of current pharmaceutical activity suggests that more research should be devoted to the areas of industrial pharmacy and synthesis using chemical compounds with pharmacological activity and products of natural origin.

GUYANA

The solid efforts now being made to increase significantly the level of output of pharmaceutical products should be continued, without detriment to the extension of analytical quality control procedures, especially as the exporting of products is envisaged. Initiation of a line of research on topics connected with these activities at university level would also be justified.

HONDURAS

Greater self-sufficiency in the pharmaceutical area is also being achieved in this country, involving not only production at a public institute and also on the basis of a public/private partnership, but also the extraction and purification of an active principle of natural origin and the installation of a pilot pharmaceutical plant at the university.

The activity in the case of the natural drug shows a distinct level of integration, from the chemical aspect of elucidation of structure to its marketing at international level as a medical speciality, including pharmacological, clinical and botanico-agricultural studies.

It is reasonable to suggest that studies of other possible natural active principles be continued, making use not only of the wide experience obtained but also of the existing research facilities, both in terms of material infrastructure and human resources.

MEXICO

The varied range of intensive and up-to-date scientific and production activities does not call for any specific and fundamental recommendations, especially as the appropriate department of L.A.N.F.I. is planning an increase in its material and human resources.

Two suggestions may, however, be made. The first relates to an integral study of the causes of high production costs of drugs in bulk, which makes it difficult to export them at competitive prices; these causes are attributable to technology and other factors. The second is a greater degree of centralization of research programmes in disciplines associated in one form or another with the production of antibiotics, in order to avoid both duplication and gaps.

NICARAGUA

The pharmaceutical industry should not only increase its output in order to cover a higher proportion of local requirements, but also increase the number of manufactured products to include antibiotics.

It is proposed that quality control of local or imported manufactured products be improved. If this cannot be implemented rapidly, for economic reasons, the possibility should not be overlooked of fulfilling this recommendation by contracting these services at subregional level since such facilities do exist.

It is recommended that the pilot plant for the production of drugs by formulation at the university be retained and developed, as this is also an excellent opportunity for the promotion of research in industrial pharmacy.

The planned multipurpose plant should also be finalized, so that production of drugs by synthesis may commence in the country, whilst projects for the extraction of active principles of natural origin should also be completed.

PANAMA

This country is also working effectively and intensively in pursuit of points 1 to 3, with the objective of proper planning of requirements and adequate control of quality and registration of pharmaceutical products.

Steps are also being taken to increase local production capacity of pharmaceutical goods.

It is proposed that the microbiological research programme be intensified, in order that other lines of research specifically related to antibiotics be added to current projects, some of which relate to this field of investigation.

b. At subregional level

All countries, with the exception of Mexico, and despite their increased needs due both to population growth and the continuous influx of more inhabitants into the areas of access to drugs, still do not have sufficient drug requirements over the medium term to justify the installation of plants in these countries, nor coverage of all products. Unilateral development of activities would lead to production surpluses of some of the products required and shortages of others.

The mission realizes that it is much easier to make these recommendations than to implement them, but it remains totally convinced that without such subregional planning the success of many enterprises may be limited by the relatively small size of the individual markets.

The subregion also needs to eliminate certain customs barriers which cannot be justified in this type of trading, although valid in other fields, and also standardize policies in respect of patents in the pharmaceutical sector.

As well as this planning role the subregion should also stimulate multinational studies and operations which involve a high degree of integration. The pharmaceutical industry offers many possibilities for this type of operation, since processes can be integrated throughout by multiphase technology. Thus a natural product extracted in one country may be processed by chemical methods into another substance in a second country, whilst a third may carry out its pharmaceutical formulation. A country may specialize in the production of a particular raw material which, in turn, may constitute an input for a second.

There are examples of favourable experience in this respect. One of the most recent instances is the integration of pharmaceutical needs by the various countries in the Caricom group, resulting in greater benefits due to the larger quantities purchased.

It may be concluded from the evaluation made of study and research centres in the subregion, details of which are given in the relevant section, that the intensity and extent of their activities lead to the assumption that integration based on cooperation by all of them, for a common purpose, can be achieved by subregional action directed towards the utilization of this potential.

Whilst this mission has a very precise objective, namely to obtain the greatest amount of data on which to base definitions, it is considered that these recommendations should also indicate the many possibilities for the subregion, which are not being fully exploited, very probably due to lack of communication. It has been shown that studies and even activities carried out in a country which satisfy its priorities have remained unused, whereas it would have been extremely interesting to pursue lines of cooperation with another country.

It was with real satisfaction that this mission uncovered facts which could be of great use if divorced from the national level and applied at subregional level. It was also found that all countries could assist each other. Examples can be given. A study of the market carried out in one country at the highest scientific level would fill a gap in others. It would simply be necessary to transfer the computer program so that others could obtain the necessary data.

Research skills in respect of natural products in one country and marine products in another would be another example. The excellent quality control work and bio-availability practised with ease in one case could be extended as services to others.

Moreover, an analysis of the production needs for antibiotics obtained by fermentation over the short term indicates a shortfall of the order of 1,100 tonnes of penicillin, 330 tonnes of tetracyclines and 36 tonnes of erythromycin. The shortfall in semi-synthetic penicillins will reach 180 tonnes. In ten years needs will have doubled. Countries where current consumption is below the minimum economic size for a plant will feel the need to install their own production centres, without seeking the cooperation of certain other countries. If the times relating to the implementation of a research and development centre are listed in the form of a time-table followed by those for a production plant, no further recommendations will be necessary, except for the compilation of a very active programme in order that an important stage will have been completed by the time needs will have doubled.

However, the Centre should also provide several complementary services, which could be implemented very quickly, and which the subregion needs today.

These services are fully defined in the section dealing with the design and organization of the Centre. In these recommendations referring to the Centre we will briefly list the areas of activity in which it is proposed that the Centre be engaged:

1. To provide technical, commercial and legal information.

2. To make available expertise so as to advise the subregion, via evaluations, meetings and solutions to specific problems in various areas, such as: Pharmacotechnology, Fermentation, Synthesis, Manufacturing Standards, etc.

3. Research and development relating to each phase of new technologies, new microbial strains, operating techniques, etc. Improvement of existing technologies. Replacement of traditional raw materials by others which are genuinely autochthonous. Production of plans for improved procedures.

4. Technical assistance, from initial training to refresher courses and availability of experts for the resolution of unforeseen problems at the production centres.

5. Assistance with economic, financial and legal problems, such as feasibility studies, technical certification of these, costs, negotiation of technology contracts, etc.

These recommendations concerning the field of activity should be supplemented by a careful selection of the senior staff of the Centre in all the various posts so that, with their own individual areas of knowledge being fully integrated, the Centre is able to produce results of high scientific and practical value.

In regard to these recommendations for the Centre it will be appreciated that much of this subregional activity already exists in the area. It is entirely possible that each of the items of work, when considered individually, may appear to be inadequate to solve the problems presented by the various specialities. Taking the broad view, however, the subregion possesses a considerable investigational infrastructure which, if efficiently utilized by the Centre, could multiply the results.

In saying this the mission is not suggesting that the Centre should control each of the investigational groups but, on the contrary, that requests be made that the existing activities should support it and that any duplication by the Centre of work already carried out should be avoided.

For this reason the Centre must maintain very flexible contacts with the investigational groups in the subregion and also with the industrial sectors (private and public) and with State bodies. It is therefore recommended that seminars, training courses and meetings be organized between all the various sectors listed above. In definitive terms the subregional Centre must fill the existing gap, providing an ongoing integration function.

c. At the level of international organizations

All the above-mentioned aspects require, in many cases, access to knowledge which the countries cannot always obtain for themselves. In other instances the scale of projects poses financing problems. It may also be difficult, on occasions, to obtain reliable and complete information.

All these aspects call for the participation of international agencies which promote projects and catalyse their implementation and also provide support for existing industrial activities by injecting the necessary vigour for the conquest of effective gains.

INTRODUCTION

This report has been based on material obtained by the mission, together with statistical data obtained from national counterparts, and on direct observations made during the many interviews with a wide range of top level representatives in industrial, academic and educational professions and in research, in connection with the objectives of this project, and Ministries of Health, Planning, Industry and Trade in the countries visited.

The purpose of this mission was to discover the problems, achievements and potential of the individual countries in question, as well as their role as members of the subregion.

This subregion comprises Mexico, Central America, Panama, the Caribbean and Guyana. Visits were made to the following countries:

Costa Rica
Cuba
Guatemala
Guyana
Honduras
Nicaragua
Mexico
Panama

The principal and final objective of this project was to establish a subregional Centre for Research and Development on Antibiotics.

This project is sponsored by the United Nations Provisional Fund for Science and Technology.

The Centre aims to fill the technological vacuum in the subregion in question by providing technologies, which are competitive on a worldwide scale, for the manufacture of antibiotics by fermentation and also by semi-synthesis.

The Regional Seminar on Industrial Applications of Microbiology, sponsored by UNIDO, which was held in Havana in July 1979, recommended a plan of action with a view to accelerating the process of expansion of the pharmaceutical industry and its vertical integration in developing countries, including the establishment of at least two Research and Development Institutes equipped with a Pilot Plant, the activities of which would lead to the development of new technologies, improvement of existing technologies, preparation of human resources and the replacement of traditional raw materials by others of a local nature. The result of all this would be to place the subregion in a better position to make its own decisions, to reduce dependence on imports to a minimum and enable the subregion to be capable, in time, of covering the increased demand for pharmaceutical products based on antibiotics which, according to estimates, will have quadrupled by the end of the century. Requirements in respect of penicillin, tetracyclines, erythromycin and semi-synthetic penicillins alone will total about 7,000 tonnes per annum. This is attributable to an increase in the population of the order of 2.9% and a daily increase in the number of inhabitants of this subregion with access to the respective governments' health programmes. The guidelines for the mission's activities in each country, and the support which these should receive from governments through the national counterparts was discussed and approved at the meeting held by the Advisory Group in Mexico on 20th and 21st August 1981, in the presence of members of the mission and presided over by Dr. Tcheknavorian.

The national counterparts at this meeting received suggestions on ways of assisting the mission, covering amongst other aspects contacts with relevant areas of production, planning, health, trade and industry and universities and research centres. The setting up of a National Commission to inform officials in the above mentioned areas rapidly concerning the precise reasons for this project was also advocated. It should also obtain the required information from questionnaires on patents, raw materials of local origin, university study plans, etc.

As a result of this collaboration the mission had full access to all sources of information and contacts at high level, and intelligent, impartial answers were given to the questions raised.

The mission collated the information obtained during the course of the itinerary, but endeavoured to form no preconceptions until the end of the tour, in accordance with the objective nature of its function.

At this point, the problems of the subregion were identified at national and subregional level, and were considered not only in terms of the manufacture of antibiotics in bulk, but also in respect of the entire sphere of integration of the pharmaceutical industry. It was found that, in general terms, problems throughout the subregion have a common denominator, which is the continuing high level of dependence on outside services, despite the fact that conditions and potential in the subregion are both positive and favourable. The extent of the problem and priorities do, of course, vary from country to country.

The report endeavours to define clearly the individual, subregional or international nature of the problems, achievements and future potential in the cases in question. It also seeks to show the effect of time by defining activities over the short, medium and long term.

The problems facing the subregion at national level have been defined as being the relatively small size of the market in each country, with the exception of Mexico, thus calling for subregional cooperation as a prime necessity in order to combine the needs of various countries.

Another problem is the excessively high production costs at production Centres in the area; these do not permit exporting or trading at regional level. These costs can be reduced once reliable and up-to-date technology is available.

Nevertheless, the future appears very promising if the high growth pattern of requirements and a firm policy by all governments to expand their health programmes are maintained, since this will lead to increased demand and eventually the need for more and larger plants. The high calibre of human resources available is another positive factor, with excellent university training facilities in the relevant disciplines, and also a fairly good research level. The availability of raw materials for use in modified form with suitable technologies is another favourable finding. All these positive aspects (without which the possibilities of success would be very relative) emphasize the need for a Centre which will fill the technological gaps in the subregion.

In fact, although there has been considerable progress in the production of antibiotics by fermentation and semi-synthesis in Latin America, especially in comparison to underdeveloped areas of the world, it should be noted that various producers have unfortunately ceased manufacturing operations for different reasons.

It must be concluded that the pharmaceutical formulating industry has also not been fully successful.

The common denominator of these drawbacks is the lack of competitiveness of local industry, which is unable to supply products under standard cost and quality conditions.

This situation is attributable to lack of up-to-date technologies, as well as other factors such as patents, lack of local support in opposition to the subsidies which many manufacturers obtain in their countries for the exporting of output to the region, local taxes on critical production requirements, etc.

This subregional weakness will continue to become more critical, for, as has already been stated, the market may have quadrupled within a very short time, on the basis of an annual increase in the population of the order of 2.9% and access by more people to more sophisticated drugs.

The complexity of these problems has been explained in the report, and recommendations given which could be implemented over the short term, whilst others would evolve over the medium and long term. The recommendations quoted cover a broad spectrum, thus completing those relating specifically to the development of technologies.

The sections of the report may be subdivided into three parts. The first includes a summary, recommendations, conclusions and introduction. It covers the main points of the plan, defining objectives, the current situation and the means of achieving these objectives.

The second part covers all the general factors connected with various aspects of antibiotics, separating elements of a global nature from those specifically relating to the subregion. It also includes an evaluation of these elements in the light of the mission's activities in the subregion.

The final part defines the Research and Development activities of the Centre, its broad range of Technical Assistance and its subindustrial plant.

PART I

GENERAL ASPECTS OF ANTIBIOTICS

A) THE ROLE OF ANTIBIOTICS IN MODERN MEDICINE AND THEIR SOCIAL IMPACT IN DEVELOPING COUNTRIES.

The discovery of penicillin in the forties opened up a new era in the treatment of infectious diseases and a new approach to the search for chemotherapeutic agents. The introduction of the use of penicillin for therapeutic purposes was rapidly followed by the discovery of streptomycin and extensive research programmes on micro-organisms in the soil, and other less common sources, as potential producers of antibacterial metabolites.

During the forty years following the discovery of penicillin some thousands of antimicrobial substances were identified in the broth cultures in which the isolated micro-organisms were fermented. Only a small percentage of these exhibited the necessary characteristics for human therapeutic uses.

Practically all antibiotics currently used in clinical medicine belong to families of agents which were discovered during the period 1940 - 1960, as can be seen from Table 1.

TABLE 1 - YEAR OF DISCOVERY OF STRUCTURAL CLASSES OF ANTIBACTERIAL ANTIBIOTICS

YEAR	CATEGORY	FIRST MEMBER DISCOVERED	FIRST MEMBER USED CLINICALLY
1929 - 1940	Penicillins	Penicillin F, G, etc.	Penicillins G and V
1939	Clinical peptides	Tyrothricin	Tyrothricin, Polymyxin, Gramicidin, Bacitracin.

1944	Aminoglycosides	Streptomycin	Streptomycin, Neomycin, Kanamycin, Gentamicin, Paromomycin, Spectinomycin
1947	Chloramphenicol	Chloramphenical	Chloramphenicol
1948	Tetracycline	Chlortetracycline	Chlortetracycline
1950	Macrolides	Picromycin	Erythromycin
1955	Lincomycin	Celesticetine	Lincomycin
1956	Novobiocin	Novobiocin	Novobiocin
1956	Cephalosporin	Cephalosporin C	Only semi-synthetic antibiotics (Cephalothin, Cephaloridine)
1959	Rifamycins	Rifamycin B	Rifamycin S.V.

The period 1960 - 1980 was characterised by a new strategy in the search for antibiotics. As a result of the reduction in the number of completely new antibiotics discovered research efforts were directed towards increasing the chemotherapeutic properties of antimicrobial substances by means of chemical modification.

This approach produced derivatives of the original antibiotics, commonly known as semi-synthetic antibiotics, and constitutes a major advance in the conquest of infectious diseases. Examples of the semi-synthetic antibiotics developed are given in Table 2.

TABLE 2 - MAIN SEMI-SYNTHETIC ANTIBIOTICS DISCOVERED SINCE 1960 AND CURRENTLY USED IN CLINICAL MEDICINE

ORIGINAL	SEMI-SYNTHETICS
Penicillins	Penicillinase resistant: Methicillin, Oxacillin, Cloxacillin, Dicloxacillin, etc.
	Acid stable, oral: Pheneticillin, Propycillin, etc.
	Broad spectrum: Ampicillin and its derivatives, Amoxycillin, Carbenicillin, etc.
	Injectable: Cephalothin, Cephapirin, Cephacetryl, Cephaloridine, Cephazolin.
	Injectable, active against B-lactamases Gram-negative: Cefamandol, Cefoxitin, Cefuroxime, Cefazedone.
	Oral: Cephaloglycin, Cephalexin, Cephradin, Cephachlorine, Cephadroxyl, etc.
	Recently introduced: Cefotaxime, Oxacephalosporin.
Aminoglycosides	Amikacin, Dibekacin.
Tetracyclines	Doxycycline, Methacycline, Minocycline.
Lincomycins	Clindamycin.
Rifamycins	Rifampicin.

The impact on the mortality index and the duration of the period of illness as a result of the introduction of antibiotics in the therapeutic treatment of infectious diseases has been spectacular. The mortality rate for some diseases, such as meningococcus or pneumococcus meningitis and subacute bacterial endocarditis, for example, which was 100% before the era of antibiotics, has fallen to less than 10%.

In other fields, such as tuberculosis, the mortality index has been reduced from 50% to below 10%, whilst the duration of the disease has fallen from 18 - 24 months to 6 - 9 months with suitable therapeutic treatment.

Despite these significant results bacterial infectious diseases are still one of the major causes of death; in developed countries they are listed in third place after cardiovascular and tumoral diseases. For this reason research still continues throughout the world to discover and improve new antibiotics by fermentation or semi-synthesis, with the objective of improving the chemotherapy of infectious diseases (improvement of efficacy against resistant strains or against more insidious bacteria which are less vulnerable to antibiotics, reduction of secondary effects, etc.).

It should however be mentioned that some of the new semi-synthetic antibiotics introduced in therapeutics have a less important chemotherapeutic effect than could be obtained under certain special circumstances; in many cases the commercial success of new antibiotics is not directly related to the real medical need. Thus a number of antibiotics introduced many years ago still constitute the therapeutic basis of treatment of many diseases.

Representative publications such as "Medical Letters", 1980.22.2.5 and Goodman and Gilman: The Pharmacological Basis of Therapeutics, 6th Ed. 1980, list the following main antibiotics used for the treatment of the majority of infections due to Gram-positive and Gram-negative bacteria, Chlamydiae, Micoplasm, Rickettsiae and Spirochetes:

Penicillin G
Semi-synthetic penicillins (broad spectrum, penicillinase resistant)
Tetracyclines
Erythromycin
Streptomycine
Chloramphenicol
Gentamicin

It is therefore vital that these antibiotics be made available to all people, without distinction. However, due to varying socio-economic situations throughout the world, there still exist populations without access to these essential antibiotics. These circumstances, together with other concomitant adverse factors (malnutrition, hygiene conditions, etc.) explain why the beneficial effects of antibiotics on mortality and morbidity rates have been less dramatic in developing countries than in industrialized areas.

These drugs must be made available at low cost for the purposes of the implementation of the "Health for all by the year 2000" programme. These essential antibiotics account for a high proportion of the cost/benefit ratio and it is therefore highly reasonable to give them priority. If this reduction in costs is achieved developing countries will also have access to more expensive drugs when their use is necessary from the medical standpoint.

B) SURVEY OF THE ANTIBIOTICS INDUSTRY

b.1. General

From a practical point of view the antibiotics industry should be considered as a fermentation industry. Only one widely used antibiotic, chloramphenicol, is obtained by a purely chemical process. The remainder are largely based on the fermentation method, although chemically-based processes are used at some stage of their production.

This is a highly sophisticated industry, but one which also calls for a greater accumulation of various specialities or disciplines.

It should also be said that it is one of the industries in which the greatest progress has been made, is still being made, and will continue to be made.

Prospects of improvements regarding antibiotics produced by synthesis can be determined from very simple parameters. If the combined yield is 80%, this only leaves a hypothetical improvement of 20%. The theoretical improvement compared with former results is analysed in the case of antibiotics obtained by fermentation, rather than the value of the possible improvement. If, for example, production of penicillin is expressed in units/ml of culture medium, it will be seen that improvements over the past 35 years have been:

Initial	:	200 units per ml
Recent	:	50,000 " "
Improvement	:	250 times

And expressed in terms of conversion values:

Initial	:	grammes of penicillin per gramme of glucose: 0.005
Recent	:	0.120
Improvement	:	24 times

Unfortunately, whilst this 0.12 grammes/gramme indicates improved yields there is still much to be achieved.

Certain important conclusions may be deduced:

1. As there is still much room for improvement, time and money should continue to be invested in development and research programmes.

2. As long as only a low percentage of that which is theoretically possible is achieved, no industrial operation can consider itself to be established, since it runs the risk of losing its market share if a rival company overtakes it by introducing more advanced production technology.

3. The sector where improvements could be achieved is the fermentation sector, not the chemical extraction area, since yields in this latter field are much closer to theoretical values for an industrial operation, using relatively small concentrations of antibiotics in the culture broth and a rather unstable active principle.

4. In general terms each improvement necessitates the addition of one more complication to the process, which upsets the existing economic equilibrium. If less raw materials are used, but the operation becomes more complex, running costs may increase by an amount which cancels out part of the economic value of the use of less raw materials.

5. The ratio of direct costs to total costs is very low compared with the chemical industry, even where highly sophisticated procedures are used. That is to say that total input costs (raw materials and energy) are very high for the production of antibiotics by fermentation. Fixed costs are much higher. The same applies to investment expenditure, not only in respect of the intrinsic cost of equipment, but also the low productivity of the fermenters. One batch takes no less than 180 hours to complete, and the concentration of antibiotics per litre of culture medium at the end of fermentation is no more than 40 gr. per litre. In pure synthesis batches take no more than 12 hours to complete, whilst the concentration of active principle is never less than 200 gr. per litre.

6. The use of various disciplines in the integration of the entire process is also a difficulty to be overcome.

7. The processes are very evolutionary, that is to say results will always vary unless a strict operating discipline is maintained and/or suitable control measures are applied.

Having thus defined the antibiotics industry, we will now list the areas of investigation which should be pursued, not only in order to initiate an industrial operation but also to enable it to retain its initial position once it is under way, and to provide a flow of scientific data which ensures its continuing economic efficiency.

The areas of research and evaluation of possibilities should cover the following points:

1. Technology
2. Human resources
3. Size of the operation

Technology

Technology embraces a range of disciplines which are integrated for one purpose, namely to achieve maximum productivity with minimum investment expenditure, both in terms of fixed assets (investment) and the use of consumables.

If we assume that an antibiotic is a metabolite produced by a micro-organism it may be concluded that the micro-organism forms the basis of the economic results of the operation.

On the other hand, if the micro-organism calls for certain elements for the purposes of greater efficiency, it must have the backing of technology.

However, one is dependent on the other. A modification of one certainly affects the other. There is therefore a need for integration, which is not always easily achieved, since each area considers its own contribution to be a determining factor and, even when those in charge of research achieve the desired integration, they must then convince those responsible for production of the desirability of the innovation and, if the modification implies investment expenditure, quantify the economic return. This is not to say that this does not apply in other disciplines, but not to the same extent and not at such conflicting levels. The importance of fully amalgamating research and production activities to ensure that improvements made are quickly realized can be demonstrated from a purely commercial aspect.

Scientific discoveries which have dictated the increase in general efficiency have not followed an ordered sequence. The main fields may be summarized as follows:

Microbial strain
Improvements in the culture medium
Aeration
Rebalancing of the medium
Improvements in the inoculation stage
Programmed addition of nutrients.

At the present time we would define, as the main areas of research, the strain and improvement of the process.

Of the two the main prospects lie in the field of genetic developments with a view to obtaining a strain which increases productivity without raising the cost of the inputs or the services required (stirring, air, quality control).

The other area of research, technology, which strives to reduce costs, is not always positive, since some of the parameters for improvement can only be resolved by investment. On the other hand the possibilities of substantial improvements are more remote, since technological progress already made in some operational areas has almost reached the maximum practicable limits.

Human resources

The production of antibiotics involves many specialized fields. If any one of the broad spectrum of specific activities does not function efficiently then all are affected. It may therefore be concluded that uniformity of human resources, which is important in all activities, is especially critical in this industry.

Size of the operation

If it is assumed that direct costs for the production of antibiotics are of the order of 30%, the remaining 70% will relate to the size of the operation. The manufacture of antibiotics is not a repetitive operation: production of a batch is a very lengthy procedure, involving various stages, and many decisions have to be taken with watch in hand as well as continuous analysis of data. In many cases decisions are analysed by computer. The entire range of operations connected with fermentation is more or less independent of volume. The same group of people is able to supervise and decide on the necessary course of action for one or several fermenters. It does not matter whether the capacity of the fermenter is 5 m^3 or 250 m^3. Thus within a certain range output may double and the cost fall significantly (in theory by 35%), but the curve of the cost/volume relationship tends to be asymptotic, and this criterion should therefore never be used with general factors extrapolated from other operations.

b.2. Subregional

Production of antibiotics by fermentation in the subregion was started in Mexico over twenty-five years ago by the subsidiaries of multinational companies, so placing this country amongst the leaders in this discipline within the developing countries. Years later companies backed by local capital were incorporated. All essential antibiotics are in fact now being produced. Of the three main factors (strain, technology, human resources) we would say that the first two have been brought from abroad, whilst genuinely local human resources are currently being used, although training and qualifications at executive level are also acquired abroad.

It should, however, be noted that, except for vital work on conservation of the strain, there does not exist at the plants any line of development of sufficient scope as to presuppose the existence of highly advanced operations, backed up by the latest innovations.

The despatch of more active and up-to-date strains from head offices or microbiological centres ensures that operations are maintained at a relatively competitive, but not optimal, level. The lack of integration of disciplines already mentioned can be observed, as the equipment does not have the level of automation nor the requisite instrumentation essential for maximum performance.

This factor assumes greater significance if the size of the plant is taken into consideration. We have estimated the cost sectors which depend on the size of the operation at 70%. Fermentation plants in the subregion are at the lower size limit, from the strictly economic aspect. It is therefore more important to improve the intrinsic efficiency of the process, which bears no relationship to the level of operation. Size is not always a determining factor for a production unit, since concomitant factors (market, financial capacity, etc.) cannot be changed, but efficiency can be improved: an efficient operation of limited size can be competitive.

b.3. The role of research and development

The production of antibiotics on an industrial scale cannot be maintained without continuous development work, and this in turn is fed by scientific knowledge resulting from research. This

must be interpreted from an economic approach. It should, however, be noted that, despite the fact that the world level of output of antibiotics has increased by almost 100% in the last twenty-five years, the number of companies engaged in this activity has decreased by a third. This has occurred gradually in the majority of cases, but the technologies used by organizations which do not maintain a level of research in accordance with the complexity of the topic on the one hand, and the scope for progress on the other, continue to become out of date.

Drugs produced by techniques other than fermentation do not, of course, necessitate such a high level of development and research. A producer of ampicillin from 6-APA with an optimal chemical yield only has to seek qualitative improvements (elimination of impurities) and economic improvements (less and cheaper raw materials, less energy), but will confidently be able to face the possibility of the emergence of considerable competition in respect of prices. This is not the case with fermentation. The possibilities for major improvements will continue to exist and will be achieved by those with permanent access to these improvements.

This may be attained in the subregion by the activities of the Centre in the fundamental cost areas:

- Strain
- Operating techniques, appropriate to the strain
- Energy: electricity, fuel
- Low cost raw materials
- Efficient human resources at all levels.

C) PATENTS

Protection of the results of development and research by obtaining world-wide patents is an important part of the strategy of leading pharmaceutical companies for the retention and expansion of their market share. As a direct result of the concentration of innovatory activities in such firms the registration of patents is dominated by a small number of such companies.

With regard to patents for antibiotics the four leading pharmaceutical companies hold 53% of all patents issued during the period 1965 - 1970. Only nine firms were granted ten or more patents in this field during this period*.

The patentability of pharmaceutical products is recognized by most developed countries. Some of these countries introduced this form of protection as soon as their pharmaceutical industries had achieved major developments in this field (France 1959; Federal Republic of Germany 1968; Japan 1976; Italy 1978).

However a large number of developing countries only recognize protection for processes used for manufacturing pharmaceutical products+. In other cases all protection by means of patents has been abolished (this applies to Brazil, Mexico and Ecuador). In other countries, such as India and Costa Rica, pharmaceutical patents are subject to special conditions in relation to their duration, scope and the existence of statutory licences.

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* See D. Schwartzmann. Innovation in the Pharmaceutical Industry. John Hopkins University, 1976, Tables 6 - 8 and 6 - 9.

+ See table

In general terms the limiting of the protection given by pharmaceutical patents is based on the conviction that "The overall impact of patents, especially when they also involve some form of product protection, is not beneficial for the rational and well-balanced development of the pharmochemical industry in developing countries. Protection by patents does not promote foreign investment nor local creativity, whereas their absence can stimulate the adaptation and improvement of technology locally and the gradual development of the manufacture of drugs in bulk".*

The impact of patents in the pharmaceutical industry and on marketing in developing countries depends to a large extent on the level of development achieved or desired in the country and the type of purchasing policy applied.

In countries where drugs are imported and/or only formulated locally, using imported raw materials, the existence of protection by patents compels private or state purchasers to buy them exclusively from the holders of the corresponding patents, thus preventing access to the international market. A clear example of the consequences of product patents under such circumstances was observed in Costa Rica. The Costa Rican Social Security Fund invited tenders for a certain antibiotic, subject to protection by patent in the country. The quotation submitted by the holder of the patent was 3.3 times higher than that of an Italian producer,

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* See UNIDO : "Relevant issues to be taken into account when negotiating transfer of technology agreements", ID/WG 331/2, page B.

who finally obtained the contract.* It is worth noting here that the difficulties encountered by the government in the purchase of pharmaceutical products caused Costa Rica to change the conditions of the issue of pharmaceutical patents drastically in 1978. Although patents for products and processes have been retained their duration is limited to one year, and the government was authorized to purchase supplies from sources other than patent holders when the prices quoted by the latter proved to be higher than those obtainable on the international market.

Under these conditions, that is to say where no raw materials are produced locally, the existence of patents for processes - provided they do not include the products obtained from them - does not in principle have any adverse effects. However the granting of patents for processes may be considered to be capable of adversely affecting the establishment and development of local capacity for the production of such products. In view of this situation, which only exists in a few developing countries at the present time, and in order to permit vertical integration of the industry and also the use of local resources, the best policy seems to be not to recognize either patents for products or processes, as has been the case in Brazil, Mexico and Ecuador during the last decade.

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* This led to a lawsuit brought by the holder of the patent (which was finally decided against the exporter of the product). See J.C. del Bello: "Technological dependence in the case of a Central American economy: Licencing agreements and Patents of Invention in Costa Rica". Technological Institute of Costa Rica. October 1979, page 113.

DEVELOPING COUNTRIES WHICH DO NOT GRANT PROTECTION BY PATENTS FOR PHARMACEUTICAL PRODUCTS

1980

ARGENTINA
BENIN
BOLIVIA
BRAZIL[a]
CAMEROON
CENTRAL AFRICAN REPUBLIC
CHAD
CHILE
COLOMBIA
CONGO
ECUADOR[a]
EGYPT
GABON
GHANA
GUYANA
HONDURAS
INDIA
INDONESIA[b]
IRAN
IRAQ
IVORY COAST
KOREA
KUWAIT
LEBANON
LIBYA
MOROCCO
MEXICO[c]
NIGERIA
PARAGUAY
PERU
SENEGAL
SYRIA
THAILAND
TOGO
TUNISIA
UPPER VOLTA
URUGUAY
VENEZUELA
YUGOSLAVIA

Notes: (a) Patents for processes are also excluded
(b) There is no patent law in Indonesia
(c) Processes cannot be patented, but an invention certificate may be obtained.

D) PRICE STRUCTURE

It is interesting to analyse some aspects of price structure in the area of bulk antibiotics.

Errors are often made by failing to take into account certain very special aspects of this activity.

Most antibiotics (with the exception of penicillin and streptomycin) were originally sold in their final pharmaceutical form as branded products. The price structure was based on vertical integration, whereby the sector producing bulk antibiotics did not sell the products in this form but transferred them to the pharmaceutical production area. Access to these drugs in bulk form was impossible, not only because of the marketing policy of the producers, but also due to the existence of patents for products and processes.

Antibiotics were branded products.

The majority of production plants in the subregion and in other developing areas were owned by transnational companies which applied this marketing policy.

With the expiry of patents, and due to the existence of countries which did not recognize patents, antibiotics in bulk form began to appear on the international market at increasingly competitive prices as technological progress led to increased efficiency to offset increases in the price of raw materials, wages, electricity, fuel, taxes and financing costs.

Products became "commodities" and therefore subject to the following very special circumstances:

1. Absence of a secure market providing fair conditions to the typical supplier.

2. Temporary surplus stocks, with the result that goods are offered at lower prices.

3. Lack of stocks, due to accidental reasons, with consequent price increases.

4. Variation in quality.

5. Price expressed as kg of final product in many cases rather than as kg of active principle.

6. Existence of policies offering export incentives, allowing products to be sold at net cost in order to obtain the benefits of these incentives.

7. Market penetration programmes, seeking markets based on binational agreements.

It should not be inferred that competition would not result in a fall in prices, but it must first of all be understood that these advantages are not always reflected in the final product and, secondly, that they are rarely manifested in a similar way to negative factors. However these characteristics should not be ignored when carrying out a feasibility study for a project, as they may affect it, especially during the early years. It should not be forgotten that implementation of a project of this type is a lengthy process and ties up large capital sums. It should therefore be effective from the outset, and generous financial backing should be granted.

Another aspect to be taken into consideration is the existence of a double-edged weapon known as "drawback" which, from a positive standpoint, allows exporting by way of importing intermediate products, on which no duty is paid, and then rapidly processing these and selling them abroad, for a small investment. From the

negative aspect it favours a manufacturing industry to the detriment of a production industry which requires a large infrastructure, and thus leads to loss of local sales. The former exports labour and some services, whilst the second bases its activities in the country of origin.

The extremely favourable terms of financing obtained when purchasing goods abroad (up to 180 days) should also be noted, since this operates to the detriment of the cost of monetary assets in the subregion and in developing countries in general.

All these implications are mentioned objectively with the purpose of reaffirming the idea that the production of antibiotics in bulk should be efficiently managed to prevent the occurrence o such difficulties. This does not mean that these problems need necessarily be manifestations of unfair trading practices. They are simply problems which have to be taken into account and solved.

E) SIZE OF THE OPERATION : COST IMPLICATIONS

The size of the operation may be analysed from two aspects:

e.1. Technical
e.2. Economic

In each case reference may be made to:

F = Fermentation
SS = Semi-synthesis

e.1. Technical, Fermentation

There are no technical limits regarding the main parameters involved in the achievement of high levels of efficiency in fermentation which are affected by size:

Stirring
Air supply
Temperature control
control of pH
Sterility
Continuous collection and programming of nutrients, precursors and correctives.

All these are feasible, both with a bench top fermenter and with the largest industrial model. Moreover, there is no significant variation in the investment value per unit of volume.

e.1. Technical, Semi-synthesis

As in the case of pure synthesis the technical aspects of the operation are not affected by size.

e.2. Economic, Fermentation

The total cost of fermentation is significantly affected by the size of the operation.

If we analyse the elements included in the cost the following values will be obtained as a percentage of sales, assuming a high level of technical efficiency.

	SIZE	
	100 m^3	500 m^3
Direct (raw materials, energy, labour)	22.4%	24.5%
Recirculated (labour for services, maintenance)	30.6%	11.4%
Structural (fixed costs)	38.3%	34.0%
Profit before depreciation	8.7%	30.1%
Total cost US$/kg	38.3	27.9
Total sales at US$ 40/kg	4,500,000	22,500,000
Depreciation	1,200,000	5,000,000
Profit after depreciation	(1,008,750)	1,806,250
Total output kg/year	112,500	562,500
Investment	6,000,000	25,000,000
Profit on investment	-	7.2%

Although these are hypothetical values they are representative of the implications of the size of the operation in respect of results and their effect on costs. They indicate that the ideal fermentation capacity for a well-balanced operation would be of the order of 200 - 250 m^3 or 225 - 280 tonnes/year. It would be as risky to base conclusions on general factors obtained from large plants and reduced proportionately for a smaller plant as to apply the reverse procedure. A specific study must be carried out in each case, with production costs and the price structure calculated very carefully, especially in the case of small plants.

It should in any case be noted that the cost/size relationship is an asymptotic curve, extrapolations from which are only correct for one section. This can be seen from the curve in Figure 1.

It may be concluded from an analysis of all these factors that the smaller a plant, the greater are the requirements for the desired yield.

The subregion finds itself in this situation, so that it is doubtful if an operation can be successful in the absence of the latest technologies, which also reaffirms the thesis justifying the setting up of a centre capable of supplying these technologies.

Finally, a safe operating zone will be found in a compromise situation relating size to efficiency, as can be seen from Figure 2.

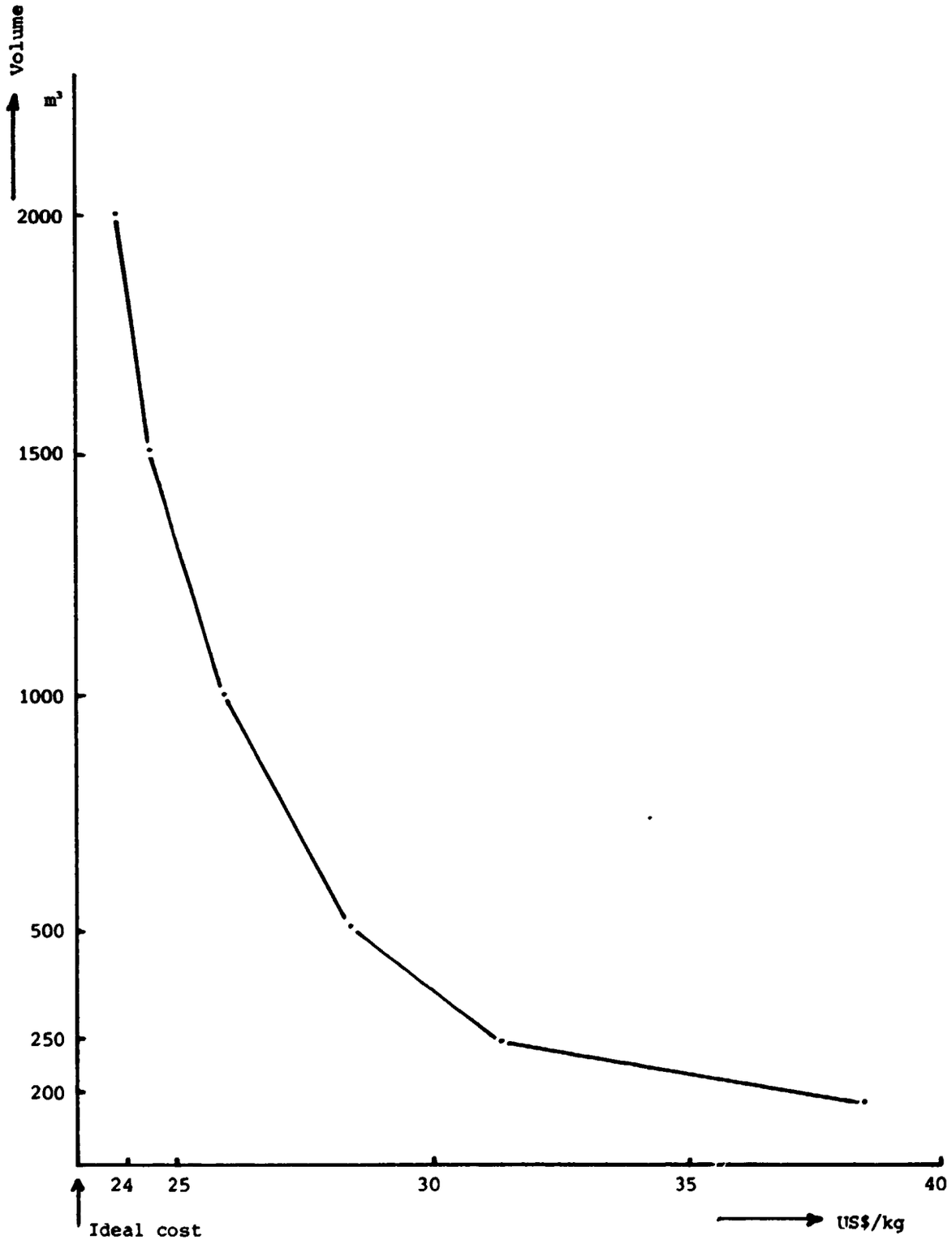
e.2. Economic, semi-synthesis

The case of semi-synthetic penicillins is very different, since the incidence of direct costs is very high and size is not as critical.

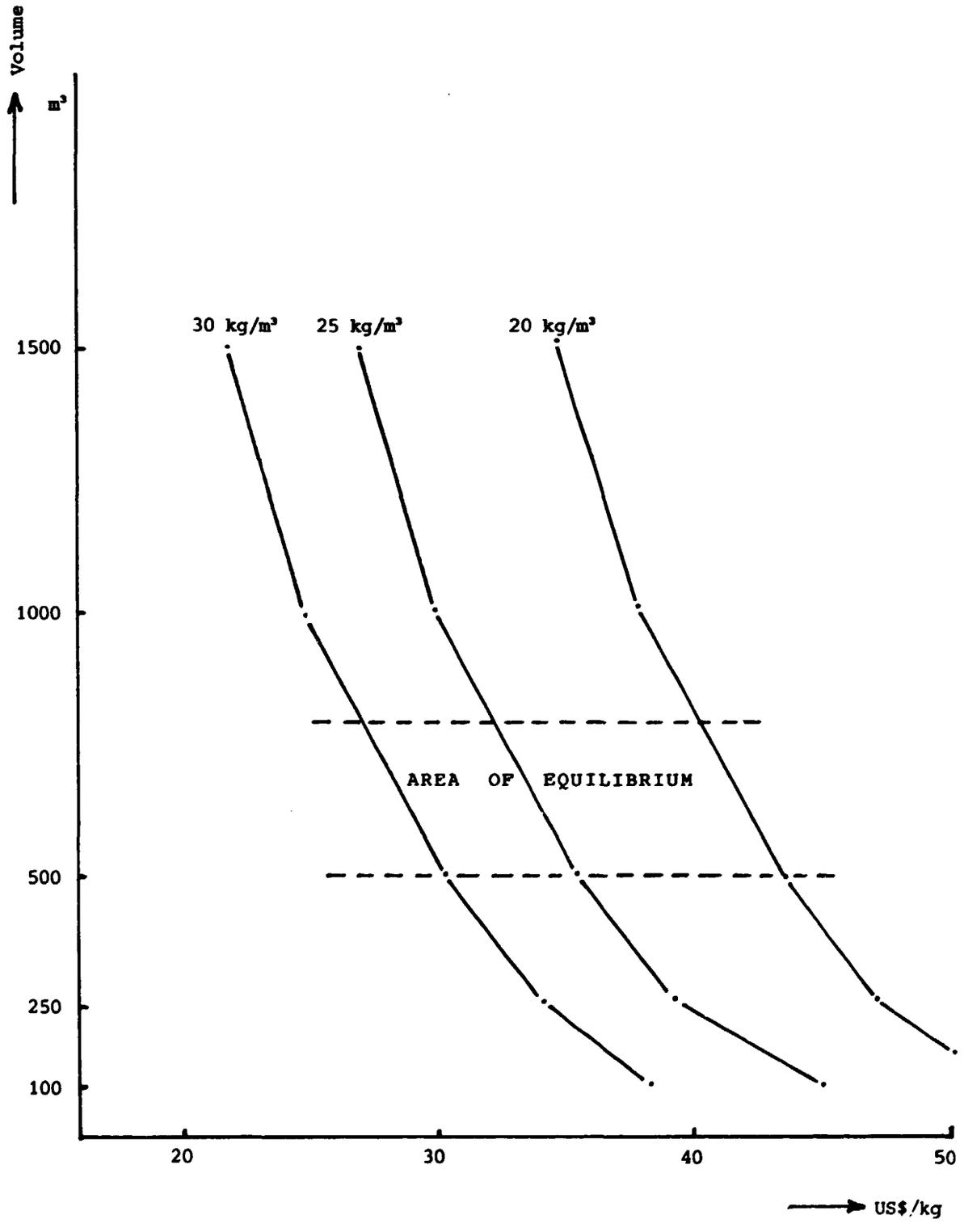
The cost structure for a semi-synthetic penicillin is as follows:

COST COMPONENT	PERCENTAGE OF TOTAL COST
Direct (raw materials, energy, labour)	80.0
Recirculated (indirect labour, maintenance)	10.2
Structural (depreciation, fixed costs)	9.8

GRAPH 1 : RELATIONSHIP BETWEEN COST AND VOLUME



GRAPH 2 : RELATIONSHIPS BETWEEN COST, EFFICIENCY AND VOLUME



All these values relate to plant specifically designed for one type of activity (fermentation-synthesis) and the production of antibiotics in the simplest form (bulk - not sterile - no derived products or more profitable commercial forms).

More interesting solutions can be found from thorough feasibility studies on the integration of various manufacturing operations, such as, for example, antibiotics in their final pharmaceutical form (capsules, sterile vials, syrups, etc.) and also integration of the fermentation plant with one for pure synthesis which not only produces antibiotics but also the more costly derivatives (insoluble penicillin salts, injectable forms of semi-synthetic penicillins, tasteless bases, etc.).

Furthermore if the integrated plant operates within a pharmochemical complex for the production of pharmaceutical products it can be demonstrated that the points of equilibrium apply to smaller sizes. What never varies is the need for the best technology available.

F) DESIGN

This topic should be analysed from two aspects: one specifically associated with production requirements, the other relating to the economic implications.

The first aspect merely calls for conformity with manufacturing standards, which do not vary as much for the production of antibiotics in bulk as for the manufacture of pharmaceutical forms. The most specific requirement relates to contamination between plants producing both penicillin and other antibiotics. Other operating requirements in respect of quality must of course also be observed.

All aspects of technical design, which must conform with the particular technology without overlooking general design principles, should also be mentioned, namely:

1. Capacity for extension

2. Flexibility for adaptation to new production alternatives.

3. Reliability

4. Easy maintenance which does not interfere with production operations

5. Protection of the environment.

With regard to the economic implications of design the incidence of fixed costs and depreciation on total costs should be taken into account; these are greater the smaller the size of the plant.

An analysis of the different sectors shows that there are two areas where the size of a fermentation plant does not relate greatly to volume: the microbiological sector and the extraction sector. In the fermentation sector, however, size is directly proportional to the desired capacity. It may therefore be supposed that fixed costs will always be fully absorbed in this latter area, whilst extraction may have a high level of inactivity. A balanced design of all sectors is then applicable without involving sumptuary or excessive investment expenditure. It should be noted that the cost of this type of operation can normally be expected to be written off within 5 years, and great importance is therefore placed on results.

Milan, 2 December 1981

NOTES ON THE PROPOSED INSTALLATION OF PLANT AT THE RESEARCH CENTRE

1) Area and volume

1.1 - The Centre comprises two different blocks, linked by a corridor:

- one block between the levels of -4 m and +9 m, where the pilot plant will be installed;
- one block between the levels +0.00 m and +9 m, where the laboratories, offices and services for personnel will be located.

1.2 - The respective areas are:

1.2.1. - Fermentation	160 m^2
- Pilot chemical plant	192 m^2
- Ionic exchange columns, solvent recovery and storage	192 m^2
- General services	156 m^2
- Workshop and storage of mechanical equipment	120 m^2
TOTAL area occupied by pilot plant	820 m^2

It should be noted that both the chemical area and the fermentation area are subdivided into various working levels (see plans OC-10-01; OC-10-02; OC-10-03; OC-20-01; OC-20-02).

The area in question therefore corresponds only to the horizontal projection of the area occupied by each department, without taking into account the metal grilles between working levels.

The total volume is as follows:

- Fermentation chamber	2,080 m^3
- Pilot chemical plant	1,728 m^3
- Solvent recovery, etc.	2,496 m^3
- General services and workshop	700 m^3
approximately	7,000 m^3

1.2.2 - The area occupied by the research laboratories is as follows:

- Chemical and analytical laboratory	740 m^3
- Microbiology laboratory (part of which is connected with the pilot plant)	740 m^3
- Manager's office, administration, services for visitors, etc.	277 m^3
	1,757 m^3

Corridors, stairs and other ancillary spaces are included in the above figures.

1.2.3 - About 100 m^2 must be added to the above figures for the boiler and water treatment section, as well as another 300 m^2 for tanks, effluent treatment, etc.

1.2.4 - The Centre will then require around 2,900 m^2, 2,500 m^2 of which will be within the two main blocks (floor area covered: 1,332 m^2) and 400 m^2 outside.

2) Main characteristics of the pilot plant:

2.1 - The main services production points (compressed air, cold water, brine at -20°C) are very close to the main installations, that is to say within the pilot plant.

The main electrical energy supply point is situated between the two services production centres mentioned, in order to reduce distribution costs to a minimum.

The calculated areas are sufficiently large to allow for future expansion, although part of the workshop area could also be used for expansion purposes if required.

The alternative of situating the services production points outside the area housing the pilot plant would be much more costly.

2.2 - The fermentation plant has been designed in "cascade" form for two reasons:

- in order to avoid any dead point in the unloading of the fermenters (with the exception of the 3,000-litre fermenter where the broth has to be pumped into the storage tanks). (Note 1).
- in order to utilize the area required by large items of fermentation equipment (3,000-litre fermenters) for the installation of various items of equipment for the separation of solids/liquids, without involving any excessive increase in the building area nor the use of land.

2.3 - The fermentation levels will be utilized as follows:

- level +5.50: 8 x 50 l fermenters (or 16 x 30 l fermenters) and 6 300-litre fermenters;
- level +3 : base of one 300-litre fermenter and upper section of 3,000-litre fermenter; centralized analytical facilities and computerized system, and possibly a thermostatically controlled bath for 5-litre fermenters (with corresponding autoclave).

  This level communicates directly with the microbiology department.
- level 0.00 : storage tank and press filter (or similar apparatus)

  This level communicates directly with the chemical department.
- level -2.50: rotary vacuum filters, decanters, centrifuges, etc.
- level -4/ -4.50: various units for the separation of solids/liquids (centrifuges, spray dehydrators, etc.).

2.4 - The chemical plant is subdivided into two levels ($\pm$0.00 and +2.50), the latter being used to house all the storage and mixing tanks, whilst the lower level will be equipped with various units for the treatment of liquids, freeze dryer, vacuum dehydrators, etc.

The adjoining department will house the solvent recovery (and will therefore be near the solvent storage tanks) and chemical equipment requiring large vertical spaces, such as the ion exchange resin columns.

This department will be subdivided into no less than three levels (+3,000, $\pm$0.00 and -4.00) to provide various possibilities for the organization of operations.

2.5 - Tanks for storage of used broth and recovery of solvent dissolved in the broth (azeotropic distillation or some other system) are situated near the chemical plant, so that the final biological treatment plant does not handle any solvent-containing broth.

2.6 - Space has been allocated in the basement for the workshop, which is absolutely essential for a centre of this nature.

The area is sufficiently spacious for the storage of mechanical parts (such as rods, pipes, steel sheets, etc.) and to allow additional space for future expansion of the services production centres (see 2.1).

Access to the workshop at level -4.00 will be via a ramp, and there will be enough parking space for manoeuvring of lorries.

2.7 - Simply operated apparatus for lifting the covers from the fermenters, including the largest units, should be installed in the roof of the fermentation section. The corresponding loads must be taken into account when calculating the strength of the roof, and the space between levels +3 and +9 should be without columns so far as is possible.

2.8 - It has been assumed that the Centre will not use any other existing installations, for example, an external heating source. A boiler room near the fermentation area has therefore been included in the design as a separate installation, integrated with the system for the chemical treatment of water which will be used in the Centre. Space for storage tanks for fuel and water has also been provided for in the design.

2.9 - The treatment of effluent should not pose any special problems at the Centre, given that:

- the amount of solid effluent will be very small;
- gaseous effluent may only pose problems (unpleasant odours) if the Centre is built in an urban zone, in which case these can be easily solved by building a suitable chimney.
- Liquid effluents will have to be treated in order to:
  - remove the solvents (see point 2.5);
  - reduce the biochemical oxygen demand by means of biological treatment;
  - eliminate any trace of antibiotic in case the water is discharged into the municipal water treatment system.

In this case additional chemical treatment units may be necessary. Nevertheless the volume of liquids used is very low (a few thousands of litres daily).

Liquid effluents from the chemical laboratories should preferably be stored in stainless steel tanks and the contents removed periodically and sent to special companies for the elimination of wastes by heat treatment.

3) Main features of the laboratories:

3.1 - Microbiology and genetics laboratory.

This laboratory occupies the entire +3.00 level, and communicates directly with the main level of the pilot plant.

For this reason ample space has been reserved for the preparation and sterilization of culture media and glass apparatus, etc., for the laboratory and plant.

As this is the main floor of the building the library and conference room will be installed here.

The central area of this floor has been designed for the installation of general services for the entire building (cold rooms, installations for distilled and deionized water) and for the specific needs of the microbiology laboratory (thermostatically controlled rooms, collections of strains, etc.).

3.2 - Chemical laboratory

This comprises the pilot chemical plant and the installations for the separation of solids/liquids from the fermented broth.

A very long and deep chemical laboratory has been designed which is situated next to the pilot chemical plant, in order to develop the production of semi-synthetic penicillins at laboratory level.

This level contains installations for the chemical and analytical laboratory; in this case the central space has also been utilized for the installation of the main items of general research and analytical equipment, such as balances, spectrometers, etc.

3.3 - General services

There will be washrooms on each floor; a spacious recreation room for staff has been provided at level +0.00.

A third partial level has been included in the design to house the general management, administrative offices and to provide rooms for visitors, advisors, etc.

This level may be extended to provide the same area as the laboratories.

The three floors are linked by a passenger lift and a goods lift (near the stairs). The fire escapes are situated opposite the pilot plant.

4) Possibilities for expansion

Plan OC-10-03 indicates the way in which the plant and laboratories could be extended, and also includes a general diagram of the proposed allocation of space (this part of the design work should only be carried out after the site has been selected).

5) Schedule of costs

See attached plan M-20-03.

6) List of critical items of equipment for the pilot plant. (Note 2).

In order that the pilot plant Centre can begin to operate the following items of equipment will be required as a minimum:

6.1 - Pilot plant: Fermentation

- 1 thermostatically controlled bath for 4 5-litre fermenters;
- 4 50-litre fermenters;
- 3 300-litre fermenters;
- 1 3,000-litre fermenter;
- 2 300-litre storage tanks and 1 300-litre storage tank with stirrers and outer envelope;
- 1 autoclave for the 5-litre fermenter and other items;
- thermostatically controlled rooms with rotary stirrers;
- microbiology laboratory for the preparation of culture media.

6.2 - Pilot plant for the separation of solids/liquids;

- press filter
- rotary drum filter
- disc centrifuge
- 2 tank centrifuges
- 1 small tank supercentrifuge, with refrigeration
- 1 decanter
- basket filters
- 300 and 3,000 litre tanks.

6.3 - Pilot extraction plant:

- 300 and 3,000 litre tanks, with stirrers and outer envelope
- 1 liquid/liquid separator
- 1 counter-current extractor
- 1 vacuum evaporator

6.4 - Precipitation and chromatography:

- thin film evaporator
- various tanks with stirrers and outer envelope
- 100-litre reactors with glass lining
- stainless steel chromatographic column
- free-drying unit
- vacuum dehydrator

6.5 - Ancillary services:

- equipment for solvent recovery (from used broth)
- tanks for solvent storage
- treatment of wastes
- workshop

6.6 - General services:

- electricity
- compressed air
- brine at -20° C
- water from local reservoir
- cold water at $+3^{\circ}$C
- air conditioning plant
- steam

6.7 - Miscellaneous:

- Raw materials for the production of batches, sufficient for a minimum period of three months or the continuous operation of a 3,000-litre fermenter.
- Spares for the main items of equipment and for the services production centres.
- Fuel for three months.

6.8 - Equipment with long delivery periods:

- Computer CPU:	8 to 12 months
- 300 and 3,000 litre fermenters:	4 to 6 months
- tank and disc centrifuges:	4 to 6 months
- rotary drum filter:	6 months
- various containers:	4 to 6 months
- stainless steel chromatographic columns	8 months
- air conditioning system (installed)	6 months

The air compressors, boiler, cooling equipment and workshop machinery should be available within a period of three to six months.

NOTE 1:

The 3,000-litre fermenters should be designed in accordance with the attached diagram, that is to say with extensible elements so that various height/diameter coefficients may be applied. Space should also be allowed for two tower-type fermenters.

NOTE 2:

The main items of equipment, without which the plant cannot function, and also those with a long delivery period, are "critical". Another obstacle could be the possibility of obtaining the equipment in the country selected for the Centre, although this matter could be resolved by means of a study of the market. There does not appear to be any difficulty in the case of Mexico.

LIST OF PLANS APPENDED

No. OC-10-01: Plan of plant at levels -4.00 to 0.00

No. OC-10-02: Plan of plant at levels +3.00 to +6.00

No. OC-10-03: Plan of plant at +9 and perspective drawing

No. OC-20-01: View of fermentation chamber

No. OC-20-02: Cross sections

No. M-20-03: Schedule of costs

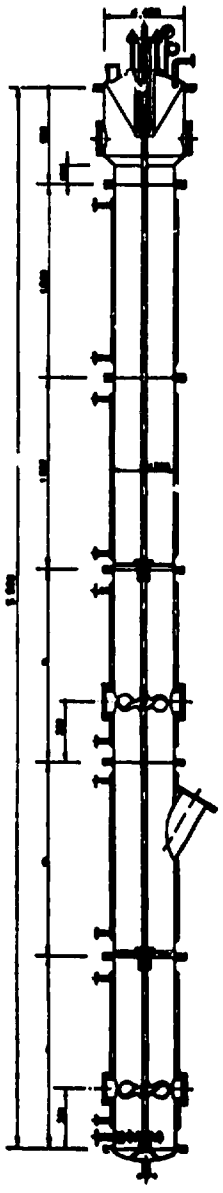


Fig. 6 COLUMN FERMENTER

All the parts are interchangeable: some are provided with apertures for inserting measuring instruments, as shown in the figure.

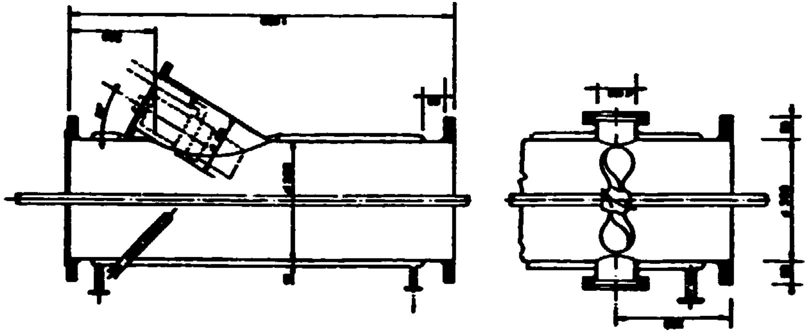
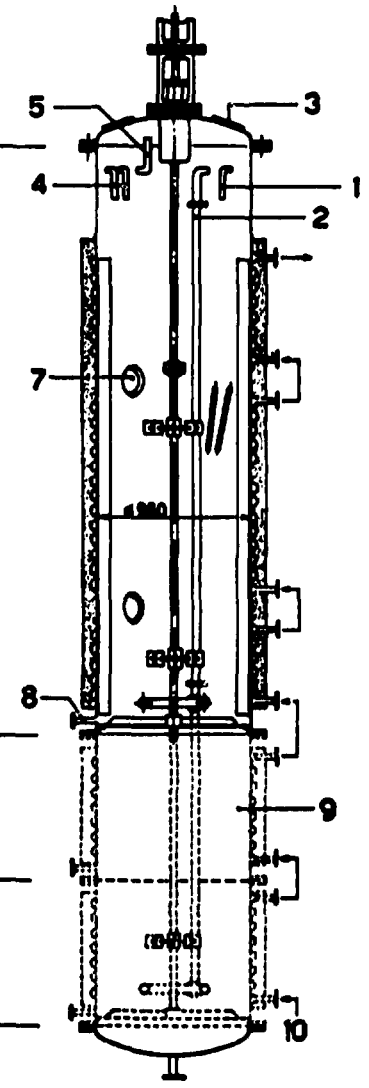


Fig. 7 FERMENTER WITH TOTAL CAPACITY OF 3000 litres AND WITH EXTENDABLE ELEMENTS (7)

(7) CHAIN, E.B., FALINI, R., GUALANDI, G. and RICCI, G.F. : forthcoming publication.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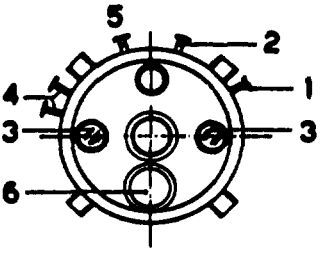
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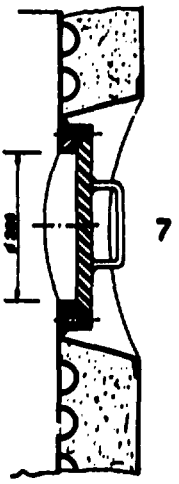
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G) FUTURE PROSPECTS

With the exception of a few and generally little-used antibiotics the remainder have entered the category of commodities, and are accordingly considered more suitable for manufacture than basic production. Improvements have in fact been very substantial, and this has enabled prices to be kept well below increases in the costs of raw materials and other products of similar complexity.

There has, however, been a reduction in the number of manufacturers, but an increase in overall output, that is to say the size of each surviving operation has increased by taking advantage not only of the improvements achieved, but also the proportional reduction in costs due to better absorption of fixed costs which, as has been seen, constitute a considerable percentage of the total cost.

At world level there should be greater natural selection of manufacturers with a higher production volume for each unit, and e continuation of research with a view to further improvements in productivity and efficiency, in the knowledge that a great deal remains to be achieved.

A company which wishes to enter this field should have access to the latest technologies and should continually seek further improvements. Commencement of production operations using inferior technology and equipment will lead to irrecoverable losses.

On the other hand, a considerable proportion of the world's population still does not have permanent access to these sophisticated drugs. Figures for the projected increase in needs are high,

thus justifying the expansion, or rather the increase in productivity, of existing plants. The actual size of plants has increased to such an extent that those used at the beginning of the antibiotics era could be regarded as pilot plants today.

The main research priority is increased productivity and savings on raw materials the second most important factor. The reason for this classification is that the success of the former determines a reduction in costs without necessitating investments and at the same time leads to an increase in total production capacity so that, as investigation of the strain is the best approach, a good proportion of research efforts are directed towards microbiology in general and genetics in particular.

H) RAW MATERIALS

There is little that is new at world level where this topic is concerned, since the supply of raw materials is determined by price, quality and reliability of the source.

Allowing for the fact that a number of raw materials have to be used and handled for every kilo of antibiotics produced, especially solvents (which are recovered), it may be concluded that even small differences in price will be important. This acquires more significance when applied to the subregion, since where it is necessary to import raw materials from distant areas, freight alone could generate a cost increase which will diminish the feasibility of the operation.

The subregion has a wealth of raw materials which can be regarded as nutrients, but there is a lack of others, especially solvents of petrochemical origin.

It should also be remembered that, even though the area has an abundance of raw materials, a study will be necessary to suggest improvements in those which are not of optimal quality, in order that the required specifications may be satisfied.

I) INDUSTRIAL PROFILE

The world industry profile can be summarized as follows, following the descriptions given in previous sections:

1. Continuous increase in size, in order to reduce the effect of indirect costs.
2. Continuous development, both of the strain and of methodology
3. Rapid transfer of new developments to production.
4. Maximum integration of research/production activities is necessary if 3. is to be effective.
5. Search for long-term sales contracts to guarantee production plans which will permit consistent and maximum use of the productivity of the plant.

At subregional level the industrial profile calls for the attainment of the following requirements:

1. First-class technology and suitable equipment.
2. Trained and motivated human resources in the fields of:
   - 2.1. Microbiology in all its disciplines.
   - 2.2. Operating personnel (Fermentation, Extraction and Synthesis)
   - 2.3. Maintenance and services
   - 2.4. Chemical control (quality and analysis during process)
   - 2.5. Production services (Planning-Supplies)

2.6 Highly qualified executive staff (with scientific base).

3. Access to raw materials at suitable price and quality.

4. Rational relationship between size of plant and market in order to be able to maintain an economic system which is competitive at a world scale.

5. Government support in respect of patents and unfair practices (under-invoicing of imports, incentives, etc.).

6. Clear government policies, avoiding as far as possible the levying of taxes, even indirect taxes (energy, fuel) and those which may affect the necessary raw materials (carriage charges, consular fees, prior deposit, etc.).

7. Good financial backing, especially during the initial period when investment capital is tied up. Also to finance working capital in order to be able to compete with the long term arrangements offered by international companies.

8. Ongoing technical assistance.

9. Rapid and ongoing access to technological innovations.

10. Flexibility of use, with possibilities for plant expansion.

11. Search for maximum integration in order to obtain a product of higher added value and related disciplines.

12. Pharmacotechnical support (via Centre) to clients, encouraging them to replace imports by finished products.

13. Subregional cooperation.

SUB-REGION

* SOCIO-ECONOMIC SKETCH
* PROFILE OF THE PHARMACEUTICAL INDUSTRIES

SOCIO-ECONOMIC SKETCH

COSTA RICA

CUBA

GUATEMALA

GUYANA

HONDURAS

MEXICO

NICARAGUA

PANAMA

SOCIO-ECONOMIC SKETCH

C O S T A R I C A

By tradition and history Costa Rica has always been the most democratic country of Central America; the one which, consequently, enjoys the highest political stability in the subregion. With a high rate of survival and an extremely low level of illiteracy Costa Rica enjoys the reputation of being one of the countries with the highest cultural level in Latin America.

Its main export, around which its economy revolves, is coffee, followed by other food products such as bananas, sugar and meat.

Costa Rica maintained a steady growth rate during the seventies. In the year 1978 its gross national product was $3.2 billion, which then fell abruptly to $2.2 billion. Its public debt is $1.27 billion, and the level of its exchange reserves fell to $158 million at the end of 1980. The constant depreciation of the national currency reflects the economic difficulties through which the country is passing. In spite of having a high proportion of energy from hydro-electric sources imports of oil certainly affects for the worse its external trading balance.

C U B A

Cuba is a planned state economy, founded and fashioned in accordance with a plebiscite carried out in 1976. Since the revolution which assumed power at the beginning of 1959 the country has put into effect a profound transformation of the social structures directed towards the establishment of a socialist society.

The backbone of the Cuban economy has always been the production of sugar. However the reformists of the latter part of the nineteenth century pointed out the advantage of diversifying agricultural production in order to reduce the dependence of the country on a single export product. Several attempts have been made more recently to stimulate the cultivation of other vegetable species, such as rice at the beginning of 1960. This initiative was not continued, and so sugar continues to be the main export.

The production of sugar in Cuba in 1980 reached a figure of 8 million tonnes, a fact which reflected the efficiency of the Government in overcoming the difficulties which arose at the beginning of the revolutionary period. The production of tobacco constitutes another import source of income for the country. The temporary difficulties which reduced the yield of the tobacco crop because of agricultural pests have now been overcome. As regards coffee, which is grown chiefly in the eastern provinces, Cuba has become self-sufficient for its domestic requirements. An intensive campaign for the production of 600,000 tonnes of milk is under way. The cultivation of citrus fruits has been greatly stimulated, and it is expected that the country will become one of the major exporters of these in the near future.

The development of the fishing industry has been extraordinary, having reached 230,000 tonnes in 1978. Despite the fact that the country possesses a variety of mineral resources, for example iron, chrome and manganese, the mining of nickel is the most important. Cuba is one of the largest producers of this mineral in the world.

Total exports in 1975 accounted for $2.95 billion, chiefly agricultural

products and raw materials. Sugar represents 90% by value of all exports. 68% of the exports went to socialist countries, the rest to industrialized countries, amongst which Canada, Japan and Spain were the largest importers.

In 1975 imports accounted for $3.11 billion: the main suppliers were the socialist countries, which contributed 51% of these.

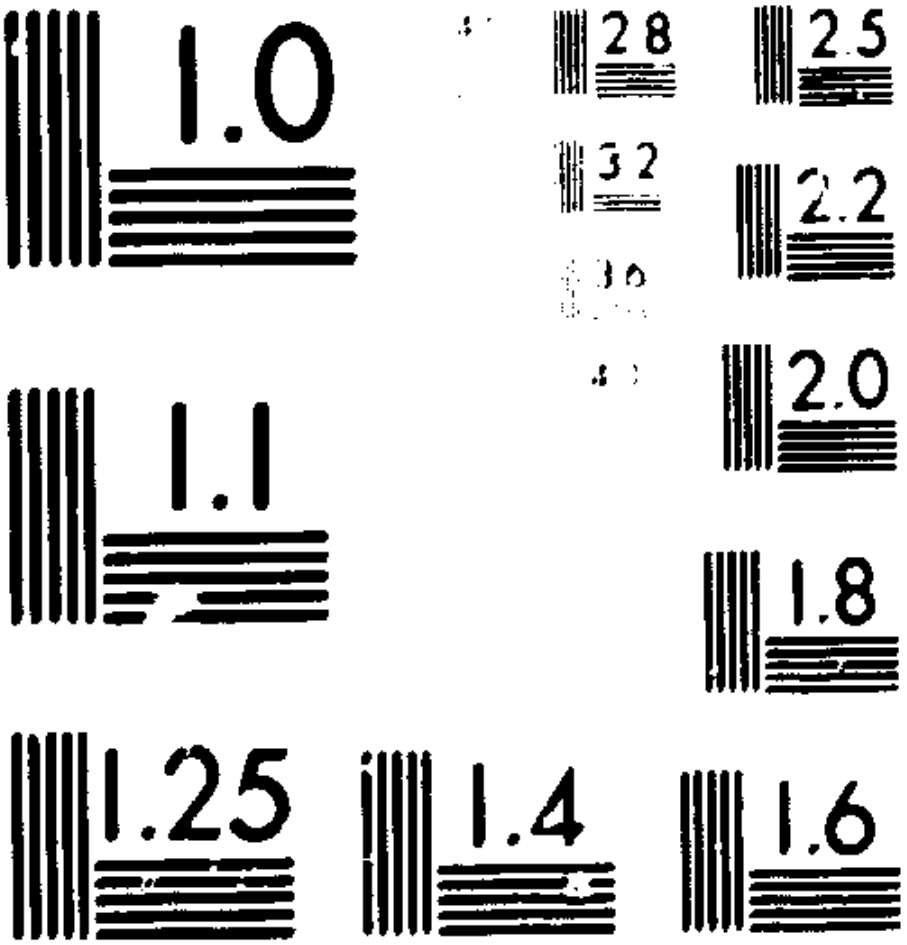
In spite of the many difficulties which the country has passed through, owing chiefly to its economic isolation, its strong determination and its faith in the future will provide the necessary elements to resolve many problems. It should be pointed out that Cuba has made extraordinary progress in many fields, particularly in the areas of education and public health, with firm plans for research aimed at the achievement of technologies of its own.

G U A T E M A L A

Guatemala was chosen some time ago by a large number of foreign corporations to set up subsidiaries with the main aim of exporting manufactured products to the countries of the Central American Common Market.

Since securing its independence at the beginning of the nineteenth century Guatemala has experienced long periods of governments not elected by suffrage. Those governments, although they have introduced material improvements, in fact delayed the prccess of democratic development. At the present time Guatemala enjoys relative political stability.

Guatemala is an eminently agricultural country, and consequently two-thirds of its population live in rural areas.



MICROCOPY RESOLUTION TEST CHART
NATIONAL BUREAU OF STANDARDS

Its main export is coffee, which represents 40% of all exports, followed by cotton and bananas. Exports to Central American countries were $253.8 million in 1978, which represents 18% of its total exports: these were made up of consumer articles valued at $1.36 billion. Total exports in 1980 were $1.75 billion against imports of $1.97 billion. At the end of 1980 its international reserves were $208 million.

G U Y A N A

Guyana, the "land of many rivers", consists of four clearly defined geographic regions: the low, agricultural regions of the coastal plains, used mainly for the cultivation of rice and sugar; the zone formed by sand and clay hills, underneath which lie immense natural resources of high-grade bauxite and low-grade iron ore; the gold-bearing sands of the moderately high zones, and the rolling savannahs devoted to the rearing of cattle. In the coastal zones possible oil deposits are being investigated. The innumerable rivers of the country possess many waterfalls, which represent a potential of hydro-electric energy.

The population of Guyana enjoys maximum political freedom under a form of republican constitution which provides for a multi-party system and regular elections. The most outstanding aspect of the political machinery of Guyana is its social stability which rests on the fact that an overwhelming majority of its various racial groups subscribes to a single political philosophy based on socialist principles and practices, aimed at guaranteeing that all the population of the country constitutes the principal beneficiary

of its progress and its development, and that the fruits of that progress are distributed equitably amongst the population.

At sub-regional level Guyana is a firm supporter of integration and has played a major role in the promotion of the Caribbean Community (CARICON), being an active member of the Latin American Energy Organization (O.L.A.D.E.).

The agricultural sector has been regarded as the main element in the Government's development plan. The main crops, in terms of employment and of added value, continue to be sugar and rice which, combined, contribute 24% to the Gross Domestic Product and 60% to the income from foreign trading.

Economic growth in the mining sector is strongly influenced by the activities of the bauxite industry, which contributes 15% to the Gross National Product.

To safeguard the economy of the country the Government has established greater controls on imports, since its foreign exchange reserves have fallen to an extremely low level. In 1980 exports only reached the figure of $470 million, whilst imports were $530 million. The public debt at the end of 1979 was $480 million.

H O N D U R A S

Like the rest of the Central American countries Honduras is a primarily agricultural country whose main products are bananas, coffee, beans, rice and timber. Cattle-raising is relatively important.

A total of 66% of its area is covered with woods. Its chief exports in 1975 were timber ($19 million), coffee ($37 million) and bananas ($19 million). Its most important mineral resources are silver, lead, gold, zinc and copper: exports of lead and zinc in 1975 accounted for $10 million.

The Gross National Product of Honduras in 1980 was $1.24 billion. This figure fell substantially in the years 1975/76 owing to natural disasters. Its exports in 1980 were $920 million and its imports $1.12 billion. The public debt of Honduras in 1979 was $740 million.

M E X I C O

Mexico has undergone a process of economic development since 1925, during which year the bases of its advance were established. Throughout the following 55 years Mexico has made enormous advances in the area of economic development: nevertheless many deficiencies of a structural order still remain. In many areas of the country the progress achieved has been below expectation, and many sections of the population still live at subsistence levels since the economic activity of Mexico continues to be concentrated in a relatively small number of areas.

One of the serious problems of a structural type, since its repercussions go beyond all sectors of the economy, is that the annual increase in population outstrips the resources of the farmland. This situation is made even worse by the fact that the excess population finds no place in other sectors of the economy, such as industry or the building sector, which have reflected patterns of dynamic growth during recent years.

Mexico has experienced a period of sustained economic development during the last 15 years, with an annual average growth of 7.4% in real terms. Meanwhile its population has increased at a rate of 3.4%, a relatively high rate compared with international standards. This circumstance has compelled the Mexican authorities to increase investments in social services. The Government has given priority to the development of production and hence the maintenance of regional disparities. The industrial sector has remained in the lead, both in the size and in the development of its performance.

Stimulated by the growth of the domestic market and by the policy of substitution of imports - hard to achieve - the industrial sector has become the biggest sector in Mexico. Petroleum and petrochemicals, energy and building, have participated in the dynamism of the manufacturing sector, displaying an extraordinary degree of co-ordination of efforts in the public and private sectors. These sectors, together, grew at an annual average rate of 8.7% between 1954 and 1980, which can be considered highly satisfactory.

In spite of the fact that agricultural development has been slower some structural changes such as self-sufficiency in basic foodstuffs (which was attained around the year 1965) have been successfully achieved. This was a consequence of the massive investments in irrigation projects in the northern regions and exporting of agricultural products and livestock, which have continued to increase at a satisfactory rate. Nevertheless agriculture has not progressed outside the irrigated agricultural regions as was hoped, and consequently the productivity and income of the agricultural population have remained at low levels. This has given rise to one of the most

discussed problems in Mexico today.

Taking into account the fact that 58% of the economically active population derives its subsistence from agricultural activities the structural framework of the Mexican market can easily be understood. This illustrates clearly why half of the total market of Mexico in consumer goods and services depends largely on agriculture. It must be pointed out, however, that 70% of the cultivatable land of the country is located in poor areas with exhausted land and in non-irrigated regions of limited productivity.

The panorama sketched above constitutes an enormous economic and social burden for all the other sectors of the Mexican economy, limiting the possibilities for growth of the country. As 46% of the work-force and their families live in rural areas at subsistence levels on the fringes of the national economy, and as almost 4 million Mexicans live at a minimum wage level, it is easy to understand that one of the peculiarities of the Mexican domestic market, which is orientated towards manufactured products, confronts large masses of population without adequate purchasing power, so making it difficult for Mexican industry to produce at efficient levels of output. This situation leads to a structure of high costs and prices.

This structure of high costs and high prices, the result of the small production runs, has prevented Mexican industry from competing advantageously in the international market with the mass production of industrialized countries, supported by the latest technological advances. If Mexican industry could sell a greater part of its production, reflected in an increase in its exports, this would help it to reduce costs and, consequently, its prices, on the domestic market.

As the prices of the national industry are frequently above prices on the international market it is compelled to depend mainly on the domestic market and, owing to the structural difficulties already noted, it is difficult for it to reduce costs to acceptable levels.

With few exceptions, therefore, Mexican industry operates successfully on the domestic market only when restrictions are imposed on the entry into the country of products of foreign origin, by means of various measures such as the imposition of import licences or tariff increases which force the price of the imported product far above that of a product manufactured within the country. This system of protection has been one of the ways by which Mexico has promoted the development of local industry.

These structural parameters resemble the characteristics by which international economy describes the majority of developing countries, including Mexico, and which have contributed towards restricting income from foreign trading, creating an obstacle to Mexico's chances of exporting industrialized products on the one hand, and on the other of operating its industries at high productive levels. It is important to emphasize that the industrial sector is by far the most dynamic within the process of economic development of the country, both in terms of production and potential absorption of additional labour.

These serious limitations of structure in the operations of the industrial sector, which restrict its growth, have meant that industry has been unable to provide new jobs in sufficient quantities

to accommodate these to the rapid increase in population. These factors, together with the unequal distribution of the national income and high bank rates, form obstacles to the process of capitalization and seal the vicious circle formed by the basic problems of the Mexican economy.

In spite of all the comments made in this sketch, the Government of Mexico has made enormous progress in innumerable areas where the development of the country is concerned.

It must be pointed out, however, that the balance of probabilities indicates that the Mexican economy will continue to enjoy stability as in the past, and that the factors which have prevented Mexico from achieving some pre-established objectives will be overcome.

N I C A R A G U A

The oligarchy which governed Nicaragua for several decades was catastrophic for the economy of the country, disrupting social order, increasing poverty and thereby contributing to preventing conditions favourable to the establishment of positive changes.

Simultaneously with the economic chaos, aggravated by many years of government lacking popular support, the progressive deterioration of the education and health systems brought in its train an increase in the level of illiteracy, together with a deterioration in health programmes and, consequently, in an inadequate supply of essential medicines.

After the revolution overthrew the dominant minorities which had held power for so many years the consumption of medicines, both

in the public sector and in the private sector, showed major increases.

In Nicaragua agriculture is the most productive sector of the national economy. This activity, together with forestry and fishing, contributes about 25% of the Gross National Product and 55% of all exports. Other exports are cotton, coffee, sugar and meat.

Inefficient administration of the resources of the country, before the present political structure, produced fatal effects for the economy, and these will call for much hard work in years to come if they are to be overcome. The public debt in 1979 was $930 million. During the year 1980 exports accounted for $520 million, as against imports of $920 million. For that reason exchange reserves have fallen to a minimum level, which will make the supply of a certain number of basic products difficult.

P A N A M A

The Republic of Panama has enjoyed lasting political and economic stability.

Panama is the country preferred by many corporations throughout the world.

Its main agricultural exports are sugar, rice, tobacco and coffee. The fishing industry grew thirtyfold between the years 1948 and 1979. Last year fishing reached the level of 139,000 tonnes.

In spite of the fact that its imports and exports are not properly balanced - in 1980 exports were $1.3 billion and imports $1.7 billion -

the national currency maintains its parity in relation to the dollar.

SOCIO-ECONOMIC AND DEMOGRAPHIC SUMMARY OF THE SUB-REGION

SOURCE: LATIN AMERICA STATISTICAL YEARBOOK

	COSTA RICA	CUBA	DOMINICAN REP.	GUATEMALA	GUYANA	HONDURAS	MEXICO	NICARAGUA	PANAMA
POPULATION (1980) x 10^6	2.21	9.73	5.94	7.26	0.88	3.69	69.75	2.73	1.89
AVERAGE GROWTH (1970 - 1980)	2.5	1.5	3.3	3.0	2.2	3.4	3.4	3.3	2.9
LIFE EXPECTANCY 1975-1980 (YEARS)	69.7	72.8	60.3	57.8	69.1	57.1	64.4	55.2	69.7
ILLITERACY (1970) %	11.6	-	33.1	53.8	8.6	40.5	25.8	42.1	21.7
(1980) G.N.P. (US$ x 10^9)	2.20	-	3.33	4.05	-	1.24	81.42	N.A.	N.A.
EXPORTS (1980) (US$ x 10^9)	1.18	-	1.22	1.75	0.47	0.92	24.31	0.52	1.30
IMPORTS (1980) (US$ x 10^9)	1.63	-	1.90	1.97	0.53	1.12	25.06	0.92	1.71
PUBLIC DEBT (1979) (US$ x 10^9)	1.27	-	0.82	0.48	0.46	0.74	28.80	0.93	2.10
INTERNAT. RESERVES (1980) (US$ x 10^6)	158	-	208	468	13	150	3408	-	117
INFLATION (ANNUAL) 1970-1980	10.8	-	10.7	9.6	10.5	7.8	16.5	19.5	6.8

PROFILE OF THE PHARMACEUTICAL INDUSTRIES

C O S T A R I C A

Costa Rica is a major importer of finished medicines; 75% of the apparent consumption of pharmaceutical products in 1975 came into the country in finished form, and only the remainder was made up locally. By value 45.8% of local formulations was exported to the area of the Central American Common Market.

The largest consumer of medicines is the public sector through the Caja Costarricense del Seguro Social (Costa Rican Social Security Fund), which provides medical cover, including medicines, to 90% of the population of the country.

The annual consumption of medicines in 1981 is estimated at $22 million, 66% of that being in the public sector. In spite of the fact that the Caja del Seguro Social has a formulation plant, 70% of the medicines distributed are imported in the finished form.

The largest quantity of pharmaceutical formulations comes from three subsidiaries of multinationals. Two of these subsidiaries exported 80% of their local formulation to the area of the subregion in 1978. The value of the production of the pharmaceutical formulation industry in 1977 was $17.98 million, 82.2% of which came from foreign firms.

The consumption of antibiotics by the public sector, expressed in weight of active substance, was 14.39 tonnes in 1978. Assuming that 33% of that consumption corresponds to the private sector, and applying a growth factor of 1.44, the requirements of the country for 1981 would be 36 tonnes.

The consumption of the main antibiotics, expressed as active substance, is as follows: semi-synthetic penicillins 55%, griseofulvin 19%, tetracycline 14% and erythromycin 8.7%.

C U B A

The pharmaceutical industry in Cuba is state-owned, and therefore the production, distribution and supply of medicines is the responsibility of the state.

Up to a short time ago the country was involved solely in formulating operations, which provide 90% of the national requirements. In addition the country has been producing biliary acids on a small scale, dedicated to domestic consumption. Cuba also produces gonadotrophins and prostaglandins, the latter from certain species of coral and at the pilot plant stage. A project sponsored by UNIDO is being implemented which envisages the construction of a multi-purpose plant which will produce a range of synthetic drugs. The extraction of ecogenin from Agave species for the production of steroids, sponsored by UNIDO, will begin shortly.

The most ambitious project in the Caribbean area has been the installation of a state plant which for some time now has been producing semi-synthetic penicillins. The production of this plant will cover the national needs for semi-synthetic penicillins, plus a surplus for export.

It should be added that the Cuban pharmaceutical industry has now begun the stage of retrospective integration, the results of which will become plain in the years to come. It also has its own areas of pharmaco-technical research.

G U A T E M A L A

Guatemala is the Central American country where there is the greatest concentration of transnational pharmaceutical formulating firms. That is why twelve of the largest pharmaceutical companies in the world have subsidiaries in Guatemala.

In 1978 the country imported bulk antibiotics to a total value of $3.99 million; 78% of all the antibiotics were imported from the United States, the rest from other industrialized countries. Exports of antibiotics in finished form were $13 million in 1978.

The formulation of antibiotics in 1978, expressed in active substance, used 48.4 tonnes of drugs valued at $4.46 million. Annual consumption of all antibiotics, including insignificant quantities exported to the Central American Common Market, was 37.2 tonnes with a value of $3.5 million.

Extrapolating the consumption of antibiotics the annual demand for all medicines has been estimated at $40 million.

G U Y A N A

The importing, distribution and manufacture of pharmaceutical products is a state monopoly under the control of the Guyana Pharmaceutical Corporation. In 1978 imports reached a sum of $10.5 million, acquired from international tenders. Imports of antibiotics represented around 10% of that total.

All the pharmacies and hospitals in the country are supplied by the

state pharmaceutical company. This company has a turnover of about $3 million in popular products. At the present time the Guyana Pharmaceutical Corporation only supplies about 5% of the country's needs, since its installations were almost completely destroyed by a fire. At the present time it is restoring its plant and acquiring a new one on a "turnkey" basis. It is hoped that this company will supply at least 40% of the country's needs by the year 1983.

The annual consumption of antibiotics for 1981-1982 is estimated at 4.7 tonnes; 54% of this consumption corresponds to semi-synthetic penicillins, 27% to tetracycline and 10% to penicillin G.

The state pharmaceutical company makes up, under licence, the medicines of some transnational firms. At the same time it carries out a programme on the use of medicinal plants in the preparation of drugs based on traditional medicine in order to reduce imports of the raw materials used in modern medicine.

There is no other manufacturer of pharmaceutical products in the country. Formulating on a small scale is carried out in pharmacies in the private sector and in government dispensaries.

H O N D U R A S

As in all the Central American countries the production of medicines in Honduras is restricted to formulating activities which were begun around 1960. Nineteen firms are involved in such activities. The majority of these are located in Tegucigalpa and in San Pedro Sula.

The value of the production of the seven largest formulators was $7.85 million in 1978, which represents 90% of the estimated production of the pharmaceutical industry, equivalent to $8.75 million. At the present time local formulations supply only 25% of the needs of the country, the remaining quantity being imported in finished form.

Imports of pharmaceutical products in 1978 were $39 million, which represents 4% of the total imports of the country. The most important suppliers of finished pharmaceutical products were Guatemala and Costa Rica, which supplied 31% of imports, followed by the United States with 14% and West Germany with 8%. Exports of medicines in 1980 accounted for $1 million, chiefly parenteral solutions to Nicaragua.

Detailed information about imports of antibiotics is not available since they are often grouped with sulphanides. The combined figures, which include exports of antibiotics plus antibacterial agents, reached a figure of $5.9 million in 1978. Total imports of medicine for veterinary use were $2.35 million in 1978.

The public sector accounts for 50% of the consumption of medicinal products.

A mixed public-private company is completing the commissioning of a new pharmaceutical formulating plant, so that in the very near future the needs of the public sector will be covered completely from local supplies.

M E X I C O

The industry producing bulk basic drugs in Mexico has undergone

extraordinary progress during the last 30 years. Both the range and the quality of the drugs produced in the country reflect the guidance of the government towards attaining self-sufficiency in a large number of essential drugs, which otherwise would need to be obtained from external sources of supply. Mexico is classified amongst the leading countries of the developing world as a major producer of essential drugs. The Mexican basic production industry embraces not only the production of antibiotics by fermentation and semi-synthesis, but also that of a wide range of other therapeutic agents, of which the steroid group constituted a significant segment of world production for several years.

The size of the annual demand for medicines in 1980, expressed in value, is estimated at $1.3 billion at retail prices. The annual growth rate of the pharmaceutical sector is 18.7%; the per capita consumption of medicines in 1981 is estimated at $27.65.

The annual value of the production of drugs in bulk in 1980 was $208.4 million, its annual growth rate being 14.1%. Production of antibiotics in 1977 was $36.04 million. Exports of drugs in bulk reached a figure of $53.8 million in 1980.

Mexico is self-sufficient for 45% in value of its needs for drugs in bulk and for 97.8% of its formulations. Investment in the pharmaceutical industry (both in basic production and in formulation) is $338.9 million; the proportion of Mexican capital is 43%. The profits of the pharmaceutical industry are estimated at 7.7% on annual sales of finished products and 12.9% on sales of drugs in bulk. Profits on capital invested are estimated at 14.7% yearly in the area of formulations and 21.1% yearly in the production of basic drugs.

Projected investments in the production of raw materials amounts to $140 million; 80% of this will be supplied by the Mexican private sector. With the expected level of production Mexico will be self-sufficient in 68% of its needs for bulk drugs by the year 1984. When it attains these goals Mexico will have reached the level of an industrialized country in this sector.

As regards the production of antibiotics it must be pointed out that the largest segment of the production of semi-synthetic penicillins corresponds to national manufacturers. It is the same where the production of Penicillin G is concerned. About 50% of the production of erythromycin is in the hands of a Mexican company: the production of all antibiotics is in the private sector.

N I C A R A G U A

The pharmaceutical industry in Nicaragua has not reached an adequate level of development. Even though a number of laboratories are involved in formulating activities, including a state company, a large quantity of medicines is imported in finished form from Central American countries, from the Caribbean and from the industrialized countries. Basic production of bulk drugs is not undertaken, nor are drugs extracted from natural sources. These circumstances highlight the country's marked dependence on external sources if it is to be able to guarantee a regular flow to supply its medicinal requirements.

The consumption of medicines, expressed in value, may be estimated at $55 million yearly.

The availability of government exchange reserves for importing raw materials intended for the pharmaceutical industry for the first

half-year of 1981 was only $1.65 million, 27% of which was for the state firm.

As regards antibiotics the annual consumption of the public sector has been estimated at $4.6 million, of which about 50% corresponds to penicillin and semi-synthetic penicillins. The yearly requirement for antibiotics for the whole of the country for 1981, expressed in weight, was 61 tonnes, about 43 tonnes of this being penicillin and semi-synthetic penicillins. The size of the annual consumption of antibiotics, expressed in value, was estimated at $9.2 million.

Several earlier missions identified priorities tending to reduce imports of medicines, such as the increase of local formulating up to a minimum of 60% of the national requirements by extending the operations of the state pharmaceutical company. The installation of a multi-purpose plant for synthesising a number of essential drugs is under study.

P A N A M A

The situation of the pharmaceutical industry in Panama is very similar to that in several of the countries of Central America, in the sense that the country has neither started the production of bulk basic drugs, nor achieved self-sufficiency from local formulating.

The size of the annual consumption of medicines, expressed in value, is $24 million for 1980; 70% of this is channelled through the public sector. Imports of antibiotics in bulk during the same year were 2.8 tonnes, supplemented by antibiotics imported in finished form, giving a total of 14 tonnes; this represents the

total annual consumption of antibiotics.

A breakdown of the annual consumption of antibiotics gave the following results:

semi-synthetic penicillins	33.7%
penicillin G	32%
erythromycin	7%
streptomycin	4.8%

The consumption of tetracycline, at least in the public sector, appears to be very small.

ESTIMATED ANNUAL CONSUMPTION OF ANTIBIOTICS*

SUBREGION

	1981		2000	
	US$**	Tonnes	US$***	Tonnes
COUNTRY				
COSTA RICA	2.2	36.0	8.11	129.9
CUBA	2.3	36.5	8.23	131.7
GUATEMALA	2.3	37.2	8.39	134.3
GUYANA	0.3	4.6	1.03	16.6
HONDURAS	0.5	8.0	1.80	28.8
MEXICO	109.3	1,750.0	394.84	6,317.5
NICARAGUA	3.8	61.1	13.78	220.6
PANAMA	0.5	6.7	1.51	24.2
TOTAL	121.2	1.940.1	437.69	7,003.6

* Future consumption has been calculated using the factor 1.07/year.

** An estimated price of US$ 62,500/t has been used.

*** Assuming constant prices.

PRODUCTION AND INSTALLED CAPACITY

MEXICO 1981

CAPACITY IN TONNES

PLANT	A	B	C	D	E	F	G	I
AMPICILLIN	40	30	-	110	-	-	-	60
OTHER SEMI-SYNTHETIC PENICILLINS	5	8	-	-	-	-	-	10
ERYTHROMYCIN	-	50	32	-	-	-	-	-
LINCOMYCIN	-	-	-	-	22	-	-	-
PENICILLIN G	-	-	-	-	-	-	120	-
TETRACYCLINES	-	51	-	-	-	100*	-	-
GENTIAMYCIN	-	1	-	-	-	-	-	-
FERMENTATION CAPACITY m^3	-	500	230	-	260	175	400	-

* Total capacity in tetracyclines. Part is used at the present time for a non-antibiotic industrial fermentation.

PART II

SUBREGIONAL EVALUATION OF THE PHARMACEUTICAL INDUSTRY

EVALUATION OF THE PRODUCTIVE SECTORS

EVALUATION OF THE EDUCATIONAI AND RESEARCH CENTRES

EVALUATION OF SECTORS PRODUCING EQUIPMENT

EVALUATION OF THE AVAILABILITY OF RAW MATERIALS

REPORTS ON VISITS TO INDUSTRIAL CENTRES

PATENTS

EVALUATION OF THE STATE OF THE PHARMACEUTICAL INDUSTRY IN THE SUBREGION

The mission had the opportunity of evaluating the state of development of the pharmaceutical industry in the subregion.

1. All the governments of the countries visited are working towards better control of the appropriate use of medicines and of their price. From a general point of view there is adequate control over medicines for the public sector (social security), leaving some freedom for the private sector, but there is still considerable room for improvement.

2. In Costa Rica, Cuba, Mexico and Panama there are, at the present time, central laboratories for the quality control of medicines. In Guatemala there is a laboratory employed on the approval of new products.

3. The situation in regard to formulating in the public and/or private sectors is as follows:

Costa Rica	25%	of the	national requirements
Cuba	90%	"	"
Guatemala	70%	"	"
Guyana	30%	"	"
Honduras	25%	"	"
Mexico	98%	"	"
Nicaragua	20%	"	"
Panama	10%	"	"

In order to improve the quality and productive capacity of local pharmaceutical production it would be advisable to promote the establishment of Centres for Pharmaco-technical Research for the acquisition and distribution of technologies and the training of personnel. The Cuban pharmaceutical industry has its own laboratory

for the pharmaceutical development of formulations. There are other initiatives in this field: The Faculty of Pharmacy of Nicaragua (University of León) and that of Panama (University of Panama) have departments of pharmaceutical industry, organized with pilot production units. The Faculty of Pharmacy of Honduras is in the process of organizing a similar department.

4. As regards production plants for natural medicinal products all the countries of the subregion have indicated their keen interest in developing this field, which makes the better exploitation of local resources possible. Up to now only Mexico has achieved a high level of production of drugs from natural resources by the exploitation of diosgenine and steroid derivatives. Cuba produces biliary acids and human gonadotropin, whilst Honduras produces the active substances contained in the Calaguala. In all the countries there are programmes for development and research in different stages of advancement in the field of natural medicinal products which must be supported whilst, at the same time, improving their organibation. Thus for example many groups concentrate their efforts on the chemistry of natural products without receiving any support from a pharmacological laboratory which would make it possible to evaluate the pharmacological potential. This means that no major discoveries of new therapeutic agents are possible, and that the greater part of the work is of only academic value.

5. As regards the production of basic drugs in bulk by synthesis only Mexico has achieved a considerable productive level. Cuba has recently begun the production of semi-synthetic penicillins and is in the process of installing a multi-purpose synthesis plant.

In the other countries there is no bulk production of synthetic drugs, despite the existence of a good level of knowledge in organic

chemistry. It may be that this field is underdeveloped because the public and private sectors have not carried out technical and economic feasibility studies for the erection of production plants for synthetic drugs.

The production of semi-synthetic antibiotics must be taken into account as part of the bulk production of synthetic drugs.

6. The basic production of antibiotics in bulk by fermentation shows Mexico as the sole producer of a series of antibiotics in bulk (Erythromycin, Tetracycline, Gentiamycin, Linomycin and Penicillin G for the production of semi-synthetic penicillins).

In spite of the relatively high level of Mexican production, the new requirements of the sub-region in 1986 (not covered by the present capacity of the production plants) have been evaluated as of the order of 1,160 tonnes of penicillin G, 330 tonnes of tetracycline and 36 tonnes of erythromycin. The total value of production of these three antibiotics is US$ 55 million.

There is therefore no doubt about the need for a considerable increase in the production of the subregion.

SUBREGIONAL EVALUATION OF THE PRODUCTION OF ANTIBIOTICS

The mission had the opportunity of visiting the industrial establishments involved in the production, by fermentation and synthesis, of those antibiotics which are manufactured in the subregion.

It also had full access to the highest levels of higher education and of research centres.

In the area of manufacture of equipment for the industry it investigated the possibilities open to manufacturers for the local supply of elements necessary to their activity. The activities of civil engineering and installation were also evaluated.

Another constitutive element of production is raw materials. The national counterparts have also supplied this information.

This information covers the most important elements of industrial activity in the field of the manufacture of antibiotics:

- Technology
- Equipment
- Human resources
- Raw materials

In addition, and in the specific case of the subregional centre for research and development, a primary factor is the knowledge of the present level of the respective technology and the existence of human resources already possessing the required disciplines.

It can be stated that, in general terms, the subregion shows activities, in the areas mentioned, which qualitatively cover all fields but which, quantitatively, are found at different levels when they are analysed over all the subregion; they demonstrate a real need for improvement so that the future productive activity may be competitive and can approach self-sufficiency.

2. Evaluation of the productive sectors

Two countries of the subregion produce, in bulk, the antibiotics most used in therapeutics.

2.1 Antibiotics by fermentation

This technique is used in Mexico by five firms, two of which are national and three transnational. However, in relation to the volumes of fermentation installed and the working volumes 59% is in the hands of nationals.

The following antibiotics are produced:

- Penicillin, technical grade for conversion into 6-aminopenicillanic acid
- Erythromycin
- Tetracycline
- Oxytetracycline
- Gentiamycin
- Lincomycin

The present total production is in the order of 500 tonnes per year, a very high figure. The fermentation capacity is 1525 m^3, and it is estimated that, with the exception of one plant which allocates part of its capacity to a non-antibiotic fermentation operation, the remainder work at full capacity.

In general terms it can be stated that the technologies have been obtained by transfer from abroad. In the case of the transnational firms this was from their head offices; national firms acquired them from firms not belonging to that category.

Production facilities, which were mostly constructed more than 20 years ago, have not undergone fundamental changes, which makes it possible to conclude that substantial technological changes have been introduced which maintain competitiveness with abroad as far as the subregional market is concerned. This aspect is seen most clearly in the case of penicillin, in which not only is it not exported but there is a marked local shortage.

This competitive inferiority is shown by the protection which the producers enjoy.

Immediate expansion programmes have not been identified, even though the shortage of antibiotics is imminent or even, more accurately, present if the analysis is applied to the subregion.

There are no serious problems regarding human resources, raw materials and the supply of equipment.

Some sectors, however, have stated that the human resources, although they possess a good basis of theoretical knowledge, lack specific production experience.

A lack of research dedicated to and focussed on the production of antibiotics by fermentation, which keeps this activity completely competitive by giving it access to the most profitable techniques, can be observed. On the other hand the mission was able to learn, from the comments made by manufacturers, about the difficulties presented by the acquisition of advanced technologies from responsible international firms.

All this amounts to a vicious circle which a subregional centre could break, giving rise to a self-sufficient industry, able to export on a basis of price and quality.

Finally it must be added that another pitfall is represented by the size, critically limited, of the plants at present in operation, only one of which has a volume of 500 m^3.

2.2 Antibiotics by semi-synthesis

Two countries in the subregion, Cuba and Mexico, produce semi-synthetic penicillins from their own manufacture of 6-aminopenicillanic acid.

Five plants are in operation, four in Mexico and one in Cuba; one is multinational and of the national ones, one is in the public sector.

Combined present production is in the order of 280 tonnes, but it may be estimated that, if required, the potential capacity is rather larger than this.

These figures refer to semi-synthetic penicillins in themselves, but to these must be added that needed to produce the 6-aminopenicillanic acid which would be approximately 170 tonnes.

The various products produced are:

- Ampicillin (trihydrate, anhydrous and sodium)
- Amoxycillin trihydrate
- Cloxacillin
- Dicloxacillin
- Hetacyclin
- Cephalexin
- 6-aminopenicillanic acid from penicillin.

This segment of the production of antibiotics does not present any particular difficulties, and all the firms seem to operate normally. However the mission discovered peculiarities which call for comment. In the first place, only the transnational firm uses the enzymatic method for the production of 6-aminopenicillanic acid, which would indicate a slight technological backwardness of the national firms which, although they are not affected economically, their final products have a certain reserve as far as their quality is concerned. In addition, the equipment would seem a little rudimentary, requiring the use of some costly production factors such as nitrogen, because of insufficiency of the cold benches. The recently commissioned Cuban plant on the other hand, presents a good balance of design.

Another comment is that, in general, no experimental work on the improvement of existing technologies or development of new ones has been detected. In this discipline no difficulties have been observed in obtaining human resources.

A high proportion of the equipment has been manufactured locally. Worthy of special mention is a freeze-drying plant of local design and very novel conception for sodium ampicillin.

EVALUATION OF THE EDUCATIONAL AND RESEARCH CENTRES

INTRODUCTION

A research and development centre for obtaining antibiotics by fermentation and semi-synthesis requires close collaboration among scientists orientated towards industry and specialized in various disciplines, so that they may make use of well-equipped laboratories, including an experimental plant, and work in stimulating conditions, for example by making contacts outside the centre and exchanging knowledge with the academic and industrial communities.

In another part of the report is a general description of the laboratory services necessary for the functioning of the centre.

Here the main qualifications of the technico-scientific personnel which the centre needs will be indicated schematically, and an attempt will be made to evaluate the potential resources of the subregion to locate or train the personnel who possess the necessary scientific preparation.

The centre needs personnel with the following qualifications:

- Microbiologists for basic work in regard to industrial microbiology (from the isolation and maintenance of the cultures to the study of their growth, and the production and testing of antibiotics);
- Geneticists with experience not only in the classical mutagenic methods but also in the most recent techniques (protoplast fusion, amplification of genes), who could serve as a basis for improving the future output in the fermentation of antibiotics;
- Biochemists-enzymologists, with experience in bacterial biochemistry, in bacterial enzymology and in the techniques of industrial enzymology (enzymatic or cellular immobilization);
- Bio-engineers with experience in the adaptation of the processes of fermentation to the industrial scale, the design of fermenters and the management of pilot plants;
- Organic chemists, with experience in extraction and purification techniques and in the chemistry of natural products (in particular, antibiotics);
- Analytical chemists with experience in the most modern physico-chemical instrumental analyses.

It would be valuable to have available a statistician, specialized in computers, who would be responsible for the correct installation of computers, the data preparation and experimental design.

The evaluation of the mission regarding the potential possibility of locating or preparing personnel suitable for the needs of the centre in the various countries of the subregion must be regarded with some reservations.

All the visits to the research and academic centres have necessarily been limited to interviews with those in charge of the centres, and these were generally followed by a visit to the laboratory installations. It is evident that, in order to evaluate the level and the quality of the research activity and/or the educational programmes, a detailed examination would have been necessary of the criteria, plans and output of the research and educational programmes, which was not possible for reasons of time, confidentiality and professional ethics. Taking also into account the differing demographic and socio-economic conditions of the various countries of the subregion, the mission's visit was guided in some cases by local personnel towards laboratories and institutes which have only the slightest connection with the project. In addition, in one country (Mexico) the mission necessarily limited its visits to the most competent centres in concrete spheres.

These facts must be taken into account if the evaluation which follows is to be correctly interpreted.

UNIVERSITY AND EDUCATIONAL CENTRES

As regards the university and higher education centres of the subregion, which offer studies in the disciplines necessary for the project, the situation may be described schematically as follows, bearing in mind that the levels of the graduation degrees are only approximate (for example, it has been assumed that university study for four to five years corresponds to a degree, whilst the postgraduate courses correspond to a doctorate).

Costa Rica

The Faculties of Chemistry, Pharmacy and Microbiology of the University of Costa Rica prepare for degrees in organic chemistry, analytical chemistry, biochemistry and microbiology (directed chiefly towards clinical microbiology and the microbiological control of drugs and foodstuffs, and to biochemical analysis).

Cuba

University of Havana: degrees and doctorates in chemistry and biochemistry, with specialization in microbiology and genetics. IPSIAE (Higher Polytechnical Institute): degrees in various specializations of engineering, including food technology (with courses in biochemistry, microbiology and fermentation engineering and chemical engineering.

National Research Centre: a research institute which prepares for doctorates in organic chemistry and the biomedical sciences, which include microbiology and genetics.

Outside Havana the Central University, in Villa Clara, and the East University in Santiago de Cuba, prepare for degrees in chemistry and biology.

Guatemala

The Faculty of Chemistry and Pharmacy of the University of San Carlos prepares for degrees in organic chemistry, analytical chemistry, biochemistry and microbiology (directed towards the control of drugs and foodstuffs).

Guyana

The Faculty of Natural Sciences of the University of Guyana prepares for degrees in organic chemistry, analytical chemistry, biochemistry and microbiology (directed towards the control of drugs and foodstuffs).

Mexico

In Mexico City: the Autonomous University of Mexico (UNAM) -

- Faculty of Chemistry: degrees and doctorates in organic chemistry, biochemistry and degrees in analytical chemistry.
- Biomedical Research Institute: degrees and doctorates in various branches of the biomedical sciences, including biotechnology and molecular biology.
- Higher Studies Division of the Faculty of Medicine: degrees and doctorates in molecular biology, biochemistry and microbiology.
- Universidad Autónoma Metropolitana. degrees in biochemistry and molecular biology.
- Instituto Politécnico Nacional (IPN): degrees and doctorates in biochemical engineering.
- Research and Higher Studies Centre of the IPN: degrees and doctorates in organic chemistry, biochemistry, genetics and molecular biology, bioengineering and biotechnology.

Outside Mexico City:

Universities and polytechnic schools in various places in the Mexican Republic train for degrees (and in some cases for doctorates). For example:

- Industrial microbiology (Univ. Autón., State of Morelos; Univ. Autón., Nayarit; Univ. Autón., Nuevo León).
- Biomedical sciences (Univ. Guadalajara; Univ. Autón., State of Mexico).
- Organic chemistry (Univ. Autón., Guadalajara; Univ. Autón., State of Morelos; Univ. Autón., Nayarit; Univ. Autón., Nuevo León; Inst. Técn. y Estudios Superiores, Monterrey).
- Analytical chemistry (Inst. Técn. y Estudios Superiores, Monterrey: Univ. Autón., Nuevo León, Monterrey).

Nicaragua

The Faculty of Pharmacy and the Faculty of Chemistry of the University of León prepare for degrees in organic chemistry, analytical chemistry, biochemistry and microbiology (directed towards the microbiological control of drugs and foodstuffs, and towards biochemical analysis).

Panama

The Faculty of Natural Sciences and Pharmacy (School of Pharmacy and School of Chemistry) of the University of Panama trains for degrees in organic chemistry, analytical chemistry, biochemistry and microbiology (directed towards the microbiological control of drugs and foodstuffs, and towards biochemical analysis).

RESEARCH ACTIVITIES CARRIED ON IN THE REGION

Research activities in spheres related to the project may be summarized as follows:

Costa Rica

A Centre for Research into Natural Products, in which researchers from the faculties of Chemistry, Pharmacy and Microbiology participate, constitutes an example of a multi-disciplinary team. University professors are increasingly interested in actively participating in projects of economic usefulness for the country, especially in the pharmaceutical sector. In the Faculty of Pharmacy a project for studies on biological availability of drugs, expressed in terms of formulations of antibiotics, is being examined.

The Technological Institute of Costa Rica, situated at Cartago, carries out research in various technological spheres and has available a centre of technical information and documentation connected with international data banks.

The Quality Control Laboratory of the Social Security Department, although not, strictly speaking, a research centre, plays an important part in the drugs policy of Costa Rica and is an institution that countries which import large quantities of drugs ought to possess.

Research is not carried out in the specific sphere of industrial microbiology.

Cuba

The National Research Centre, created in 1965, is a vast modern institution which carries out research in the sectors of biomedicine, bio-engineering, chemistry and electronics. In the areas of interest to the UNIDO project mention must be made of the departments of microbiology, genetics, bio-engineering, organic chemistry of natural products and electronic instrumentation.

Amongst the main areas of research are:

- The biochemistry, physiology and genetics of yeasts (S.cerevisiae, Candida utilis);
- Isolation of mutants of high yield for the production of methionine and lysine, resistant to temperature, some of them produced industrially;
- Studies on the hydrolysis of cellulose and other by-products of the sugar-cane industry;
- Studies on the production of proteins for feeding stuffs from husks and the bark of sugar-cane, and on the reduction of nucleic acids in yeasts for human consumption;
- Other projects on molecular engineering are planned.

Chemical and pharmacological studies on the active principles of native plants.

The Departments of Electronic Instrumentation produces some components for scientific equipment, including for bio-engineering.

There is a small experimental plant with fermenters of up to 200 litres, completely equipped.

Institute of Chemistry and Biology, Cuban Academy of Sciences. The scientific activity is directed chiefly towards the exploitation of natural resources.

Amongst the different research programmes the following are relevant to the UNIDO project:

- Isolation and mutational selection of microorganisms for industrial use;
- Studies of the production of proteins by non-conventional methods;
- Bacterial enzymology;
- Biochemistry and physiology of microorganisms.

In the field of pharmaceutical chemistry interest is concentrated on the products prepared from marine organisms, in particular prostaglandines which are obtained from corals and the chitin and chitosane of crustaceans.

- Faculty of Biology of the University of Havana. In this faculty the Department of Microbiology has carried out laboratory studies on enzymes, production of antibiotics and enzymatic immobilization. The laboratory is equipped with some fermenters (3 to 10 l).
- Sugar-cane Research Institute. This is a large research institute aimed at the better utilization of sugar-cane: 60% of the research projects are directly related to the industrial demand.

  With respect to the areas of interest for the UNIDO project:

  Collection, isolation and genetic mutation of microorganisms for industrial use.

  Studies on the production of industrial enzymes (cellulose, invertase, nucleotidase).

  Biotechnical studies on the production of alcohol, including the use of non-conventional techniques (enzymatic immobilization) and the production of dextran.

  Control and analytical studies of all raw materials and final products. The Institute is equipped with some glass fermenters (4 l) and a 30-litre stainless steel fermenter constructed in the existing workshop of the Institute.
- Research Institute for the Food Industry. This is a vast institute for research, control and analysis of industrial processes of preparation of foodstuffs, which works in close collaboration with the food industry.

  With regard to the spheres related to the UNIDO project.

  Collection of industrial microorganisms;

  Studies on fermentations of foodstuffs, enzymes (amylase, invertase, pectinase), enzymatic and cellular immobilization and by-products of yeast.

  The Institute is equipped with small and large fermenters (of up to 7,200 l) for the production of yeast.

Unfortunately it was not possible to visit the laboratories because the Institute is planning to move elsewhere.

- Empresa Mario Muñoz

This is a plant dedicated chiefly to the production of some pharmaceutical raw materials (bioextractive), such as chorionic gonadotropin and biliary acids. It is the research laboratory of the Cuban pharmaceutical industry which works with natural products.

There is no research activity related to the UNIDO project. Another research laboratory of the Cuban pharmaceutical industry deals with problems of formulation.

Guatemala

- ICAITI (Central American Institute for Research and Industrial Technology).

This is a vast institute for applied research, founded in 1955 by the governments of the Central American republics in order to give technico-scientific support to the industrial development of the interested countries. It works in various spheres of industrial technology, market research, analysis and certification of quality of industrial products, and gives assistance to industries on technical, financial and organizational matters.

With regard to the sectors of interest for the UNIDO project the ICAITI deals with the microbiology of foodstuffs and alcoholic fermentation (it has obtained a patent on a process of alcoholic fermentation from sugar-cane, which is used industrially). The ICAITI has extensive administrative and political experience in the running of a centre linked with several countries.

- INCAP (Institute of Nutrition of Central America and Panama).

This is a vast institute for research and control of foodstuffs, with considerable experience in food microbiology and chemistry and well equipped laboratories.

In the INCAP a laboratory has been set up recently for the control of drugs (LUCAM: Unified Laboratory for Control of Foodstuffs and Medicines) which has chemical and microbiological sections.

Guyana

- Institute of Applied Science and Technology.

This is an institute, situated within the university campus, which carries out research into mineralogy, ceramics and the preparation of foodstuffs. Recently it has been concentrating its interest on the up-to-date technology of alcoholic fermentation. Research is not carried out in the field of industrial microbiology in connection with antibiotics. Some technicians have received training in bio-engineering in the University of London, and possess great motivation for working in this field.

Honduras

- The Faculty of Pharmacy promotes a research programme on medicinal plants. CONRAD is an institute for research, development and production, well equipped, with work based on the discovery of the antipsoriasis effects of the oleaginous extract of a plant called Calaguala.

  In Honduras research is not carried out in connection with industrial microbiology. It is of value to cite the case of CONRAD as an example of the possibility of creating a research and technical development group, even in a small country, when there is definite motivation.

Mexico

- Institute of Biomedical Research of the Autonomous University of Mexico.

  The Department of Biotechnology is working on various research projects, most of them of possible interest to industry:

  Making the production of antibiotics and aminoacids subject to regulations;

  Enzymatic technology (for example, production of 6-aminopenicillanic acid by enzymatic or cellular immobilization; enzymatic hydrolysis of cellulose);

  Fermentation technology for steroids, vitamin B12;

  Application of genetic engineering to the production of unicellular proteins, insulin, enzymes (for example, penicillin, amydase).

  The Department has achieved practical successes in developing processes used on an industrial scale.

  The Department of Molecular Biology, although it is more orientated towards basic research, undertakes several projects of possible practical interest in collaboration with the Department of Biotechnology (for example, genetics of industrial microorganisms, molecular engineering studies for the production of enzymes, etc.).

  A pilot plant is being constructed with a fully equipped fermenter of 1,000 litres which has been designed by the Department of Biotechnology. At the present time the plant works with a battery of fully equipped fermenters of 20 litres.

  National Polytechnic Institute.

  The Research and Higher Studies Centre, with its two Departments of Biotechnology and Bio-engineering, promotes research programmes in the field of fermentation, directed chiefly towards the production of unicellular proteins from agricultural wastes.

  The Centre has an internationally recognised collection of cultures of industrial strains, and is equipped with a battery (8) of fully equipped 16-litre glass fermenters and a 60-litre stainless steel fermenter.

In a year's time a pilot plant with a 1,000-litre fermenter will be completed.

Metropolitan University, Department of Biotechnology.

It has several research projects in the field of industrial microbiology, suitably linked with industry, for example: studies on the production of lactic acid and on the genetics of lactic bacteria.

Studies on the production of nucleotides from yeasts.

Studies on the production of tryptophane.

It works actively on solid fermentation.

In the pharmaceutical sphere research is conducted into new sources of steroids and into alkaloids extracted from native plants.

A 1,000-litre stainless fermenter and other connected items of equipment will come into operation.

The Department of Industrial Microbiology of the Faculty of Chemistry of the Autonomous University of Nuevo León, Monterrey, promotes research programmes into the hydrolysis of cellulose, pectinases, penicillin and amydase.

It is equipped with a battery of new glass fermenters (two of 20 l and three of 14 l).

Technological and Higher Studies Institute of Monterrey.

The Department of Chemistry promotes an intensive research programme into natural products extracted from plants and, in addition, into phytopathological fungi and the cultivation of pines to stimulate the production of mycorrhizas.

The extensive National Laboratories of Industrial Promotion (LANFI), Mexico City, devote themselves to applied research and were established to give technical and scientific support to the industrial development of the country. They work chiefly in the spheres of food technology, minerals, chemicals, cellulose and packing materials. In the sphere of chemicals the Laboratories are orientated particularly towards pharmaceutical products obtained by fermentation. They have a research unit which works on the microbiological conversion of steroids, which is equipped with fermenters of 10, 14 and 40 litres. At the beginning of 1982 one 150-litre fermenter and two of 16 litres will be installed, all of them fitted with complete set of instruments, together with various items of primary recovery equipment (e.g. centrifuges).

The research of this department also concerns the utilization of agro-industrial wastes, the production of microbial enzymes and microbial polysaccharides.

The Analytical Section of LANFI is equipped with the most modern scientific instruments.

The Information Department has a good library which provides national and international publications and books dealing with biotechnology and pharmacy.

The Department of Chemical Processes has a pilot plant with fully-equipped reactors, distillation column and other equipment for chemical processes. A plant is being installed at the present time for the preparation of foodstuffs.

Nicaragua

In the National University of León a group is being trained to work on the preparation of natural products from native plants.

The Food Technology Laboratory of Managua is an institute for applied research into foodstuffs control and processes, including food microbiology. It is interested in working in collaboration with the UNIDO centre, even though it is situated in another country. Research is not conducted in spheres connected with industrial microbiology for the production of antibiotics.

Panama

The Laboratory Specialized in Analysis (LEA) is a vast institute situated within the university campus, devoted to the chemical, pharmaceutical and pharmacological analysis of drugs, cosmetics and foodstuffs. It is well equipped and in the analytical sector undertakes research which includes studies on immunity tests using radioactive methods and on the biological availability of formulations of drugs in volunteers.

The LEA Laboratory, together with the Costa Rica Quality Control Laboratory, constitutes a notable example of the policy followed by the health authorities in exercising scrupulous control of drugs, especially when they have to be imported in large quantities via the social security system.

Specific research is not conducted in the spheres connected with industrial microbiology for the production of antibiotics.

CONCLUSIONS

On the basis of this brief survey of the educational and research institutions of the subregion, which, it is assumed, would provide the technico-scientific personnel who possess suitable preparation for the research and development centre for antibiotics to function with success, the following comments may be made and conclusions drawn:

In all the countries visited research and/or educational activities are eing carried on which cover at least a part of the scientific disciplines which bear on the project.

This is pertinent because, regardless of the country in which the centre is going to be located, the other countries could have an opportunity for their own personnel to work in the regional centre and to contribute to its training programmes and to its practical success, benefiting at the same time from such activities.

Only a few countries have research and/or educational institutes which cover the wide spectrum of the scientific knowledge necessary for a typical centre which comprises multiple disciplines and which works on research and technical development in the field of antibiotics.

Amongst those countries Mexico and Cuba could provide the centre with the greater part of the scientific personnel trained in disciplines such as industrial microbiology, genetics and bio-engineering. It would be very difficult to establish a qualitative comparison between the respective scientific and technical competence of the personnel trained in these disciplines in the two countries. As pointed out in the introduction it is impossible to evaluate the educational levels on the basis of a brief visit and the written curricula of university studies.

As far as research activities are concerned it is also very difficult to make any evaluation since many parameters have to be taken into consideration when judging the performance of a research group: publications, patents, technical knowledge, training programmes, assistance to industry and various other results generated by the group, in relation to the number of researchers. Nevertheless, although it is true that a qualitative comparison cannot be made on the basis of the information available, what can be said from the quantitative point of view is that there are scientific and technical personnel in Mexico with basic knowledge in all the range of disciplines which the centres require, and that that personnel is much more numerous than in Cuba. This will permit a better selection of the personnel and an acceptable rotation.

In addition the important possibility, mentioned in the introduction, of proceeding to beneficial interaction and interchange with technical personnel with wide experience in the industrial production of antibiotics by fermentation, only exists in Mexico.

EVALUATION OF SECTORS PRODUCING EQUIPMENT

The supply of equipment differs whether one links it to centres of research or of production.

A research centre has a large number of items, the majority of them of high individual value, of rapid delivery because they are mass produced. Very few pieces have to be constructed to drawings.

On the other hand, industrial plants require a wide range of items which are generally designed on the basis of demands by the technology employed.

The subregion shows Mexico, with a major metal fabricating infrastructure, to be capable of producing the greater part of the industrial parts. Traditional companies have production facilities in that country.

Cuba has a large workshop, specialized in stainless steel and capable of making a major contribution to the pharmaceutical industry.

As regards the servicing which the instruments require, both in the area of research and for industrial plants, Mexico has specialized companies which represent most of the world brands.

The mission visited, by way of sample, two large firms.

VISIT TO THE PFAUDLER PLANT

Location	Mexico D.F.
Ownership	Private sector, multinational (Sybron)
Field of activities	- Production of stainless steel reactors with glass lining, heat exchangers, receivers and other related pieces of equipment, and systems of tubes and conduits. Standardized sizes and technical characteristics - Detailed engineering - Supervision of the installation
Technology used	In all work procedures the techniques used in the United States parent company are followed.
Workshops	All the equipment necessary to construct the products, including cutting installations, welding, etc. Refractory furnace for applying glass compounds to the steel (glass lining) capable of receiving tanks of up to 7,500 litres. Quality control which includes inspection by X-rays.
Production line	Medium pressure vats, with glass lining, up to 7,500 litres. Stainless steel reactors according to customer's specifications. All kinds of jackets, heat exchangers, instruments and stirrers.
Human resources	All the necessary workers, supervisors and executive personnel from the respective schools, and personnel available with prior experience.

TALLER METALMECANICO

Location	Industrial district of Havana
Ownership	Public sector
Field of activities	Metal fabricating work in stainless steel
Technology used	Lavac (Sweden)
Production installations	- 5 induction furnaces of 400 kg for the production of stainless steel. Moulds are produced automatically, although some manual operations are carried out to meet special orders. - Welding equipment, automatic current control. Inert gases may be used if necessary. - Cutting tables. Plasma installations. - Pressure-moulded covers and bases.
Quality control	Suitable equipment for controlling production. Inspection by X-ray not available.
Factors which would affect production	There is some lack of specialized personnel, which makes it impossible to arrange a second shift.
Production line	- Stainless steel tankers, intended chiefly for the dairy industry, insulated with foam polyurethane (isothermal). Volume: up to 20 m^3. Sanitary finish. - Stainless steel tanks, international container type, for the export of rum. Volume: 20 m^3. - Equipment for the processing of sugar-cane, especially the handling and transport of materials. - Supply to order of supplementary equipment for imported plants, such as storage tanks, small reactors, etc.
Supply of equipment	All the plant was imported from Japan.
Raw Materials	All the raw materials, stainless steel sheets, electrodes, etc. are imported.

LIST OF EQUIPMENT MANUFACTURERS, MEXICO

Reactors

Pailmack International
Cortec S.A.
Hersil Ingenieros S.A.

Steam Boilers

Babcock Wilcox de México
Termomax de México
Calderas Mexicanas Oslec

Stirrers

Lightnin de México
Operaciones unitaris S.A.
M y B S.A.

Centrifuges

Sharples-Stokes
Bird-Macorvi S.A.
Westfalia Separator Mexicana
Trialta S.A.
Escher Wyss S.A. (Sultzer Hnos. S.A.)

Filters

Air:

De Vecchi Ingenieros S.A.
Veco S.A.

Rotary

Stockonle Mexicana

Liquid

AMF-Cuno (Filtración) S.A.

Sterile Air

Veco S.A.

Pumps

Gaulin-México
Worthington de México
Bombas GOULD
Peerless Tisa S.A.

Vacuum

Penwalt S.A.

Plate heat exchangers

A.P.V. Paraflow

EVALUATION OF THE AVAILABILITY OF RAW MATERIALS

The raw materials necessary for producing antibiotics by fermentation may be divided into two groups:

1. Natural products: for the greater part connected with the food industry; in some cases they are used in their natural state and in others as by-products of other processes, or specially prepared to obtain a specific quality. The most common examples are animal or vegetable oils, molasses, macerated maize (liquid, concentrated and/or dried), cereal meal, etc.

2. Chemicals:

   2.1 Basic industrial chemicals such as acids, antifoams, etc., inorganic or organic;

   2.2 Solvents, most of which are petrochemical products.

The mission has evaluated the quantity and quality of the materials available and has arrived at the conclusion that the subregion possesses potentially the greater part of the raw materials of Group 1, very few of Group 2.1 and hardly any of Group 2.2.

Mexico constitutes an exception, since it has the necessary chemical infrastructure and industrial plants which have been producing antibiotics during the last two decades. Some statements by production executives in Mexico regarding local raw materials do not differ from the remarks made by production personnel in industrialized countries.

In addition, it is fitting to underline the need for the raw materials to satisfy the specifications required in all consignments since, otherwise, one must expect high losses, including those due to the immobilization of the plant because of rejection of raw materials.

Consequently one of the objectives of the subregional Centre is to adapt technologies to existing raw materials and to recommend to local producers the most suitable way of improving the quality of the products manufactured and the compliance with specifications.

Some remarks must be made about the prices of local raw materials. Unfortunately in many cases they would be slightly higher than international prices, should special specifications be demanded, owing to the reduced volume of orders in relation to the volume of production of standard quality.

The following table shows the availability of raw materials in the subregion:

A SELECTION OF RAW MATERIALS USED IN FERMENTATION PROCESSES AND AVAILABLE IN THE SUBREGION

Costa Rica	Cuba	Guatemala	Guyana	Honduras	Mexico	Nicaragua	Panama	
								A. Natural products
	x				x			Maize maceration water
x	x			x	x			Maize starch
x	x	x	x	x	x		x	Liquid tallow
	x				x			Soya oil
				x	x			Maize oil
	x				x			Sunflower oil
x				x	x		x	Palm oil
					x			Cerelose
x	x	x	x	x	x	x	x	Sugar
	x				x			Glucose (Syrup)
	x				x			Soya meal
		x			x	x		Cotton meal
x	x			x	x	x	x	Maize meal
x	x			x	x	x	x	Molasses
					x			Filter aids (diatomaceous earth)
								B. Chemical
					x			Isopropanol
					x			Methanol
x	x	x	x	x	x	x	x	Ethanol
					x			Butanol
					x			Amyl acetate
					x			Butyl acetate
								Methylene chloride
x					x	x		Calcium carbonate

REPORT ON VISITS MADE TO PRODUCTION PLANTS IN THE SUBREGION

The mission was able to visit a large number of industries, some specifically linked to the production of antibiotics and others to processes of the same technological type but producing other non-medical substances.

In the following pages a report is given on the key elements of the operations in each of the plants producing antibiotics in bulk.

FERMIC PRODUCTION PLANT

Location: Iztapalapa, Mexico. Industrial district

Ownership: National private sector

Field of activities: Production of various antibiotics by fermentation and semi-synthetic penicillins.

Technology used: At first technology acquired from Italy was used. The yield of the fermentation procedures is apparently slightly below international levels. As regards the semi-synthetic penicillins the yield is satisfactory, although some comments about the purity are not out of place owing to the fact that the 6-aminopenicillanic acid is produced chemically, and for that reason the finished products contain dimethylamiline.

Production installations: Storage area for solvents and other raw materials. Production department with the equipment necessary for the preparation of inocula, fermentation of seed, fermentation, extraction and synthesis.

- Quality control during and after the process
- Sterile area
- General services and others

The plant was approved by the Federal Drug Control Authorities.

The volume of the fermenters is as follows:

Five of 37 m^3

Four of 75 m^3, that is an approximate total volume of 500 m^3

There is no automation.

For this purpose a pilot plant of five fermenters of 5 m^3 and two of 10 m^3 was not used, owing to the fact that the equipment proved inadequate.

Research or technical development activities: There are no activities in the chemical sector. Very basic microbiological work.

Factors which affect production:

- Failures in the electrical energy supply
- Shortage of human technical resources, need for continuous internal training.
- Problems posed by some raw materials (imported raw materials, etc.)

Production capacity:

Fermentation:

- Erythromycin 50 t/a
- Tetracycline 50 t/a
- Oxytetracycline for veterinary use 1 t/a
- Gentiamycin 1 t/a

Semi-synthetic penicillins:

- Ampicillin 30 t/a
- Dicloxacillin
- Cephalexin 8 t/a

Others:

- Zootechnical products (dried mycelia)
- Sterile preparation of antibiotics (tetracycline)

Destination of the production: The products manufactured are sold to the manufacturers of finished pharmaceutical products in the country.

Control of environment: There is no effluent treatment.

Supply of equipment: The fermenters and reactors are manufactured locally.

PLANTA DE PRODUCCION DE QUININAS DE MEXICO

Location: Xalostoc, Mexico. Industrial district.

Ownership: National private sector.

Field of activities: Production of semi-synthetic penicillins as follows:

- ampicillin (Trihydrate, anhydrous and sodium) (injectable grade), cloxacillin and dicloxacillin.

6-aminopenicillanic acid from imported penicillin, technical grade.

Technology used: The greater part of the procedures have been developed by the plant's own scientific personnel, complemented with technology acquired in some of its phases.

The efficacy of the processes seems reasonable as far as the volume of production is concerned, but the quality is not fully satisfactory owing to the fact that the 6-aminopenicillanic acid is obtained by the chemical route and, consequently, the final product is not free from dimethylaniline, even though that is precipitated in the form of naphthalene sulphonate.

Production installations:

- Storage area for solvents and other raw materials.
- Production department with the equipment necessary for synthesis, drying by purification and solvent recovery.
- Quality control during and after the process.
- Sterile area for the production of sodium ampicillin by freeze-drying of the product in bulk.
- General services and others.

Production capacity: In three daily shifts and a week of five working days, the production capacity is 48 t per year for the semi-synthetic penicillins, plus 32 t per year of the 6-aminopenicillanic acid needed.

Destination of the production: The products manufactured are sold to manufacturers of finished pharmaceutical products in the country.

Control of the environment: There is no effluent treatment.

Human resources: The company encounters no problems in this respect. The plant supervisors themselves undertake training and the improvement of productivity.

Supply of equipment: The greater part of the production equipment has been imported. The drying and freeze-drying equipment is manufactured locally.

VISIT TO ORSABE

Location	Cuernavaca, State of Morelos, Mexico
Ownership	Public sector. Multinational (Beecham)
Field of activities	Production of various semi-synthetic penicillins, such as: Ampicillin (trihydrate, anhydrous and sodium) Amoxycillin Cloxacillin Dicloxacillin Flucloxacillin 6-aminopenicillanic acid, enzymatic route.
Technology used	It was received from the parent company. It is the only plant in Mexico which uses the enzymatic route for the production of 6-aminopenicillanic acid; consequently the quality of the finished products is noteworthy.
Production installations	- Storage area for raw materials and solvents - Well installed and instrumented production equipment - Quality control during and after the process - Sterile area for sterile products - General services and others - There is no recovery of solvents. Used solvents are sold. The laboratory equipment is used strictly for production control. Totally dependent on the Beecham parent company.
Production capacity	In three daily shifts and a working week of five days the production capacity is 110 t; the necessary 6-aminopenicillanic acid is 70 tonnes.
Destination of the production	The whole of the production is transferred to its own pharmaceutical division. It is not sold to other companies.
Control of the environment	There is no effluent treatment.
Human resources	The executive personnel of the plant is of Mexican nationality. The remainder of the personnel, with training to high school level, is taken on locally.
Supply of equipment	The greater part of the equipment was imported.

PRODUCTION PLANT OF FERMENTACIONES Y SINTESIS S.A.

Location	Saltillo
Ownership	Private, national
Fields of activities	Production of various semi-synthetic penicillins Ampicillin (trihydrate, anhydrous and sodium) Amoxycillin trihydrate Cloxacillin Dicloxacillin Hetacyclin 6-aminopenicillanic acid by the chemical route
Technology used	The necessary technology was acquired, and at the present time a small team is engaged on improving the process. Glass apparatus has been installed of the size used on laboratory benches. The efficacy of the process is reasonably satisfactory; production levels are somewhat below international levels. As regards quality, the only observation that must be made is the presence of dimethylaniline in the finished product owing to the use of 6-aminopenicillanic acid obtained by the chemical route.
Production installations.	- Storage area for raw materials - Recovery and storage of solvents - Production department with large size reactors, drying station and sterile area for sterile products in bulk - Quality control during and after the process - Fully equipped laboratory to give technical support to the industrial operation - General services and others
Production capacity	In three daily shifts and a working week of five days, the production capacity is 60 t per year plus 40 t of 6-aminopenicillanic acid from technical penicillin.
Destination of the production	The greater part of the production goes to reet the needs of the associated pharmaceutical firms of the Benavidez group. The remainder is sold to local manufacturers of finished products.

Control of the environment	The gaseous effluents are not treated. The liquids are collected by a municipal system of treatment.
Human resources	Obtaining staff is beginning to be difficult because of the installation of other manufacturing plants in the neighbourhood. All the production executive personnel are of Mexican nationality.
Supply of equipment	Most of the equipment was manufactured locally on the basis of detailed engineering acquired with the technology.

VISIT TO CIBIOSA

Location	Saltillo, Mexico
Ownership	Private sector, national
Field of activities	Production of technical grade potassium penicillin G.
Technology used	The technology was acquired in Japan. The plant is confronted by difficulties of various kinds (maintenance of the productivity of the strains, mechanical problems, etc.) and each sector is being reviewed at present. They receive technical assistance from the Japanese supplier of the technology and from a consultant in the United States, who gives information to the owner.
Production installations	- Storage of raw materials and solvents - Production of culture media and continuous sterilizations station - Two seed tanks of 10 m^3 and 4 fermenters of 100 m^3 - Service tanks for the addition of precursors and nutrients - Vacuum filtration unit - Two-stage extraction - Crystallization - Drying - Inoculum laboratory - Control during the process There is practically no automation or instrumentation.
Production capacity	Owing to the reviews and technical problems the present capacity is very low. Taking the installed capacity into account the normal levels of annual production, expressed as technical grade, could be from 285 to 300 tonnes.
Destination of the production	All the present production of technical grade potassium penicillin G is sent to Farfinsa (an associate company of the Benavidez group) for the manufacture of 6-aminopenicillanic acid.
Control of the environment	Treatment of liquid effluents is done in a municipal treatment plant.
Human resources	The executive personnel of the plant is of Mexican nationality. The skilled workers have been trained in the plant, because personnel with the necessary experience could not be found.

Supply of equipment	The fermenters and the corresponding tanks were manufactured locally. Standard equipment (centrifuges, vacuum rotary filters, etc.) is imported.

VISIT TO THE ABBOTT PLANT

Location	Tlaxcala
Ownership	Private-multinational sector
Field of activities	Production of erythromycin
Technology used	Depends totally on the parent company in the United States. The strain is supplied in freeze-dried flasks, ready for the preparation of the inoculum.
Production installations	- Storage of raw materials - Storage and recovery of solvents - Inoculum laboratory - Preparation of culture media and continuous sterilization - Six fermenters of 38 m^3, seed tanks and ancillary equipment - Extraction sector with Podbielniak counter-current separators Chemical sector for the production of miscellaneous salts The equipment is fully instrumented, with automated control panel.
Production capacity	Since 1973, starting from 6 t per year, production capacity has been increased, following a programme, to produce 32 t in 1981 (approximately 61% of the whole of the Mexican market, public and private). Plans for the future involve increasing the fermentation volume by 60%.
Destination of the production	The erythromycin produced is sold to local manufacturers of finished products, although a large proportion is sent to the Abbott pharmaceutical division.
Control of the environment	The treatment of effluents is properly carried out. Liquid effluents are treated by biological breakdown methods.
Human resources	There are no problems. The executive personnel of the plant is of Mexican nationality, trained at the parent company.
Supply of equipment	A considerable percentage of the equipment is imported.

VISIT TO PFIZER

Location: Toluca

Ownership: Private sector - Multinational

Field of activities: Production of terramycin and tetracycline, including the grade used as a food supplement.

Technology used:

It was received from the parent company. No important improvement programme is under way. Completely dependent on the parent company for research and technical development.

Production installations:

As the departments of fermentation, extraction and refining are situated in the industrial complex which comprises the sectors of pharmaceutical formulation, veterinary science and proteolytic enzymes, services such as final and process quality control, general services, maintenance, storage, etc. are centralized.

The fermentation plant comprises the inoculum laboratory for the preparation of culture media and three fermenters of 35 m^3 with the corresponding equipment. Automation and instrumentation are satisfactory and centralized on a wall panel.

The extraction sector comprises extraction in a rough state, refining and the production of derivatives (tasteless bases, salts).

Production capacity

No information was given on this side of things, and as part of the fermentation equipment is used for the production of proteolytic enzymes it is useless to calculate the theoretic capacity.

Destination of the production

Wholly allocated to their own production of pharmaceutical and veterinary products.

Control of the environment

No information was given on this point.

Human resources

The executive personnel of the plant is of Mexican nationality and has been trained at the parent company in the United States.

There is a problem of considerable turnover of personnel.

Supply of equipment

Most of the equipment is produced locally, using their own detailed engineering.

VISIT TO UPJOHN

Location	Cuernavaca, State of Morelos, Mexico
Ownership	Private sector - multinational
Field of activities	Production of lincomycin
Technology used	Received from head office in Kalamazoo, although processes are being perfected locally as regards yields and economy. The technology makes the intensive use of local raw materials possible. Maintenance and improvement of the strains is undertaken directly in Kalamazoo.
Production installation	- Storage area - Inoculum laboratory - 4 fermenters of 65 m^3, with the corresponding fermentation equipment - Ample extraction area and equipment for applying a very complicated multi-phase procedure - Quality control during and after the process - General services and others
Production capacity	22 t of lincomycin per year
Destination of the production	Sent in its entirety to their own pharmaceutical division
Control of the environment	Liquid waste is sent to the municipal treatment plant
Human resources	The executive personnel of the plant is of Mexican nationality. The qualified staff is taken on locally and is trained up to high school level. Internal training. Considerable technical interchange with other Upjohn plants, (Kalamazoo - Puerto Rico), which stimulates rivalry among the different branches.
Supply of equipment	The greater part of the equipment was manufactured locally.

"8 DE MARZO" PRODUCTION PLANT FOR SEMI-SYNTHETIC PENICILLINS

Location	Cotorro - Havana Province
Ownership	Public sector
Field of activities	Production of various semi-synthetic penicillins: Ampicillin trihydrate Anhydrous ampicillin Amoxycillin trihydrate Sodium cloxacillin Sodium dicloxacillin Hetacyclin 6-aminopenicillanic acid to meet their own needs, by chemical route Part of the production encapsulated and in blister packs.
Technology used	Supplied by IBI (Italy), including technical assistance. The production volume and quality are very satisfactory, although the finished products contain small quantities of dimethylaniline owing to the use of 6-aminopenicillanic acid.
Production installations	- Storage of raw materials - Suitable area for recovery and storage of solvents - Production equipment: 2 stainless steel reactors of 4,500 litres, with condenser 2 stainless steel reactors of 4,500 litres 2 basket centrifuges of 1,400 mm diameter - Nitrogen storage and tanker - General services, including a brine refrigeration system - Good system of steam evacuation, with purifying tower - Encapsulation sector (hard pack), including the packing of the production in powder and in blister packs - Quality control during and after the process - Development laboratory.
Production capacity	60 to 70 t per year, in three daily shifts and a working week of five days.
Destination of the production	Chiefly to pharmaceutical plants belonging to the Government. The remainder is exported to IBI as part payment.
Control of the environment	Only gaseous effluents are treated.

Human resources	Both the personnel who fill key posts and the workers are nationals of the country. The training of the former takes place in Italy. Commissioning was the responsibility of the local personnel with foreign assistance.
Supply of equipment	The production and general services equipment was imported but the supplementary equipment, such as that for storage and maturation and the tanks, was manufactured locally.

PATENT PROTECTION IN THE SUBREGION

Situation by countries

Unlike the rest of the Latin American countries the majority of Central American countries grant some form of protection of patents in the pharmaceutical sector. The legal position of the countries considered in this report may be summarized as follows:

a) Costa Rica

i) Legislation: Copyright Law of 26 June 1896 (amended 1921 and 1922); Decree 6129 of 19 April 1978.

ii) Patentability: In accordance with Decree 6129/78 patents may be granted on products and pharmaceutical procedures only if the products are manufactured or the processes are applied in Costa Rica. The application for a patent must include a certificate on which it is stated that the respective product has been registered by the Ministry of Health. Revalidation of foreign patents is allowed, provided the patent is registered in the country of domicile of the applicant.

iii) Duration: pharmaceutical patents only last one year (the period of validity of patents in all other fields is 20 years from the date they are granted).

iv) Exploitation requirements: as indicated in i) above exploitation of the product or process is a condition for granting a patent in the pharmaceutical sector.

b) Cuba

i) Legislation: Patent Law No. 805 of 4 April 1963, Law No. 618 of 1939, Law No. 914 of 4 January 1961. Cuba is a member of the Buenos Aires Convention and of the Paris Agreement for the Protection of Patent Rights.

ii) Patentability: both pharmaceutical products and processes are patentable. The law permits revalidation of foreign patents ("import patents").

iii) Duration: 17 years from the date of issue. Foreign patents revalidated in Cuba may last up to 17 years, or up to 10 years when they are registered three years after having been granted in the foreign country.

iv) Exploitation requirements: patents originally filed in Cuba must be exploited within three years of granting, but three successive extensions of one year may be obtained. If the patent has not been exploited after this period, a licence may be offered for one additional year. The patent expires if an application for a licence is not submitted. Patents revalidated in Cuba must be exploited within a year of the date of granting.

v) Compulsory licences: It is important to bear in mind that, in accordance with Law No. 618 (1958), compulsory licences may be obtained after one year from the granting of a patent when it is in the interest of the national economy.

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* On the basis of information available at the present time it is not clear whether these conditions apply also to patents registered in accordance with the regulations of the Paris Agreement, or whether they have been replaced by article 5A of the latter.

c) Guatemala:

i) Legislation: Law of Invention patents, Decree No. 20011 of 18 August 1931. Guatemala is a member of the Buenos Aires Convention.

ii) Patentability of pharmaceutical products: both the products and the processes are patentable. The law permits revalidation of foreign patents.

iii) Duration: The duration of a patent will not exceed 15 years (or until the expiry of the first foreign patent in the case of import patents).

iv) Exploitation requirements: If, after one year from the granting of a patent, it is not exploited industrially, a compulsory licence may be granted at the request of a third party. However, the licence can be cancelled after 2 years if the holder of the patent (or his .....) begins to exploit the patent.

Rule 5 II of the Guatemalan law on patents should be mentioned. In accordance with this, the patent has no effect against "..... a third party who, for the purpose of experiment or study ..... which in no way implies commercial exploitation, manufactures a product or utilizes a process identical to the product or process patented".

d) Guyana

i) Legislation: Patents and Design Act of 9 May 1937.

ii) Patentability: Substances prepared or produced by means of the use of chemical processes, or for use in medicine are not patentable. However, the processes or methods for the manufacture of such substances are patentable. This protection extends to products produced by the processes described in the patent application. Revalidation of foreign patents is granted on the basis of applications made within three years from the granting of those patents in a foreign country.

iii) Duration: sixteen years from the date of application. This period may be extended by the Supreme Court for 5 or 10 additional years. Revalidated patents expire at the same time as the original patents.

iv) Exploitation requirements: a compulsory licence may be obtained by an interested third party if the patent is not exploited commercially within 3 years; the Director of the Patent Office may, however, defer the decision on a licence application when, for reasons of the nature of the invention or for other reasons, the time which has elapsed is insufficient to permit exploitation of the invention.

v) Compulsory licences: In addition to the compulsory licence referred to in the preceding paragraph a compulsory licence may be granted (or the patent be revoked) three years from a patent being granted, in the event of abuse of monopoly rights, as in the following cases:

a) if the refusal of the patentee to grant a licence on reasonable terms would prejudice trade and the establishment of an industry in Guyana, and granting of the licence was in the public interest.

b) if trade and industry is unfairly prejudiced by the conditions imposed by the patentee for the purchase, hire, licence or use of a patented article or for using or exploiting the process patented;

c) if the existence of a patent - connected with an invention relating to a process which involves the use of materials not protected by the patent or with an invention relating to a substance produced by such process - were used unfairly by the patentee for prejudicing the manufacture, use or sale of such materials in Guyana.

(e) Honduras: Law of Invention Patents, Decree 125 of 15 April 1919, amended by Decrees 151/35, 39/57, 43/57 and the Decree of 9 March 1976. Honduras is a member of the Buenos Aires Convention.

ii) Patentability: In accordance with the reform of 1976 pharmaceutical products are not patentable, and processes may obtain protection only if the applicant can prove that he is using the process in Honduras and can place the product on the market under reasonable conditions of quantity, quality and price. Foreign patents may be revalidated in Honduras for the period up to the expiry of the first patent obtained abroad.

iii) Duration: 10, 15 or 20 years, depending on the importance of the invention and the applicant's application.

iv) Exploitation requirements: As mentioned in ii) above, exploitation is a condition for the granting of pharmaceutical patents. The latter expire, moreover, if they are not exploited within a period of one year.

(f) Mexico

i) Legislation: Law of Inventions and Trade Marks of 19 February 1979. Mexico is a member of the Paris Convention.

ii) Patentability: Mexico is the only country, amongst those considered here, which does not recognise patents, either for pharmaceutical products or processes. Processes to obtain chemico-pharmaceutical products and medicines may, however, be protected by an "inventor's certificate". This is a term created by the Mexican Law of 1976; it does not confer on its holder an exclusive right to use the invention (as patents do) but only the right to receive royalties from any third party who may use the protected invention. In the absence of an agreement between the parties the royalties are determined by the competent administrative authority. Such certificates last ten years.

(g) Nicaragua

i) Legislation: Law of Invention Patents of 14 October 1899, amended by the Decrees of 20 march, 30 July, 18 September 1925; of 21 December 1955 and 3rd and 6th April 1968. Nicaragua is a member of the Buenos Aires Convention.

ii) Patentability: Both pharmaceutical products and processes are patentable. Foreign patents may be revalidated in Nicaragua for the unelapsed period of the original patent.

iii) Duration: 5 to 10 years.

iv) Exploitation requirements: Patents may be revoked if they are not exploited within a year of being granted. This period may be extended if the reason for the lack of exploitation is justified. Expiry may be avoided if an offer is made to sell the rights of patents, or of the articles patented, through advertisements published in The Gazette.

(h) Panama

i) Legislation: Administrative Code, Law 9, 3 July 1961 (articles 1987 to 2004): Decree No. 1 of 3 March 1939.

ii) Patentability: Both pharmaceutical processes and products are patentable. Revalidation of foreign patents is allowed (for not more than 15 years).

iii) Duration: 5, 10, 15 and 20 years, at the option of the Executive.

iv) Exploitation requirements: Patents must be exploited within one third of the period for which they have been granted. Exploitation is not required for import patents.

2. Evaluation

A proper evaluation of the situation relating to the protection of patents in the sub-region, with the object of recommending the most suitable location for the Centre, must consider not only the existence or non-existence of patents on products and/or processes, but also other aspects of the legislation, such as the revalidation of foreign patents, the duration of the patents, the conditions of exploitation, and the existence of obligatory licences. The

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* Likewise exploitation would seem not to be required when a foreign patent is effectively exploiting the invention in its country of origin.

actual implications of a system of patents depend largely on the characteristics of these aspects just mentioned. As discussed below, in particular for the case of two countries, the duration of the patents and other conditions imposed by the law can, in practice, seriously limit legal protection and consequently reduce the possibility of patents being used as potential restrictions on the activities of third parties in importing or producing pharmaceutical products.

Table 1 summarizes the situation with regard to patentability in the countries considered in this report. According to the type of patents granted these countries may be grouped as follows:

I.	Completely non-patenting	Mexico
II.	Patenting of processes only	Guyana, Honduras
III.	Patenting of products and processes	Costa Rica, Cuba, Guatemala, Nicaragua, Panama

It is clear, on the basis of this classification, that Mexico is the only country without any protection of patents. It must be remembered, however, that inventor's certificates may be obtained in Mexico for processes for the manufacture of pharmaceutical products. This may imply the need to pay compensation to third parties for the use of a certificate, as well as the possibility of charging royalties for the use of certificates possibly obtained and registered in the name of the Centre itself.

Although Guyana and Honduras belong to the same group (II) their situations are markedly different. In the first country protection of the process extends to the products produced by the application of such process. Thus, the holder of a patent can prevent imports of such products manufactured abroad using the patented process. In contrast to this reinforced protection the conditions

imposed in Honduras for granting patents on pharmaceutical processes would probably make it rather difficult to obtain them.

Table 1

Patentability in the pharmaceutical sector

Country	Product	Process
Costa Rica	Patentable (only for one year, and if the product is produced in Costa Rica)	Patentable (only for one year if the process is applied in Costa Rica)
Cuba	Patentable	Patentable
Guatemala	Patentable	Patentable
Guyana	Not patentable	Patentable (protection extends to substances produced using the processes described in the application)
Honduras	Not patentable	Patentable only if the applicant can prove that he is using the process in Honduras and can place the product on the market under reasonable conditions of quantity, quality and price)
Mexico	Not patentable	Not patentable (an inventor's certificate may be obtained)
Nicaragua	Patentable	Patentable
Panama	Patentable	Patentable

PART III

THE CENTRE

OBJECTIVES, PERSONNEL AND EQUIPMENT

1. INTRODUCTION
2. OBJECTIVES
3. AREAS OF ACTIVITY
4. ORGANIZATION OF THE CENTRE: DEPARTMENTS AND PERSONNEL
5. EQUIPMENT
6. SERVICES
7. BUILDINGS
8. SCHEDULING
9. ECONOMIC ANALYSIS
10. LEGAL ASPECTS

1. INTRODUCTION

It is well known that the largest and most profitable companies allocate a sizeable percentage of their sales (of the order of 10% or even more) to research and development with the aim of achieving continual innovation in products and ongoing improvement of their production processes. The investment in each of these areas varies according to the firms, but as a general rule the amount allocated to new products is greater than that allocated to process improvements. We can quantify, therefore, the percentage allocated to process improvements at between 2 and 5% of the value of sales. This figure, from an accounting point of view, is charged to the industrial cost of the product benefiting from that improvement.

The problem of planning the size, personnel and material facilities of a new independent Centre lies in the fact that neither the investment nor the operating expense can be charged, from an accounting point of view, to existing or highly probable sales but have to be charged to future attainment in terms of technologies generated by the Centre.

The value of these technologies must be such that the cost of the Centre may be reasonably charged to the industrial products which may be produced by industrial plants, using technologies from the Centre. In this way the Centre will be financially self-sufficient and will be able to increase its programmes and facilities.

From another aspect it must be agreed that it will produce intangible advantages for the subregion, such as the training of personnel, distribution of information, advice, analytical control, etc., which it will not be possible to charge to the technologies but to the industrial operations under the general heading of technical assistance.

The new potential requirements for 1986 have been calculated at approximately $70 million/year, represented by Penicillin, semi-synthetic Penicillins, Tetracyclin and Erythromycin; if those requirements are to be covered by the production achieved in plants installed in the subregion, an investment of the order of 5% on estimated sales will be justified. That being so, the Research and Development Centre may be reasonably designed taking as a basis a budget of $3.5 million per year.

Although a detailed economic study of the Centre is beyond the scope of this report, the preceding figure agrees with general values for this type of activity.

A general study in terms of personnel, material facilities is therefore presented for a Research and Development Centre capable of working on three or four basic projects for the development of fermentation, enzymatic and synthetic technologies for antibiotics, as well as other connected activities. The details of personnel, buildings and equipment are given by way of guidance and must be adapted to the reality of the programmes which will be decided on at the appropriate time.

2. OBJECTIVES

2.1 To provide technologies for commencing the production of selected antibiotics

Bearing in mind that the Centre's budget has been evaluated on the basis of 1986 sales of Penicillin, semi-synthetic Penicillins, Tetracyclin and Erythromycin, the Centre's programme must be designed to achieve the technologies for the antibiotics mentioned. That means that, within the time-table for construction, the evaluation of the available know-how and, therefore the nature of the programmes to be developed, must be placed at its end.

The selection of the know-how most suitable for commissioning and its adjustment to local conditions, in terms of raw materials and transfer to the industrial plants that by 1986 may have been installed in the subregion, may represent the challenge for the first five years of operation of the Centre (including the two years which are reckoned to be necessary for installing it); experiments at pilot level will be essential for the transfer of technology to the industrial plants.

2.2 To provide technical assistance

In the industrial operation of producing antibiotics by fermentation many parameters must be kept under control. This is part of the task of the production personnel, but very often it is required to carry out a careful investigation into various production problems. The Research Centre must assist production in all its technical aspects. Technical assistance comprises all this ongoing work for the improvement of strains, cultures and better conditions for fermentation. In addition the transfer to plant scale of all this activity must be made after prior work at a pilot scale.

2.3 Training of technical personnel for the Centre itself and for industry

One of the problems of the subregion is the shortage of personnel trained in fermentation technology. This may be one of the initial problems in the organization of the Centre. A few persons must be taken on with prior experience acquired in this field. The candidates must preferably be selected from persons working in the industrial area and who have suitable experience in

disciplines of pilot plant, bio-engineering and industrial microbiology in industries producing antibiotics. This may prove costly, but is unavoidable. Besides this small nucleus the other researchers may be recruited from amongst the best graduates from the universities in the region. If these appointments are successful in about two years all the personnel of the region will be in a position to handle the Centre's projects and proceed with the training of operatives for the industry.

2.4 Provide technology for the production of other antibiotics

In the course of the next five years the use of other antibiotics, such as the cephalosporins, may reach such a level, in the subregion, as to justify the inclusion of projects for that purpose in its programmes.

2.5 Research in other fields of Bio-engineering and Industrial Microbiology

Industrial Microbiology is in continuous evolution in terms of objectives and technical proposals. The fermentation of antibiotics represents, today, only a small segment of the use of microorganisms for the production of substances for consumption by humans. The Centre must identify the most important sub-regional objectives and, in a second stage, devote its efforts to attaining them, acquiring in the meantime the most sophisticated techniques (e.g. molecular engineering) which are necessary for that purpose.

Emphasis must be given to the fact that the Centre must, in the long term, fill the gap which exists between the developing world and the developed world in the field of Industrial Microbiology.

3. AREAS OF ACTIVITY

The Centre will have as its mission the development of technologies in their fullest sense, that is to say covering all the elements which may be defined as technology: strains, cultures, parameters to be taken into account in carrying out fermentation, collection and extraction techniques, final purification, quality analysis, evaluation of results, necessary equipment, the role and quality of personnel, etc.

However, as has been stated in various parts of this report, the infrastructure of the Centre in itself will allow services, related in one way or another to the pharmaceutical operation of the subregion, to be provided.

The following areas covered by the Centre may be specifically mentioned:

1. INFORMATION

1.1 Technical

1.1.1 Pharmacotechnology
1.1.2 Pharmaceutical chemistry
1.1.3 Unit processes
1.1.4 Quality. Stability. Specifications and methods of analysis.
1.1.5 Pharmacology
1.1.6 Engineering
1.1.7 Raw materials
1.1.8 Packing. Materials. Techniques
1.1.9 Sources of technology

1.2 Commercial

1.2.1 Prices of raw, intermediate and finished materials

1.2.2 Suppliers

1.2.3 Markets. Trends

1.3 Legal

1.3.1 Patents

1.3.2 Methods of negotiation and contracts

2. ADVICE

2.1 Evaluations

2.2 Audits

2.3 Solution of specific problems in pharmaceutical areas, fermentation, raw materials, etc.

3. RESEARCH AND DEVELOPMENT

3.1 Development of new technologies in all areas

3.2 Improvements in existing technologies

3.3 Raw materials. Replacement of traditional by local materials

3.4 Programme of improvements: energy, solvent recovery, by-products, etc.

4. TECHNICAL ASSISTANCE

4.1 Training programmes

4.1.1 On site

4.1.2 At the Centre

4.1.3 At places set up by the Centre

4.2 Re-training programmes

4.3 Experts available for solving problems linked with the technologies developed by the Centre (permanent, or from a list held by the Centre).

5. ECONOMIC AND FINANCIAL

5.1 Feasibility

5.2 Costs

5.3 Detection of problems in this area and solutions

6. SUB-INDUSTRIAL PLANT

6.1 Fermentation

6.2 Extraction

6.3 Synthesis

6.4 Natural products

6.5 Miscellaneous (Packing, formulations, etc.)

4. ORGANIZATION OF THE CENTRE

1. OPERATIONAL LEVEL

A working Director, who must cover all organizational aspects and the attainment of objectives.

2. CORPORATIVE CONTROL LEVEL

A representative of each member country who, in accordance with the Statutes of the Centre, will exercise Political and Industrial operative control over the corporation.

3. ADMINISTRATIVE LEVEL

A manager, who must cover all aspects connected with Personnel, Accounts, Purchases, minor Contacts with the Government where the centre is located, and Public Relations.

4. TECHNICAL MANAGEMENT

A non-executive Director, capable of identifying the technical goals of the Centre. Not only must he be knowledgeable in his own right but must have a capacity for channelling the enquiries and specific knowledge of the area managers. He must maintain contact with those advisors whom the Centre appoints for temporary missions, and also keep updated a list of persons capable of carrying out tasks of technical assistance and of solving problems in the various areas of activity of the Centre.

5. TECHNICAL AREA MANAGERS

Under the general oversight of the Technical Management the technical area managers will carry out everything related to their speciality,

with personnel at lower level reporting directly to them. They will periodically report their findings and, when there is a call for it, they will issue provisional and/or final reports. They will be responsible for the self-administration of their area, supporting the administrative manager so that the latter may summarize all the non-technical activity in his reports and accounts.

Each specific discipline will have an area manager:

MICROBIOLOGY AND GENETICS

BIOCHEMISTRY

CHEMISTRY (Synthesis and Natural Products)

QUALITY in all its aspects (Centre itself, and Assistance)

ENGINEERING (Design, operation and supervision of the Centre's own services)

SUB-INDUSTRIAL PLANT

6. ANCILLARY SERVICES

These will be responsible for:

Library and Information

Secretarial Support

Maintenance and Services

7. SUB-INDUSTRIAL PLANT

In addition to the essential need for the technologies, developed at laboratory level, confirming their capacity for being used at industrial level, this semi-industrial Plant would be designed in such a way that, when circumstances required, it could produce, in a routine or ad hoc way, products whose quality and quantity made them suitable for sale.

1. MANAGEMENT - 6

1 WORKING DIRECTOR

1 ADMINISTRATOR

1 LIBRARY, INFORMATION

3 SECRETARIES - ADMINISTRATIVE ASSISTANTS

2. DEPARTMENT OF MICROBIOLOGY AND GENETICS - 12

5 MICROBIOLOGISTS AND GENETICISTS

4 TECHNICIANS

3 OPERATIVES

3. DEPARTMENT OF CHEMISTRY - 3

2 ORGANIC CHEMISTS

1 TECHNICIAN

4. DEPARTMENT OF BIOLOGY - 3

2 BIOLOGISTS

1 TECHNICIAN

5. ANALYTICAL DEPARTMENT - 8

1 CHEMIST

1 MICROBIOLOGIST

3 TECHNICIANS

3 OPERATIVES

6. SUB-INDUSTRIAL PLANT - 14

1 BIO-ENGINEER

1 MICROBIOLOGIST

1 CHEMIST

4 TECHNICIANS

7 OPERATIVES

7. DESIGN AND PROJECTS DEPARTMENT - 4

1 BIO-ENGINEER

1 CHEMICAL ENGINEERING

2 TECHNICIANS

5. EQUIPMENT

THE BASIC PIECES OF EQUIPMENT ARE LISTED BELOW. IT MUST BE POINTED OUT THAT THIS LIST DOES NOT INCLUDE:

- OFFICE FITTINGS
- TOTALLY EQUIPPED LABORATORY BENCHES (WATER-VACUUM-GAS-COMPRESSED AIR - DEIONISED WATER)
- COMPUTER TERMINALS OR DATA PROCESSORS
- GLASS APPARATUS, REAGENTS AND OTHER ITEMS OF WHICH AN INVENTORY CANNOT BE MADE
- LIBRARY, WITH THE NECESSARY BOOKS AND PUBLICATIONS

5.1 DEPARTMENT OF MICROBIOLOGY AND GENETICS

3 REFRIGERATORS (200-350 l)
2 S.S. STEAM AUTOCLAVES (200 l)
2 DRY HEAT STERILIZERS (100 l)
5 STAINLESS STEEL TANKS WITH STIRRERS FOR PREPARATION OF MEDIA
1 ANALYTICAL BALANCE
1 SEMI-ANALYTICAL BALANCE
6 WATER-BATHS (4 l)
1 ELECTRICAL WATER DISTILLER
3 pH METERS
2 LABORATORY CENTRIFUGES (ONE REFRIGERATED)
1 HIGH-SPEED REFRIGERATED CENTRIFUGE
3 LAMINAR FLOW STERILE VESSELS
1 VESSEL FOR MUTAGENS, GASES OR SOLVENTS
1 MERCURY LAMP, BACTERICIDAL, LOW PRESSURE
1 CALIBRATED ULTRA-VIOLET INTENSITY GAUGE
1 NEPHELOMETER
1 PHASE-CONTRAST MICROSCOPE WITH MICROPHOTOGRAPHY
1 MICROMANIPULATOR
1 STEREOSCOPIC MICROSCOPE
1 AUTOMATIC COLONY COUNTER
8 STIRRERS WITH THERMOSTAT

5.2 DEPARTMENTS OF BIOCHEMISTRY AND ORGANIC CHEMISTRY

1 SPECTROPHOTOMETER, RECORDING, UV AND VISIBLE

1 SPECTROPHOTOMETER, UV AND VISIBLE

2 pH METERS

1 APPARATUS FOR AUTOMATIC TITRATION

1 ELECTROPHORESIS APPARATUS

1 ANALYTICAL BALANCE

1 SEMI-ANALYTICAL BALANCE

4 ELECTROMECHANICAL STIRRERS

4 MAGNETIC STIRRERS

4 BATHS WITH THERMOSTAT

3 VESSELS FOR GASES AND SOLVENTS

3 REFRIGERATORS (200 l)

1 FREEZER (300 l)

2 LABORATORY VACUUM PUMPS

2 LABORATORY CENTRIFUGES

1 PREPARATIVE CENTRIFUGE

1 ULTRAFILTRATION EQUIPMENT

2 APPARATUS FOR CELL DISINTEGRATION

1 COMPLETE TLC UNIT

1 COMPLETE PC UNIT

2 MULTI-CHANNEL PERISTALTIC PUMPS

1 AUTOMATIC COLLECTOR FOR FRAGMENTS, REFRIGERATED

1 VACUUM DRIER, HEATED

4 VACUUM EVAPORATORS, ROTATIVE

5.3 ANALYTICAL DEPARTMENT

5.3.1 BIOLOGICAL TESTING

2 AUTOMATIC DILUTION UNITS

2 LAMINAR FLOW STERILE VESSELS

2 UNITS FOR READING COLONY DIAMETERS

2 BATHS WITH THERMOSTAT

1 S.S. STEAM AUTOCLAVE, (33 l)

2 REFRIGERATORS (100 l)

4 INCUBATORS

1 AUTOMATIC WASHING-MACHINE FOR GLASSWARE

1 BENCH-TOP COMPUTER

5.3.2 PHYSICAL CHEMISTRY

2 AUTOANALYSERS

1 COMPLETE MICRO-KJELDAHL UNIT

1 MELTING POINT UNIT

2 SPECTROPHOTOMETERS, UV AND VISIBLE

1 SPECTRO-FLUORIMETER

1 NMR SPECTROPHOTOMETER

1 CHROMATOGRAPHY UNIT

1 EQUIPMENT FOR HPCL

1 GAS-LIQUID CHROMATOGRAPH

1 COMPLETE TLC UNIT

1 COMPLETE PC UNIT

1 ATOMIC ABSORPTION ANALYSER

1 POLARIMETER

2 pH METERS

1 KARL-FISHER UNIT

1 LABORATORY CENTRIFUGE

2 ANALYTICAL BALANCES

1 SEMI-ANALYTICAL BALANCE

5.4 SUB-INDUSTRIAL PLANT

5.4.1 FERMENTATION

16 GLASS FERMENTERS (10 1)

16 STAINLESS STEEL FERMENTERS (30 1)

6 STAINLESS STEEL FERMENTERS (300 1)

2 STAINLESS STEEL FERMENTERS (3,000 1)

ALL THE FERMENTERS MUST BE EQUIPPED WITH ABSOLUTE FILTERS, pH AND TEMPERATURE RECORDERS AND REGULATORS, DISSOLVED OXYGEN AND ABSORBED POTENCY MONITORS, FOAM-ANTIFOAM AND AIR STREAM. THREE OF THE SIX FERMENTERS OF 300 1 AND THE TWO OF 3,000 1 MUST IN ADDITION BE EQUIPPED WITH CONTINUOUS MONITORS OF THE O_2 and CO_2 CONTENT OF VENTED AIR.

1 FILTER FOR STERILIZATION OF LIQUIDS

2 STAINLESS STEEL CONTAINERS (50-100 1), STIRRED AND FITTED WITH EXTERNAL JACKET FOR PREPARATION AND STERILIZATION OF CULTURE MEDIA FOR THE GLASS FERMENTERS

2 CONTAINERS WITH STIRRERS FOR MEDIA PREPARATION (2,000 l)

2 BENCH pH METERS

2 LABORATORY CENTRIFUGES

1 STERILE LAMINAR FLOW VESSEL

2 BALANCES (10 kg)

1 SCALES (250 kg)

1 ANALYTICAL BALANCE

1 SEMI-ANALYTICAL BALANCE

1 REFRIGERATOR (200 l)

1 COLD ROOM

AIR FILTERS AND PREFILTERS

PUMPS

WATER DEIONIZER

5.4.2. FILTRATION

2 STAINLESS STEEL VESSELS (3,000 l) FOR STORAGE OF MASH

2 STAINLESS STEEL VESSELS (3,000 l), WITH JACKET, FOR FILTERED MASH

1 ROTATING VACUUM FILTER, 1 m^2

1 FILTER PRESS

2 PORTABLE STAINLESS STEEL VESSELS (300 l) WITH INTERNAL COIL AND STIRRER

1 SOLID-LIQUID CENTRIFUGAL SEPARATOR (500 l/h)

5.4.3 EXTRACTION

1 CENTRIFUGAL EXTRACTOR, COUNTER-CURRENT (100 l/h)

2 LIQUID-LIQUID SEPARATORS (100-500 l/h)

3 S.S. VESSELS (300 l), WITH INTERNAL COIL

2 LABORATORY ROTATING VACUUM EVAPORATORS

2 BATHS WITH THERMOSTAT

1 VESSEL FOR SOLVENTS

5.4.4 PURIFICATION

1 VACUUM PUMP (2 mm)

1 FILM CONCENTRATOR, GLASS, MULTICOLUMN (50-150 l/h)

1 FILM CONCENTRATOR, GLASS, SINGLE COLUMN (3-8 l/h)

4 PERISTALTIC PUMPS, 50-200 l/h and 1-10 l/h

2 VITREOUS-LINED REACTORS (100 l), WITH VARIABLE STIRRING, CONTROL OF TEMPERATURE AND SUITABLE FOR VACUUM WORK

2 BASKET CENTRIFUGES

1 STAINLESS STEEL COLUMN (100 l)

5 GLASS COLUMNS (12-120 cm)

5 GLASS COLUMNS (8-80 cm) WITH JACKET

1 CENTRIFUGAL PUMP (300 l/h)

5.4.5. CHEMISTRY

2 VITREOUS-LINED REACTORS, COMPLETELY EQUIPPED (100 l)

2 COMPLETE REACTION UNITS, GLASS (50 l) AND COMPLETELY EQUIPPED

1 VITREOUS-LINED REACTOR, COMPLETELY EQUIPPED (300 l)

1 STAINLESS STEEL REACTOR (316 l), COMPLETELY EQUIPPED

1 FLUID BED DRIER (15 kg), GLATT TYPE

1 BUCHNER TYPE TABLE FILTER, 50 cm DIAMETER, STAINLESS STEEL, 316 l

1 BASKET CENTRIFUGE

1 VACUUM DRIER, HEATED (300 l)

1 VACUUM UNIT, WITH WATER RING PUMP OR STEAM EJECTOR

ALL THE EQUIPMENT IN SECTORS 5-4-3, 5-4-4 and 5-4-5 MUST BE RATED FIRE AND EXPLOSION PROOF.

6. SERVICES

1 STEAM GENERATOR, 1 t/hour, COMPLETE, WITH FUEL TANKS, CONDENSATE, WATER AND WATER SOFTENER, ADDITION OF ADDITIVES, PRESSURE AND OUTPUT RECORDERS

2 AIR COMPRESSORS, OIL-FREE, 5 m^3/MINUTE, COMPLETE WITH CONDENSATE SEPARATOR, POST-COOLER, PALL PRIMARY FILTER AND TEMPERATURE, PRESSURE AND STREAM RECORDERS.

1 AIR COMPRESSOR, OIL-FREE, DRY, 1 m^3/MINUTE

1 COLD UNIT, BRINE, 10,000 F/M

1 AIR CONDITIONING UNIT

1 WASHING UNIT FOR GASEOUS EFFLUENTS

1 PRE-TREATMENT UNIT FOR LIQUID EFFLUENTS, CHEMICAL METHOD

7. BUILDINGS

THE CIVIL ENGINEERING MUST BE BASED ON THE REQUIREMENTS SET OUT IN THE FOLLOWING TABLE

SECTOR	m^2
1. ADMINISTRATION AND SOCIAL	
1.1 GENERAL MANAGEMENT, DOCUMENTATION, ADMINISTRATION	200
1.2 SOCIAL, CONFERENCES, CLOAKROOMS	400
1.3 STORES	200
2. MICROBIOLOGY AND GENETICS	200
3. CHEMISTRY AND BIOCHEMISTRY	100
4. ANALYTICAL	150
5. SUB-INDUSTRIAL PLANT	800
TOTAL	2,050

8. SCHEDULING

The following approximate schedule has been prepared on the assumption that all the bodies listed must collaborate to the full.

Two phases are considered: one phase linked with the international agreements, the other with the technical aspects of the installation and operation of the Centre. It is recommended that, owing to the long period required, steps be taken to bring forward the beginning of 2. before the end of 1, and this could be discussed at the next meeting of the advisory group. This would, of course, affect the requirements for funds.

1. ACTIONS TO BE TAKEN IN THE AREA OF INTERNATIONAL AGREEMENTS

ACTION	TIME IN MONTHS PART	TIME IN MONTHS CUMULATIVE
- Meeting of Advisory Group	-	-
- Examination of proposal by the national and international bodies	3	3
- Preparation of the Centre's statutes	2	5
- Examination of the statutes by the national and international bodies	4	9
- Meeting of representatives to approve the statutes	-	9
- Constitution of Executive board and director	2	11
- Preparation of Design, Programme and Budget, and distribution to the national and international bodies	4	15
- Examination of the proposal by the Board	4	19
- Commencement of construction	-	-

2a. CONSTRUCTION AND OPERATIONS OF THE CENTRE

- Preparation of the project	4	4
- Tendering	6	7 (1)
- Selection of equipment. Placing purchase orders	10	14 (1)
- Construction	12	17 (1)
- Receipt of equipment	8	18 (1)
- Installation	9	21 (1)
- Commissioning	3	24

2b. RECRUITMENT OF STAFF

- Selection and appointment of the initial group (2)	6	6
- Selection and appointment of 2nd group (3)	18	24
- Selection and appointment of remainder of personnel	9	36 (1)

2c. NEEDS FOR FUNDS (in $ millions)

	YEARS					
Type of expense	1st	2nd	3rd	4th	5th	TOTAL
Investment	2.5	2.5	0.5	0.3	0.2	6.0
Operating expenses	0.6	1.2	2.5	3.5	3.5	11.3
Annual Total	3.1	3.7	3.0	3.8	3.7	17.3

(1) The time for completion of the action is indicated, but this is begun before the end of the preceding one.

(2) 1 Director, 2 Secretaries, 1 Administrator, 2 Microbiologists, 1 Biochemist, 1 Organic Chemist, 1 Analytical, 1 Bio-engineer, 1 Chemical Engineer.

(3) 2 Microbiologists, 2 Organic Chemists, 1 Biochemist, 1 Bio-engineer, 6 Technicians, 6 Operators.

9. TECHNICO-ECONOMIC ANALYSIS OF THE INCREASE IN PRODUCTION NECESSARY FOR THE SUB-REGION IN 1986: IMPLICATIONS FOR THE CENTRE

An economic evaluation of the Centre has been carried out on the basis of the information collected by the mission.

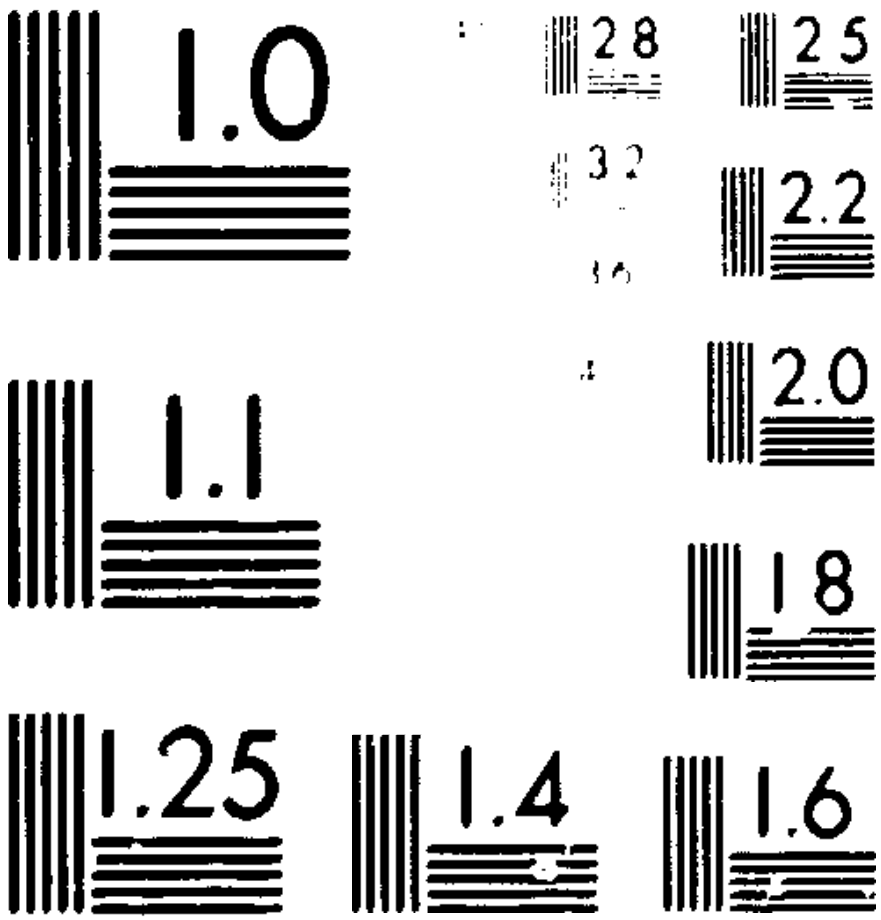
The consumption of the sub-region in the year 1980, in tonnes, was found to be as follows:

	BY FERMENTATION				
COUNTRY	PENIC.G.	TETRA	ERYTHRO	TOTAL	SEMI-SYNTHETICS
MEXICO	926	224	74	1,224	341
CUBA	14.17	19.77	8.15	42.09	3.60
NICARAGUA	22.6	3.7	6.18	32.48	20.83
GUATEMALA(1)	17.70	6.70	2.20	26.60	10.60
COSTA RICA(2)	14.0	5.07	3.07	22.14	20.70
PANAMA	2.07	9.80	0.23	12.10	0.70
HONDURAS	1.45	1.35	0.30	3.10	2.90
TOTALS	998.49	270.69	94.15	1,363.33	402.83
PENIC. from 6-APA	74.85			74.85	
FINAL TOTAL	1,073.34			1,438.18 "T"	

(1) Sub-division in accordance with the average of the subregion from the total figure available.

(2) Estimated from 1981.

Assuming one or more plants are installed they would be available by 1986 in accordance with the following plan:



MICROCOPY RESOLUTION TEST CHART

1982 - Taking of decisions feasibility and consideration of legal and financial aspects.

1983 - Design engineering, selection of site, contractors and suppliers of technology.

1984-85 - Construction

1986 - Commencement of operations.

Consequently, the production capacity of that plant will meet the demands of the subregion by the year 1986 (assuming that the increase in consumption during the following years will be covered by an increase in productivity of the new antibiotics Centre).

It has been assumed that consumption will increase at an average of 7% per year (in weight of active substance), which means that the figure shown as "T" (of 1,438.18 tonnes per year in 1980) must be increased to 2,158 tonnes per year in 1986.

In order to determine the size of the industrial plant the present fermentation capacity must be taken into consideration. In fact only Mexico possesses fermentation plants which operate with a capacity of 1,525 cubic metres and which produce 635 tonnes of the three antibiotics enumerated (the penicillin is of technical grade). Apparently the productivity of those plants is very low, since it does exceed 0.055 kilogrammes per cubic metre/hour. This output would be increased if we excluded one of the plants, increasing productivity to 0.075 kilogrammes per cubic metre/hour. An increase in local production of 65 tonnes by 1986 has been estimated, which would place local production in 1986 at 700 tonnes.

When the new plant or plants operate at full capacity their production would be 1,248 minus 700, that is to say 1,458 tonnes per annum. The size of the production facilities could be estimated on the basis of 25 kilogrammes of final product obtained in 200 hours of fermentation, or 0.125 kilogrammes per cubic meter/hour. Operating 7,500 hours per year the production of a cubic metre of fermentation capacity would reach 937.5 kilogrammes per cubic metre. Therefore the production capacity would be $\frac{1,458}{937.5}$ = 1.555 cubic metres of usable volume.

This capacity is purely theoretical, since it refers to an ideal antibiotic (quite close to technical penicillin). In order to determine a plant size with greater accuracy the following breakdown could be considered (based on an annual increase in consumption of 7%):

1.1 Consumption of penicillin in 1986 = 1,073 x 1.5007 = 1,610 tonnes
Less present production - 337
Production necessary by 1986 1,273 t
Estimated productivity in 1986 = 0.9375 t/m^3/year
Usable fermentation volume $\frac{1,273}{0.9375}$ = 1,358 m^3

1.2 Consumption of tetracycline in 1986 = 406.2 tonnes
Less local production in 1986 - 75
Production required in 1986 331.2 t
Productivity in 1986 = 20 kg/m^3 in 200 hours = 0.1 kg/m^3 hour or 0.75 t/m^3 year
Usable fermentation volume necessary = 331.2/0.75 = 441.6 m^3

1.3 Consumption of erythromycin by 1986 = 141.22 tonnes
Less local production in 1986 - 105.5
Production necessary in 1986 35.72 t
Productivity in 1986 = 0.187 t/m^3/year.
Usable volume necessary = $\frac{35.72}{0.187}$ = 191 m^3

1.4 Fermentation capacity subtotal

Penicillin	1,358 m^3
Tetracycline	441 m^3
Erythromycin	191 m^3
	1,990 m^3

1.5 Semi-synthetic penicillins

Present consumption is 400 t/year and the annual estimate for 1986 is 600 tonnes. Present production (Mexico and Cuba) is 280 tonnes per year, which could increase to 420 tonnes in 1986. The quantity which needs to be produced would be 180 tonnes.

1.6 Value production:

The following production values (preliminary estimates) for 1986 are taken from the figures mentioned above:

				US$/tonne	US$ millions
Penicillin G	1,273	t/year	x	35,000	= 44.555
Tetracycline	331.2	"	x	35,000	= 11.592
Erythromycin	35.7	"	x	80,000	= 2.85
Ampicillin	180	"	x	100,000	= 18.0
Less penicillins for semi-synthetics	220	"	x	35,000	= -7.7
				Value US$	69.29 millions

2.1 This figure, which must be regarded as approximate, gives an idea of what the size of the operational volume would be, part of which would be used for research and development. Based on that part, it would be possible to determine the size of the Centre.

2.2 The fundamental parameters for the setting up of the Centre are:

In broad outline, the part of productivity which could be allocated to research would be around 10%. Half of that share would be reserved to research into new products, which constitutes one of the objectives of the Centre, the rest would be used in technological and microbiological development and in assistance in areas directly related to the production of antibiotics. This means that $3.5 million/year could be used to cover the operating cost of the Centre.

2.3 The above sum may be broken down as follows:

- Assuming that the cost of buildings, equipment and installations of the Centre did not exceed the sum of $6 million, and that financial and depreciation represented 20% of that sum, these would represent $1.2 million.

- It is possible to evaluate the operational cost of the Centre (excluding personnel). A preliminary estimate is as follows:

	US$
Electrical energy, 500 kW/h x 7,500 h/year x 6 cents kW	225,000
Steam, 100,00 cal x hour x 7,500 h x 3 cents/1,000 cal	25,000
Engineering assistance (5% of the value of the plant	300,000
General and administration expenses (10%)	350,000
Raw materials and chemicals	100,000
Total cost of the operations	1,000,000

- The cost of salaries for the personnel may be estimated at US$25,000 per person/year; then 52 x 25,000 US$ 1,300,000
- Depreciation, 20% on 6,000,000 US$ 1,200,000
- Operating cost per annum US$ 3,500,000

2.4 Although a reliable estimate of the investment necessary requires having a finished project available, an approximate idea may be obtained by using conventional factors.

		US$
2.4.1	Laboratories 450 m^2 at 3,000/m^2	1,350,000
2.4.2	Pilot Plant 800 m^2 at 2,000/m^2	1,600,000
2.4.3	Offices 250 m^2 at 1,000/m^2	250,000
2.4.4	Equipment, Pilot Plant	1,600,000
2.4.5	Services and Stores 500 m^2 at 1,000/m^2	500,000
2.4.6	Central Services (45% of 2.4.4)	700,000
	TOTAL	6,000,000

10. LEGAL ASPECTS

In a preliminary manner it is possible to define a group of aspects to be taken into account in the constitution of the Centre. Amongst these the following deserve special attention:

10.1 Regional character

A basic feature of the Centre will be its regional character. The countries of the subregion must participate on a footing of equality, or in accordance with the method which is adopted for the implementation and functioning of the Centre. This participation should be reflected both in the contributions, in the allocation of the managerial functions and in the nationality of the plant personnel.

10.2 Creation by means of treaty

The Centre should be set up by means of an international treaty, which will determine its functions, management, administrative structure, contributions and other features of the respective statutes.

10.3 International legal staff

The Centre should be provided with its own legal staff, qualified to contract for and execute all acts proper to its purpose. Independently of the legal staff that may be assigned to it, in accordance with the standards of the country where it is located, the Centre should be provided with international legal staff. This would result, amongst other things, in its employees enjoying certain immunities in the countries party to the treaty.

10.4 Institutional form

Given the functions that the Centre should perform, and the need to generate funds for its maintenance, the possibility should not be excluded of the Centre charging for the sale of its services, technology or products, to include a reasonable profit margin. The Centre could establish itself as a multinational company* with powers to carry out all commercial operations which come within its activities. The alternative is the setting up of an intergovernmental entity. The relative advantages of one or other organizational form should be studied in greater detail, in particular regarding the possibility of receiving direct or indirect help from national or international bodies for financing the Centre's programmes.

10.5 Contributions

Examination of this question should include, at the proper time and when more concrete discussions between the countries have been held, the following aspects:

I) Public or private character: in principle, and in accordance with the proposed characteristics of the Centre, it is to be assumed that this would be set up completely or fundamentally with public contributions from the participating countries. Possible participation of private investors in the capital should not, however, be excluded, if the Centre takes the form of a company. Of course, the public character of the

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* an interesting precedent of a multinational company is the creation of MULTIFERT under the auspices of the Latin American Economic System.

contributions would not imply that the services of the Centre would be directed solely to the public sector. Its activities would be directed towards satisfying the requirements of the private or public sector of the subregion, without distinction.

II) Nature: Financial contributions, or contributions in kind (buildings, equipment, etc.), could be accepted. If the Centre is set up as a company then in principle, and except for extension of the capital, contributions should be made at the time of constitution. If it were an intergovernmental entity, it is possible to consider an initial contribution and annual quotas in accordance with the amount of each country's contribution.

III) Participation by countries: If the form of a company is chosen, the participation of each country could be graded in accordance with its interest. The constitutive treaty ought to lay down the respective shares but closing the door to new members. In the case of an intergovernmental entity the countries should negotiate and the treaty should fix the measure of each country's share. This could be established on the basis, for example, of the relative contribution of each country to the international organizations. The degree of development of the pharmaceutical industry, the consumption of antibiotics and other more specific variables could also be taken into account.

IV) Non-transferability: The participating governments will not be able to transfer their share in the Centre to third parties, except to public institutions in the same titular country.

10.6 National and preferential treatment

The Centre ought to receive the same treatment in the home country as national firms or entities for fiscal purposes, or for obtaining promotional benefits (for example, for exports). In addition the constitutive treaty could establish special benefits for the activity of the Centre in the subregion, such as exemption from import duties and income tax, immigration formalities for its employees, etc.

10.7 Conditions for the transfer of technology for the production of antibiotics

a) Pre-contractual phase

The negotiation of a contract of transfer of technology for the manufacture of antibiotics may be preceded by a preliminary stage in which the potential supplier passes to the potential recipient general information about the process he possesses, knowledge of which he is prepared to hand over.

In this case it is usual to sign a "confidentiality agreement", the sole purpose of which is to communicate such information as the potential recipient must keep secret. That information must enable the latter to make an evaluation of the technology he is going to receive, by means of a general profile of the variety, including details about the quality standards of the product, the productivity to be obtained, if it requires or does not require special equipment, the stability of the process and some features of the art of manufacture.

In the pre-contractual phase the potential recipient should supply the supplier with information about the equipment and raw materials which he would use and about other general conditions that may affect the application of the process.

b) Contractual phase

Most of the considerations put forward in the document discussed during the First Consultation Meeting on the Pharmaceutical Industry, ID/WG.331/3, "Preparation of Guidelines. Background Paper" (23rd September 1980) apply. The agreements relating to production of antibiotics present, however, some specific characteristics which it is fitting to point out.

1. Secret know-how has a key role in the contract. Although patents may be in force, and it may therefore be necessary to include a licence for the use of them in the agreement, secret processes constitute an element without which production could not be envisaged in a profitable way. This applies also to antibiotics whose patents have expired, or are about to expire, and with which the proposed Centre could deal basically.

2. The confidentiality of the information passed on will on account of what has been said, be a normal requirement of the supplier, which the recipient must negotiate suitably, with a view to requiring a precise specification of those parts of the information regarded as secret, excluding from the range of the causes knowledge already divulged or already possessed by the recipient, and establishing a reasonable duration for the obligation.

3. It is important that the guarantees be negotiated which the supplier is willing to grant and which have some particular features in these contracts. Generally the supplier should give a laboratory demonstration (preferably in the recipient's laboratory and with raw materials provided by the latter) and arrange for the commissioning of production in the recipient's plant, guaranteeing the fulfilment of certain parameters (consumption of raw materials, input/output relationship, consumption of energy, quality of the product obtained according to the standards accepted in the contract, etc.), in a given number of batches. Non-fulfilment of these guarantees should normally give rise to cancellation of the contract, since the recipient should not be obliged to maintain a contractual relationship which does not meet the technical and economic conditions agreed on.

4. In general, the firms which may transfer technologies on antibiotics are not producers of intermediates. Tied purchase clauses would, in principle, be infrequent in such contracts. However, the supplier could try to arrange for fulfilment of the guarantee to be conditional on supplies being obtained from a given producer. In fact, if the raw materials supplied by the recipient comply with the supplier's specifications, there are no reasons for accepting such a requirement.

5. The training and definition of the tasks of the personnel responsible for the fermentation is an important aspect of the contract. There are certain aptitudes and knowledge of the experienced technician which can only be passed on by means of demonstrations and personal communication.

6. In addition, it may be advisable to agree on technical assistance being provided by the supplier over a reasonable period. It is improbable that, after a year's operation, problems will arise which have not occurred in this period, which might be a suitable period for the duration of this obligation. When production is not continuous it may be preferable for the obligation for technical assistance to continue until a given quantity of the product has been produced.

7. The price for the technology transferred may be agreed on as a lump sum (in one or several payments) or as royalties (on selling price, or according to the amount produced). The norm would seem to be an initial payment on receiving the know-how, plus additional payments or a royalty for the duration of the contract.

8. As pointed out under point 6 from the technical point of view a year may be sufficient to correct defects that may arise in the production, but a longer duration of the contract may be agreed for the purposes of calculation of a royalty and the maintenance of the obligation of confidentiality.

II. Implications of patent rights legislation on the setting up and operation of a subregional Centre

The consideration of this subject requires the analysis of two main aspects:

(a) The limitations which the recognition of patents is likely to impose on the operation of the Centre, and

(b) The possible protection that the Centre may seek for the results of its research and development.

The first aspect is no doubt of greater importance, since it refers to restrictions which the Centre may potentially face. The nature and importance of these restrictions will depend on a certain number of factors, chiefly on the type of activities developed by the Centre and on the type of products and technologies with which the Centre will work.

The existence of protection of patents would not affect, in principle, the mere carrying out of research and development activities, even in those countries where the processes or products are protected. However, to the extent that these activities involve the use or production (even if on a limited scale) of such processes or products, some implications may arise in accordance with the range of the protection existing in the country.

The production of raw materials may be impeded or prevented where patents are in force which cover the products themselves or the methods of manufacture which must be applied to obtain them.

The importing of raw materials may be prevented* when the product is covered by a patent in the country of importation and when the law extends the protection of the process to the products manufactured, by means

* This would be the case if the product were bought from sources other than the holder of the relevant patent.

of its use.*

Assuming that the Centre will envisage the acquisition of technology from firms abroad, the existence of patent protection may also negatively affect its negotiating position when it has to discuss the terms and conditions of the transfer of technology agreements. The possession of patents (especially patents on products) confers on their holder a monopolistic position from which he can generally impose restrictive clauses and high prices on the licensee.

The impact of patent legislation would also vary, as mentioned above, in accordance with the type of technologies and products with which the Centre deals. There will be no difficulties - even if patent protection exists - if the activities of the Centre are concentrated on products for which the patents have already expired. Although this may be the situation for a wide range of products with which the Centre will deal - as is recommended - at least during its initial period, in the longer term the existence of patent protection may involve the consequences stated above.

As regards the possible protection of innovations made by the Centre, the second important aspect already mentioned, it does not seem likely, in the view of the technical experts, that the Centre can achieve substantial innovations in the short or medium term in the field of antibiotics. Although longer term considerations ought also to be considered in this respect it does not seem that the possibility of obtaining protection of patents in the country where the Centre is located should constitute a decisive factor in determining its most suitable location. In the first place it is likely that any development undertaken by the Centre will consist chiefly of improvements and adaptations of know-how rather than new discoveries of a patentable nature. Secondly and given the territorial character of patent rights, the possible protection of the invention in the country where the Centre is located will not be sufficient, in any case, to forestall its

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* Amongst the countries considered in this report, Guyana recognises this form of "protection of the product by the process".

copying or use of the invention in other countries unless the patent protection is obtained in such countries.

In conclusion, and to the extent to which the activities of the Centre are limited strictly to research and development and do not involve the use or manufacture of patented processes or products, the existence of patent protection will not have significant implications for the operation of the Centre. However, if the Centre had to import or produce raw materials, or wanted to acquire technologies which are covered by patents, a number of restrictions will very probably emerge.

Although it could be argued that the existence of patent protection in the country where the Centre operates would make safeguarding of the technical results achieved by the Centre possible it is clear not only that this is a remote possibility but also that, in any case, the potential negative effects arising from the existence of such protection would greatly outweigh the possible benefits that it might ensure.

Therefore when evaluating the most suitable location for the Centre the non-existence or existence of limited patent protection in a country ought, in principle, to be regarded as an important advantage of that country when establishing the Centre in question.

In accordance with the analysis undertaken earlier (see point i) above) Mexico seems to offer very suitable conditions for the establishment of the Centre, at least from the point of view of the absence of possible restrictions on some of its possible activities. Costa Rica and Honduras, although they formally recognise patents on products and/or processes, in practice have made them subject to a special system, particularly in Costa Rica, which seems to eliminate or to a large extent neutralise the possible adverse effects of the exercise of patent rights by third parties.

Again Guatemala, Nicaragua and Panama do not, in this respect, seem to offer the desired conditions. It should be noted, however, in the case of Guatemala, that its law expressly permits the use of inventions

registered for experimental and scientific purposes (see point above). Cuba and Guyana, although for different reasons, may be placed in an intermediate position between these countries and those mentioned in the preceding paragraph.

III. Protection and Supply to Third Parties of Technology created, adapted or improved by the Centre

a) Patenting of innovations by the Centre

As stated earlier the technological developments to be carried out by the Centre could - ahtough this does not seem probable, at least during the initial period of the Centre - possibly constitute inventions that can qualify for the obtaining of patents (or inventor's certificates in the case of Mexico).

The concept of "invention" that exists in the majority of the countries considered in this report is based on "objective" criteria of "novelty"* and industrial applicability. Mexican legislation - which is the most recent - is the only one which has introduced the additional registration of "inventive activities" as a condition for obtaining patents or inventor's certificates. In other words, and except for the latter country, the patentability requirements would seem to be less strict in the area than in the majority of developed countries.

The registration of patents in the subregion could be facilitated by existing international conventions on patent rights. As shown in Table 2, Costa Rica, Cuba, Guatemala, Honduras and Nicaragua belong to the 1910 Buenos Aires Convention. In accordance with this Convention an application may be lodged, and obtain priority in the country which is part of the Convention within a year of the date of its presentation in another country which belongs thereto.**

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* In Costa Rica, Honduras, Guatemala and Cuba "universal" novelty is apparently required. Only local novelty would seem to be required in Guyana, Nicaragua and Panama.

** This right of priority would apparently apply even if the first application had not been made in a country which was part of the Convention.

Furthermore Cuba and Mexico are members of the Paris Convention for the protection of patent rights, as revised in Stockholm in 1977. According to this Convention applicants from either of these countries have one year's priority when making an application for a patent in the other country.

b) Regulations on the transfer of technology

Mexico is the sole country - amongst those considered here - which has specific regulations on contractual agreements for the transfer of technology. In the other countries* contracts on the transfer of technology are not, in principle, subject to any specific regulations and their content may therefore be freely decided on by the parties.

Mexican legislation (1972 Law on the Transfer of Technology) applies to the domestic transfer of technology, that is to say agreements where both the supplier and recipient are domiciled in Mexico, and also to agreements for importing technology (that is to say when the supplier is domiciled abroad). Agreements for exporting technology from Mexico do not have to comply with the said legislation.

In accordance with this law all agreements which include the licensing of patent rights, the transmission of know-how and the provision of engineering and other services may be registered in the National Register of Transfers of Technology. Registration is granted after evaluation and approval of the agreement, which constitute the conditions of validity of the latter. Evaluation of the agreement consists of an examination of the reasonableness of the price and the identification of clauses which could be considered restrictive. An agreement may or may not be approved if it contains one or more of the following conditions :

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* The case of Cuba, given its system of centrally planned economy, is of a different nature. In this case the importing of technology is dealt with through the appropriate administrative bodies.

Clauses which permit the supplier to regulate or to interfere, directly or indirectly, in the administration of the recipient of the technology.

The obligation to hand over to the supplier of the technology, freely or for a charge, patents, trade marks, innovations or improvements obtained or made by the recipient.

Limitations on research and development by the recipient.

The obligation to acquire equipment, instruments, parts or raw materials solely from a given supplier.

Prohibitions or restrictions on the exporting of goods or services on the part of the recipient of the technology in a manner which is contrary to the interests of the country.

Prohibitions on the use of complementary technology.

The obligation to sell the goods produced by the recipient solely to the supplier of the technology.

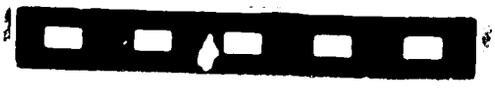
Requirements to employ permanently personnel nominated by the supplier.

Limitations on the volume of production or the imposition of sale or re-sale prices on goods produced by the recipient for domestic or external markets.

Obligations on the recipient to sign contracts for exclusivity in sales or representation with the supplier and in respect of the national territory.

The establishment of excessively extended periods of application. In no case may the period exceed ten years as an obligation for the recipient of the technology.

The requirement that litigation arising from the interpretation or compliance with the agreement be submitted to the jurisdiction of foreign courts.



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