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09428

Distr.
LIMITED

UNIDO/IOD.336
31 January 1980

English

UNITED NATIONS INDUSTRIAL
DEVELOPMENT ORGANIZATION

Pharmaceutical Meeting on the Production of
Essential Drugs in Developing Countries

Balatonfured, Hungary, 16-23 September 1979

DRAFT REPORT*

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INTRODUCTION

The Lima Declaration and Plan of Action for Economic Co-operation and Development calls for the share of developing countries in the total world industrial production to increase to at least 25 per cent by the year 2000. The world production of pharmaceuticals in 1976 amounted to US$ 42.3 billion out of which about 10 per cent was the share of developing countries. As the national health programmes gain momentum, the requirement of pharmaceutical products in the developing countries is bound to grow. The main objective of the pharmaceutical industry in developing countries therefore, is to make available the essential medicines required for the social health programme.

In most of the developing countries, the pharmaceutical industry is confined to formulation and packaging of drugs. In view of this, UNIDO has been endeavouring to move towards a more integrated pharmaceutical industry involving advanced scientific and technological skills. The major problems encountered by the developing countries in the matter of development of an integrated pharmaceutical industry are the non-availability of the required technology as well as economics of scale. In light of the above, the exchange of information on technological capabilities and experience amongst developing countries assumes considerable importance.

In view of the above and as follow up action to the Regional Seminar on the Industrial Application of Microbiology in the Pharmaceutical Industry which was held in Havana, Cuba in July 1979, the pharmaceutical meeting on the production of essential drugs in developing countries was organised by UNIDO in co-operation with the Hungarian Pharmaceutical Union. The purpose of this meeting was to provide information on different processes involved in the production of essential drugs, sources of technology and its transfer, investment and raw materials required and to discuss with experts from developing countries the

problems related to the essential drugs to be produced in their respective countries with a view to promoting the production of drugs in developing countries at national and regional level in order to attain self-sufficiency in essential drugs within the country.

Organisation of the meeting

The meeting, which took place in Balatonfured, Hungary from 16-23 September 1979, was opened by Dr.Lajos Csurgai, Deputy Minister, Ministry of Heavy Industry, Dr.Lorand Palvdi, Executive Director, Chamber of Commerce, Dr.T.Sömjen, Chief of Department of International Organisation in Secretary of International Relations, Dr.György Csakvari, Director, Union of Hungarian Pharmaceutical Industries, Dr.Ferenc Toldy, Deputy Director, Medimpex, Dr.Vagó, Vice-President, Union of the Hungarian Pharmaceutical Industry and Dr.A.Tcheknavorian-Asenbauer, Chief, Pharmaceutical Industries Unit, UNIDO.

Each of the speakers emphasised the importance of "Health for All by the Year 2000". Mrs.Tcheknavorian stressed that this meeting would give the opportunity to evaluate the existing technologies for the production of essential drugs; it would also give the opportunity to identify which were the most essential drugs for developing countries.

Mrs.Tcheknavorian suggested that, after the presentation of the consultants' papers, detailed discussions be carried out by the participants in order to develop a Plan of Action.

Dr.Vagó was elected Chairman of the meeting and Mrs.Tcheknavorian the Vice-Chairman; two secretaries to the meeting were Mr.Hortobage and Ms.A.Povrie.

Adoption of the Agenda

The agenda was adopted without any changes being made. In general, it was agreed that the length of the presentation of papers and the duration of the ensuing discussions be kept flexible according to the interest shown.

FORWARD

Special thanks are due to Messrs.Szentpülöpi, Lorand, Sõmjen, Miklovics, Vagó and György without whose tremendous efforts and co-operation this meeting would not have taken place, nor would it have been such a success.

PRECIS OF THE MEETING

10 consultants from Hungary presented papers on antimalarial drugs, antidepressives, antibiotics, antituberculotics, antileprotics, sera and vaccines, analgetics, vitamins and multipurpose plant. Topics included in these papers were the different processes involved in the production of essential drugs, sources of technology and its transfer, investment and raw materials required. A discussion also took place with medical doctors who talked about the medical aspects of each drug.

After presentation of the papers, detailed discussions ensued. Summaries of the papers are given below together with some important comments which are relevant to the subject and which supplement the papers. The summaries of the papers are as follows:

1. Antimalarial Agents by L.Pallos and P.Benkó

The study, prepared on the basis of instructions given by UNIDO, was submitted to each participant in English. In the conference, Dr.L.Pallos briefly discussed the data, regarding the spreading, curing and prophylaxis of the disease. In the ensuing discussion, the technologies suitable for preparing Chloroquine and pyrimethamine were discussed in detail. The investment costs and the most essential factors to be taken into consideration when selecting the most economical method, were pointed out. Some important data relevant to the purchasing and preparation of the base materials and intermediates was also mentioned.

Summing up the study, it was concluded that, on the basis of the information obtained, chloroquine is the most widely used antimalarial of the developing countries. Therefore, it was agreed by the representatives of the different countries that the preparation of this medicament should be an important task of their countries. From the technologies given, they judged that the Hungarian one would be the most reliable one.

* Q: What would be considered a minimum size for chloroquine phosphate?

* A: An average size would be 55 tons/year but this can be either higher or lower depending on the circumstances.

Q: Re. the production of the end product from novaldiamine; how many patents are available for this production?

A: Approximately 4 or 5 main ones - Hungary, USA, UK, Japan and Germany.

Q: Would the price of production from primaquine be less?

A: The prices of the production processes cannot be compared. However, chloroquine determines the price within this group.

Q: Re. resistance to chloroquine diphosphate; does this mean that this drug will become obsolete?

A: Resistance to chloroquine diphosphate depends on the type of malaria. If chloroquine diphosphate is alternated with primaquine then the resistance can be overcome.
(All participants stated that chloroquine diphosphate was used in their countries and that no resistance had been shown).

* Questions raised during the discussion on this subject;
Q = question, A = answer

2. Antidepressives by L.Pallos and P.Benkó

A study was prepared by the authors according to the requirements of UNIDO and it was submitted to each participant in advance.

Dr.Benkó discussed in his lecture the disorders of the psychic life and listed the medicaments suitable for their treatment.

Amitriptylin was discussed in detail due to its high significance. The possible ways for its preparation were described, while a special emphasis was put on the economic technology used in Hungary.

The author gave a lecture on Lithiumcarbonate, used world-wide in the treatment of manic depression. He described the raw material, its processing, purification and use as a medicament.

After the lecture, the representatives of the developing countries expressed their views regarding the preparation and marketing of the antidepressives. The final conclusion was that there is a very low number of patients suffering from depression in these countries, therefore they do not think that the preparation of these medicaments is basically needed by them.

Q: How much does technical lithium carbonate cost?

A: US$ 0.95/Lb. but it has to be purified before it can be used for pharmaceutical purposes.

Q: Is the investment justified for developing countries?

A: No.

Q: How much would purified lithium carbonate cost?

A: About 4-5 times that of technical lithium carbonate i.e. US$ 4-5/Lb.

3.a. Antibiotics by J.Gyimesi

Some outstanding members of the most important groups of antibiotics i.e. penicillins G and V, oxytetracycline, chloramphenicol, erythromycin, gentamicin C complex, were demonstrated and some of their semi-synthetic derivatives (ampicillin, oxacillin, doxycycline, amikacin). Their chemical structure, synthesis and chemotherapy were discussed and the price situation.

The problems in the location of a fermentation plant and the main points to choose from given fermentation technologies were also included into the paper. Comparisons of some technologies of important products from an economical point of view were made.

A list of antibiotics and an index to manufacturing companies was also presented.

3.b. Antibiotics by K.Pólya

1. The size of a profitable fermentation plant = 6 x 50 Kl = 300 Kl (in stainless steel fermentors).

2. Energy consumption (in tropical zone) for penicillin.

a)	Steam - (0,4 MPa (t:142°C))	average: 3,4 t/h max: 12,5 t/h
b)	Electricity - (6KV)	average: 3,6 MW max: 4,6 MW
	Pressurised air (0,3 MPa)	average: 9900 Nkl/h max: 12000 Nkl/h
	Cooling energy (t-20°C metonol)	average: 2,9 x 10^6 k cal max: 3,4 x 10^6 k cal

3. Water consumption — average: 1375 Kl/day; max: 230 Kl/hr.

4. Waste water (which may need treatment) — average: 103 Kl/day; max: 230 Kl/hr

Dollar production of 1 kl fermentor capacity/day:

penicillin	31
oxytetracyclin	30
neomycin	36
bacitracin	30
gentamycin	45
tobramicin	140
ceph-C-7ACA	250

Q: What is the contamination per centage in fermentation?

A: 5 - 10%; the longer the fermentation process the greater the possibility of fermentation. Fermentation takes 10 days, therefore the figure of 5 - 10% contamination is very high.

Q: Are continuous sterilisers used to sterilise the media?

A: Yes.

Q: What would be the cost of setting up a minimum capacity plant?

A: Approximately US$ 40 million; this price would include the cost of everything.

4 Antituberculotics by I.Kocska

Today's therapy of TB consists of the joint administration of two or more effective antituberculotics.The efficacy in the tuberculosis therapy my be influenced to a considerable degree by economic factors.The cost factors for individual antituberculotics are very different.The compounds exhibiting cross-resistance/its mode of action is similar/should never be used jointly or in combination,since they do not promote therapy in this form and may affect it even adversely.Primary drugs:Isonicotinic-acid-hydrazide/INH/,streptomycin/kanamycin/,rifampicin,ethambutol;secondary drugs:p-amino-salicylic-acid/PAS/,thioacetazone,thiocarlide,viomycin,cycloserine,ethionamide,prothionamide,pyrazinamide.Antibiotics:streptomycin/kanamycin/,rifampicin/semisynthetic/, viomycin,cycloserine,the others chemotherapeutic agents. The joint administration or combination of the members of the two groups is favorable.

INH is the most frequently applied antituberculotic.Isonicotinic acid is the key starting material of INH manufacturing.It my be prepared fom gamma-picoline,4-ethyl-pyridine, 4-cyano-pyridine.

Point of view	gamma-picoline	4-ethyl-pyridine	4-cyano-pyridine
yield	60%	70%	40-60%
cost of raw material	1.7	21.0	4.0 $ US
Invest.+ cost	±	±	+
danger	–	±	+
contamination of environment	–	±	+

+ =favourable, ± =medium, – =disadvantageous

Rifampicin is the mo st active antitub.agent,but its manufacturing is the mo st expensive.Rifamycin is produced by fermentation processes.Rifampicin is prepared by semisynthesis starting from Rifamycins.

The production cost of ethambutol is a function of the price of d-2-amino-butanol-1.
The best pharmakon for the treatment of all kinds of leprosy is DDS = DAPSON and its derivatives.

Q: What is the recommended period of treatment?

A: 1½ years.

Q: Would it be possible to find a new drug in order to shorten this period?

A: No. It is not a question of finding a new antituberculotic; it is more a question of teaching physicians how to use the existing ones properly.

5. Prevention and treatment of infectious diseases by immunization.
by J.Bösszörményi

1. Characteristics of immunologicals

Although the production of immunologicals belongs to the pharmaceutical industry, it has also some special aspects, e.g.

1.1. immunologicals are always made of living or natural materials, like microbes, human or animal blood,

1.2. immunologicals are mostly used for prevention and not for treatment,

1.3. the use of immunologicals is directed mostly by the health strategy of a country and not by medical practitioners.

2. Choice of technologies

The possibilities to choose between different technologies is rather limited, because the applicability of a certain technology is determined by the technical conditions and stage of development.

It is recommended to plan a stepwise development /as detailed in the paper/.

3. Type of manpower

The production of immunologicals is never a simple adaptation of one or two technologies on a large scale, but it is a multifold activity applying many methods mostly on laboratory scale. Therefore such a plant needs a team of scientifically interested biologists, pharmacists, biochemists, veterinarians

accompanied by a group of well trained technicians and skilled workers.

4. Hints for the selection of the place

4.1. Needs of the plant

4.1.1. necessity of clean air, free from dust and smoke

4.1.2. vicinity of a sloughter house or farm for supplying materials for media preparation

4.1.3. easy connection to blood bank for getting human plasma

4.1.4. vicinity of a town, where technical maintenance services are available

4.1.5. contacts with university laboratories, hospitals, health authorities, etc.

4.2. Requirements of the environment for preventing environmental pollution

4.2.1. Infections. Serious and efficient precautions should be taken to prevent any infection originating from the laboratories.

4.2.2. Bad smell is a possible polluting factor due to processing protein containing materials /meat, blood, etc./ and functioning of animal house.

4.2.3. Spoiling the common drainage by discarded and putrescible proteins.

4.3. Conclusions regarding the location.

A plant for immunological production should be located in close vicinity of a big town, preferably to a capital. It should not be inside the residential or industrial area, but rather in a suburb near to agricultural areas or forests but with reliable transport facilities.

Q: What equipment would be required to install a vaccine production unit?

A: microscopes, vials, glassware and 3 autoclaves of 200-300 l capacity; these units can be located in the most simple of buildings.

Q: What quantity could be produced in this installation?

A: 1.3 million units (for diphtheria, typhoid and cholera) and approximately 1 million units of BCG.

It was generally agreed that the most important item is the existence of trained personnel. Once one has skilled personnel then the investment and equipment are rather simple and the scale of production can increase. It was also pointed out that the same skilled personnel can supervise either simpler or more advanced production.

6. Analgetics and/or Antiinflammatory Drugs by K.Harsányi

Summary

The following drugs were mentioned in the lecture delivered at 20 September, 1979: morphine, codeine, N-allyl-nor-morphine, meperidine, methadone, dextropropoxyphene, pentazocin, nefopam, buprenorphine, butorphanol, phenacetine, paracetamol, noramidopyrinium-methansulfonate-Na, aminophenazone, salicylic-acid, aspirin, N-aryl--anthranilic acid derivatives, phenylbutazone, indometh--acin, diclofenac, ibuprofen, allopurinol, sulfinpyrazone.

Among these the syntheses were reviewed for the underlined compounds. On a raised question the structure and synthesis of azapropazone was discussed. The subjects of the debate after the lecture were: how can the production of the salicylic acid and derivatives be profitable? In generally can the foundation of the own industry be worthy with old, traditional drugs, in spite of their high consumption level?

The lecturer emphasized his point of view, that the production of drugs of hundred tons /acetanilides, pyr--azolones, salicylic acid/ without own organic intermediate industry can hardly achieve economically. Some of the more modern drugs offer better profitability, but the quantity and the permanence of the manufacture less. In this connection one of the attendant warned the audience, that the pyrazolones could cause heavy damages of the kidney and their outlook might worsen.

Q: What sort of products should the developing countries concentrate on producing?

A: Those from poppy culture. If the organic intermediate industry is well developped, then this industry could be economic. Anti-inflammatory drugs is an area in which developing countries can produce economically.

Q: What would be the smallest economic capacity of an installation for producing proferic drugs?

A: Approximately 20 tons/year for indometacin and ibuprofen

Q: What would the investment be?

A: For 600 tons/year of acetylsalicylic acid, the investment would be US$ 2 million; this includes the cost of production, equipment and land. The percentage of this amount required for equipment is approximately 14%, about 7% for transfer of technology and 10% for a detailed engineering fee.

7. Vitamins by L.Feuer and G.Lugossy

The vitamin A requirement of the developing countries can be ensured to a certain degree from the extract of some natural substances. Cod-liver oil and shark-liver oil are the most suitable for the purpose, but they contain also some vitamin D apart from vitamin A.

Although vitamin A is present in palm oil also, there is no method known for its industrial extraction. Vitamin B_1 can be prepared synthetically, while vitamin B_{12} can be prepared by fermentation.

It was concluded that the preparation of vitamins in the developing countries could take place economically in the co-operation between some of them since their economy depends greatly on the size of the producing plant i.e. ANDEAN group. It must also be noted that it is advisable to produce at least two vitamins at one time.

With respect to the fact that the production of vitamins requires rather special technologies, the establishment of high-capacity plants is advisable, but it is very difficult to establish a multipurpose plant for vitamin producing purposes. It may happen in the case of the parallel production of vitamins A and E.

With respect to the fact that vitamins are continuously needed, there is no danger of terminating or changing the production.

The preparation of nicotinic acid amide from agricultural wastes is possible theoretically in some of the developing countries. Such waste is for example the tobacco powder which remains after production of cigarettes and cigars. Nicotine can be obtained from it by steam distillation and transformed relatively easily to nicotinic acid and nicotinamide respectively but, until now, economic plants are built on petrochemical bases.

Q: What system of purification of vitamins A and B_1 is used?

A: Purification of vitamin B_1 is done by the solvent method but molecular distillation is better.

Q: What would be an economic size of a vitamin A and B plant?

A: For vitamin A: minimum size would be 200 tons;
for vitamin B_1: minimum size would be 100 tons.

Q: What would the investment be for a minimum size?

A: Vitamin A: US$ 8 million;
" B_1: US$ 4 million;
Vitamin B_2: US$ 2.5 million (synthesis);
" US$ 5 million (fermentation);
" B_6: US$ 3 million;
" C: US$ 25 million;
" D_2: US$ 0.5 million;
Nicotinamide: US$ 10 million.

This investment only includes equipment, since vitamins can be produced in any normal plant with the simple addition of enamelled autoclaves.

Q: Has the technology during the last 10 years developed a great deal?

A: Technology in the field of vitamins does not change much at all, therefore it is a good investment for the future.

8. Medical Aspects

Four medical doctors, Dr.T.Jávor, Dr.H.Graber, Dr.A.Zádor and Dr.Vidor talked about the various aspects of each group of drugs from a medical point of view. The following were their comments:

Antimalarials - chloroquine diphosphate is the cheapest and most effective with only mild side effects such as headache and disturbed vision; these side effects appear in 1.7% of the cases.

Antidepressants - amitriptyline is a safe drug with no serious side effects.

Analgetics - paracetamol shows signs of liver toxicity and can lead to aggressive hepatitis.

Vitamins - vitamins are not given to patients of calcium depletion.
Vitamin A group given to sufferers of cirrhosis of the liver;
Vitamin B group given to sufferers of diabetes;
Vitamins A and D can be dangerous if taken in excess; it can lead to hepatic failure.

Antituberculosis - thioacetazone has not been used in Hungary for the past 20 years because of toxicity and side effects such as hepatic failure. Rifampicin together with ethambutol is a recommended combination but the best treatment is isoniazid together with ethambutol as well as streptomycin.

Antibiotics - the toxicity of chloramphenicol is dose-related. The most effective antibiotic is penicillin because it is completely selective and has no toxicity. The only disadvantage is that it can cause allergies. Gentamycin can only be administered parenterally and therefore is not so important for developing countries.

3. Multipurpose plant by I.Szentpéteri

As compared to other industries, pharmaceutical industry looks back upon a relatively short past. Though the curing of the ailing and the preparation of medicines are as old as humanity, development to an industrial grade took a fairly long time.

Synthetic processes applied in the pharmaceutical industry generally can be reduced to such unit operations that demand the use of duplicators, coolers, receivers, filters, homogenizers, evaporators, crystallizers or complete units of them in various groupings. With a view to this the relatively prompt obsolescence of pharmaceuticals should also be considered. The production of new pharmaceuticals will be needed before the buildings become decayed and the changing over might require substantial reconstructions. This gives a choice between two alternatives: either we should erect such buildings which can be amortized in unusually short terms and may be pulled down afterwards, or we build such hall systems in which the groups of apparatus can be readily replaced so as to permit the variations of technology closely to follow the variations of the pharmaceuticals (so called type halls) or else, such units of halls should be erected, in which the frequently occurring standard reactions of the pharmaceutical industry can be performed in the apparatus groups separately, independently from the actual sequence of operations, and in such halls, occasionally with the moving of the particular phases inside the production hall, the operations required by the manufacturing

technologies are performed. Such halls are called flexible operation halls.

A thorough study of the various technologies of synthetic medicines has demonstrated the fact - otherwise known - that, after some simplifications, even the most diversified synthetic manufacturing processes can be reduced to relatively few fundamental operations. Following this we believed that, provided adequate groups of apparatus can be formed for the performance of various operations through the appropriate selection of their dimensions, the production of an equipment in which the synthetic manufacturing technologies can be broken down into operation - steps become possible. This method implies that the sequence of the operational units is not arranged to suit the demands of the technology of a particular medicine.

This, although it might result in a surplus of material handling inside the hall, yet, at the same time, the full palette of the various operations becomes possible to be performed. When grouping the apparatus consideration was given to dimensions and materials. This has rendered the demands of apparatus of the same type of the various operations easier to survey and to satisfy. Such an operation hall is practical and indispensable for any such plant in development which does not possess a definitive list of synthetic products yet or, even at the beginning of the development, it desires to perform the finishing operations of several sorts of products. In other words, we might say that such a hall can be considered as a large scale pilot plant where technological steps which had been put to the test before should be performed with the available fleet of apparatus.

During the lecture the use of the type- and flexible-halls was demonstrated in practice with photographs.

Several pharmaceutical processes have been examined according to the "unit operations" and the results are shown in the following table:

Basic organic process	occurrence	% distribution
1. Halogenation	40	12.5
2. Sulfonation	18	5.6
3. Nitration	14	4.3
4. Production of amines	33	10.5
5. Alkylation	71	22.2
6. Friedel-Crafts reaction	16	5.0
7. Esterification	28	8.8
8. Hydrolysis	38	11.9
9. Hydrogenation, reduction	24	7.5
10. Oxidation	12	3.7
11. Acylation	19	5.8
TOTAL	320	100.0

Q: Re.the transfer of intermediates in multipurpose plants; how practical is this?

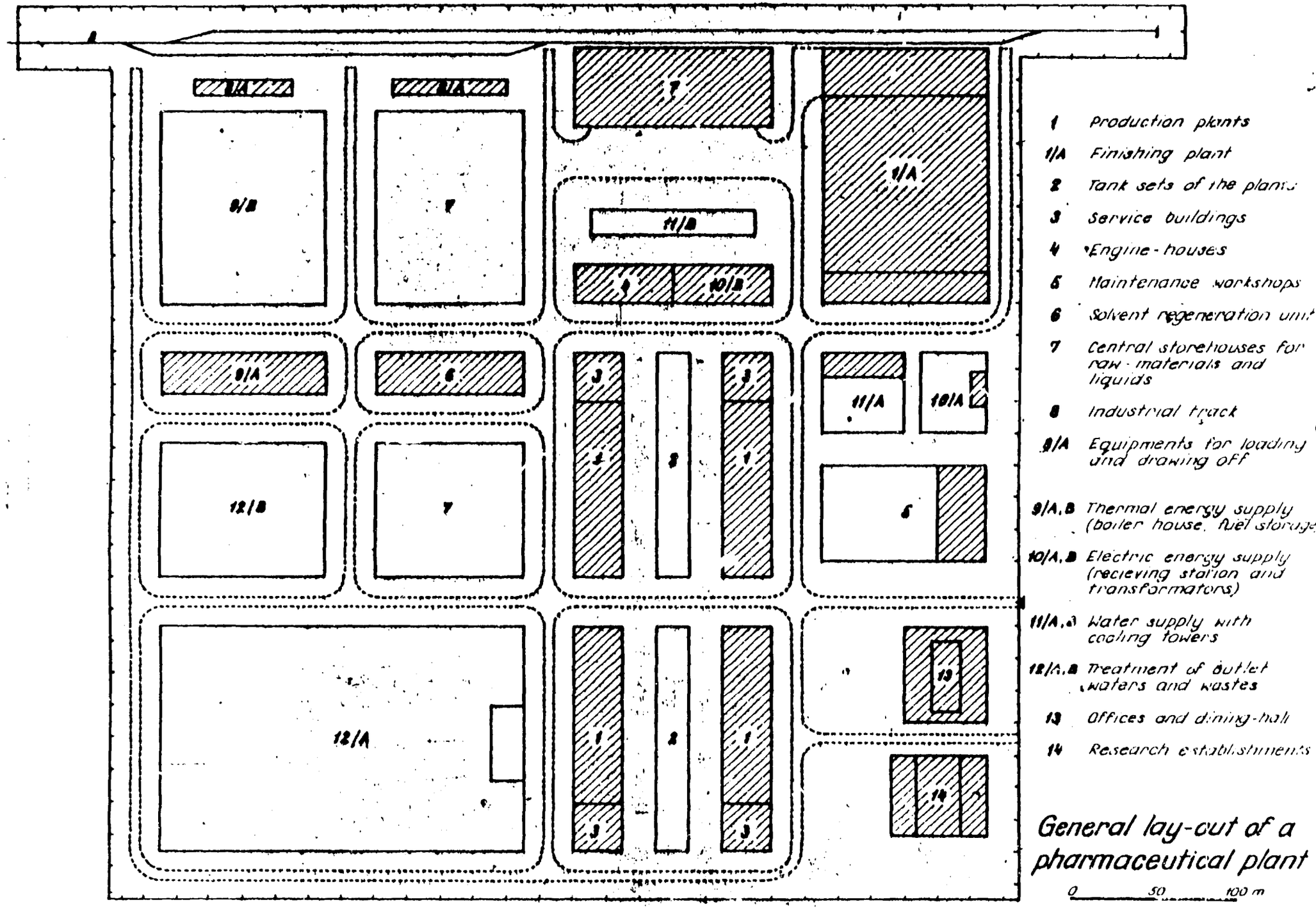
A: For liquids, flexible tubes are used; for solid substances the transfer would be difficult.

Q: What happens if the solvent is aggressive to the tubes?

A: The tubes are lined with teflon and this makes the process 99% sure but is rather expensive.

Q: What is the optimum size of each hall in a multipurpose plant?

A: 24m x 18m.



1 Production plants
1/A Finishing plant
2 Tank sets of the plants
3 Service buildings
4 Engine-houses
5 Maintenance workshops
6 Solvent regeneration unit
7 Central storehouses for raw-materials and liquids
8 Industrial track
9/A Equipments for loading and drawing off
9/A,B Thermal energy supply (boiler house, fuel storage)
10/A,B Electric energy supply (recieving station and transformators)
11/A,B Water supply with cooling towers
12/A,B Treatment of outlet waters and wastes
13 Offices and dining-hall
14 Research establishments

General lay-out of a pharmaceutical plant

0 50 100 m

10. The Production of Essential Drugs and UNIDO's role
by A.Tcheknavorian-Asenbauer

Mrs.Tcheknavorian gave a description of what UNIDO is, its aims and objectives, the structure of the Organisation, with special reference to the activity of the Pharmaceutical Industries Unit. She highlighted the increase of the interest of developing countries in this industry, which is reflected in the increase of projects within the Unit.

Mrs.Tcheknavorian also emphasised the importance of producing some of the essential drugs in developing countries from raw materials or intermediates in order to develop the technological and industrial infrastructure and also to increase the technological capabilities in the developing countries. It was also pointed out that much of the basic production is not possible in developing countries due to low consumption and the size of the market. Therefore, the use of the multipurpose plant concept would be a positive method towards the development of the basic pharmaceutical industry. Mrs.Tcheknavorian also emphasised the important role of screening and evaluation of different technologies which are available on the market, according to the needs, size, simplicity and the availability of starting materials on the international market. The choice of the right technology is therefore the first step towards a successful industrial production which will affect the final price of the product.

Developing countries are sometimes not well informed about the different technologies which are available on the market or about their suitability. This is one reason why this meeting has been organised, in order to give the developing countries the opportunity to learn about the technologies which are available for the 20 main essential drugs, identified at the Cairo meeting. This will give the developing countries the opportunity to choose the best and most appropriate technology for their production in their

respective countries. In this connection, papers were prepared by the Hungarian consultants and presented the different technologies for the various therapeutic groups which are available on the international market. These technologies were compared, from a technological and economic point of view, with the idea that developing countries could benefit and be informed about the best technologies, from the point of view of their effectiveness and appropriateness. This would eventually lead to the production of the final drugs at the lowest possible cost, since this can only be achieved if the right technology and the right design have been considered before starting up the industry.

Mrs. Tchelnavorian asked the consultants to revise the Cairo drug list; this will be the basis for the Global Preparatory Meeting to be held in 1980 and for consultation which, in turn, will be the basis for negotiating for the transfer of technology.

11. Background papers presented by the participants

Participants from Brazil, Cuba, Egypt, Ghana, India, Indonesia, Iraq, Kenya, Mexico, Peru, Philippines and Thailand presented a background paper on the situation of the pharmaceutical industry in their country. Summaries of the papers are given below:

Brasil, H.Cardoso

The paper presents the situation of the pharmaceutical industry in Brasil. The economical situation in 1978 is appreciated with figures due to import/export balance. Inflation and its effects are discussed as well as the measures adopted by the Government. Data on the Brasilian pharmaceutical market is presented for the last four years.

The share of the market by national and foreign companies is, respectively 22.9 and 77.0% in 1979. The growth of the market in 1979 (16.66%) is above the inflation index of 13.8%.

Several considerations on price control and sanitary control are made, showing the difficulties faced by private pharmaceutical industries at present in Brasil. The influence of the state agency CEME is analysed in figures.

The distribution of manufacturers in the different regions of the country as well as the number of drugs, grouped in the different therapeutic classes, were discussed.

The basic raw materials for essential drugs for local production were reviewed. Further considerations concerning health care expenditure and drugs were made.

Cuba, M.Sanchez Osuna

During the past few years, Cuba has created the basis for the future development of the pharmaceutical industry. The old facilities were remodelled and modern manufacturing and packaging machines were acquired. Some investment was also made in order to attain, as far as possible, the modernisation fo the industry.

In 1978, the Cuban pharmaceutical industry was able to produce large and small volume parenterals, infusion equipment, oral powders for suspension, tablets, dragees, ointments, sterile powders for injections, eye glasses, contact lenses, blood derivatives, raw materials from slaughterhouse by-products, human urine and other land and sea natural resources. During 1978, the growth of the national pharmaceutical industry was 24% in value related to that of 1977.

The development of the Cuban pharmaceutical industry is one of the main objectives in the national development programme. The main research lines which are being carried out today are the following: antibiotics by semisynthesis and fermentation, medicinal plants, products of the sea, slaughterhouse derivatives and synthetic drugs.

The Government needs to maintain and increase the level of medical assistance and it is impossible to keep importing large quantities of active substances. Therefore, the Cuban pharmaceutical industry is working to accelerate the investment plans and to increase the national research activities.

Egypt, S.M.Shaddad

The pharmaceutical industry in Egypt is regarded as one of the vital and strategic industries directly related to the field of socio-economic development of today. The development of this industry is continuing rapidly, taking into consideration the importance of the drug, availability and the correct quality. In 1952, 10% of the drugs required in Egypt were locally manufactured. Today, Egypt produces 80% of its requirements and all in dosage form. About 2500 drugs are now available on the Egyptian market, while in 1952 it was about 20000 specialities without any plan to ensure safeguarding the health and economic resources of the country.

In the field of raw materials, only about 15% of those required are manufactured locally in Egypt. Therefore, Egypt still requires foreign technology in this field.

There is also in Egypt a defined system and policy for drug distribution to ensure fair distribution of drugs in the country. The average individual's annual share of drugs in Egypt was about 4.21£E while in 1952 it was approximately 0.22£E.

As regards the field of quality control, the pharmaceutical industry in Egypt is controlled by either the quality control which is carried out in the factory starting from the arrival of raw materials and the in process quality control and finally the control of finished goods and/or the governmental control from the governmental organisation specialised in this field.

The main drawback in the rapid development of the pharmaceutical industry in the developing countries is the lack of proper and relevant information. There is therefore a need to set up a good drug information centre which could provide the following:

1. Sources of basic raw materials and intermediate chemicals together with prevailing prices as well as prices of finished goods in other countries.
2. Institutions which can offer the required technology and all relevant information concerning the pharmaceutical industry.
3. Information on new drugs which are scheduled for clinical trials and the regions where these trials are to be carried out.

UNIDO could help to set up a scheme of registration of new drugs in developing countries.

Ghana, J.Blukoo-Allotey

Until approximately 20 years ago, all drugs used in Ghana were imported from overseas manufacturers. Today, however, there are 8 pharmaceutical formulation factories which produce 60% of the total volume of drugs used in hospitals, clinics and homes.

The most important groups of drugs which are produced in the formulation factories are antibiotics, antipyretic analgesics and antimalarials and these 3 groups account for approximately 60% of the total drug production. It is also in these three areas that priority consideration is being given for the establishment of multipurpose synthetic and fermentation plants for the production of basic essential raw materials such as tetracycline, paracetamol, chloroquine phosphate etc.

The Government of Ghana has already set up a Plant Research Institute which is currently collecting and collating the therapeutic profiles of all the known useful herbs in the country and it is anticipated that very useful medical gains may accrue from this institute when the active principles contained in these herbs are identified and isolated.

The Government is also giving serious consideration to the setting up of a vaccine production plant. As a first stage it is planned that essential vaccines be purchased in bulk for local dilution and filling into ampoules, vials etc. During this stage it is envisaged to embark on intensive training programmes in the quality control of vaccines for the staff who will eventually form the nucleus of the vaccine unit.

India, A. Ramchandran

Since independence in 1947, the growth of the pharmaceutical industry has been very rapid. From US$ 12.5 million, it has risen to US$ 800 million. The industry is mainly divided into 3 sectors i.e. public sector (owned by the state), private sector, small scale sector. While the public sector has concentrated on the production of basic drugs, other sectors have gone for formulation i.e. finished products.

There is a price control of drugs and formulation in the country. The prices are printed on each package. The State has categorised the drugs; the essential drugs like penicillin have been earmarked to the public sector, while other drugs are given to the private and small scale sectors.

Most of the drugs such as antibiotics, synthetic drugs and vitamins are produced in the country from the basic stage. IDPL makes antibiotics, 40 synthetic drugs, 200 formulations. IDPL also has a large research division and design organisation and can share complete technology of all the drugs it produces or can even accept to erect the plants on a turnkey basis. IDPL exports drugs and formulations to Arab countries and Europe.

Indonesia, Dr.Djasman

The pharmaceutical industry in Indonesia has developed extraordinarily fast if compared with other industries. In the past ten years since the First Five Year Development Plan commencing April 1969, until today when Indonesia has just entered the Third Five Year Development Plan in April 1979, the pharmaceutical industry has shown a remarkable growth. With the rapid growth of the pharmaceutical factories in Indonesia no problem is encountered to meet the domestic need of drugs, as almost all the drugs have been produced locally. Therefore approximately four years ago the Ministry of Health of the Republic of Indonesia banned the import of drugs which can already be manufactured locally in an endeavour to give protective measures to the local industry.

However, more than 90% of the pharmaceutical raw materials and excipients required for the processing of finished drugs up until now are still imported, and in order to stimulate the manufacture of these pharmaceutical raw materials, the Government grants certain facilities or benefits to those willing to invest in this field. At the present stage, the kind of basic raw materials produced is around ten, the majority of which is only to meet the manufacturers' own requirement. Only quinine and its salt have been produced in large scale for domestic requirement as well as for export.

The medicines manufactured are in generic form and in the past the number of medicines produced was limited due to the restricted funds made available.

Quality control system has also been introduced by the Ministry of Health on the drugs sold in Indonesia by way of taking random samples from the factories, distributing companies or the market; samples taken are analysed at government owned laboratories.

Prices of drugs are beyond the reach of the majority of the people, and even though there is no price control on drugs in Indonesia, it is hoped that prices will indirectly be controlled through the supply and demand equilibrium and by way of expanding the use of drugs in generic form.

Iraq, M.Haider

The pharmaceutical industry is one of the most important industries in Iraq. Some important raw materials available are: Meniral acids, alcohols (Ethyl, Methyl), starch, rice, potato, maize, kaolin, glycerin, sulphur, sulphur ammonium, urea, oils fixed and volatile, paints etc. The total pharmaceuticals import of the country is approximately £18 million (1978) as follows:

The state organisation of drugs "KIMADIA".

The medical supplies.

The state organisation of drugs "KIMADIA" also co-ordinates imports of the local drug manufacture done almost exclusively by the SDI and its capacity £ 18 million.

SDI is a large enterprise having the one multiple storage building for different pharmaceutical production - fermentation plant for antibiotics, laboratories comprising research and development laboratories, pharmaceutical analysis laboratories, quality control, microbiological, pharmacology and toxicology laboratories. Other main buildings include administrative, steam generation, stores, sewage treatment plant and others. SDI employs 1200 people between administrative, technical and workers. The annual consumption of medicines in Iraq is estimated at about £ [illegible]lion - the consumption per capita is approximately £3/person/year.

The laboratories of SDI are authorised by the Ministry of Health to issue official certificates for its products and sometimes for rechecking important ones.

The main governmental control laboratories are called the "Central laboratories" and are sited in Baghdad. There are also two research centres in Baghdad.

The actual problem facing the pharmaceutical and antibiotic production is the lack of highly trained personnel especially workers who need extensive programmes to familiarise themselves with highly sophisticated machinery and complex procedures. There are several research programmes which might lead to positive results, but this will of course need a lot of work and time. There are 6 universities in Iraq each with its own research projects leading to higher degrees.

The policy of SDI management at present is to produce products of international drug companies under special licenced agreements. The quality, of course, is subject to the approval of the licensor and a new factory will be built to produce a new drug under licence.

Technicians from SDI are sent abroad to the companies granting the licence for training both in the field of production and analysis. Engineers are sent to train on automatic lines of production being purchased from abroad. The amount of people in Iraq employed in the pharmaceutical industry is increasing rapidly through these experiments. SDI exports some of its pharmaceutical products to other Arab countries.

Kenya, A.Mathenge

The pharmaceutical industry in Kenya consists mainly of the distribution of imported finished dosage forms. However, a number of plants have started formulating locally a small range of those drugs required in large quantities.

There is no production of raw materials or intermediates. A few auxilliary materials for pharmaceutical use and some packaging materials are available locally. Manpower with basic scientific knowledge is available but would require specific training in various fields for the pharmaceutical indsutry.

Approximately 6000 formulations are circulating in the market. Plans are underway to reduce this number through drug registration which is currently non-existent.

The main problems encountered in the supply of pharmaceuticals are:

a) dependence on the importation of all our drug requirements;

b) the high cost of drugs;

c) a large multiplicity of formulations of doubtful quality.

The Government is committed to the encouragement of local pharmaceutical production and is already a partner in a joint venture in the largest of the formulation plants.

Technical assistance from UNIDO and other agencies will be sought to develop this industry.

Mexico, F.Fernandez Viana

The total consumption of drugs in Mexico in 1978 was US$ 750 million. The governmental institutions buy 35% in values and 50% in units.

The total production of active ingredients was US$ 80 million and US$ 40 million were imported in the same year.

Mexico has 350 enterprises in formulation activities, 10 in fermentation, 15 in synthesis and 12 in other procedures in this industry.

Since 1978, Mexico has had the Interministerial Commission in the Pharmaceutical Industry. This organisation comprises 5 ministers and 2 directors from the social security institutions and is in charge of the complete policy in the pharmaceutical industry.

The Commission has established the programme of development and promotion for the industry with clear incentives, mainly in the active ingredients' area. These policies include such areas as prices, foreign trade, desentralisation of the industry and the development of the basic drugs.

Peru, J.Ecos

A brief account of the pharmaceutical industry in Peru was given. It refers to the development of this industry from the initiation of its activities to the present. Also, the main characteristics of this industry and the characteristics of the market were pointed out.

It is mentioned that technical dependence still exists; research and development are done in only a few foreign companies abroad; imports of raw materials and auxiliary materials and inadequate growth are the main problems affecting the pharmaceutical industry in Peru.

The setting up of a modern quality control laboratory (National Health Institutes - Ministry of Health) is a programme to promote the manufacturing and trade of generic drugs. The founding of an Institute for Industrial Research and Technical Standards (ITINTEC) and the integration process carried out by five ANDEAN countries - Peru among them - are important steps relevant to the pharmaceutical industry, which have been carried out by the Government of Peru.

Philippines, G.Lleander-Chanco

At present, the Philippine pharmaceutical industry is purely a compounding/formulation industry. The local industry has the following salient features:

1. The industry imports about 90% of its bulk active raw materials primarily from the United States, Europe, Japan and Australia;
2. The local industry is characterised by a very well established compounding or formulating operation utilising semi-automatic machinery and employing skilled to highly skilled labour;
3. The industry has facilities for the manufacture of
   a. solid preparations such as tablets and capsules
   b. liquid preparations such as dispersion, liquid galenicals and parenteral fluids
   c. semi-solid preparations like creams and ointments;
4. The local drug industry services not only the domestic needs of the country but also export to other countries like Thailand, HongKong, Indonesia and Malaysia;
5. In 1976, the sales of the industry rose to ₱1.7 billion which includes export sales as well as domestic;
6. Industry sources estimate that the industry will have a growth rate of 12-14%.

Based on imports, the rank order of drug imports in 1976 of the top five (5) therapeutic classes in terms of money equivalent (FOB value), is as follows:

1. Antibacterials (including antibiotics and sulfas)	US$	12,872,039
2. Vitamins and minerals		5,027,751
3. Hormones		1,207,145
4. Immunologicals		1,117,194
5. Analgesics, antipyretics		1,087,052

The total Philippine import of drugs in 1976 amounted to US$ 22,211,188 (FOB). For the same year, the rank order of drug imports of the top five (5) therapeutic classes by weight equivalent, is as follows:

1.	Vitamins and minerals	1,437,348 kilos
2.	Antibacterials	316,581
3.	Analgesics, antipyretics	83,274
4.	Narcotic analgesics	82,140
5.	Immunologicals	62,969

Availability of raw materials and auxiliary materials for the pharmaceutical industry - As a recent development in the local industry, a pioneering project is envisaged for the local manufacture of semi-synthetic penicillins. The proposed project, which will be operational by 1981, will have a rated capacity of 25 MTPY and will service the domestic market. The project is privately owned, but has received government assistance by way of availment of tax and non-tax incentives. Ancillary industries to the drug industry are the packaging industries which make boxes and cartons, plastic and glass containers, metal closures etc.

Distribution of pharmaceutical products

Pharmaceutical products reach the consumer through two main outlets:

1. The distributor/wholesaler and
2. The direct sales outlets which include small and large drug stores, hospitals, clinics, medical centers, government institutions, physicians, industrial institutions and others.

Principal problems of current operation in the drug industry

The problems currently facing the industry are:

1. The increased cost of production and the increases in labour and freight costs;
2. Larger financing requirements because of high current rates of borrowing;
3. Foreign exchange problems and tight credit facilities.

Government policy towards the establishment of pharmaceutical industry

The Government through one of its agencies, the Board of Investments, is looking into the possibility of establishing a fine chemicals multipurpose plant which will serve the domestic requirements of the pharmaceutical industry. The Government is encouraging the manufacture of antibiotics, sucrochemicals and cocochemicals as preferred areas of investment.

Thailand, P.Setrapongse

Pharmaceutical products sold in Thailand are imported as either raw materials which the local pharmaceutical manufacturers formulate into the form of finished products or intermediates of finished products which have been blended and packaged by domestic manufacturers. There are about 183 domestic pharmaceutical manufacturers but only one state-owned - the GPO. Our sales amount to US$ 250 million per year.

At present there is no raw materials' production of pharmaceuticals in Thailand. The GPO has planned to develop an antibiotic plant in the near future.

The problems which the pharmaceutical industry faces at the present are:

1. The availability of raw materials from abroad;
2. The price of raw materials which are higher because of the oil crisis;
3. The technology to produce the raw materials ourselves.

Pharmaceutical Meeting on the Production of Essential Drugs in Developing Countries

PLAN OF ACTION

In most of the developing countries, the pharmaceutical industry is confined to formulation and packaging of drugs. In view of this, UNIDO has been endeavouring to move towards a more integrated pharmaceutical industry involving advanced scientific and technological skills. The major problems encountered by the developing countries in the matter of development of an integrated pharmaceutical industry are the non-availability of the required technology as well as economics of scale. In light of the above, the exchange of information on technological capabilities and experience amongst developing countries assumes considerable importance.

In view of the above, the pharmaceutical meeting on the production of essential drugs in developing countries has been organised by UNIDO in co-operation with the Hungarian Pharmaceutical Union. The purpose of this meeting is to provide information on different processes involved in the production of essential drugs, sources of technology and its transfer, investment and raw materials required and to discuss with experts from developing countries the problems related to the essential drugs to be produced in their respective countries with a view to promoting the production of drugs in developing countries at national and regional level in order to attain self-sufficiency in essential drugs within the country.

In the course of the meeting the Hungarian experts presented papers on the following topics, indicating the technical, engineering, medical and economic aspects:

- Antibiotics;

- Analgesics;
- Antituberculotics;
- Antimalarials;
- Sera and vaccines;
- Antidepressives;
- Vitamins;
- Antileprosy drugs.

The participants also presented papers on the status of the pharmaceutical industry in their respective countries. After presentation of the papers an interesting discussion took place in the course of which the main problems have been identified as indicated below:

1. non-availability and/or high cost of technology;
2. insufficient knowledge for the assessment and evaluation of the suitable technology;
3. insufficient market size for economic production;
4. lack of trained personnel and infrastructure;
5. high price of raw materials and intermediates and their availability;
6. lack of knowledge regarding licencing and contractual agreements.

The above factors are constraints in the way of the growth and development of the pharmaceutical industry in developing countries. In view of this the meeting devoted its attention to find ways and means to overcome the above problems and reached a concensus on the remedial steps to be taken based on which recommendations have been made. The meeting also reviewed, as a first step, the essentiality of the illustrative list of 20 drugs identified by the inter-regional preparatory meeting held in Cairo. Based on the above the following recommendations have been made:

1. List of essential drugs recommended for production:

Therapeutic Groups		Technology Required?	1st. priority	2nd. priority
1. Analgesics:	acetylsalicylic acid	x	x	
• Non-narcotic	paracetamol	x	x	
	indometacin	x		x
2. Anthelmintics:	piperazine		x	
	bephenium	x	x	
	mebendazole	x		x
3. Antibacterial:	benzylpenicillin	x	x	
	tetracycline	x	x	
	oxytetracyclin	x		x
	erythromycin	x	x	
	ampicillin	x	x	
	gentamicin			x
	chloramphenicol	x		x
	streptomycin	x	x	
	sulfadiazine	x		x
	sulfadimidine	x	x	
4. Antifilarial:	diethylcarbamazine	x	x	
5. Antileprotic:	dapsone	x	x	
6. Antimalarial:	chloroquine phosphate	x	x	
	primaquine	x	x	
7. Antituberculotic:	isoniazid	x	x	
	ethambutol	x	x	
	para amino salicyclic acid			x
	rifampicin			x
8. Antihypertensive:	methyldopa	x	x	
	reserpine	x	x	
9. Diuretics:	furosemide	x	x	

		Technology Required?	1st. priority	2nd. priority
10. Antidiabetics:	insulin	x		x
	tolbutamide	x	x	
11. Oral contraceptives:	norethisterone+ ethinylestradiol	x	x	
12. Immunologicals:	blood fractioning	x	x	
13. Vaccines:	dry B.C.G.			x
	dry typhoid vaccine			x
	smallpox			x
	dry liquid cholera vaccine D+B			x
Sera:	tetanus antitoxin			x
	diphtheria antitoxin			x
	snake antivenom			x
14. Vitamins:	A	x	x	
	B_1			x
	B_2			x
	B_6			x
	B_{12}	x	x	
	C	x	x	
	D_2			x
	PP			x

Non essential

Antidepressives.

2. UNIDO is requested to work in close co-operation with the Hungarian Pharmaceutical Industry. The latter agreed to make available technology for the following drugs at reasonable prices and terms:

Vitamin B_1, Vitamin B_{12}, Vitamin C, Vitamin D_2, oxytetracycline, chloramphenicol, antidepressives, penicillin G, penicillins, semi-synthetic penicillins, indomethacin, isoniasid, ethambutol, chloroquine diphosphate, pyrimethamine, blood fractioning, methyldopa, digitoxin, norethisterone and ethinylestradiol.

UNIDO is requested to locate other suitable sources for transfer of technology.

3. It is recommended that wherever the market size for the production of drugs for a given industrial scale of operations are not adequate

a) a multipurpose plant should be utilised for the production of a group of essential drugs. For this purpose, UNIDO is requested to work with the Hungarian Pharmaceutical Industry and others on the basic designs for different sizes of multipurpose plants which can accommodate groups of essential drugs separately for synthesis and fermentation;

b) pooling of markets at sub-regional level in creating a common market to make industrial scale production feasible. In view of this, co-operation amongst developing countries is recommended. UNIDO is also requested to assist the establishment of national pharmaceutical associations in the different regions.

4. The lack of infrastructure including roads, energy resources, water supply and communications is hampering the development of the pharmaceutical industry and this should be addressed to the governments concerned, for the creation of the necessary infrastructure. UNIDO should concentrate on the development of trained manpower in different skills and the establishment of pharmaceutical centres equipped with pilot plants for the above essential drugs for the purpose of demonstration, training and process development.

5. One of the most crucial factors hindering the development of an integrated pharmaceutical industry is the high prices of the raw materials and intermediates, which in some cases, are even higher than the price of the finished products. UNIDO is, therefore, requested to organise a system of consultations between developed and developing countries for negotiating a reasonable price of raw materials and intermediates in order to make the production of the above mentioned essential drugs feasible.

6. It is recommended that UNIDO integrate into the pharmaceutical industry programme, an activity to make information available on the sources, suppliers, prices, trends etc. in the international market of raw materials, intermediates and drugs.

7. On account of a lack of knowledge about licencing and contractual agreements, the developing countries sometimes enter into contracts which in the long run would prove disadvantageous to them and limit further growth of the pharmaceutical industry. Hence a knowledge of licencing agreements and contracts is an essential prerequisite for the development of this industry. So UNIDO is requested to prepare guidelines for the evaluation of technology and also, through a system of consultations, to negotiate favourable terms and prepare a model contract for the use of developing countries.

8. The Hungarian Pharmaceutical Union, as well as the Hungarian Government, have extended co-operation for the transfer of technology wherever they can, to train personnel and make available intermediates for the production of these essential drugs and finished drugs at reasonable prices.

9. It is recommended that such meetings be held periodically for follow up and to maintain continuity; for this reason, it is preferable that the same participants be invited, as far as possible.

ANNEX I

AGENDA

Sunday, 16 September	Arrival
Monday, 17 September	
9.00	Opening session
10.30	Antimalarials by Dr. Pallos and Dr. Benkó
12.00	Lunch
14.00	Antidepressives by Dr. Pallos and Dr. Benkó
	Brazil, Cuba and Ghana country papers.
Tuesday, 18 September	
9.00	Antibiotics by Dr. Gyimesi
Afternoon	Visit to toxicological department, Veszprém
Wednesday, 19 September	
8.00	Antituberculotics and antileprotics by Dr. Koczka
	Egypt country paper.
Afternoon	Visit to Lacta EGYT factory, Körmend
Thursday, 20 Septmeber	
9.00	Sera and vaccines by Dr. Böszörményi
	Iraq and India country papers
12.00	Lunch
14.00	Analgetics by Professor Harsányi
Friday, 21 September	
9.00	Vitamins by Dr. Feuer and Dr. Lugosi
12.00	Lunch
14.00	Medical aspects with Dr. Jácor, Dr. Graber, Dr. Zádor and Dr. Vidor
Saturday, 22 Sáptember	
9.00	Multipurpose plant by Dr. Szentpéteri
11.00	Plan of Action
Sunday, 23 September	Departure

Name	Participant/Observer	Home address	Office address	Telephone/telex no.	Profession
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H.M.J.Haidar	participant	Iraq-S.D.I. Samarra Iraq	Iraq-S.D.I Samarra Iraq	8888I42	Pharmacist
C.Ferreira de Almeida	participant	SQS II2 Brasilia D.F. Brasil	Ministry of Health Brasilia Brasil	Home:24408655 Office:2268803	Medical doctor, Public Healt
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Dr.Djasman	Participant	Bendhilir G II/I3 Jakarta, Indonesia	Percetakan Negara 23 Jakarta, Indonesia	4I5395 582233	Pharmacist
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F.Nieto Colin	Participant	Escultores 22 Col.Satelite Mexico	Hermosillo 26 7 Piso Mexico 7 D.F.	584 85 24 564 OI 77	Chemical Engineer
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Dr.L.Pallós	EGYT Pharmacochemical works Hungary	Expert in antimalarials and antidepressives
Dr.P.Benko	Research Department EGYT Pharmacochemical Works Hungary	Expert in antimalarials and antidepressives
Dr.J.Gyimesi	Head of microbiological Department in Institute for Drug Research, Budapest, Hungary	Expert in antibiotics
Dr.I.Koczka	Head of Dept.of Chemotherapy Institute of Drug Research Budapest Hungary	Expert in antituhercolotics and antileprotics
Dr.J.Böszörményi	Director Institute of Sera and Vaccines HUMAN Hungary	Expert in vaccines and sera
Dr.K.Harsányi	Gedeon Richter Chemical Works Hungary	Expert in analgetics
Dr.L.Feuer	Director of Dept.of development Chinoin Pharmaceutical works Hungary	Expert in Vitamins
Dr.G.Lugosi	Head of Research and Development Laboratory, CHINOIN, Budapest, Hungary	Expert in vitamins
Dr.T.Jávor	Pécs University Budapest, Hungary	Expert in internal medicine
Dr.H.Graber	Head of Dept.of Medicine and clinical pharmacology Municipal Hospital Péterfy Budapest, Hungary	Expert in antibiotics

Dr.A.Zádor	Medical Director and Head Physician Budapest,Hungary	Expert in antituberculotics
Dr.Vidor	Budapest, Hungary	Expert in tropical and infectious diseases.

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SUMMARY OF TECHNICAL INFORMATION FROM EXPERTS' PAPERS

ANNEX III

SUBJECT	TECHN.SOURCE	TYPE OF PROCESS	MAIN RAW MATERIALS	LENGTH OF PROCESS	PRICE	MAIN EQUIPMENT
1. Antimalarial agents by Pallos+Benkó						
Chloroquine	ICI Ph.,Winthrop Bayer, May+Baker in USA Hilton Davis Chem., UK Medimpex,Hungary	Chem. Sythesis	Dichloroquinoline + novoldiamine	1 - 2 steps		enameled and iron autoclaves, vessels, vacuum distillating, centrifugal pumps, heat exchangers, centrifuges.
			or m-chloroaniline, diethyl, 2 keto succinate + novoldiamine	6 - 7 steps		
			or diethyl-ethoxy-metilen malonate, m-chloraniline + novaldiamine.	3 - 4 steps		
			m-chlororoaniline, methyl-acrilate + novoldiamine	5 - 6 steps		
Pyrimethamine	Burroughs Welcome +Co. USA Deutsche Welcome, Germany Medimpex,Hungary	"	Ketonitrile, guanidine	2 - 3 steps		enameled reactors + vessels,acidproof centrifuge,air lay dryer
			or p-chlorobenzyl cyanide, ethyl propionate, guanidine	3 - 4 steps		
2. Antidepressives by Pallos+Benkó						
Amitriptyline	Merck Sharp+Dohme , USA Hoffman-LaRoche+ Troponwerke, FRG Medimpex, Hungary	"	dibenzosuberon, dimethyl aminopropyl chloride	2 - 3 steps		steel, enameled and corobon reactors, heat exchangers,filters centrifuges, air-lay dryers, liq.-liq. extractor, evaporator
			or benzalphtalid, dimethyl amino propylchloride	4 - 5 steps		
			or phtalic acid anhydride phenylacetic acid, dimethyl amino propyl chloride	5 - 6 steps		

SUBJECT	TECH.SOURCE	TYPE OF PROCESS	MAIN RAW MATERIALS	LENGTH OF PROCESS	PRICE	MAIN EQUIPMENT
3. Antibiotics by I.Gymesi						
Penicillin	more than 36 companies from USA, Sweden, India, Italy, Spain, Japan, Argentina, FRG, England, Austria, Hungary, Portugal, Mexico, Finland, Holland, Danemark, USSR, Bulgaria, France, etc.	Fermentation recovery, purification	sacharose, C.S.L. or peanut flour, soy bean oil, phenyl or phenoxi acetic acid, inorganic salts, solvents	1 week/batch	US$35/kg	fermentors, vessels, heat exchangers, filters extractors, dryers, laboratory for inoculum .
Ampicillin	almost the same	Chem.synth,	6 APA, phenylglycyl chloride-chlorohydrate	2-3 steps	US$72,5/ kg	enamelled reactors condensers, extractors, filters, centrifuges, vacuum dryers.
Erythromycin	more than 13 companies from USA, India, Italy, Portugal, Spain, England, Mexico, France, etc.	Fermentation, recovery, purification	starch, soybean meal, C.S.L., propionate, inorganic salts, solvents	1 week/batch	US$ 90/kg	fermentors , vessels, heat-exchangers, filters, extractors, reactors, dryers, laboratory for inoculum .
Gentamicin	more than 7 companies from Argentina, Hungary, Mexico, FRG, Bulgaria, Italy, USA, etc.	- " -	starch, sucrose, yeast extract, CSL, palm oil	5-6 days/batch	US$ 7236/kg	fermentors , vessels, heat exchangers, filters, ion exchange columns evaporators, laboratory for strains .

SUBJECT	TECHN.SOURCE	TYPE OF PROCESS	MAIN RAW MATERIALS	LENGTH OF PROCESS	MAIN EQUIPMENT	PRICE
4. Antituberculotics + Antileprosy agents by I.Koczka						
INH-isonicotinicacid hydrazide	Bayer,Merck Darmstadt FRG,Rhone Poulenc France, Carlo Erba,Farmitalia Italy,A.B.Bofors Sweden, Sinbiotics,India	Chem.synth.	hydrazine hydrate in sohi, benzene, pyridine	5-6 steps	enamelled reactors, vessels,condensers, extractors,distillators.centrifuges	
Streptomycin		Fermentations, recovery,purification	starch,soybeanmeal, C.S.L. ,inorganic salts	1 week/batch	fermentation,vessels heat exchangers, filters,ion exchange columns,evaporation, lab. for strains.	
Rifampicin	Lepetit,Italia	Fermentation, chem.synthesis	soybean meal,solvents	1 week/ferm. batch 6 steps, synthesis	- " -	
Ethambutol	Lederle Japan,Themis India,Ital-Syntex,Pharchemn, Co.Pharmaceutica Milanese,Italy	chem.synth,	d-2 amino butanol-1, dihalo ethane	1-2 steps	enamelled reactor, vessels,heat exchangers,vacuum distillation,centrifuges, dryers.	
Dapsone		chem. synth .	p-nitro chlorbenzene	5-6 steps	enamelled reactors, heat exchangers	
5. Immunologicals by J.Böszörményi						
vaccines,sera,blood derivatives	Human Hungary	extraction ,fermentations, blood fractioning,tissue culture,etc.	animal glands from slaughter houses,blood, culture media, laboratory animals, etc.		mainly laboratory + small size equipment and animal-house ,freeze dryers, filling + labeling equipment,autoclaves, sterilizers,cold rooms, etc.	

SUBJECT	TECHN.SOURCE	TYPE OF PROCESS	MAIN RAW MATERIALS	LENGTH OF PROCESS	PRICE	MAIN EQUIPMENT
6. Analgetics and/or Antiinflammatory drugs by E. Harsányi						
6.1 Morphine + derivatives Codeine, Papaverin	USA, UK, USSR, Hungary, Evans Medical, Philip Harris, Alkaloida, Calmic	extraction	Papaver somniferum (poppy)			
6.2 Piperidine derivatives:						
Meperidine	Winthrop, Wyeth, Lilly,	Chem. synthesis	phenylacetonitrile	3-4 steps		
Methadone	Bertalanffy, Autriche Hoechst, etc.	-"-	diphenylacetonitrile	1-2 steps		
6.3 6-7 benzomorphans: Pentazocin		-"-	3-7 dimethyl-pyricline	8-9 steps		
6.4 Non-narcotic analgetics w. antipyretic action:						
Phenacetin	Bayer, Braun + Herberg, FRG, Iwaki Seijaku, Japan Lederle Spain, Leciva, Czechoslovakia	-"-	p-chloro-nitrobenzene	3-4 steps		
Noramidopyrin	Hoechst, Winthrop, Galénica Pharmacia, Lagap, etc,	-"-	ethylacetoacetat, phenyl hydrazine	7-8 steps		
6.5 Analgetic, anti-inflammatory drugs :						
Aspirin	Bayer, FRG; Frosst Dorval Canada; De Angeli Guidotti Italy ; Kwizda Austria, etc.	-"-	salicilic acid	1 step	not profitable	
			or			
			sodium phenolate	2 steps		
Indomethacin	Sumitomo Osaka; Kowa Tokyo, Meiji Seika Kaisha Tokyo, Japan; Lifasa Spain; Merck Shap + Dhome, FRG; Polfa Poland;	-"-	p- methoxy-phenyl hydrazine, levulinic acid, ester.	5-6 steps		
			or			
			phenyl hydrazine, acetal dehyde, p-chlorobenzoil chloride	4-5 steps		
			or			
			p-chloro-benzoate, p-metoxiphenylhydrazine sulfonic acid sodium salt	2-3 steps		

SUBJECT	TECHN.SOURCE	TYPE OF PROCESS	MAIN RAW MATERIALS	LENGTH OF PROCESS	PRICE	MAIN EQUIPMENT
6.6 Drugs for control of hyperuricemia: Allopurinol	Tanabe Tokyo,Japan; Desitia,Hennig,Fresenius,Gerot,Austria;Siegfried Zofinge ,Switzerland	Chem.synthesis FRG;	cianoacetic acid ester, orthoformic acid ester	3-4 steps		
7. Vitamins by Feuer + Lugési						
Vitamin A	BASF,Bayer,Merck FRG; Pfizer,Gral Mills,Hoffman La Roche,USA; AEC France; Phillips Holland;	extraction of βionone	lemon grass oil		US$24,50/kg	
		chem.synth. from βionone	βionone,ethyl chloracetate,Grignardreagent C 15 aldehyde,LiAlH4, methylcrotonicacid-triphenyl-phosphonium bromid	7-8 steps 2-3 steps		fully automated operation;special equmts.for extremely large amounts of heat evolved;severe safety demands;
			or βionone,formyl-crotonic acid ester	3-4 steps		
Vitamin B 1 (thiamine HCl)	Hoffmann La Roche Switzerland;Merck USA;Takeda Tanabe Sankyo Kongo,Japan;Rhone Poulenc, Bayer,France;Bayer,E.Merck FRG;	chem.synth.	βethoxy ,propionitrile, malonitrile,acetamidine	10-11steps	US$ 23/kg	enameled autoclaves,acid resistent,steel autoclaves + film evaporator;
Vitamin B 2 (Riboflavine)	Grain Processing Corp. Diamond Shamrock,Merck USA; Bayer FRG;Hoffmann La Roche Switzerland	chem.synth. Fermentation	3.4-dimethylaniline, Dribose molasses (free of iron)	4-5 steps	US$ 40/kg (USP) US$ 20/kg (animal feeding)	special equmt. for catalytic hydrogenation; fermentation, vessels,filters;

SUBJECT	TECHN.SOURCE	TYPE OF PROCESS	MAIN RAW MATERIALS	LENGTH OF PROCESS	PRICE MAIN EQUIPMENT
Vitamin C	Merck Pfizer ,Hoffmann La Roche USA;Bayer Hoechst FRG;Takeda Japan;Rhone Poulenc France; Pliva Jugoslavia	Chem.synth. Fermentation	D-glucose	7-8 steps	US $ 10/kg traditional equmt. of chem.industry+ some special for catalytic hydro-genation;
Vitamin PP (Nicotinamide)	Merck,Hoffmann La Roche, Parke Davies USA;Carlo Erba Italy;Bayer FRG;	Chem.synth.	Nicotine or Quinoline or Picoline	2-3 steps	US $ 7/kg traditional equmt. + reactor tube for oxidation; high degree of instrumentation