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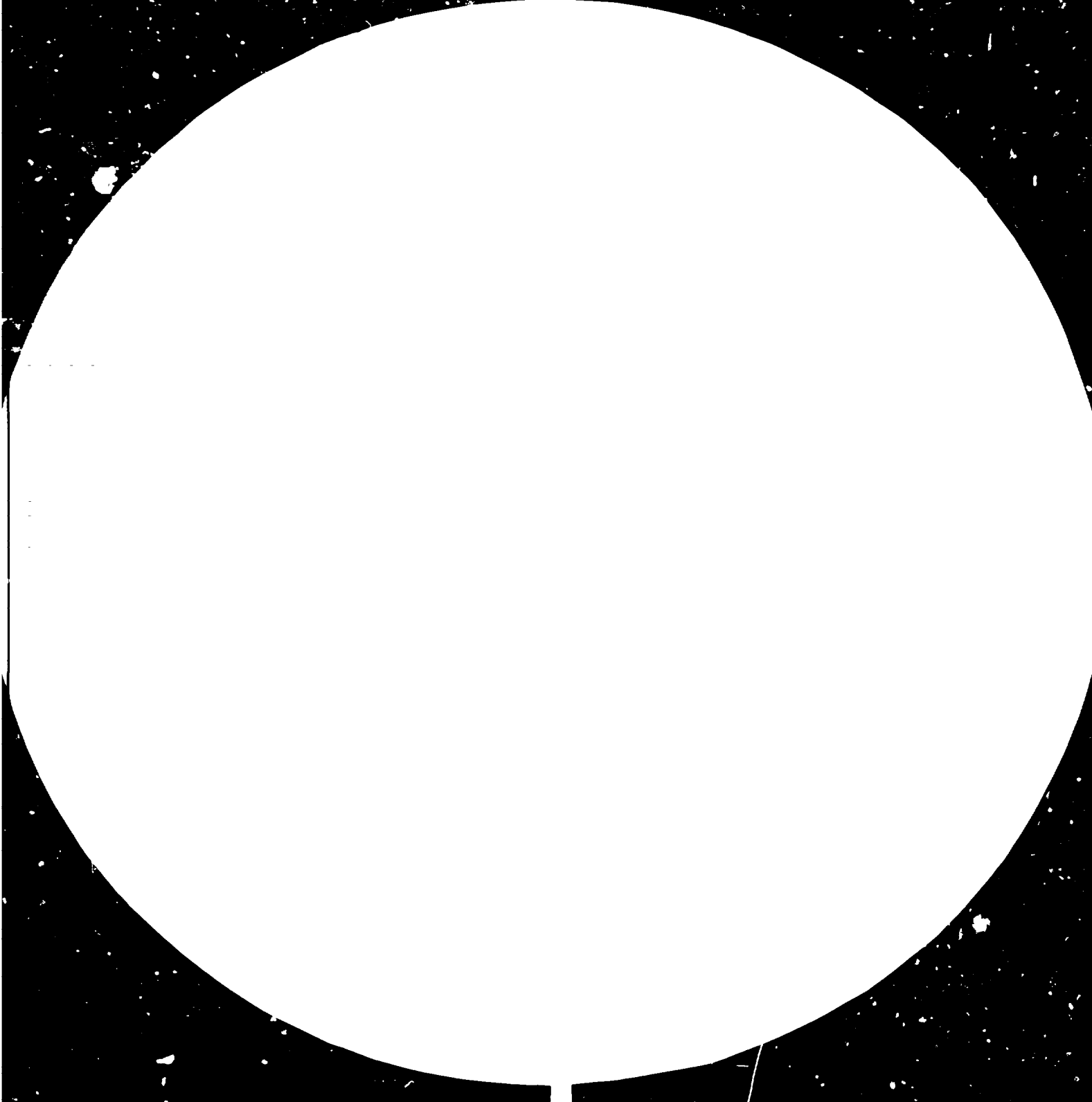

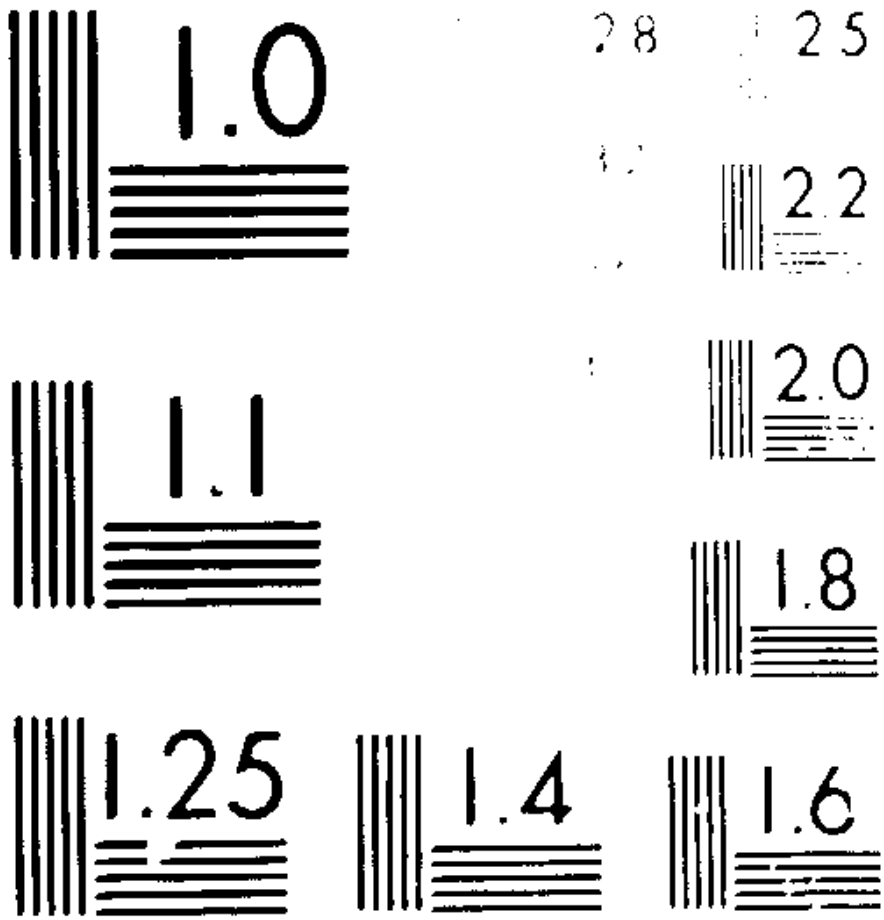
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APPROPRIATE INDUSTRIAL TECHNOLOGY FOR DRUGS AND PHARMACEUTICALS

UNITED NATIONS INDUSTRIAL DEVELOPMENT ORGANIZATION
Vienna

Monographs on Appropriate Industrial Technology
No. 10

APPROPRIATE INDUSTRIAL TECHNOLOGY FOR DRUGS AND PHARMACEUTICALS

UNITED NATIONS
New York, 1980

EXPLANATORY NOTES

A full stop (.) is used to indicate decimals.

A comma (,) is used to distinguish thousands and millions.

A slash (/) is used to indicate "per", for example t/a = tonnes per annum.

A slash between dates (for example, 1979/80) indicates an academic, crop or fiscal year.

A dash between dates (for example, 1970–1979) indicates the full period, including the beginning and end years.

References to dollars ($) are to United States dollars.

References to rupees (Rs) are to Indian rupees. In October 1978 the value of the rupee in relation to the dollar was $1 = Rs 7.90.

The word billion means 1,000 million.

The word lakh means 100,000.

The following notes apply to tables:

Three dots (. . .) indicate that data are not available or are not separately reported.

A dash (–) indicates that the amount is nil or negligible.

A blank indicates that the item is not applicable.

Totals may not add precisely because of rounding.

In addition to the common abbreviations, symbols and terms and those accepted by the International System of Units (SI), the following have been used:

Economic and technical abbreviations and symbols

c.i.f.	cost, insurance, freight
EDTA	ethylene diamine tetraacetic acid
ft	foot (1 ft = 30.5 cm)
ft^2	square foot (1 ft^2 = 9.290 dm^2)
in.	inch (1 in. = 2.54 cm)
in^2.	square inch (1 in^2. = 6.45 cm^2)
INH	isoniazid
IR	infra-red
PAS	*p*-Aminosalicylic acid
psi	pound-force per square inch (1 psi = 6,895 Pa)
UV	ultraviolet

EXPLANATORY NOTES *(continued)*

Organizations

AHRTAG	Appropriate Health Resources and Technologies Action Group (London)
BNF	British National Formulary
BP	British Pharmacopoeia
BPC	British Pharmacopoeial Codex
CAEME	Camara Argentina de Espitialedades Medicinales
IP	Indian Pharmacopoeia
ITDG	Intermediate Technology Development Group Limited (London)
NFI	National Formulary of India
USP	United States Pharmacopoeia
WHO	World Health Organization

The concept of appropriate technology was viewed as being the technology mix contributing most to economic, social and environmental objectives, in relation to resource endowments and conditions of application in each country. Appropriate technology was stressed as being a dynamic and flexible concept, which must be responsive to varying conditions and changing situations in different countries.

It was considered that, with widely divergent conditions in developing countries, no single pattern of technology or technologies could be considered as being appropriate, and that a broad spectrum of technologies should be examined and applied. An important overall objective of appropriate technological choice would be the achievement of greater technological self-reliance and increased domestic technological capability, together with fulfilment of other developmental goals. It was noted that, in most developing countries, a major development objective was to provide adequate employment opportunities and fulfilment of basic socio-economic needs of the poorer communities, mostly resident in rural areas. At the same time, some developing countries were faced with considerable shortage of manpower resources; in some other cases, greater emphasis was essential in areas of urban concentration. The appropriate pattern of technological choice and application would need to be determined in the context of socio-economic objectives and a given set of circumstances. The selection and application of appropriate technology would, therefore, imply the use of both large-scale technologies and low-cost small-scale technologies dependent on objectives in a given set of circumstances.

Report of the Ministerial-level Meeting. International Forum on Appropriate Industrial Technology

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Annexes

Foreword

As part of its effort to foster the rapid industrialization of developing countries, the United Nations Industrial Development Organization (UNIDO), since its inception in 1967, has been concerned with the general problem of developing and transferring industrial technology. The Second General Conference of UNIDO, held at Lima, Peru, in March 1975, gave UNIDO the specific mandate to deal in depth with the subject of appropriate industrial technology. Accordingly, UNIDO has initiated a concerted effort to develop a set of measures to promote the choice and application of appropriate technology in developing countries.

Appropriate industrial technology should not be isolated from the general development objective of rapid and broad-based industrial growth. It is necessary to focus attention on basic industrial development strategies and derive from them the appropriate technology path that has to be taken.

The Lima target which, expressed in quantitative terms, is a 25 per cent share of world industrial production for the developing countries by the year 2000, has qualitative implications as well. These comprise three essential elements: fulfilling basic socio-economic needs, ensuring maximum development of human resources, and achieving greater social justice through more equitable income distribution. Rapid industrialization does not conflict with these aspirations; on the contrary, it is a prerequisite to realizing them. But, in questioning the basic aims of development, we also question the basic structure of industrial growth and the technology patterns it implies.

Furthermore, it is easy to see that the structure of industrial growth that should be envisaged and the corresponding structure of technology flows should be different from what they are today; a fresh approach is called for. This does not mean that the flow of technology to the modern sector and the application of advanced technologies are unnecessary. On the contrary, it is essential to upgrade the technology base in general, and it is obvious that to provide basic goods and services, there are sectors of industry where advanced or improved technology is clearly necessary. It would be difficult to envisage a situation where the dynamic influence of modern technology is no longer available for industrial growth and development in general. However, an examination of the basic aims of industrial development leads to the conclusion that there must be greater decentralization of industry and reorientation of the design and structure of production.

Such decentralized industry in the developing countries calls for technologies and policy measures that often have to be different from those designed for the production of items for a different environment, that of the developed countries. As a result, there is a two-fold, or dualistic, approach to

an industrial strategy. Morever, the two elements in such an industrial strategy need to be not only interrelated but also integrated.

In approaching the question of appropriate industrial technology from an examination of basic development needs, a mechanism is necessary to link and integrate appropriate industrial technology to the overall development process. Through such a process the concept of appropriate industrial technology could be placed in the mainstream of the industrial development effort.

It is hoped that these monographs will provide a basis for a better understanding of the concept and use of appropriate industrial technology and thereby contribute to increased co-operation between developing and developed countries and among the developing countries themselves.

It is also hoped that the various programmes of action contained in the monographs will be considered not only by the forthcoming meetings of the United Nations Conference of Science and Technology for Development and UNIDO III but also by interested persons working at the interface over the coming years.

Abd-El Rahman Khane
Executive Director

Preface

To focus attention on issues involved in choosing and applying appropriate technology, UNIDO organized the International Forum on Appropriate Industrial Technology. The Forum was held in two parts: a technical/official-level meeting from 20 to 24 November 1978 at New Delhi and a ministerial-level meeting from 28 to 30 November 1978 at Anand, India.

In response to a recommendation of the ministerial-level meeting, UNIDO, with the help of a generous contribution by the Swedish International Development Authority, is publishing this series of monographs based mainly on documents prepared for the technical/official-level meeting. There is a monograph for each of the thirteen Working Groups into which the meeting was divided: one on the conceptual and policy framework for appropriate industrial technology and twelve on the following industrial sectors:

Low-cost transport for rural areas
Paper products and small pulp mills
Agricultural machinery and implements
Energy for rural requirements
Textiles
Food storage and processing
Sugar
Oils and fats
Drugs and pharmaceuticals
Light industries and rural workshops
Construction and building materials
Basic industries

The monograph on the conceptual and policy framework for appropriate industrial technology also includes the basic part of the report of the ministerial-level meeting and some papers which were prepared for the Second Consultative Group on Appropriate Industrial Technology, which met at Vienna, 26-29 June 1978.

PART ONE

Issues and considerations

Note by the secretariat of UNIDO

INTRODUCTION

World sales of drugs in developed market economies are concentrated in the hands of transnational corporations. The table shows the increasing share in the production of drugs by developing countries from 1960 to 1980.

SHARE OF ECONOMIC GROUPS IN THE PRODUCTION OF PHARMACEUTICALS
(Percentage)

Economic grouping	*1960*	*1975*	*1980*
Developing countries of Africa, Asia and Latin America	8.4[a]	12.0[b]	14[c]
Developed market and centrally planned economies	91.6	88.0	86
Total	100.0	100.0	100
Value (billion dollars)	7.9	37.5	...

[a]Estimated distribution: Africa, 0.2; Asia, 3.4; Latin America, 4.8.
[b]Estimated distribution: Africa, 1.3; Asia, 4.4; Latin America, 6.3.
[c]Indicative only; estimates extrapolated on the basis of share increases during the period 1960–1975 would lead to shares ranging from 13.2 to 14.5 per cent.

This increase in production will involve much higher capital investment than normally envisaged, because, of 110 developing countries, only about 10 have formulation and bulk production plants, while some 50 have only formulation plants and the rest only import the finished products. Therefore, most of them now only carry out the final stages of manufacture, that is, formulating imported bulk drugs into finished preparations or repacking imported finished drugs. Backward integration of industries in these countries to go into more basic stages of manufacture will involve considerable capital investment without reflecting significantly on the value of output. Ancillary industries such as the production of packaging materials and associated engineering industries for making simple equipment must also be established. These measures will result in a considerable increase in the value added and reduce dependence on imports. With a simultaneous development of the chemical and chemical-based industries, where feasible, the developing countries will have more self-sustaining industries.

The trends from 1980 onwards are difficult to forecast because of political, social, economic and technological factors that are likely to play increasing roles

in the development of the pharmaceutical industry throughout the world. The growth of the industry will probably be more regulated to meet the urgent health needs of each country instead of the *laissez-faire* policy followed at present in many countries, especially as the right to health care will become widely established as a major socio-political goal. This development will also mean higher levels of government economic controls on prices, profits and foreign capital investment. To correct the present concentration of drug distribution in urban centres and make drugs available in the rural and more remote parts of developing countries, the trend will be towards public acquisition of the drug distribution systems. Smaller, dispersed plants will supplement the existing larger ones that operate in urban centres in the more advanced developing countries. Traditional medicine will also play a more important role in the health services, and greater attention will have to be paid by governments to the standardization and upgrading of products from this source.

I. OBJECTIVES

The major objectives in promoting pharmaceutical industries in developing countries are:

(a) To provide, in adequate quantities, products essential to health care at prices within reach of most of the population;

(b) To set up relatively independent drug industries that will allow developing countries more freedom to form health care policies relevant to their particular needs at minimal cost, using locally available raw materials and production facilities, and also utilizing the existing traditional forms of medicine;

(c) To contribute to the national economies of the developing countries;

(d) By taking steps appropriate to the stage of development of the industry in these countries, i.e., formulation of drugs in dosage forms, operation of multipurpose plants, production of bulk drugs of plant and animal origin or production of drugs from intermediates, to establish a self-sustaining industry. The industry can be designed for a variety of end-products, thus giving it a commercial and economic advantage over other industries. The technology for establishing such production is fairly well diffused and can be obtained relatively easily from small developed countries or advanced developing countries in forms adapted to the needs of developing countries;

(e) To have a catalytic effect on industrial development in general. The pharmaceutical industry usually spearheads the development of chemical and chemical-based industries, as well as the ancillary products and engineering industries required to supply their needs;

(f) To provide educational opportunities for young men and women in new disciplines of science and to provide employment for trained people.

II. FORMULATION UNITS

The choice and adaptation of appropriate technology in promoting the pharmaceutical industry in different groups of developing countries are

discussed in the first of the papers in Part Two. Even in developing countries that are fairly advanced, where products are made in economically sized units and located where the necessary infrastructure, such as the chemical and engineering industries, exists, it is possible for semi-industrial units dispersed over the rural and remoter parts of the country also to be set up to formulate basic drugs relevant to the region, to meet the local needs and to draw their requirements of raw materials from multipurpose factories located nearby. The size of these semi-industrial units, their capital cost and the testing facilities required to maintain quality are indicated in the paper. These units will supplement the major production plants and cater to the needs of the population of rural areas which now receive hardly any of the benefits of modern medicine.

The size of the formulation unit suggested in the paper is based on what the average control laboratory can cater to. If, however, it becomes necessary to set up smaller units, depending on demand, it will become necessary to link two or more formulation units to one control laboratory, provided the distances over which the samples must be moved are not too great. The use of raw materials and marketing of finished products in such cases will, however, have to await clearance of samples of each batch by the control laboratory.

It is necessary to ensure that the products turned out by these units have the required bio-availability and, for this purpose, assistance from other well established units or institutions within the country will be necessary. A small product-development laboratory (a research laboratory attached to the control laboratory) to work out any problems that may be encountered is also suggested in the paper.

While formulation facilities can be economical in small markets, and assist in developing skills to undertake backward integration into basic manufacture, economies of scale become very important in the production of antibiotics, drug intermediates and synthetic drugs. Many developing countries have already developed technological capability and adapted an improved technology to their specific needs and environments. Some have by their local R and D efforts improved the productivity of important processes. In such cases, however, there is also a well developed chemical industry, including a petrochemical industry, to supply the basic chemicals and integrate development of chemical-based industries such as dyes, plastics, synthetic fibres, pesticides, rubber chemicals and surfactants, which makes the production of common chemical intermediates feasible, thereby linking the gaps between the chemical industry and intermediates for drugs, dyes and the like.

In developing countries, a large proportion of the population depends on the indigenous systems of medicine. To improve their usefulness, such systems must be standardized and upgraded after proper screening. In addition to improving the reliability of the products, it will be necessary to weed out many useless preparations. The methods to be adopted by different countries will not be the same, but some indications to developing countries as to how they can improve these systems of medicine and make them more effective are suggested in the paper.

III. MEASURES

The following are the principal measures to be taken to achieve the objectives:

(a) Establishment of a national list of drugs as a basis for rational development of the pharmaceutical industry in relation to the health needs of the population;

(b) Improvment and strengthening of the scientific base for development and production of the traditional medicine and household remedies;

(c) Development of repacking and formulation plants;

(d) Development of manufacturing plants for sanitation products, in particular water-treatment agents, pesticides and disinfectants;

(e) Formation of an intrasectoral framework to advance the development and production of bulk drugs, including immunologicals and antibiotics, as well as their related basic materials such as intermediates, biologicals, plant products, chemical precursors and various nutrient media;

(f) Study and establishment of standards for tropical conditions, chemical engineering plant facilities and layout structures. Dosage forms also should be designed to withstand the high temperature and humidity conditions in tropical countries;

(g) Development of manufacturing plants for dosage packaging (for example pharmaceutical glass) and various other types of packaging materials;

(h) Establishment of a comprehensive quality assurance system, including specifications of standards and procedures, training of specialized personnel, information training to all persons concerned, in-plant quality assurance systems, inspection and auditing and verification methods relating to the total materials and products stream including the storage, administration and use of drugs. A system of registration that takes into account both the usefulness of a drug and its associated risks should be established. This could be done on a regional basis for smaller countries that cannot afford the elaborate facilities needed;

(i) Establishment of regulations relating to domestic and foreign corporate ventures and the importation of foreign drugs, intermediates and know-how;

(j) Establishment of model manufacturing units in less developed countries and in the rural areas of more advanced developing countries. These units will formulate selected indigenous drugs, household remedies, antiseptics, infusions and other simple formulations, depending on the common ailments prevalent in the area;

(k) Establishment of multipurpose plants to produce drugs from intermediates for a group of model manufacturing units;

(l) Establishment of units for the extraction of active ingredients of plant products that can be cultivated in developing countries instead of the present practice of exporting them as crude drugs. This will improve the value added of the products exported to developed countries and give the developing countries the necessary foreign exchange reserves to import intermediates and other

substances required for the manufacture of drugs to combat diseases common in the area.

The measures above reflect the main elements of the alternative technological development strategies for establishing a pharmaceutical industry, taking into account the development requirements of a particular country.

IV. ROLE OF INTERNATIONAL CO-OPERATION

In the pharmaceutical industry there is a high rate of obsolescence of products, not only owing to the development of new and improved products or cheaper substitutes, but also because over a period of time, the users become sensitized to certain drugs or the micro-organisms against which the drug action is directed develop resistance to it. In these circumstances, efforts to update the technology used and products manufactured by the larger units and government research institutions, which can afford the expenditure involved on R and D, are essential. Large manufacturing units in developed countries which have established modern research laboratories and spend a considerable portion of their sales revenue on R and D are the main source of information on both improved processes and strains and new drugs; they will hold a commanding position in this regard for quite some time. Association with such units and maintenance of the flow of information is therefore essential.

In less-developed countries, both special experience in management methods and technical expertise in operating pharmaceutical units are lacking. Manufacturing operations must be carried out under hygienic and often sterile conditions, with scrupulous attention to quality, and personnel must be trained to work in such an environment. The developing countries should therefore seek assistance in this regard from international companies. Training facilities for managerial personnel and technical staff at the factory level are therefore essential, and international co-operation in this regard will be most useful to developing countries.

For dissemination of scientific information to the medical profession on the action of newly introduced drugs, toxic effects, treatment of toxic effects and precautions necessary, based on experience encountered during clinical trials and those reported from time to time, the developing countries essentially depend on their foreign collaborators. A flow of information from the international firms concerned is essential in this respect.

International collaboration therefore still plays an important role in this industry, and for developing countries to obtain greater benefits from such collaboration, guidance is necessary. Governments can also establish certain guidelines in regulating collaboration arrangements to obtain the maximum benefits in this regard.

Report of the Working Group

I. DEVELOPING A PHARMACEUTICAL INDUSTRY

Most of the developing countries are at present dependent almost entirely on imports for their requirements of drugs and pharmaceuticals. The technological range and sophistication and high capital intensity of the industry make it nearly impossible for these countries to establish a conventional pharmaceuticals industry in the near future. On the other hand; governments must ensure that adequate supplies of drugs essential to the health of the population are available to the largest segment of it. For this, drugs would have to be progressively manufactured within the developing countries themselves with a view to achieving a measure of self-sufficiency in this key area. A beginning can be made by adopting appropriate technological alternatives by which the benefits of modern drug technology are available to larger segments of the population of the less developed countries, especially to people in rural and remote areas.

Simultaneously, the production of drugs used in traditional and local systems of medicine should be encouraged and integrated with the general programme of medical care. These would, however, need to be standardized and further developed. The cultivation of medicinal plants in the developing countries should be encouraged, and, where possible, facilities for extraction should be established to isolate the active principles for domestic and export markets.

If appropriate technology is selected and adopted for the development of a pharmaceutical industry it would be possible to establish sound structural linkages with auxiliary industries such as packaging materials and engineering goods industries.

Small-scale pharmaceutical units

The pharmaceutical industry should be considered from the standpoint of the country's health requirements, rather than as a commercial proposition. Despite the existence of more than 3,000 drug manufacturing units in India, for instance, the basic requirements of the rural population have not yet been met. The fact that there is a well-established pharmaceutical industry in any developing country does not by itself guarantee that the drug requirements of the most vulnerable sections of the population will be met. Small manufacturing

units and hospital pharmacies should therefore be set up in the rural and remote areas to produce the common drugs and simple household remedies needed in those areas.

Such small manufacturing units could provide employment opportunities for young people and increase the familiarity of the local population with drug manufacture. Such a strategy would also help developing countries to produce more sophisticated drugs in due course. Developing countries without a pharmaceutical industry could begin with units of this kind, which also include small infusion plants. They could become growth nuclei and progressively develop into an organized pharmaceutical industry even in the least-developed countries. Advantage should be taken of the offers of some countries to provide simple bulk drugs and equipment at minimum cost for establishing and operating such model manufacturing units. See the paper "Medicine for the rural population in India" in part two of this monograph for details of the equipment required and its approximate cost in India.

Many of the products that can be manufactured in such small-scale units are listed in the pharmacopoeia and formularies for treatment of common ailments and can be produced in the form of tablets, capsules, ointments, syrup and other liquid preparations. The background paper mentioned above presents such a formulary, developed after interviews with a large number of physicians serving in the rural areas either under the Indian Medical Association or through social organizations. A plan for small pharmaceutical units is also included. Each unit is initially supposed to serve 2 million people and to produce medicaments at an average cost of one rupee ($0.12) per person per year.

It is, however, essential that the formulary should be reduced to a small list of products required in the rural areas by a large majority of the population. This list could vary from area to area within the same country, as well as from country to country, according to local requirements and conditions. Once the products have been identified, it would be possible to manufacture them in small factories near the local hospitals. Small formulations units could be as economic as the high-value, small-sized manufacturing units. For hospital supplies and other bulk requirements, standard formulations and packaging lists should be prepared and products could then be manufactured on a contract basis by manufacturing units within the country. This system has been developed successfully in Brazil and Peru and has resulted in considerable savings on essential drugs.

In Sri Lanka, the State Pharmaceutical Company, which is government owned, invites tenders for the products listed in the formulary approved by the National Formulary Committee. After purchase these are distributed to the central drug stores, which in turn distribute them to the smaller stores in the outlying districts.

Zambia imports but also has its own small formulation units. The Government gives preference to local production; mark-ups as high as 12 per cent over the cost of overseas supplies are charged. The medicines are then passed to the medical stores and from there to the provincial medical stores and district hospitals. In this way a fairly wide distribution is achieved. The medicines are supplied free of charge by hospitals. In addition, there is commercial distribution through drug stores, wholesalers, retail shops,

supermarkets and grocery shops. What restricts supply is not poor distribution but insufficient production.

Packaging

Packaging is an important and integral part of the total technology of drug production. Sufficient information on packaging technologies suitable for different climatic conditions and distribution methods and systems is available. However, packaging institutes should be established in those developing countries which still do not have such institutes. Information on the kind of help that the existing institutes could provide in packaging pharmaceuticals for rural areas could be collected by UNIDO and be made available to interested developing countries.

Training

The developing countries generally lack special experience in management methods and technical expertise in operating pharmaceutical units. Drug-manufacturing operations must be carried out under hygienic and often sterile conditions, with scrupulous attention to quality. Personnel engaged in pharmaceutical units must be adequately trained in both management methods and production operations. Training facilities for managerial personnel and technical staff at the shop-floor level are therefore essential. International co-operation in this regard would be most useful.

Integrated training centres should be set up on a regional and sub-regional basis to provide training in management, pharmaceutical manufacturing, quality control and packing. These centres should be equipped with small research and development (R and D) and pilot-plant facilities to help solve the specific problems.

Drug research

In view of the rapid obsolescence of drugs and the special requirements of the developing countries, particularly for drugs to treat communicable and tropical diseases, it may be necessary to establish drug centres or institutes in the developing countries as joint or regional ventures.

These institutes should be able to make clinical evaluations of drugs. The development of new drugs to fight tropical diseases is often delayed because of the lack of facilities for their clinical evaluation in developed countries, where such diseases do not exist. The research centres should also undertake the evaluation and standardization of traditional remedies and plant products.

Regional co-operative centres

In would be helpful for the development of the pharmaceutical sector in developing countries if regional co-operative pharmaceutical centres, each

serving a group of countries, were established. Work of this kind has already been initiated by UNIDO and the United Nations Conference on Trade and Development.

These centres could also provide the following services:

Information on available sources of technology
Assistance in arranging for technological training
Market intelligence
Regional market and national resources surveys
Management training
Product information

Information

The developing countries depend on their foreign collaborators for the supply of scientific information to the medical and pharmaceutical professions on the action of newly introduced drugs, their toxic effects and their treatment, and the necessary precautions. This information is based on experiences encountered during clinical trials and those reported from time to time. A flow of information in this respect from independent sources is also highly essential. International collaboration therefore still plays an important role in this industry.

Role of international co-operation

The pharmaceutical industry is characterized by a high rate of obsolescence of its products, not only owing to the the discovery and development of new ones or of less costly substitutes, but also because, over a period of time, users become immunized to certain drugs or, what is equally important, the micro-organisms against which the drug action is directed tend to develop a resistance to the drug. In either case the drug loses its efficacy and becomes obsolete. Therefore, sustained efforts to improve and modify the technology used and to manufacture new products are needed. This is possible only with the assistance of large pharmaceutical companies and government research institutions that can afford the R and D expenditures involved.

The development of process technology for pharmaceuticals and basic drugs requires a great deal of research. It is therefore necessary for the developing countries to establish strong R and D capabilities in this field to keep abreast of global developments.

II. PROGRAMMES OF ACTION

The programme of action at the national level should include the following elements:

(a) An industrial policy that clearly outlines the short- and long-term plans

for the development of a pharmaceutical industry and a production plan based on a list of drugs to be taken up for priority production;

(b) The establishment of a drug control organization with a testing laboratory. The cost of such an elementary control laboratory is estimated to be $25,000;

(c) Carrying out of feasibility studies of small pharmaceutical formulation units. Adequate fiscal and other incentives to the private sector to establish such units in rural and remote areas. In the conditions prevailing in most developing countries, a lead will have to be given in this aspect by governments themselves. The capital cost of establishing a small pharmaceutical manufacturing unit would be approximately $200,000. An infusion unit could cost an additional $300,000;

(d) An organization for the collection, cultivation and processing of domestic medicinal plants;

(e) Research on the standardization and preparation of products used in traditional systems of medicine;

The programme of action at the international level should include the following elements:

(a) Regional pharmaceutical centres set up on a co-operative basis until separate national centres can be established. These centres would provide training in scientific management and production methods. Some of the existing organizations in more developed countries could be developed into regional or subregional centres. These centres could have small R and D outfits to undertake studies of certain types of operational problems;

(b) Examination of the offers made by developed countries to supply at cost bulk drugs to be formulated in the proposed small manufacturing units with a view to promoting the establishment of such units in selected developing countries on a trial basis;

(c) Assistance of the major pharmaceutical firms and research institutions in the developed countries in updating the technologies used in developing countries and also in developing new products suitable to the local conditions in and the needs of developing countries;

(d) Suitable forums for the exchange of the technological experience of developing countries in establishing pharmaceutical industries;

(e) Institutes that can make clinical evaluation of new drugs in developing countries. They should be established on a regional or subregional basis and should also undertake to standardize traditional remedies and phytochemical products.

III. RECOMMENDATIONS

1. Each developing country should accept a commitment to establish a strong local pharmaceutical industry including adequate capabilities for repacking and formulation. The goal should be to offer as wide a range of drugs as may be required by the medical profession. However, in order to utilize

limited resources and to assist in establishing a local industry, it is essential to develop a national list of drugs. Local production of such drugs would bring the benefits of technological advances in the manufacture of pharmaceuticals to the people who do not yet have access to them. The criteria for selecting drugs for local production may include the following:

(a) The drug is widely used or required by the health authorities to treat prevalent diseases;

(b) Its efficacy and safety in the treatment of diseases has been demonstrated;

(c) The cost per treatment is low enough for the population to afford;

(d) There are other special advantages of local manufacture as opposed to imports (lower costs of transport, availability of raw materials, saving of foreign exchange etc.);

(e) A feasibility study of the project should indicate that economic production could be ultimately attained including the meeting of regional and interregional demands;

(f) The manufacturing process is appropriate to the conditions prevailing in the country;

(g) The know-how for manufacture is available for production.

2. The scientific base for the development and production of preparations based on traditional systems of medicine and household remedies should be improved and strengthened.

3. An intrasectoral framework to promote the development and production of bulk drugs, including immunologicals and antibiotics as well as their related basic materials such as intermediates, chemical precursors and various nutrient media should be established.

4. Arrangements should be made for the collection of suitable animal by-products from modern abattoirs for medicinal purposes.

5. Standards for chemical and pharmaceutical engineering plants and layouts for structures for tropical conditions should be studied and elaborated.

6. Dosage forms and packages should be designed to withstand the high temperature and humidity conditions encountered in tropical countries.

7. Ancillary industries for pharmaceutical packaging materials, pharmaceutical machinery, auxiliary materials and suitable refrigerated transport facilities should be developed.

8. A comprehensive quality assurance (QA) system, including the specification of standards and procedures particularly suited for local conditions should be established. This programme should also include the training of specialists in in-plant QA systems and in inspection, auditing and verification methods relating to the materials and products stream.

9. Special consideration should be given to the storage conditions, distribution and usage of drugs.

10. A system of registration of new drugs should be established. Such a system could be set up on a regional basis for smaller countries that cannot individually afford the elaborate facilities needed.

11. Guidelines relating to the transfer of technology to produce drugs and intermediates should be drawn up.

12. Small model pharmaceutical units for formulation in less developed countries and in the rural and remote areas of more advanced developing countries should be established. These would include selected drugs of the traditional systems of medicine, household remedies, antiseptics, infusions for rehydration, and other simple preparations: tablets, capsules, ointments, syrups to treat ailments common in the area. These units should not attempt to produce high-potency drugs. The location of such units would depend entirely on government policy on the dispersal of industries. Infusion plants in local settings such as hospital pharmacies would be useful and could help the rural population and prevent loss of life from dehydration. These manufacturing units should also produce sanitation products such as water treatment agents and disinfectants. Such small pharmaceutical manufacturing units could, in specific cases, become nuclei for future expansion.

13. Multipurpose plants to produce drugs from intermediates should be established in developing countries wherever feasible.

14. The cultivation of medicinal plants in developing countries should be encouraged, and where possible, facilities should be established for the extraction of active ingredients of plant products for domestic or export markets instead of the present practice of exporting them as crude drugs to developed countries.

PART TWO

Selected background papers

Choice and adaptation of appropriate technology for the production of pharmaceuticals in developing countries

*B. Shah**

To meet the requirements of a country's medical and health services, its pharmaceutical industry needs to produce drugs of adequate quality in sufficient quantities and at reasonable prices. Developed countries are flooded with innumerable preparations; it is not possible for any developing country to market all of them within its limited resources. It is recommended, therefore, that each developing country establish a national list of drugs to meet the needs of the majority of its population. The drugs included in such a list would differ from country to country depending on many conditions, such as the pattern of prescription, common diseases, type of health services, available personnel, financial resources and genetic, demographic and environmental factors.

CHOICE OF TECHNOLOGY FOR DIFFERENT GROUPS OF COUNTRIES

After the preparation of a national list, the manufacturing method chosen will depend on the development stage of the country's industry and its technical base. The developing countries have been broadly classified into five groups, depending on their stage of development, as follows:

Group	*Description*
I	No manufacturing facilities and dependent on imported, finished pharmaceuticals
II	Packaging of formulated drugs and production of simple formulations
III	Formulation of a broad range of drugs in dosage form; production of simple drugs from intermediates
IV	Production of a broad range of drugs from intermediates and manufacture of some intermediates from local raw materials
V	Manufacture of intermediates and production of the plant and equipment required

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GROUP I COUNTRIES

Group I countries not only have no manufacturing facilities for pharmaceuticals, they also have limited public health services and poor distribution channels. The steps they should take are:

(a) Establish procurement procedures for the items in the national list of drugs to take advantage of bulk purchasing;

(b) Develop quality-control facilities to ensure the quality of the drugs purchased (see annex I for a list of control and formulation equipment);

(c) Establish units for repackaging formulated drugs which will help build auxiliary industries for producing packaging materials and standardize their production (see annex II for list of packaging materials);

(d) Set up units to produce infusion solutions and simple formulations on a semi-industrial scale (see annex I for the necessary equipment).

GROUP II COUNTRIES

Group II countries already package formulated drugs and produce simple formulations. The steps they should take are:

(a) Establish formulation units to convert bulk drugs into dosage forms such as tablets, capsules, liquid preparations, ointments and infusion solutions (see annex I);

(b) Establish facilities to control quality from the raw material to the finished product (see annex I);

(c) Set up the requisite organization to monitor drug stability. When products fail to meet specifications they should be recalled from the market.

To achieve these steps, it is essential to train industrial pharmacists to set up and operate semi-industrial units and to establish test facilities. This is a very important part of the infrastructure. UNIDO has been assisting in this area by providing training at certain universities. For example, over the last five years, trainees from 82 nations have participated in courses at the University of Ghent, Belgium, obtaining the expertise to begin the production of simple preparations, set up and operate small infusion-producing installations and introduce semi-industrial formulation facilities for tablets, capsules, ointments, ampoules and the like. Several of the more advanced developing countries have similar facilities and are co-operating with less advanced ones in this field.

Semi-industrial plants need no elaborate equipment. The technical assistance and equipment for them are not difficult to acquire within the developing countries themselves. Such units should also undertake production of simple antiseptic solutions to help prevent the spread of infection. The infusion solutions referred to above are essential for treating severe cases of dehydration caused by diarrhoea; unless they are administered immediately, lives are lost. It would cost more to import such solutions, which contain nearly 95 per cent water, than to produce them locally at hospital pharmacies. A list of equipment required for making such infusions and simple formulations is given in annex I. The ancillary products required to formulate drugs are given in annex III.

Types of formulations

The various ingredients involved in making simple formulations are described below.

Tablets

Various types of tablet are made, such as plain, chewable, sugar-coated, press-coated, layered, film-coated and sustained-release.

The tablet form offers several advantages:

Ease of dispensing and administering

Ease of packaging and shipping

Accuracy of dosage

Preservation of drug activity

In addition to the active drug or drugs, the other ingredients in tablets are diluents, binders, lubricants and disintegrating, colouring and flavouring agents:

(a) Diluents. Many synthetic and natural drugs are highly potent; only extremely small quantities are required per dose. In order to be able to make a tablet for administering such small quantities, certain inert materials called diluents are included. Some examples are lactose, starch, sucrose, mannitol, dicalcium phosphate, calcium sulphate and micro crystalline cellulose;

(b) Binders. Substances that keep the components of the tablets together in the tablet form after compression are known as binders. Examples of common binders are gum acacia, gum tragacanth, gelatin, starch paste, sodium carboxymethylcellulose, ethylcellulose, polyvinyl pyrrolidone and sodium alginate;

(c) Lubricants. These are substances that prevent adhesion of the powder to the punches during compression and ensure smooth ejection of the tablets from the dies. Some commonly used lubricants are talcum powder, liquid paraffin and stearic acid and its salts;

(d) Disintegrating agents. Substances that help break up tablets after administration to the patient are called disintegrating agents. Some commonly used ones are cornstarch, gum guar, methylcellulose, sodium carboxymethylcellulose, micro crystalline cellulose and alginates. The pharmacopoeias prescribe a limit of 15 minutes for the disintegration of common tablets after administration;

(e) Colouring agents. Colour, in addition to making tablets look more attractive to patients, also helps to distinguish different medicines. Only certified food and drug colours are normally used;

(f) Flavouring agents. To make tablets more palatable, various flavouring agents are incorporated into them.

All ingredients must be tested for their compatibility both with each other and with the active drug or drugs.

Capsules

Capsules are solid dosage forms in which the drugs are enclosed in hard or soft shells of gelatin. (The gelatin shells themselves are also called capsules.) As a dosage form, capsules have advantages over tablets in that:

(a) They retain drug potency without complex formulation techniques;

(b) They give more protection from the atmosphere by holding each dosage in a sealed container;

(c) They mask the taste and odour of the active drug;

(d) They disintegrate in the stomach in less than five minutes, thus making the drugs available for quick absorption.

Capsules are largely used to market single active drugs such as antibiotics. However, mixtures of drugs, either as made or in granules, are also marketed in capsule form (for example, vitamins). Capsules come in a variety of sizes. The choice of size depends on the bulk density of the mixture for a single dose. The colouring of capsules is adopted extensively as a method of identification for proprietary products. In damp conditions, capsules tend to stick together, so it is recommended that they be stored in a dry and cool place.

The general process for manufacturing hard gelatin capsules containing drugs involves four operations: preparing the powder mixture, and filling, sealing and cleaning of the capsules.

The drug for capsules is blended in a blender, with a diluent if necessary, and with a little lubricant to ensure free flow of the powder while filling the capsule. The blended material is then filled in semi-automatic or automatic machines that are now available even in several developing countries. The machine first separates the top and bottom parts of the empty capsule, delivers an accurate weight of the blend in the bottom part and then replaces the top part.

Sealing is achived in a machine that applies a solution of gelatin at the joint of the top and bottom parts of the filled capsule. Such machines are easily available. Self-locking capsules, however, do not need sealing. Some of the pharmaceutical houses also print their capsules to identify their products. This can be done before or after filling.

Liquid preparations

Liquid preparations have these major advantages:

(a) Ease of handling when the active drug is a liquid;

(b) Flexible administration, as with small or large doses, as required by the physician;

(c) Quick action–the drug is available for absorption immediately after administration;

(d) Ease of formulation–liquid preparations can be sweetened or flavoured to facilitate their administration, particularly for children and old people.

Parallel with these advantages, however, there are certain disadvantages:

(a) For single doses, liquids are bulkier than equivalent solid dosage forms, resulting in higher costs;

(b) Deterioration of drugs such as antibiotics, vitamins and hormones is much faster in the liquid form than in solid dosage forms.

Liquid dosage forms are mainly of three types: solutions, emulsions and suspensions.

Solutions

Solutions are made by dissolving a drug or drugs in a compatible solvent. The product should be a homogeneous, clear mixture, free from suspended particles. Water, alcohol, sugar syrup, glycerin and sorbitol (70 per cent) are the most common solvents.

Apart from the active drugs und diluents, other ingredients involved are sweetening, colouring and flavouring agents as described in the discussion of tablets. Also, preservatives are added to prevent the growth of moulds and bacteria to which liquid preparations are susceptible. Commonly used preservatives are alcohol, hydroxybenzoates and sorbic acid.

Emulsions

Emulsions are two-phase systems prepared by combining two immiscible liquids, one of which is uniformly dispersed in the other. In order to keep this emulsion stable for a considerable time, emulsifying agents, such as benzalkonium chloride, glyceryl monostearate and gum acacia are added. The last of these is the most commonly used natural emulsifying agent.

Suspensions

Like an emulsion, suspension is a two-phase system, but it involves a solid phase finely suspended in a liquid phase. In order to keep the solid well suspended, certain chemicals are used, among them sodium carboxymethylcellulose, methylcellulose, polyacrylic acid and sodium alginate. The natural suspending agents include gum acacia and gum tragacanth.

Ointments

Ointments are soft, semi-solid preparations usually containing medicinal agents intended for application to the skin or eyes. All ointments should be sterile.

While it is not possible to give full manufacturing details here, the general method of ointment manufacture involves three types of material besides the active drug or drugs:

(a) Diluents or bases constitute the major portion of ointments and influence the absorption of the drugs through the skin. Various types of bases are used, for example:

(i) Oleagenous bases consisting of mineral, animal or vegetable oils, among them soft paraffin, liquid paraffin, lard, olive oil and cottonseed oil;

(ii) Absorption bases, for example hydrophilic substances such as wool fat (lanolin);

(iii) Washable bases are water soluble and are easily removable from the skin by washing with water. Common examples are the polyethylene glycols. They are compatible with a wide range of active drugs;

(iv) Emulsion bases are of two types. In one, water is the internal phase and oil the outer (W/O–water-in-oil emulsion); the other contains oil in the inner phase and water in the outer (O/W–oil-in-water emulsion). An example of a W/O emulsion is hydrous wool fat; stearic acid soap is an example of an O/W emulsion. Agents that help in forming emulsions for both the oil and water phase are called emulsifying agents. Sodium lauryl sulphate is an example;

(v) Emulsifying waxes are waxes that form O/W emulsions when fused with water. Examples are cetyl alcohol, stearyl alcohol and glyceryl monostearates;

(vi) Silicon bases include products that contain silicon compounds such as bentonite;

(b) Antioxidants are sometimes added to ointments to prevent oxidative deterioration. Their selection depends on factors such as toxicity, irritancy, potency, compatability, odour, discolouration, stability and solubility. Common antioxidants are butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA) and propyl gallate.

(c) Preservatives are added to ointments to prevent contamination, deterioration and spoilage by bacteria or fungi. The most common are esters of *p*-hydroxy benzoic acid (methyl ester or propyl ester) and sorbic acid.

Infusions and other parenterals

Popularly known as injections, parenteral preparations, including infusions, are sterile pharmaceutical dosage forms that can be administered intravenously or intramuscularly. Pharmacopoeias recognize four main types of parenteral products:

(a) Solutions of medicaments ready for injection. This is the most common form (such as glucose, saline) and are commonly known as infusions;

(b) Dry solid medicaments that make up into solutions by the addition of suitable solvents just before administration. These are mostly antibiotic preparations such as penicillin;

(c) Suspensions of solid medicaments ready for injection. These are mostly drugs in colloidal or micronized form such as hydrocortisone;

(d) Dry, solid medicaments that yield suspensions upon addition of suitable vehicles such as procaine penicillin.

Parenteral preparations offer the following advantages over the other dosage forms:

(a) They are the only way certain drugs can be absorbed in active form as with streptomycin and neomycin;

(b) They offer more predictable absorption because they are independent of the vagaries of the gastro-intestinal system;

(c) Their effective dose can be more accurately selected and the desired blood concentrations obtained quickly;

(d) They permit immediate action in emergencies, for example for unconscious or unco-operative patients. This is usually achieved by intravenous injection;

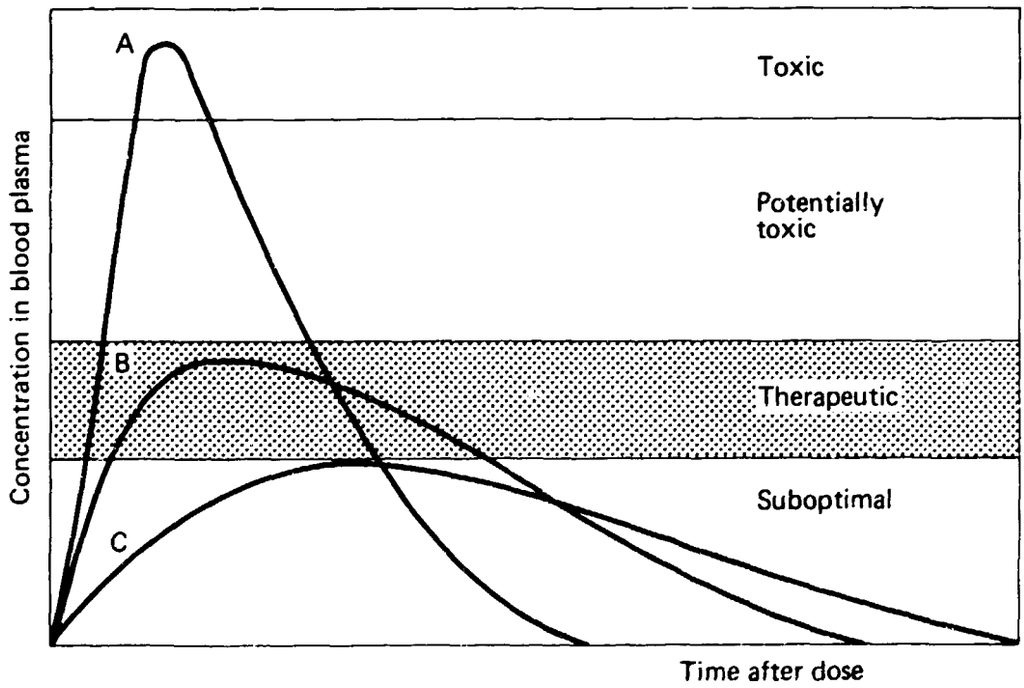
(e) The intravenous parenteral route offers the only method of rapidly increasing blood volume in cases of dehydration;

(f) They are the only possible method of administering drugs when patients are unable to take or retain drugs orally;

(g) The intramuscular and the subcutaneous parenteral routes can be used to prolong absorption of a drug, especially where sustained release is needed.

Supplies to primary health centres in rural areas

To improve supplies to the primary centres at reasonable cost, hospital pharmacies must be established to undertake simple formulations, infusions and the like. The selection should be made with special reference to the diseases prevalent in the area. A formulary of drug preparations commonly required in rural hospitals will have to be prepared, based on the national list of drugs. The facilities needed for organizing such production are:



Types of variation of bio-availability of drug formulations, depending on the nature of auxiliary ingredients, particle size and method of formulation. All three drug formulations, A, B and C, release the same total dose into the bloodstream, but drug A is released so quickly that it reaches toxic levels, while drug C is released so slowly that it never reaches the level at which it has any effect. Only drug B is medically useful

(a) Small infusion installations that could initially serve the needs of a group of hospital pharmacies;

(b) Semi-industrial formulation facilities for producing tablets, ampoules, ointments, antiseptics (such as sodium hypochlorite, potassium permanganate, chloramine and cresol) and solutions. These semi-industrial facilities would supply local needs. Their production would entail no transport difficulties and could therefore be distributed on regional and local bases;

(c) Quality control (chemical and bacteriological) laboratories connected with the hospital pharmacies or semi-industrial units.

These hospital pharmacies or semi-industrial plants would have the great advantage that locally trained industrial pharmacists could undertake the work very easily. Development of the human skills needed to carry out the operations involved under hygienic and aseptic conditions and operate testing facilities, however, needs special emphasis and can be achieved only by proper training. Essential technical help should be available to these units and other institutions within the country, especially to ensure that the preparations they produce have the necessary bio-availability. A given quantity of active ingredient can produce differing results if not properly formulated, as illustrated in the figure.

Proper supply and storage of immunologicals is also necessary. These are heat-sensitive products that lose their effectiveness with time. Their storage therefore needs special attention; otherwise the rural population receives hardly any benefit from them for prevention and treatment of epidemics. In a later stage, rural centres can undertake the work of preparing individual doses from bulk shipments under sterile conditions.

Other preventive measures at the rural centres include supply of water-treatment chemicals, pesticides and disinfectants. These could also be formulated locally in a separate unit to meet local requirements.

GROUP III COUNTRIES

Group III countries formulate a broad range of bulk drugs in dosage form and have also begun to produce simple bulk drugs from intermediates. The steps to be taken by them are:

(a) Establish multipurpose plants to produce the bulk drugs required for health programmes by manufacturing products, using production processes involving similar chemical reactions;

(b) Set up units for extracting active ingredients from indigenous medicinal plants, growing wild or cultivated;

(c) Set up centres to utilize slaughterhouse by-products, for example, extracting active ingredients from animal glands and organs and production of surgical catgut;

(d) Set up units to produce immunologicals both for prophylaxis and treatment.

Multipurpose plants

The advantage of multipurpose plants in countries where demands are limited is that the facilities can be utilized throughout the year by changing from one product to another. Demand for each product will always vary from season to season and from year to year, depending on epidemics etc.

Groups of simple bulk drugs can be made from intermediates in one multipurpose plant designed to carry out similar processes and operations. Among the major synthetic drugs are, for example, the sulpha drugs. They are chemically similar and are usually produced with the same type of equipment, starting from the same or similar chemical intermediates.

A list of equipment for a multipurpose plant that can be used to produce a large number of bulk drugs starting from late intermediates is presented in annex IV. To withstand corrosive reactions, the reaction kettle should preferably be glass-lined, but many reactions can be carried out in stainless-steel equipment, using only small, all-glass equipment for the final corrosive stages, thus reducing capital outlay. By changing intermediates and varying the reactants and reaction conditions, it is possible to use such equipment to produce, at the rate of about 200 t/a, the following drugs: aspirin, lidocaine, isoniazid, nicotinamide, methyl salicylate, paracetamol, phenacetin and phenylbutazone, the demands for which vary with market conditions.

It is also possible to set up such multipurpose plants to meet the demands of groups of semi-industrial formulation units or hospital pharmacies. They have the advantage of low overheads and few distribution problems compared to large manufacturing units set up in urban centres.

Botanical extraction units

The design of extraction units for recovering active ingredients from plants depends on the kind of plants available and of the products to be obtained from their extracts. Many developing countries now export crude herbs to developed countries and in turn import the active principles. Even exporting semi-processed products would improve export earnings.

Later, as experience is gained, the active ingredients could be isolated within the country of origin and be used for medical treatment as well as for export. In such cases, the value added increases many times. It would be an important step in redeploying industry from developed to developing countries and would help to improve the share of industrial production of developing countries.

In recent years greater attention has been given to plant products because plants synthesize complicated molecules from simple ones by means of highly specific reaction mechanisms that would be either too difficult or too costly to duplicate by classical chemical methods. In the case of steroid hormones, the partial synthesis of finished hormones starting from the very closely related naturally ocurring product diosgenin is more economic than total synthesis. Therefore, collection of wild or cultivated *Dioscorea* root for extraction of diosgenin is undertaken on a large scale, and plantations have been developed in many developing countries with suitable climatic and soil conditions. *Dioscorea* root grows wild on the Mexican and Himalayan mountains. Its collection for the extraction of diosgenin has however, depleted the lower and more accessible

ranges. One solution, therefore, is scientific cultivation of *Dioscorea* tubers and other plant genera such as *Solanum*, whose berries contain solasodine. Extraction of hecogenin from sisal waste can also form a starting point for the synthesis of steroid hormones. Another example of partial synthesis is that of vitamin A, starting from the citral present in lemon-grass oil. Guatemala, India and other subtropical countries have suitable climatic and soil conditions for cultivation and offer great scope to supply plant materials.

There are also certain phytochemicals that it is more advantageous to extract as active ingredients of plant products than to obtain by synthesis. Some of these can exist in different steric forms, and their chemical synthesis, therefore, yields a mixture of isomers that is very difficult to separate. The products thus obtained by synthesis may be toxic and have different therapeutic properties. In plants, these reactions take place at normal biological temperatures and pressures, so that the type and quantity of the substances produced will be those that they need for their own metabolism and hence are normally free from toxic ingredients. In view of these factors, there is great demand for certain plant products in the world despite the advances in chemical technology and the appearance of cheaper synthetic substitutes.

Some of the drugs extracted from plants obtained either by cultivation or collection from the wild are the following:

(a) Strychnine and brucine. The dried ripe seeds of *Strychnos nux vomica* yield two important alkoloids, strychnine and brucine. Although strychnine is a very powerful central nervous system stimulant and has been used therapeutically, it has now been replaced by other, safer drugs. These are produced in large quantities (mainly for export), from seeds collected in the forests of India, Israel and other countries;

(b) Atropine, hyoscyamine and scopolamine. These drugs are mydriatic alkaloids obtained from *Solanum* sp. Scopolamine is additionally used as a sedative and a tranquillizing depressant to the central nervous system. As a first stage, the extraction of crude extracts can be undertaken in the developing countries where the plants grow wild, for export to developed countries;

(c) Quinine. The *cinchona* tree is cultivated over large areas in India as in Darjeeling, the Nilgiris and also in Indonesia. The factories attached to these plantations in India alone have a total quinine production capacity of 61 t/a. The output is very much greater in Indonesia. Efforts can still be made to increase production of quinine salts to meet the growing demand from foreign markets. Although the use of quinine as an antimalarial drug has decreased, it is used increasingly for the production of quinine, which is used against cardiac ailments such as auricular fibrillation and ventricular tachycardia, and as a bitter in aerated waters and non-alcoholic beverages;

(d) Reserpine. Reserpine from *Rauvolfia vomitoria* roots is a tranquillizer that induces sedation without somnolence. It is used in psychiatry for the treatment of schizophrenia and paranoia. Its wide use in drugs against hypertension is well known. *R. vomitoria* is cultivated in Africa and in India, in Darjeeling, Kerala and other places. Extraction prior to isolation of reserpine is fairly simple;

(e) Emetine. Plantations have been established in Darjeeling, India, to

produce ipecac at the rate of 20 t/a of dry roots and are largely meeting the requirements for the production of emetine. Emetine is extracted at two factories (in Bombay and Calcutta) with a combined capacity of 590 kg/a. It is principally used in the treatment of amoebic dysentery and in small quantities in expectorants, emetics and the like;

(f) Digitalis glycosides. In India, two units for extraction of digoxin, a cardiac drug, from locally grown *Digitalis* leaves have been set up in Bombay. In this case, the cultivation of *Digitalis* and the application of modern extraction technology were necessary for its manufacture. In particular, it has been grown successfully on slopes near tea plantations but not considered suitable for the cultivation of tea. Although developing countries may not be in a position to isolate the active principle, they can make crude extracts for export to countries that produce cardiac preparations;

(g) Caffeine. In regions where tea is extensively grown, caffeine can be easily extracted from tea wastes and tea prunings with such solvents as benzene, chloromethanes or chloroethanes. Although caffeine is made synthetically in large factories in developing countries, natural caffeine is preferred in certain drug preparations. As an ingredient of aerated soft drinks, it fetches a high price. Several extraction units exist in India near the tea-growing centres of Assam and Kerala. Coffee husk is another source for caffeine extraction. Caffeine is also a by-product of the production of decaffeinated coffee;

(h) Ephedrine. This drug can be extracted from *Ephedra* shrubs, which grow wild in the arid Himalayas in Afghanistan and Pakistan. It has many uses in the production of cough syrups and antiasthmatic preparations. Here, also, there is competition from synthetic ephedrine, but the natural alkaloid enjoys certain preference;

(i) Schillarin. The bulbs of squill *(Scilla)* grow wild in many subtropical regions and need only be converted into a crude extract to supply countries that make a cardiac drug that is very effective for patients who do not respond to digoxin;

(j) Other extracts. Multipurpose plants for the extraction of the active ingredients of senna (laxative), belladonna (for colic), podophyllum (for cancer) and the like are also possible. All of the active ingredients of some of these plant products are already being extracted in India and some other countries. A new unit in India will, in addition, isolate the active constituents.

Utilization of slaughterhouse by-products

The production of sera and vaccines from slaughterhouse by-products is linked with the upgrading of abattoirs in large cities and the setting up of primary extraction centres in their immediate vicinity. The by-products must be collected frozen and preferably processed immediately after slaughter.

For example, in the production of insulin, which is essential for controlling diabetes, the pancreatic glands are removed from cattle carcasses immediately after slaughter and frozen below −10°C. Insulin is isolated by repeated extraction of the pancreas with cold acidulated alcohol in special mincing equipment. The extract is filtered to remove biological matter, and the insulin-alcohol solution is concentrated initially in a special rising-film

evaporator and later at reduced pressure in a vacuum still. Chilling the alcoholic concentrate leads to the separation of residual fat, which is removed by filtration. The insulin is salted out from the filtrate as the crystalline hydrochloride, called salt cake, which is then dissolved in water. Crystalline insulin is precipitated by adjustment of the pH to the isoelectric point of insulin.

Many active ingredients of glands and organs of slaughtered animals, such as epinephrine and other hormones, pancreatin, pepsin and other enzymes, and liver extracts, can be similarly recovered. Catgut required for surgery and other uses can be produced from sheep intestines. Many intermediary products such as cholesterol can be obtained from the spinal cord or wool fat. Cholesterol can be used for the synthesis of steroid hormones and vitamin D_3. Bile can also be used to produce the bile acids required for synthesis of hormones and the like. Most of these raw materials are wasted but at the same time there are heavy demands for the limited output of such products produced in the developed and a few of the developing countries.

Biologicals such as the sera, vaccines, antitoxins and toxoids necessary for both prophylaxis and treatment can be produced by public health laboratories with simple equipment. The list includes vaccines against smallpox and cholera, anti-tetanus serum and toxoid, anti-diptheria serum and toxoid, anti-rabies vaccine, triple antigen and oral polio vaccine.

GROUP IV COUNTRIES

Group IV countries are those that already produce a broad range of bulk drugs from intermediates and manufacture some intermediates, using local raw materials. The steps to be taken by them are:

(a) Set up units for the production of antibiotics by fermentation;

(b) Set up plants for intermediates that also cover the needs of other chemical-based industries.

The steps involve both a significantly more sophisticated technology, for example the production of antibiotics, and an infrastructure of a developed chemical industry capable of manufacturing intermediates for drug production.

Antibiotics

Unlike synthetic drugs, antibiotics are made with the help of micro-organisms using fermentation technology. However, chloramphenicol and some of the newer, semi-synthetic penicillins such as ampicillin are produced industrially by chemical methods. Despite their complete lack of chemical similarity, they all exhibit antibiotic activity, that is, they can interfere with the metabolic processes of specific micro-organisms in that the growth of these organisms is either retarded or suppressed. Again, unlike the production of synthetic drugs, which needs a large number of chemicals and a complicated series of chemical reactions, the production of antibiotics needs mainly nutrient media and certain solvents. It is therefore easier to produce antibiotics than synthetic drugs in developing countries, provided the technology and equipment for their manufacture are available and that workers are trained to maintain

strict hygienic and sterile conditions. The raw materials required for the manufacture of antibiotics are shown in annex V.

The large-scale production of antibiotics by fermentation involves growing the antibiotic-producing organism in a liquid medium. The correct pure strain of the micro-organism is chosen and then grown from the master culture in a series of intermediate transfers from laboratory shake flasks to seed tanks of increasing size and finally to the fermentor. Each vessel contains a liquid medium with sufficient nutrients for the optimum growth of the organism. Transfer of the growth from a smaller to a larger tank is carried out at 5 to 10 per cent of the volume of the larger vessel. All transfers are made under aseptic conditions and, in fact, there are facilities not only for steam sterilization of the vessels, but also all outlets from the tanks are continuously exposed to flowing steam so as to prevent contamination of the broth by other organisms. The plant equipment is made of iron or, preferably, of stainless steel, and the tanks are equipped with mechanical agitators and dip tubes for aeration of the broth, so as to obtain uniform growth of the micro-organism. Aeration is carried out with compressed air, which is first sterilized by filtration through suitable cartridge filters. Strict temperature control at all stages of the fermentation is maintained. The pH is also controlled between narrow ranges by addition of acids or buffer salts. The fermentor has sampling devices so that the progress of the fermentation can be monitored with suitable analytical procedures. These depend on the type of fermentation being carried out.

Once analytical assay has indicated the antibiotic concentration in the broth has reached an optimum, the batch is harvested. Usually the antibiotic is in solution, so the broth is filtered to separate it from the mycelia, which are discarded. The filtrate is then solvent extracted to isolate the antibiotic prior to final purification. Purification procedures depend on the nature of the antibiotic.

Chemical intermediates for synthetic drugs

For the basic production of drugs from locally available raw materials, integrated development of all the chemical raw materials for the chemical-based industries is necessary. In developing countries, the development and production of chemical intermediates means a series of exercises in import substitution, which has to be progressively achieved.

This step can be undertaken as more and more basic chemicals become available and the expansion of a chemical-based industry makes it possible to set up economical units for the production of intermediates. Many co-products will be involved in such manufacture, and they will have to find proper uses in allied industries. This is therefore a continuous process, akin to solving a gigantic jigsaw puzzle; it involves not only development of a drug industry but also of dyes, plastics, fibres, synthetic rubber, pesticides and the like.

The basic raw materials involved are the chemicals based on alcohol, coal and petroleum. Not only must these resources exist, but there must also be production units for making alcohol-based and coal-based chemicals and petrochemical reformers and crackers. Such developments are not possible when these resources are lacking or if the country is too small to undertake such projects. The problem can only be solved by regional co-operation between countries that have these resources and the setting up of regional units located at

the most convenient centres, whose production can then be shared by the countries within the region. The exchange of chemical intermediates produced where natural facilities exist between developing countries can also be examined as an alternative.

The problem is not so acute in the production of antibiotics, plant products and those based on animal by-products. The nutrients required by the antibiotics industry are mainly agricultural products, and their supply depends on overall agricultural production. The other raw materials such as solvents, precursors and filter aids are not difficult to import from other producing countries at reasonable prices. Similarly, plant products are based on local resources and, with the required climatic and soil conditions, can be cultivated or, if they grow naturally, collected from wild sources. Animal by-products need proper organization of abbatoirs and the collection and storage of glands, organs and the like under proper conditions to prevent the deterioration of active ingredients before they are extracted. If proper attention is given, these products can be undertaken by developing countries more easily than setting out to make chemical intermediates for the production of synthetic drugs from basic raw materials.

GROUP V COUNTRIES

Group V countries manufacture the intermediates required for the pharmaceutical industry and also produce the plant and equipment required. They also undertake local research in order to develop new products and improve manufacturing processes. The steps to be taken by them are:

(a) Expand the range of intermediates and the volume of production to be able to meet other developing countries' requirements;

(b) Expand the production of chemical plant equipment and machinery both for production of dosage forms and of drugs from basic chemicals;

(c) Undertake R and D to develop new processes and screen new products.

Countries at this stage have reached near self-sufficiency with regard to basic raw materials, range of therapeutic groups, developmental and process research and effective distribution. Developing countries arrive at this level (which is comparable to international standards in production technology and the quality of products) only after many years of experience with international collaboration. Although they have not reached a stage where they can be self-sustaining with regard to the discovery of new products they have achieved a strong technical base and the capacity to produce different chemical intermediates (and thereby improved their negotiating power). They can select the processes best suited to their conditions and have the capacity to absorb any new technology and improve on it with their local R and D facilities.

Their capacity to produce machinery and equipment depends on how well the co-ordinated development of other engineering industries has taken place. Just as the manufacture of basic drugs using primary raw materials depends mainly on the level that the chemical industry has attained in the country, the ability to build capital goods to produce drugs depends on the level that the engineering industries have achieved.

The manufacture in a developing country of the two types of machinery and equipment needed depends on there being adequate demand from associated chemical and chemical-based industries, that is, equally rapid development, especially in the fields of dyes, drugs, pesticides, fertilizers and petrochemicals. The type of equipment can be classified under four main categories (see annexes I and IV):

Pharmaceutical processing and packaging machinery

Laboratory and research instruments

Chemical plant and machinery, including specialized equipment for services and utilities

Process-control instruments

Each category includes a large variety of equipment and instrumentation. It is necessary to have a further breakdown of the different categories into individual types according to the expansion envisaged in the industries, their present status and future needs. This depends in turn on the development of consultancy, process engineering and design, and project management in the country.

After arriving at the probable requirements, other considerations include:

Plant location

Process and know-how selection

Finance planning

Detail process engineering and design for equipment and plant

Procurement of materials and planning for equipment fabrication

Manpower planning, recruitment and training

Installation of equipment

Test run and start-up of plant

Regular routine production

Such activities, however, need capable engineers with experience in a variety of design and development activities.

A list of the raw materials required for the manufacture of drugs is in annex VI.

PATENT PROTECTION AND RELATED NEGOTIATIONS

Patent protection plays a significant part in sustaining industrial development in countries that have strong patent laws covering both user and process patents. Usually in developing countries, however, there are only process patents, and in some countries there are none at all. In others, patent protection is prohibited for drugs, while still others have made the patent laws so weak in the field of food and drugs that, even if patents are granted, they are endorsed with a "licence of right" and limited with a clause for compulsory licensing. The period of validity of the licence is also much reduced.

In all of these cases, what is sustaining industrial development is access to unpatented rather than patented know-how. If a country has a technical base

adequate to unravel unpatented know-how and has access to intermediates. permission to use a patent is very easy to acquire, and if fees are paid at all in such circumstances, they are nominal.

Thus, countries that develop a strong technological base and have access to chemical intermediates are in a stronger position to negotiate to obtain the unpatented know-how to establish production. They also have the wherewithal to absorb the new technology and improve on it with local R and D facilities.

It is only the less-developed countries that do not have the appropriate background to be in a position to understand, and compare foreign know-how and are therefore unable to negotiate effectively. They often negotiate weakly and grant excessive concessions owing to inadequate information on other agreements and the lack of ability of those who negotiate, who usually are non-technical people and are therefore unaware of the technical aspects. Shortage of capital or foreign exchange and lack of managerial skills to organize and operate plants lead to projects being set up for production of non-priority items and where production is undertaken from stages which only increase the dependence on foreign suppliers of intermediate products.

Countries in this category can, however, be helped by international organizations such as UNIDO. Assistance is available on the selection of products, the type of technology best suited to the country, improved utilization of local raw materials; how to negotiate better terms and conditions for acquisition of appropriate technology. UNIDO can also help promote technical co-operation between developing countries in areas where the technology is more easily adaptable and where prevailing local conditions are similar.

The following are some guidelines that would be of help in negotiations for acquisition of technology:

(a) For drugs on which patents have expired, the cost of purchasing technology and manufacturing know-how (often expressed in terms of technical fees and royalties on sales) should be at a reasonable rate, appropriate to the product concerned in view of the patent expiry date;

(b) For drugs on which patents have not expired; the cost of buying the technology and manufacturing know-how may be higher; but nearness to the end of the patent life should be taken into account;

(c) When only the supplying of know-how for formulation is involved, such payments should be reasonable and appropriate for the information supplied;

(d) When further stages of manufacture are undertaken within the country, higher payments are admissible;

(e) The package of terms and conditions should admit different scales of royalties, taking into account the technology involved;

(f) The transfer of technology and manufacturing know-how should be as complete as possible in the sense that the developing country should be entitled to existing and new information on the medical effectiveness of the drug and improvements in the manufacturing process made by the licensor;

(g) Personnel of the developing country should be trained to manage and operate the production facility and to undertake product information, distribution and product R and D;

(h) The technology transfered should be adapted as and when required to suit local conditions by the supplier of technology, collaborating with the expertise of the developing country;

(i) When the drug is manufactured from a late intermediate, the supplier of technology should ensure that the required quantity of the intermediate shall be made available at reasonable prices;

(j) In recognition of the desire by many developing countries to develop exports, the inclusion of such export markets should be considered by both parties when negotiating each technology transfer arrangement. (It is recognized that, in several countries, the restrictions on procurement of key ingredients such as intermediates from particular suppliers need not apply. This will depend on the technological competence of the firm concerned and would, in any case, be a matter of discussion between the interested parties.);

(k) The supplier of technology should assist the developing country in undertaking the production of late intermediates within the country in a phased programme, so that all or as many stages of production as possible are undertaken within the country.[1]

PROMOTION OF DRUGS UNDER INDIGENOUS SYSTEMS OF MEDICINE

In developing countries, much of the population depends on indigenous systems of medicine. It would go a long way to meet the medical needs of these countries if some of the medicines used under these systems were standardized and upgraded after proper screening.

In addition to determining the efficacy of the products for the purposes for which they are prescribed, it is also necessary to weed out many useless preparations now offered to the public. The methods to be adopted by different countries will not be the same but some indication to developing countries as to how best they can improve these systems of medicine and make them more effective are the following:

(a) A system to screen and select the useful preparations should be established. Following this a formulary should be laid down to ensure that what is dispensed is of uniform standard and gives the required therapeutic response. Some 444 preparations have been listed in a national formulary for indigenous drugs in India, for example;

(b) Uniform standards of education concerning these systems of medicine should be evolved and a central register of practitioners should be maintained. A minimum standard of education should be laid down for those who practise the system;

(c) A post-graduate institute or department financed by the government should be established to specialize in different branches of these systems of medicine;

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[1]Report of the Second Panel Meeting of Industrial Experts on the Pharmaceutical Industry (ID/WG.267/4/Rev. 1), p. 7.

(d) A central council for research in indigenous systems should be established as an autonomous body engaged in intensive research in the various fields. The council should conduct research on drugs literature and clinics and make a survey of medicinal plants throughout the country;

(e) Herbarium sheets should be established to identify the herbs required for cultivated and experimental gardens. Folklore claims should be examined scientifically. Books containing simple remedies for common ailments should be prepared and published;

(f) Pharmacopoeial laboratories for indigenous medicine should be established to work out standards and develop tests for the single drugs and compound preparations used in these systems of medicine. A museum of medicinal plants should be set up to facilitate identification of drugs used in indigenous systems of medicine;

(g) State governments should establish their own pharmacopoeias of indigenous medicines to meet the requirements of drugs for their dispensaries and hospitals. Private pharmacies should also be encouraged;

(h) Incorporating certain modern drugs into indigenous formulations has also helped bring about improved preparations. This has the advantage of reducing the toxic effects of the ingredients and making the preparations less costly. Such useful preparations can also be incorporated in the national formulary.

Traditional medicines are extensively used in developing countries because they are cheap and within the reach of everyone, which cannot be said about most modern medicines; traditional medicine will therefore play an important part in the health services of many of these countries. How to improve the use of the locally available substances of natural origin is already receiving the attention of the governments of many developing countries.

Annex I

LIST OF EQUIPMENT REQUIRED FOR A DRUG FORMULATION UNIT[a]

Tablet department

Capacity: 1.5 billion tablets/a = 6.25 million tablets (2.5 t)/d (2 shifts)
Average tablet weight, 350 mg

Floor area: 485 m²

Equipment

Granulation

Scales
Platform, 1 t
Platform, 300 kg
Two-pan, 10 kg
Chemical, 10 kg

Powder sifter
Comminution mill, jacketed
Comminution mill, simple

Mixers
Hobart-type, with stirrer, 500 litre
Extra bowls for above (3)
Hobart-type with stirrer, 100 litre
Extra bowls for above
Steam-operated kettle, stainless-steel, 50 litre
Steam-operated kettle, stainless-steel, 100 litre
Mortar and pestle, 5 kg and 10 kg
Cabinet dryer, thermostatically controlled, 110° C, steam-operated, 48 trays (2)
Fluid-bed dryer, 120 kg
Fluid-bed dryer, 60 kg
Extra vessels for above (3)
Drying room (50 m²), thermostatically controlled, with 6 trolleys of 48 trays

Lubrication

Powder sifter, 50 kg
Granulator (2)
Hobart mixer, 500 litre
Platform scales, 10 and 500 kg

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[a]I. A. Modi, *Project Profile for a Drug Formulation Unit*, Cadilla Laboratories, Ahmedabad, India.

Compression

Press coat, 900 series
Rota press, 45-station, 8,000 tablets/min
Rotary tablet machine, 37-station, (2) 2,500 tablets/min
Rotary tablet machine, 27-station, (2) 1,500 tablets/min
Rotary tablet machine, 16-station, (2) 500 tablets/min
Single-stroke compression machine, 90 tablets/min
Hardness tester (4)
Vernier calipers (2)
Disintegration-time unit (2)
Chemical balance
Chilsonator, 250 kg/h
Tablet-dedusting unit (4)

Coating (1.5 million tablets per day)

Coating pan, 60 in. (1.5 m)
Coating pan, 72 in. (1.83 m)
Jacketed kettles (2), 20 litre
Colloid mill
Polishing pan, with drive

Dryer

Cabinet-type, 48 trays (2)
Two-pan balance, 10 kg
Two-balance, 1 kg
Chemical balance

Capsule department

Capacity: 240 million capsules/a = 1 million (300 kg)/d (2 shifts)
Average capsule weight, 300 mg

Floor area: 255 m²

Equipment

Platform balance, 330 kg
Two-pan balance, 10 kg
One-pan balance, 1 kg
Mixer, 2 × 210 litre
Doubler conc. mixer, 100 litre
Mortar and pestle, 5 kg
Chilsonator, 40 kg/h
Dryers, specially designed (2)
Vacuum dryer, 40 trays
Automatic capsule-filling machine (2), 500 capsules/min
Extra accessories for filling other sizes
Semi-automatic capsule-filling machine, 300 capsules/min
Extra accessories for other sizes
Empty capsule loader (2)
Capsule-inspection unit with belt (1 for pencillin, 1 other)
Capsule-printing machine
Chemical balance (3)
Humidity recorder (6)
Capsule-polishing unit (1 for pencillin, 1 other)

Liquid department

Capacity: 1.8 million litres/a = 7,500 litres/d (shifts) 60-ml and 120-ml packages 94,000 units/d (2 shifts)

Floor area: 890 m²

Equipment

Scales
Platform, 500 kg
Two-pan, 10 kg
One-pan, 1 kg

Mixers
Stainless steel, with stirrer
2 × 5,000 litres
2 × 1,500 litres
2 × 500 litres
Jacketed, with stirrer
2,000 litres
1,000 litres
Hobart-type, 500 litres
Colloid mill (2)
pH meter
Viscometer
Pump, 1,500 litres/h
Filter press, 2,000 litres/h
Eight-head filling unit, 48,000 units shift
Automatic capping unit
Automatic labelling unit
Automatic carton-opening machine
Conveyor belts with checking units, 2 m × 7 m
Automatic gravity filling machine for viscous liquids such as malt
Kettle, stainless steel, 500 litres

Ointment department

Capacity: 60,000 kg/a = 250 kg/d (2 shifts)
Floor area: 200 m²

Equipment

Cleaning and sterilization
Isopropyl alcohol sterilizer for tubes
Powder sterilizer, UV, cabinet, 5 kg

Manufacturing
Scales
Platform, 200 kg
Two-pan, 10 kg
One-pan, 1 kg
Chemical (sterile and non-sterile)

Preparation

Jacketed mixing tank with stirrer, 200 kg, sterile and non-sterile

Mills

Triple roll, stainless-steel
Ball, 50 kg
Edge-runner, 25 kg
Jacketed colloid
Oven (for ophthalmic preparations), 200°C, 48 trays
Autoclave, double-door

Filling and crimping

Automatic tube-filling and crimping machine, 4,000 tubes/h
Chemical balance, one-pan

Parenteral department (including infusions)

Capacity: 300,000 litres/a = 1,250 litres/d (2 shifts)
Floor area: 305 m²

Equipment

Washing

Automatic rotary-type, high-speed washing machine for ampoules and vials
Demineralization plant, 300 litres/h
Distillation plant, 500 litres/h
Rubber-stopper washing machine, 100 kg

Sterilization

Double-door autoclave with thermo-recorder, 24,000-vials capacity
Double-door dry-heat sterilizer (2), 20,000-vials capacity
Storage tank with constant temperature for distilled water (2), 1,000 litres

Manufacturing

Scales

Platform, 100 kg
Two-pan, 10 kg
One-pan, 200 g
Stainless-steel tank, jacketed, with stirrer, (3), 200 litre
Stainless-steel tank, jacketed with stirrer, (3), 100 litre
Stainless-steel pressure vessel, 2 × 100 litre
Stainless-steel pressure vessel, 50 litre
Membrane filtering units: column type (2)
    193 mm (2)
    141 mm (2)
Vacuum pump, high-capacity
Air compressor

Filling and sealing

Automatic multihead vial-filling and rubber stoppering unit with sealing unit
Three-head ampoule-filling and sealing machine (2)
Laminar-flow unit (3)

Leak test

Vacuum-operated vessel
Inspection unit for physical checking (10)

Powder and granules section

Capacity: 60 t/a = 250 kg (12,500 bottles)/d (2 shifts)
Floor area: 165 m²

Equipment (2 each, 1 for penicillin, 1 other)
Mixer, 210 litre
Dryer, 48 trays
Automatic bottle-filling machine
Conveyor belt
Semi-automatic capping machine
Granulator

Quality-control department

Chemical analysis
Balance (3)
Melting-point apparatus (2)
Hot-air oven (3)
Vacuum oven, with pump
Distilled-water unit
Muffle furnace
Oxygen flask with platinum baskets (2)
Platinum dishes and crucibles (6)
Glassware
Water-baths, electric (3)
Gas plant
Miscellaneous

Instrument analysis
Gas chromatograph
IR spectrophotometer
UV spectrophotometer
Fluorimeter
pH meter (2)
Refractometer
Paper chromatographic equipment
Thin-layer chromatographic equipment
Air-permeability apparatus for surface area
Polarimeter
Viscometer (3)
(Redwood, Ostwals and Brookfield, 1 each)
Tablet-disintegration machines (2)
Tablet dissolution-rate machine
Tablet-hardness tester
Tablet friability-test machine

Tablet-inspection belt
Karl Fischer moisture-determination apparatus
Flame photometer
Vernier calipers (2)
Micrometers (2)
Potentiometric titration unit

Microbiological analysis

Aseptic cabinet for sterility testing
Hot-air ovens (2)
Incubators (to maintain temperature from 0°–50°C) (4)
Autoclaves (sterilizer) (2)
Microscope with camera lucida
Projection microscope
Refrigerated high-speed centrifuge machine, 20,000 rev/min
Zone reader
Refrigerators (3)
Culture counter

Pharmacological analysis

Automatic temperature-recording machine for pyrogen test
Kymograph for test for depressor substances
Galvanized cages for rabbits, cats and guinea-pigs
Polypropylene or galvanized cages for mice
Animals:
  Rabbits for pyrogens (36)
  Cats for depressor test (6)
  Mice for toxicity (200)
  Guinea-pigs for toxicity (50)

R and D department (formulation)

Floor area: 150 m^2

Equipment

Tablet-compression machine, single-stroke
Rotary tablet machine, 16-station
Mixer
Granulator
Coating pan
Oven, small size, 40°–200°C
Capsule-filling machine, 200 capsules/min
Balance, 5 kg
Chemical balance, single-pan, 200 g
Triple-roller mill, small
Colloid mill, small
Jacketed vessel and stirrer, 5 litre
Ball mill, 2 kg
Tube-filling machine, semi-automatic
Tube-crimping machine, semi-automatic
Liquid-filling machine, 1–30 ml
Capping machine for vials and bottles

Mini-bottle and vial washing machine
Autoclave, small
Ampoule-sealing machine
Incubators (3), 30°C, 45°C and 60°C
Refrigerator, small
Humidity- and temperature-control cabinet
Library books and periodicals

Packaging department

Floor area: 750 m^2

Equipment

Strip-packaging machines (6 tablets) (6)
Conveyor belts (12), 5 m
Automatic tablet counting and filling machines (2)
Automatic capsule counting and filling machine
Automatic capping machines (2)
Tin-sealing machine
Gumming machines (2)
Automatic carton openers (3)
Automatic label- and carton-printing machines (2)
Automatic printing and labelling machines for vials and ampoules (3)
Heat sealers for plastic bags (3)

Maintenance and common utility services department

Floor area: 375 m^2

Equipment

Lathe, 165 mm × 600 mm
Lathe, 300 mm × 200 mm
Drilling machine (2), 2 in.
Bench grinder, 150 mm
Flexible grinder, medium
Portable drill machines (2), 13 mm and 38 mm
Portable blower, small
Electric welding machine, 12 kVA, 3-phase, oil-cooled
Gas welding set, standard
Air compressor, 20 hp (15 kW), 3-phase, 60 ft^2/min (28 litres/sec), 150 psi (10 bar)
Vacuum pump, 10 hp (7.5 kW), 3-phase, 177 ft^2/min (84 litres/sec), ultimate vacuum 0.005 (0.7 Pa)
Gas plant, 141.5 m^3/h
Boiler, 2 t
Water-treatment plant:
  Demineralizing, 1,000 litres/h
  Softening, 10,000 litres/h
  Distilling, 500 litres/h
Air-conditioning plants (3), 80 refrigeration

Annex II

LIST OF PACKAGING MATERIALS FOR PHARMACEUTICALS

Type of formulation	*Containers*	*Closures*	*Outer packaging*	*Shipping*
Sterile antibiotics, powders in vials	USP Type III vials (20 mm), 5, 10 and 20 ml	Rubber stoppers Aluminium seals	Labels Printed carrier cartons	Corrugated boxes Gummed tape
Parenteral solutions	USP Type I vials (11 mm), 5, 10 and 20 ml	Gum-rubber stoppers Aluminium seals Aluminium dust caps	Labels Printed individual cartons Inserts Carrier cartons	Corrugated boxes Gummed tape
	USP Type I glass ampoules, amber or white flint), 1, 2, 5, 10 and 25 ml	End-sealing by jet flame	Labels Carrier trays (paper or plastic) Carrier labels Inserts	Corrugated boxes Gummed tape
Sterile transfusion solutions	Neutral glass infusion bottles or special plastic bottles, 500 ml	Rubber plugs Aluminium caps Aluminium dust caps	Labels Individual cartons (printed) with corrugated liners Dispensers Inserts	Seven-ply corrugated boxes with cushion liners Gummed tape
Elixirs, syrups and suspensions; ophthalmic or solutions etc.	White or amber bottles, 10, 25, 50, 100, 250, 500 and 1,000 ml	Bakelite or metal caps with paper wads Pilfer-proof closures	Labels Individual cartons (printed) with corrugated liners Inserts	Seven-ply corrugated boxes with cushion liners Gummed tape
	Polyethylene squeeze bottles, 10 and 20 ml (printed)	Polyethylene screw caps Dust caps	Individual printed cartons Inserts	Corrugated carrier boxes Gummed tape
	"Drop-talners" with droppers	Bakelite screw caps	Labels Individual printed cartons Inserts	Corrugated carrier boxes Gummed tape

Type of formulation	*Containers*	*Closures*	*Outer packaging*	*Shipping*
Tablets, capsules, suppositories etc.	White or amber bottles	Cork or polyethylene plugs Pilfer-proof caps with silica-gel bags	Labels Printed individual cartons Inserts	Seven-ply corrugated boxes with cushion liners Gummed tape
	Polystyrene containers with polyethylene bags	Polystyrene screw caps with silica-gel bags	Printed carrier cartons (paper or plastic)	Corrugated paper boxes Gummed tape
	Printed, laminated paper; plastic or aluminium foil laminates in rolls	Heat sealing	Catch covers (printed) Inserts Carrier cartons	Corrugated paper boxes Gummed tape
	Plastic tablet dispensers (printed)		Carrier cartons (printed) Inserts	Corrugated paper boxes Gummed tape
Ointments, creams and pastes	Printed collapsible tubes (inside lacquered aluminium or tinned steel)	Bakelite or polyethylene screw caps with wads	Individual cartons Inserts Carrier cartons Carrier labels	Corrugated boxes Gummed tape
	Glass jars (amber)	Bakelite or polyethylene screw caps with wads	Individual cartons Inserts Carrier cartons Carrier labels	Corrugated boxes Gummed tape
Powders for suspension powders, granules etc.	Amber or white bottles	Rubber wads Bakelite screw caps Pilfer-proof seals	Labels Individual cartons Inserts Printed carrier cartons	Corrugated boxes Gummed tape
	Polyethylene squeeze bottles	Plastic plugs Polyethylene screw caps	Labels Individual cartons Inserts Printed carrier cartons	Corrugated boxes Gummed tape
	Polyethylene laminated paper bags, pouches etc. (printed)	Heat sealing	Inserts Printed carrier cartons	Corrugated boxes Gummed tape
Tinctures, extracts, and infusions	Amber bottles, 500 ml	Pilfer-proof caps	Labels Cellophane wrap	Wooden boxes Signod straps
Nutritional products (foods, biscuits)	Bags made of polyethylene or other laminates	Heat sealing	Inserts Printed carrier cartons	Corrugated boxes Gummed tape

LIST OF PACKAGING MATERIALS FOR PHARMACEUTICALS
(continued)

Type of formulation	*Containers*	*Closures*	*Outer packaging*	*Shipping*
	Printed tins or printed composite containers	Metal lids Paper wads		Corrugated boxes with liners Gummed tape
	Printed waxed paper or laminated aluminium foil wraps	Adhesive wrap sealing		Corrugated boxes Gummed tape
Aerosols and sprays (pressure packs)	Printed container made of tinplated steel, extruded, seamless, aluminium, coated glass or synthetic plastics with polyethylene dip tubes	Spray valves with polyethylene actuators and pistons	Inserts Printed carrier cartons	Corrugated boxes Gummed tape

Annex III

LIST OF ANCILLARY PRODUCTS REQUIRED TO FORMULATE DRUGS

Diluents
- Lactose
- Starch
- Sucrose
- Mannitol
- Dicalcium phosphate
- Calcium sulphate
- Microcrystalline cellulose

Binders
- Gum acacia
- Gum tragacanth
- Gelatin
- Starch paste
- Sodium carboxymethylcellulose
- Methylcellulose
- Ethylcellulose
- Polyvinyl pyrolidene
- Sodium alginate

Lubricants
- Talcum powder
- Liquid paraffin
- Stearic acid
- Calcium stearate
- Magnesium stearate

Colouring agents
- Certified food and drug colours only

Flavouring agents

Capsules
- Hard gelatin
- Soft gelatin
- Seamless

Emulsifying agents
- Benzalkonium chloride
- Glyceryl monostearate
- Gum acacia

Suspending agents
- Sodium carboxymethylcellulose
- Methylcellulose
- Carbopal polyacrylic acid
- Sodium alginate
- Gum acacia
- Gum tragacanth

Preservatives
- Alcohol
- Hydroxy benzoates
- Sorbic acid

Annex IV

LIST OF EQUIPMENT FOR A MULTIPURPOSE PLANT[a]

Process equipment

	Quantity
Glass-lined reactors, 1,000 litres; jacketed, with anchor agitator, condenser and 500-litre receiver	2
Stainless-steel reactors, jacketed, with stirrer, 100-litre steel receiver (500 litres)	2
Steel distillation units, 1,000 litres, with receiver (500 litres)	3
Cast-iron reactor, jacketed, anchor-type stirrer, steel receiver (500 litres)	1
Stainless-steel 316 centrifuges, 1,000-mm diameter	2
Steel rubber-lined centrifuge, 1,000-mm diameter	1
Steam-heated dryers, 72 aluminium trays (80 cm × 80 cm × 3 cm)	2
Vacuum steam-heated tray dryers with trays as above	2
Stainless-steel crystallizers with jacket and anchor-type stirrer, 5,000 litres	3
Pressure leaf-filter, stainless-steel	1

Services equipment

Water-ring pump, 80 m^3/h	1
Air compressors with receiver, 30 ft^3/min (14 litres/sec) 30 psi (2 bar), with receiver	2
Steam-generating plant, 600 kg/h with water softener and accessories	1
Refrigeration plant for chilled water, 20 refrigeration tonnes with cooling tower	1
Water-circulation pumps	6
Demineralized water plant	
Electrical distribution panel, with circuit breakers	

Laboratory equipment

Balances	2	pH meter	1
Vacuum pump	1	Glassware (1 set)	
Muffle furnace	1	Miscellaneous instruments	
Electric oven	1		

[a]Multipurpose basic pharmaceutical plant project proposal, Sarabhai International, Baroda, India.

Annex V

RAW MATERIALS REQUIRED FOR THE MANUFACTURE OF ANTIBIOTICS

Carbohydrates
- Starch
- Dextrin
- Dextrose
- Cane sugar

Protein sources
- Soya flour
- Corn-steep liquor (50%)
- Ground-nut meal

Salts
- Ammonium sulphate
- Sodium sulphate
- Ammonium chloride
- Manganese suphate
- Zinc sulphate
- Sodium biphosphate
- Sodium chloride
- Potassium acetate
- Potassium dihydrophosphate

Acids
- Sulphuric
- Nitric
- Hydrochloric
- Oxalic
- Ethylenediaminetetraacetic

Alkalis
- Calcium carbonate
- Sodium hydroxide
- Potassium hydroxide
- Calcium oxide

Gases
- Ammonia
- Chlorine
- Nitrogen
- Carbon dioxide

Solvents
- Butanol
- Butyl acetate
- Methanol
- Isopropanol
- Octanol

Quaternary ammonium compounds

Filter aid
- Dicalite/Hyflosupercel

Decolourizing agent
- Active carbon

Resins (replenishment)

Antifoamers
- Wax emulsion
- Vegetable oils

Miscellaneous
- Formaldehyde (30%)
- Potassium phenylacetate
- Phenylacetamide and phenylacetic acid

Annex VI

RAW MATERIALS REQUIRED FOR THE MANUFACTURE OF DRUGS

Raw materials	*Drug or intermediate for which it is used*
Acetanilid	Sulpha drugs
Acetaldehyde	Sulpha drugs
	Indomethacin
Acetic acid	Phenacetin
	Chloroquin
	Sulpha drugs
Acetic anhydride	Chloramphenicol
	Sulfacetamide
	Paracetamol
	Acetazolamide
	Thiacetazone
	Acetylsalicylic acid
	Vitamin B_1
	Phenacetin
Acetoacetic ester	Amidopyrine
	Noramidopyrine methanesulfonate
	4-Diethylamino-1-methylbutylamine
Acetonitrile	Sulpha drugs
Acetone	Vitamins A, B and C
	Ephedrine
	Amodiaquin
Acetophenone	*p*-Nitroacetophenone
Acetone semicarbazone	Nitrofurazone
Acetoin	Sulphamethoxazole
Acetylacetone	Sulfamethoxazole
Acetylaminophenol (paracetamol)	Amodiaquin
Acetyl chloride	Vitamin A
Activated carbon	All
Acrolein	Folic acid
Acrylonitrile	Vitamin B_{12}, sulpha drugs
Adipic acid	Iodipamide
Alcohol (absolute)	All
Aluminium metal	Chloramphenicol
Allyl bromide	Secobarbital
Aluminium chloride (anhydrous)	Chloramphenicol
	Prenylamine
Amino chlorobenzophenone	Chlordiazepoxide
	Diazepam
D-2-Aminobutanol	Ethambutol
4-Amino-2,6-dimethylpyrimidine	Sulfisomidine
Aminohydantoin sulphate	Nitrofurantoin

Raw materials	*Drug or intermediate for which it is used*
o-Aminophenol	Di-iodohydroxyquinoline
m-Aminophenol	*p*-Aminosalicylic acid (PAS) and esters
	Paracetamol
	Diloxanide
2-Aminopyridine	Mepyramine
2-Aminopyrimidine	Sulphadiazine
	Sulphadimidine
2-Aminothiazole	Sulphathiazole derivatives
Ammonium thiocyanate	Acetazolamide
	Thiacetazone
	Vitamin B_1
Ammonia gas	All
Ammonium sulphate	Antibiotics
Alanine	Vitamin B_6
Aniline	Acetanilid
p-Anisidine	Indomethacin
Anthranilic acid	Methaqualone
Anisaldehyde	Mepyramine
Beet molasses	Vitamin B_{12}
Benzene	Vitamins
	Analgesics
	Sulpha drugs
	Thiacetazone
Benzaldehyde	Chloramphenicol
	Noramidopyrine methanesulfonate
Benzoic acid and salts	Diazepam
	Chlordiazepoxide
Bromine	Chloramphenicol
	Diphenhydramine
Benzyl chloride	Chloramphenicol
	Bephenium hydroxynaphthoate
	Benzyl cyanide
	Phenobarbitone
Benzyl cyanide	Pethidine
	Phenobarbitone
	Phenylacetic acid
	Phenformin
2-Benzylpyridine	Pheniramine maleate
Boric acid	Anti-dysentery drugs
2-Bromopentane	Barbiturates
Butyl acetate	Penicillin
n-Butyl alcohol	Penicillin
	Tetracyclines
	Vitamins B_1 and B_2
t-Butyl alcohol	Hydrochlorothiazide
n-Butylamine	Tolbutamide, methyldopa
2-Butene-1,4-diol	Vitamin B_6
Diethyl butylmalonate	Phenylbutazone
Butyl oxide	Ephedrine
n-Butyl bromide	Phenylbutazone, oxyphenbutazone

Raw materials	*Drug or intermediate for which it is used*
Calcium cyanamide	Sulfamethoxazole
Calcium oxide	Antibiotics
Calcium carbonate	Antibiotics
Carbon disulfide	Tolbutamide
m-Chloraniline	Amodiaquin
	Chloroquin
	Hydrochlorothiazide
Chloral hydrate	Diloxanide
Chloracetyl chloride	Lidocaine hydrochloride
p-Chlorobenzoic acid	Analgesics
	Indomethacin
p-Chlorobenzene sulphonamide	Chlorpropamide
2-Chloroethanol	Metronidazole
1-Chloro-2-diamethylaminoethane	Chlorpheniramine maleate
Chlorofluoroethane	Acetylaminophenol (paracetamol)
	Diaminodiphenylsulphone
	Halothane
2-Chlorophenothiazine	Chlorpromazine
p-Chlorophenol	Clofibrate
2-Chloropropyl-dimethylamine hydrochloride	Chlorpromazine
Chlorosulphonic acid	Sulpha drugs, diaminodiphenylsulphone hydrochlorothiazide
	Furosemide
	Chlorpropamide
5-Chloro-2,4-disulphonamidoaniline	Chlorothiazide
Cholesterol	Ethisterone
	Spiranolactone
Citric acid	Tetracyclines
	Citrates
Cinnamaldehyde	Prenylamine lactate
Cobalt nitrate	Vitamin B_{12}
Corn-steep liquor	Antibiotics
Copper powder	Chlorpromazine
Cotton-seed flour	Amphotericin B
	Tetracyclines
Cyanoacetic acid	Theophylline
Cyanoacetic ester	Folic acid
	Sulphadimethoxazine
Cyanoacetamide	Ethionamide
Defoamers	Antibiotics
7-Dihydrocholestrol	Vitamin D
Dibutyl ether	Ephedrine
2,4-Dichlorobenzoic acid	Furosemide
Dichloromethyl acetate	Chloramphenicol
4,7-Dichloroquinoline	Amodiaquin
2,5-Dichloronitrobenzene	Chlorpromazine
Dicyandiamide	Sulphaguanidine
	Sulphadimidine
	Phenobarbitone
	Phenformin

Raw materials	*Drug or intermediate for which it is used*
Diethylamine	Diethylcarbamazine
	Lidocaine hydrochloride
	Amodiaquin
	Nikethamide
	Diethylaminoethanol
Diethanolamine	Pethidine
2-Diethylaminoethanol	Procaine hydrochloride
	4-Diethylamino-1-methylbutylamine
4-Diethylamino-1-methylbutylamine	Chloroquine
Diethyl carbonate	Furazolidone
Diethylethoxymethylene ester	Chloroquine
	Amodiaquin
Diethyl malonate	Phenylbutazone
	Diethylethoxymethylene malonic ester
	Vitamin B_2
Diethylmethylamine	Pethidine, ethionamide
Diethyl oxalate	Phenobarbitone
	Vitamin B_2
	Ethionamide
Dimethylamine	Chloramphenicol
	Bephenium hydroxynapthoate
3,4-Dimethylaniline	Anthistamines
2,6-Dimethylaniline	Antihistamines
	Sulphadimethoxazine
Dimethylaminochloroethane hydrochloride	Mepyramine
Dimethyl formamide	Antibiotrics
	Steroids
1-Dimethylamino-2-chloropropane hydrochloride	Promethazine and salts
Dimethyl sulphate	Vitamin B_1
	Noramidopyrine methanesulfonate
	Aminopyrine
	Diloxanide
Dimethyl sulphoxide	Vitamin A
	Diloxanide
Dinitrobenzal chloride	Vitamin D
Diphenyl oxide	Chloroquin
	Amodiaquin
Diphenylamine	
Diosgenin	Steroids
Ergosterol	Vitamin D
Epichlorhydrin	Xanthinol nicotinate
Ether	Vitamins and analgesics
2-Ethoxyethanol	Tetracyclines
Ethyl acetate	Vitamins
Ethyl bromide	Phenobarbitone
	Vitamin A
	Ethambutol
Ethylene dichloride	Chloramphenicol
	Isoniazid (INH)

Raw materials	*Drug or intermediate for which it is used*
Ethylene dichloride *(continued)*	Diethylcarbamazine
	Bephenium hydroxynaphthoate
	Chloroquin
	Amodiaquin
Ethylene diamine	Ethylene diamine tetraacetic acid (EDTA)
	Caffeine and thiophylline
Ethylene diamine tetraacetic acid (EDTA)	Antibiotics
2-Ethylhexanol	Antibiotics
Ethyl orthoformate	Diethylethoxymethylene malonate
Ethyl chloroformate	Vitamin B_6
Ethylene oxide	Chloroamphenicol
	4-Diethylamino-1-methylbutylamine
	Furazolidone
	Vitamin B_1
Ethylene chlorohydroin	Diethylaminoethanol
Ethyl palmitate	Vitamin A
Ethylisopropyl malonate	Amylobarbitone
Ethylmethyl ketone	Ethionamide
	Vitamins
Filter aids	All
Formamide	Hydrochlorothiazide and other chlorothiazides
Formaldehyde (30%)	Streptomycin
	Chloramphenicol
	Amodiaquin
	Tetracycline
	Isoniazid
Formic acid	*p*-Aminosalicylic acid and esters
	Diethylcarbamazine
	Vitamin B_1
	Hydrochlorothiazide
Fumaronitrile	Vitamin B_6
Furfurylamine	Furosemide
Gelatin	Vitamin A
	Gelatin capsules
Glucose (dextrose)	Vitamin C
	Calcium gluconate
	Antibiotics
L-Glutamic acid hydrochloride	Folic acid
Guanidine nitrate	Folic acid
Guanidine carbonate	Sulpha drugs
Hexamethylene tetramine	Chloramphenicol
Hydrazine hydrate	Isoniazid
	Thiacetazone
	Nitrofurantoin
Hydrazine sulphate	Acetazolamide and others
Hydrobromic acid	Methyldopa

Raw materials	*Drug or intermediate for which it is used*
Hydrogen peroxide (30%)	Tolbutamide
Hydroxyethylhydrazine	Furazolidone
p-Hydroxynapthoic acid	Bephenium hydroxynaphthoate
3-Hydroxymethylpyridazine	Pyrazinamide
Hydroxylamine hydrochloride	Hydroxy urea
	Sulfadimethazine
8-Hydroxyquinoline	Halogenated oxyquinolines
Hydroquinone	Vitamin A
Hexane	Soya-flour vitamins
Iodine	Iodochloro- and dichlorohydroxyquinoline
Isoamyl formate	Imipramine
Isopropyl alcohol	Chloramphenicol, tetracyclines
Isopropyl ether	Vitamins
Isophytol	Vitamin E
Ketoacetal	Vitamin A
Lard oil	Antibiotics
Lithium metal	Vitamin A
Lactic acid	Calcium lactate
	Calcium sodium lactate
Levulinic acid	Indomethacin
Maleic acid	Pheniramine maleate
	Chlorpheniramine maleate
Magnesium metal	Vitamin A
Malonic ester	Riboflavin
	Amylobarbitone and other barbiturates
Methoxypyridoxin	Vitamin B_6
Methyl alcohol	Streptomycin
	Chloramphenicol
	Vitamin A
	Vitamin C
	Ephedrine
	Pethidine
	Vitamin D
	Chloroquine
Methylamine (40%)	Ephedrine
	Caffeine
	Thiophylline
n-Methylalanine	Vitamin A
Methylbenzene sulphonate	Amidopyrin
	Noramidopyrine methanesulfonate
2-Methylimidazole	Metronidazole
Methyldichloroacetate	Chloramphenicol
	Vitamin A
Methyl acrolein	Sulphamerazine
Methylaminophenol	*p*-Aminosalicylic acid and esters
b-Methylaminoethanol	Xanthinol nicotinate
Methylene chloride	Vitamin A

Raw materials	*Drug or intermediate for which it is used*
Methylethylpyridine	Vitamin A
Methyl formate	Chloramphenicol
Methylisobutyl ketone	Tetracycline
	p-Aminosalicylic acid and esters
	Tolbutamide
	Chlorpropamide
Methylaminochloroacetate	Vitamin A
Methylcyanoacetate	Sulphadimethoxazine
Methylene dichloride	Antibiotics
Methylethyl ketone	Vitamins
	Ethionamide
b-Methylnapthalene	Vitamin K
2-Methyl-1, 3-propanediol	Meprobamate
Monochlorobenzene	Chloramphenicol
Monochloracetic acid	Analgesics
	Vasodilators
	Xylocaine
Monoethanolamine	Piperazine salts
Nickel catalyst	Vitamin C
	4-Diethylamino-1-methylbutylamine
Nickel alloy (Raney nickel)	Several synthetic drugs
p-Nitroacetophenone	Chloramphenicol
Nitrobenzene	Phenyl butazone
p-Nitrobenzoyl chloride	Folic acid
5-Nitrofurfuryl diacetate	Furazolidone
	Nitrofurazone
Nitromethane	Antihypertensives
Nitroethane	Methyldopa
Nitropropane	Methyldopa
Nitrogen gas	Methyldopa
o-Nitrophenol	Iodochloro- and Diiodohydroxyquinoline
p-Nitrotoluene	Thiacetazone
	Procain hydrochloride
	Imipramine
p-Nitrobenzoic acid	Procaine hydrochloride
m-Nitrobenzoic acid	Iodipamide
Novaldiamine	Chloroquin phosphate
1-Octanol	Vitamin B_{12}
Oxalic acid	Vitamin B_2
	Diethyl oxalate
	Tetracyclines
Oil (maize, peanut or soya)	Antibiotics
Palladinized charcoal	Vitamin A
Palladium chloride	Chloramphenicol
Palmitoyl chloride	Vitamin A
Pancrea[illegible] (animal gland)	Insulin
Paraformaldehyde	Vitamins
Phenol	Acetylaminophenol (paracetamol)
	Salicyclic acid

Raw materials	*Drug or intermediate for which it is used*
	Iodochloro- and Diiodohydroxyquinoline
	Bephenium hydroxynaphthoate
	Chloroquin
Phenothiazine	Promethiazine and salts
Phenoxyacetic acid	Penicillin V
Phenylacetylcarbinol	Ephedrine
Phenylacetamide	Penicillin
o-Phenylenediamine	Thiabendazole
Phenylacetic acid and its potassium salt	Penicillin
a-Phenylglycine	Ampicillin
b-Phenylethylamine	Phenformin
	Diethylcarbamazine
Phosgene	Phenobarbitone
Phosphoric acid	Antimalarials
Phosphorus oxychloride	Chloroquin
Phosphorus pentasulphide	Vitamin B_1
Phosphorus pentoxide	Nikethamide
	Ethionamide
Phosphorus trichloride	Methaquolone hydrochloride
Phosphorus pentachloride	Ethionamide
Phytyl bromide	Vitamin E
Phenyl acetone	Phenylamine
Phenylhydrazine	Sulpha drugs
b-Picoline	Nicotinic acid
	Nicotinamide
	Nikethamide
Piperazine hexahydrate	Diethylcarbamazine
	Piperazine salts
Piperidine	Ethionamide
Potassium acetate	Antibiotics
	Ethionamide
Potassium borohydride	Vitamin A
	Chloramphenicol
Potassium hydroxide	Antibiotics
	Vitamin B_2
	Synthetics
Potassium carbonate	*p*-Aminosalicylic acid and esters
	Penicillin
Potassium dihydrogen phosphate	Antibiotics
Potassium permanganate	Pyrazinamide
	Nicotinic acid
Potassium cyanate	Tolbutamide
	Chlorpropamide
Potassium cyanide	Vitamin B_{12}
Potassium thiocyanate	Tolbutamide
	Chlorpropamide
Potassium ferricyanide	Antibiotics
Procaine hydrochloride	Penicillin
Propargyl bromide	Vitamin A
n-Propylamine	Chlorpropamide
	Probencid

Raw materials	*Drug or intermediate for which it is used*
Pyridine	Sulpha drugs
Pyrazine monocarboxylic acid	Pyrazinamide
Quaternary ammonium compounds	Penicillin and other antibiotics
Quaternary ammonium compounds	Tetracyclines
Quinoline	Hydroxyquinolines
Resins	Streptomycin and other antibiotics
Salicylic acid	Acetylsalicylic acid
	Sodium salicylate
Silicones	Antibiotics
Sodamide	Pethidine
Sodium borohydride	Vitamins
Sodium benzoate	Vitamin A
Sodium bromide	Analgesics
Sodium citrate	Antibiotics
Sodium acetate	Chloramphenicol
Sodium cyanide	Phenobarbitone
	Vitamin B_{12}
	Phenylbutazone
	Diloxanide
Sodium diethyldithiocarbamate	Vitamin A
Sodium ferrocyanide	Tetracycline
Sodium hydrosulphite	Antibiotics
Sodium metal	Metamizol
	Folic acid
	Phenobarbitone
	Vitamin B_1
	4-Diethylamino-1-methylbutylamine
	Aminopyrine
Sodium methoxide	Vitamin A
	Phenylbutazone
	Sulpha drugs
	Analgesics
Sodium sulphide	Analgesics
Sodium metabisulphite	Vitamins
Sorbitol	Vitamin C
Sodium hydroxide	All
Sodium carbonate	All
Sodium nitrate	Vitamin B_{12}
	Folic acid
Sodium nitrite	Chloramphenicol
	Phenacetin
	Noramidopyrine methanesulfonate
Sodium phosphate	Antibiotics
Soya flour	Antibiotics
Sulphuric acid	All
Stearyl alcohol	Vitamin C
Stannic chloride	Analgesics
Sulphur	Anti-TB drugs

Raw materials	*Drug or intermediate for which it is used*
Tartaric acid	Chloramphenicol, sulpha drugs
Thiosemicarbazide	Anti-TB drugs
Toluene	Analgesics
o-Toluidine	Methaquolone
Trichloroethylene	Chloramphenicol
	Emetine
	Bephenium hydroxynapthoate
	Phenylbutazone
p-Toluenesulphonamide	Tolbutamide
Trimethylquinol	Vitamin E
Thionyl chloride	Procaine hydrochloride
	Pethidine
	Hydrochlorthiazide
	4-Diethylamino-1-methylbutylamine
Thiazole-4-carboximide	Thiobendazole
Triethylamine	Tetracycline
	Vitamin B
L-Tyrosine	Anti-convulsants (L-dopa)
Urea	Chloramphenicol
	Vitamin B_2
Urethane	Meprobamate
Vanillin	Methyldopa
	Anti-hypertensives
Wax emulsion	Antibiotics
o-Xylene	Chloramphenicol
	Vitamin B_2
	Phenylbutazone
m-Xylidine	Xylocaine
Zinc dust	Phenylbutazone
	Chloramphenicol
Zinc chloride	Vitamins

Provision of drugs by appropriate technology

*P. Dunnill**

INTRODUCTION

History suggests that sanitation and vaccination should be given the highest priority in achieving good health for the greatest number of people at the lowest cost. However, there are situations where only the use of drugs can be effective. The problem is that, in contrast to other factors influencing good health, such as food, water, shelter and drainage, which can generally be provided by local, simple and small-scale operations, given the vital input of proper information, many key pharmaceuticals are the products of intrinsically complex processes. Therefore, finding ways by which communities other than fully developed ones can be better provided for is particularly difficult.

With no other products are technical decisions so influenced by powerful commercial, ethical and social pressures as with drugs. For this reason a brief analysis is given of the ways in which government policies influence the provision of drugs, particularly to poor rural communities.

Technical factors shaping policy

For the present purpose drugs may be divided into two classes: *(a)* the traditional local remedies, many of which are complex mixtures of plant origin; *(b)* the modern drugs, which are mostly well-defined chemicals derived from the petrochemical or fermentation industries. A few traditional materials have, in refined forms become important drugs in all countries; examples are quinine, caffeine and ergot. Some of the remaining traditional remedies are comparable to modern cough and indigestion mixtures in that they give comfort but are not life saving. Greater claims are made for others, but their effects, which may depend on the method of administration, are unproven. Without discounting the eventual emergence of further key drugs from traditional local remedies, present needs can only be met with the aid of a small number of modern drugs. The desire to utilize local resources at times seems to be so great that it is put before sound medicine.

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The problem of providing modern drugs to a local community, often an isolated rural one in a developing country, can be considered in three parts:

(a) Provision of chemicals from which the drugs are compounded at the lowest possible cost;

(b) Compounding of the drug as a tablet, capsule, injectable etc. from the chemicals at the lowest possible cost;

(c) The provision of the drug to an individual patient with the maximum regard to local circumstances.

Production of basic chemicals, fermentation and compounding

Few developing countries have the ability to produce the range of basic chemicals needed for their key drug requirements. Some, like India, are approaching this capability. The best that many others can expect in the next decade is the ability to manufacture selected basic chemicals from local raw materials. Coal and oil are obviously being used in this way, but the production of solvents by fermentation in countries rich in sugar and starch resources is also important; it saves foreign currency even if it is not strictly economic.

Where imports are essential, it is evident that only by being better technically and economically informed about world chemical supplies and by exerting a greater degree of central government control will developing countries obtain imported chemicals at the lowest possible cost.

All countries will progress from the straight purchase of the chemicals which constitute the active ingredients of drugs to the purchase of simpler and cheaper chemicals from which the ingredients can be made. Their sources of information are the local subsidiaries of foreign companies, international agencies such as UNIDO and independent consultants. Organizations like Indian Drugs and Pharmaceuticals Ltd. (IDPL) and ITDG have a role in providing information about the use of local raw materials and small-scale production of basic chemicals.

Making basic chemicals is not simple. Many countries that have made considerable progress in the production of basic chemicals, for example Egypt, have nonetheless experienced difficulties in preparing them in the exceptional quality needed for pharmaceuticals. Quality control of the chemical steps by which the active ingredients of a drug are prepared is crucial, and the requirement for expensive analytical equipment cannot be avoided.

On the other hand, drugs produced by fermentation, expecially the antibiotics, are at first sight attractive for local production in developing countries since the principal starting material may be any number of low-cost carbohydrates such as molasses or corn-steep liquor. However, even here the quality must often be raised. Much greater problems are presented by the sophistication of the production process and by the need to obtain special strains of micro-organisms which produce high product yields. Government involvement may be essential in negotiating for these strains or initiating strain selection in local research institutes and in being prepared to underwrite an unprofitable phase of production. Independent organizations and individuals

can help by collecting basic process design information which will aid countries either in setting up their own plants or, more likely, in negotiating from a position of greater knowledge for foreign plants and know-how.

Given that a government can restrict advertising and promotion so that such overheads are eliminated, it seems quite possible that antibiotic production could be profitable on a smaller scale than is now practised in developed countries. However, the technology cannot be simplified beyond a certain level, and regional rather than local production seems appropriate.

If antibiotic fermentation is technically too advanced, a carbohydrate-rich country could begin by producing food yeast with technology closely allied to that of brewing to provide B vitamins. However, one ambitious programme to combat vitamin deficiency by this means failed on the grounds of consumer resistance to a product of low appeal. Nevertheless, a modest local programme closely linked with health clinics where a yeast product would be given with conviction and authority could be better accepted.

The compounding of drugs in appropriate forms is a field where much more radical change could occur. This step is generally done in large factories in the commercial companies of developed countries, where even small local companies could commonly process one million tablets a year. However there is ample evidence that factory-scale operation is not essential. Hospital preparation of drugs is still practised in a surprisingly large number of institutions. For example, in the United States of America in the late 1960s, 41 per cent of hospitals surveyed operated "manufacturing programmes". Though drug compounding in the local pharmacy has lost its place in many developed countries, the procedures for sound practice are recorded in the literature, and the approach is still used in developing countries with respect to simple remedies.

There appear to be no insuperable technical reasons why the hand compounding or very small machine compounding of drugs should not be the means of reducing costs and shifting the centre of gravity of manufacturing towards the local community. Quality control at this level would entail maintenance of clean mechanical handling equipment in regulated conditions with regular checking of chemical quality by a regional regulatory laboratory.

Quality control is clearly a sensitive issue, one on which physicians, conventionally trained pharmacists and industrial producers have strong views, and it is an area where government involvement is essential. International agencies can also play a role if they adopt a strictly practical approach. Inter-governmental co-operation may also reduce costs, but this development demands particularly close and harmonious relations.

The pharmaceutical auxiliary

The third requirement in providing drugs is a suitable method of transfer to the patient. It is increasingly accepted that rural communities most at risk will not have access to fully trained physicians in the foreseeable future, and that local people must be trained as medical auxiliaries to diagnose the more obvious local diseases, referring only intractable cases to regional hospitals. It therefore seems sensible to consider making the compounding of drugs from bulk

ingredients the responsibility of local people. The intention would be to train them locally to avoid the inevitable tendency of people trained in urban centres to gravitate back to them.

Pharmaceutical auxiliaries will need training and operation manuals in local languages and guidance on small-scale equipment, some of it hand-operated, including tablet punches and counters, blenders, mixers and dryers. At present, neither suitable manuals nor consumer guides specifically concerned with equipment are available.

The training of pharmaceutical auxiliaries to compound, package, label and prescribe a very limited number of drugs appears to be the only means of bringing modern life-saving drugs to rural communities. Even in India, which has over 2,000 drug manufacturing companies, with less than half the market foreign controlled, the population cannot be effectively served by conventional means. The country requires its larger firms to provide to small companies, for formulation, a proportion of drug ingredients which they manufacture. By analogy, governments can elect to ensure supply of even smaller quantities of material to rural centres for manual or very small-scale mechanical manufacture.

The provision of drugs at a rural level seems less likely to compete with powerful commercial interests than is the case in urban areas, since the rural market is commercially less attractive. It is fragmented, and its inhabitants are unable to afford drugs in the normal way. From experience of missionary and similar hospitals, patients do not show resistance to non-brand-name drugs, a common problem in commercial pharmacies.

Other technologies needed for drug production

The adequate handling of drugs by rural centres requires a number of other appropriate technologies. The assumption that chemical and biological quality is maintained after dispatch of ingredients from a central store depends not only on good stock recycling but also on adequate, low-cost, cool or cold storage. Adequate packaging of drugs is of great importance, especially in tropical conditions. Organizations in developing countries often find, for example, that a lack of suitable local glass bottles restricts preparation of even simple formulations. While strip packaging of individual tablets or capsules is expensive, the preparation of sachets of tablets by hand-sealing plastic sheets is already used, and refinement of this method to make it more reliable and convenient would be valuable. Since misuse is a major problem, ITDG and others have operated pilot schemes examining the use of pictorial labels to aid the correct self-administration of drugs.

Current objectives on drug provision

Having concluded that small-scale compounding could make a contribution and that pharmaceutical auxiliaries could provide a means of delivery, ITDG is seeking to assist such developments. The Ministry of Overseas Development of the United Kingdom has recently funded a project to survey small-scale

pharmaceutical equipment together with a survey of the litarature on how such equipment is or has been used. ITDG is also exploring with the Appropriate Health Resources and Technologies Action Group (AHRTAG) the issues involved in training pharmaceutical auxiliaries.

It is hoped that the resulting catalogue of equipment and bibliography of uses will be of wide interest, but ITDG is particularly concerned to see a specific practical outcome. It is therefore interested in collaborating with individual governments or local organizations who are prepared to establish pilot projects. With such pilot projects many of the problems of supply of bulk materials to the rural centre can be circumvented by special measures so that the central issue of local compounding can be tested. The total investment in such pilot studies will be very small, so that modifications after initial experience should not be as great a problem as it could be with major capital investments.

Government actions influencing the provision of drugs

This section deals only with those aspects of government policy which relate directly to the local compounding of drugs from constituents imported in bulk and with the employment of rural pharmaceutical auxiliaries.

The objective of government policy in this case will be to obtain bulk materials at the lowest cost possible and to transfer them in smaller unit amounts to rural centres with minimal loss of drug activity. These centres will provide guidance on compounding, some equipment and regulatory checks on the use of material supplied. The bulk purchase of drugs by non-profit agencies, governments and even groups of governments is becoming well established. Similar approaches are applied to raw drug components and containers.

The efficient importation of bulk drug components is crucial. Delays in customs clearance and transit will lead to deterioration much more rapidly than for many other commodities. Special warehousing and careful stock recycling are imperative and a central facility for re-packaging into smaller units is required. The technology required is conventional but the organizational problems can be formidable.

Delivery to rural areas is often difficult and the work initiated by ITDG/AHRTAG and others, which is supported by the World Health Organization (WHO), on vaccine transportation is relevant. It is hoped that current projects of ITDG on small-scale equipment and ITDG with ARHTAG on pharmaceutical auxiliaries will help to provide a basis for advice to local rural health centres. Close co-operation with governments will be essential to ensure that this information is made available in a useful form and in the local language.

These are some of the social, political and economic factors influencing the provision of basic drugs:

(a) Need to co-ordinate national chemical or drug buying to obtain favourable bulk purchase terms;

(b) Desirability of persuading companies to produce and package basic but low-profit drugs while allowing them to manufacture some trivial but high-profit drugs and cosmetics;

(c) Need to rely heavily on foreign company technical expertise while seeking to change the balance of drug production and packaging;

(d) Shortage of servicing facilities for equipment and analytical instruments used in drug production and compounding;

(e) Migration of entrepreneurs and skilled persons away from rural areas;

(f) Need to persuade doctors to prescribe from limited lists mostly of generic drugs;

(g) Resistance of conventionally trained doctors and pharmacists and of local folk doctors to the introduction of rural health auxiliaries;

(h) Existence of powerful fashions in medicines, for example, the use of multivitamins;

(i) Lack of experience in the use of potent synthetic drugs by rural communities and problems of prescribing to largely illiterate communities;

(j) Tendency of universities and medical and pharmacy schools to reinforce conventional approaches;

(k) Conflict of interest of middle-class urban patients and poor rural ones in terms of drug imports, packaging and health care.

TECHNOLOGY APPROPRIATE TO DIFFERENT TYPES OF COUNTRIES

Common features in many developing countries are their limited supply of capital for investment and their under-employed population. Both suggest that small, local and labour-intensive organizations are more appropriate than very large, capital-intensive and highly automated ones. However, the manufacture of pharmaceuticals provides a very severe test of this viewpoint.

Many of the most useful drugs, such as the antibiotics are complex chemicals produced by methods requiring very precise control. They are potent in action, may have to be taken by injection, and their quality control requires a degree of sophistication which is not easily attained. Stocks of pharmaceuticals must be available for rapid prescription, and medication may have to continue for extended periods. The product must also remain in an essentially unchanged state for a relatively long time after production.

Governments may accept locally produced hospital buildings of rather limited quality rather than have none for their communities; they may even accept, for the treatment of illness, the use of rather crude local remedies which have been long established. However, they are not likely to accept modern pharmaceuticals of a quality lower than those known to be produced in the most advanced facilities.

On occasions, even high-technology pharmaceuticals have been withdrawn because they were perceived to be inferior. One developing country banned the use of an imported vaccine against a common disease which was frequently fatal there. In the country of production, the vaccine had been withdrawn because it very occasionally caused encephalitis, and the disease against which it was used was mild. A government will naturally feel that what is not good enough for a so-called developed country is not good enough for its own community.

Concerning the degree of under-employment in developing countries, it is necessary to ask first whether an abundance of labour is of value in the

controlled production of complex substances such as pharmaceuticals. The answer is that it probably is not. A. E. Humphrey of the University of Pennsylvania has encouraged the development of fermentors even more highly instrumented than those used in current antibiotics production because, in his experience, the employment of operators of limited training or motivation to measure and control important parameters leads to serious errors. These errors tend to grow with the number of personnel responsible for control. Taken in isolation, this consideration argues for large, centralized production facilities with highly trained staff and fairly sophisticated instrumentation. Most of the pharmaceuticals manufactured in developing countries are indeed produced in this way by foreign-owned companies. The past record suggests that this approach has not provided adequate amounts of pharmaceuticals for those sectors of the community most in need.

The options open for the manufacture of raw materials and pharmaceuticals, and their packaging, storage and quality control depend on the general level of industrialization. It is estimated that three quarters of the total drug manufacturing operations in developing countries takes place in 12 countries; the vast majority of others have either few or no drug manufacturing facilities.

Manufacture of pharmaceutical raw materials

The precursors of many modern drugs are fine chemicals which are converted in pharmaceutical processing into tablets, capsules, injectables and other preparations suitable for administration in therapy. The variety of fine chemicals required is large, and their quality must be as high as that of the preparations into which they are to be formulated. In these circumstances, few developing countries will be in a position to manufacture the necessary range of fine chemicals.

The production of drugs directly from local natural products has been the subject of considerable interest in both the developing and developed countries. UNIDO has, as one of its pharmaceutical programmes, the utilization of extracts from medicinal plants and of slaughterhouse wastes as raw materials for pharmaceuticals.

The production of drugs from local natural products is also one of the most difficult aspects of pharmaceuticals supply to assess. Aside from the few well-known natural drugs and precursors that have been examined in detail in developed countries, there is a vast number of natural materials for which healing properties are claimed but on which little controlled study has been done. The extraordinary range of curative properties claimed for some materials might seem unrealistic in the light of accepted practice in developed countries, but it must be admitted that the natural materials are complex mixtures unlike most modern drugs. Increased production of those natural drugs and precursors of defined value and their complete processing in the country of origin is certainly to be encouraged. This would avoid loss of foreign exchange in repurchasing the final, more expensive product from a foreign manufacturing country. It may even provide a source of high-value pharmaceutical exports.

The controlled testing of the curative properties of local traditional drugs is perhaps desirable in view of their widely established use. However, the task

involves great expense. It also seems likely that the chances for the successful production of new drugs with definite curative value will be small. The advanced pharmaceutical companies of the world do not lightly dismiss promising sources of important new drugs. While the complexity and variability of the natural materials could account for some failure to recognize important materials, this only further emphasizes the difficulty and expense in assessing their potential. It would, however, be hypocritical to suggest that people of other countries should abandon the use of natural materials of "unproven" value in view of the equivalent use, for example, of digestive aids in developed countries.

It would be useful to have local assessments of those natural materials which, though not as accepted as caffeine, ergot, quinine or senna, do seem to have fairly definite benefits. (At present there appears to be a tendency to produce large lists of natural materials with no classification of the confidence in their efficacy.)

The need for assessments is illustrated by the position in India. In 1970/71, India exported drugs valued at Rs 48 million ($5,720,000 at 1975 exchange rates). To this export, psyllium- and senna-based products alone contributed Rs 33 million ($3,960,000). In the same year, crude drugs, alkaloids and other derivatives from vegetables worth Rs 14 million ($1,661,000) were imported. This indicates the extent to which imports might be substituted. Surveying the prospects for medicinal plants, Kempanna cites the rejuvenation of cinchona plantations (for quinine) through improved planting systems, better management practices and optimizing extraction techniques, as the kind of approach that is applicable to sources of drugs of proven value [1]. He notes that, of 200 tonnes of caffeine available from 8,000 tonnes of tea wastes per annum, only 80 tonnes are produced. Huge quantities of tea waste are apparently disposed of by burning. The demand for diosgenin as a precursor of steroid hormones has led to the finding of several *Dioscorea* species rich in this material.

The annual turnover in pharmaceuticals in India was Rs 2,000 million ($237.6 million) in 1972, but only 1.6 per cent of this was spent on research. About 98 per cent of research expenditure went for chemistry and the clinical aspects of pharmaceuticals; the remainder was spent on studies of the cultivation of suitable plants. However, a co-ordinated national programme has since begun to isolate improved plants and preserve collections as forests and jungles disappear. Kempanna concludes by arguing the need for careful planning to integrate the cultivation of medicinal plants with food crops, better marketing to eliminate speculation and better quality control [1]. Agricultural polytechnics (the proposed Krishi Vigyan Kendras) represent local agencies for spreading the necessary technical knowledge.

The preparation of vaccines and the production of antibiotics from micro-organisms by fermentation can be considered as the biological equivalent of fine chemicals manufacture. The technology demanded, particularly for vaccine preparation, is even more advanced than that for fine chemicals. In developed countries, the preparation of vaccines does not involve large-scale operation; but the degree of expertise and the exceptional quality-control requirements would seem to make this field too difficult to approach by any but the most advanced technology. In one less-developed country in Central Asia, a

vaccines and sera institute is already functioning under the financial auspices of a public health institute. An enlarged, independent institute is under construction with an estimated capital development cost of about $3.3 million. This is a relatively large project for the country concerned.

Fermentation is operated on an extremely large scale (up to 500 m^3). There is therefore ample scope for scale reduction. However, while the fermentative stage does not present the hazards of live-virus handling faced in some vaccine operations, the technology is still very demanding. For example, in penicillin fermentation, if the culture is contaminated at any point over a period of six to eight days, not only may the contaminating organism utilize nutrient and synthesize unacceptable substances, but enzymes may be produced which totally degrade the penicillin. In these eight days, with a vessel of 120 m^3, a volume of sterile air of 1.38 million m^3 will be required for growth, and 43,000 kWh of electrical energy will be required for agitation. The surface finish and sealing of the whole fermentor and ancillary fittings must be such that effective sterilization can be achieved and maintained during the same prolonged period. Construction is normally of stainless steel, requiring specialist fabrication, but recently a 3,000-litre plastic fermentor vessel has been tested (for other applications) where the agitation as well as the aeration for respiration is brought about by compressed air. Following this work, a 20,000-litre vessel of glass-reinforced plastic inside standard concrete pipe sections is planned.

The production and extraction of some other antibiotics produced by fermentation is not quite as difficult. However, given that for all antibiotic production some well-trained and experienced staff are required, there is little incentive to operate a small-scale facility. The question of how small a scale is technically worth while will require a detailed analysis. The assessment of economic feasibility will be unique to each case. Nevertheless, the developing countries currently face great difficulties in ensuring adequate supplies. A physician working in a less-developed country in Africa states that antibiotics account for up to 30 per cent of the annual budget. For example, Perlman, reviewing the fermentation industries, notes that penicillin G wholesale prices rose 50 per cent in 1973/74 [2]. In these circumstances, countries with adequate capital resources may be expected to set up medium-sized fermentation and production facilities.

Manufacture of pharmaceuticals from raw materials

The manufacture of pharmaceuticals from fine chemicals and the formulation of the final drug represent an area where greater use could be made of local industry. The scale of manufacture in operation in different developing countries ranges from very small (with less than ten employees) to the industrial level. Problems such as quality control are common to all scales, but the manufacturing problems are rather different. Very small-scale manufacture may involve just those compounding operations that are undertaken in hospital pharmacies.

Typical of equipment and output of such compounding units is the following description of a modest non-governmental compounding facility in a least-developed country in Africa:

"The facility processes about one 40-litre batch of liquids per working day. The tablet machine works all day most days. About one million capsules are produced annually. One trained worker from Europe and one university-trained African pharmacist control operations and two dependable and experienced secondary-level local men do most of the manufacturing work. Others assist in packaging, cleaning etc. The plant is in fact under-utilized and production could be greatly increased with little or no additional outlay for plant."

The organization supplies only its own hospitals and clinics.

Because none of the equipment is large, space requirements are small and the rooms organized according to the following functions:

Quarantine storage for incoming raw materials and batch samples

Raw-material storage

Weighing and batching

Mixing, granulating, drying

Compressing (tabletting)

Packaging

Capsuling

Ointment and suppository processing

Liquids processing

Washing-up facilities

Quality control laboratory

Office

In four rooms there will be humidity control.

Liquids are made up in 40-litre and 100-litre stainless-steel kettles. Ingredients are stirred in using small, propeller-type electric-powered stirrers; various types of small restaurant-type electric mixers are used for making pastes for suspensions. Bottling is carried out with the aid of a hand-operated self-metering filler and a hand-operated capping machine.

For tabletting, wet and dry granulation and direct compression techniques are employed. It is hoped to acquire a drum-type blender and a small oscillating granulator for powder blending. At present large stainless steel sieves are used and the material is processed by hand. Drying of granules is accomplished in a home-made cabinet with a capacity of about 25 kg. Compression is by a single punch machine.

For ointments, either the ingredients are stirred in after melting the base or a small mill is used when required.

A small capsule-filling device has an output of 12,000 to 15,000 capsules per shift with one operator.

The range of preparations possible with such limited equipment is illustrated by the following:

Analgesic balm ointment

Antist tablets (chlorpheniramine maleate), 4 mg

Baby aspirin, 75 mg tablets

Benzyl benzoate application

Calcium gluconate, tablets

Carbarsone tablets, 250 mg
Cherry cough syrup
Chloramphenicol syrup
Chloroquine syrup
Chlorpromazine, 25 mg tablets
Citrazine syrup (piperazine citrate syrup)
Codeine cough mixture (children's use)
Codeine cough syrup (adult use)
Diaminodiphenylsulfone (DDS), 5, 10 and 25 mg tablets
Diazepam, 5 mg and 10 mg tablets
Diethylcarbamazine citrate (Hetrazan), 50 mg tablets
Diphenhydramine expectorant
Elixir terpin hydrate with codeine
Folic acid, 5 mg tablets
Gripe water
Icthyol ointment
Kaolin and pectin
Neomycin wound powder
Paracetamol, 500 mg tablets
Paracetamol elixir
Phenobarbital and atropine tablets
Phenobarbital elixir
Prednisolone di-iodoquine cream
Promethazine, 25 mg tablets
Promethazine syrup
Scabex (gamma benzene hexachloride) ointment
Sim San (benzalkonium chloride)
Streptoguanine powder
Streptoguanine tablets
Sulfadur (sulfamethoxy pyridazine) suspension
Sulfanilamide ointment
Triple sulfa suspension
Vitamul (multiple vitamin) syrup
Whitfield's ointment

The borderline between such small-scale maufacture and the compounding of pharmaceuticals in what are not primarily manufacturing establishments is ill defined. The potential of compounding in hospitals, clinics and pharmacies is, however, so important that it is worthwhile examining what can be done to encourage and improve it. Two extreme examples illustrate this.

A report dealing with drug availability in a less-developed country in Central Asia notes that:

> "The pharmacy network of about 600 outlets, together with the bazaar merchants and others who sell drugs, represents a major, under-utilized group of health workers already active in every community of any size. The Ministry of Health, by exercising simple regulatory authority, may well be able to improve the availability and quality of health care through simplification of drugs sold generically".

Statistical data on manufacturing or bulk compounding in hospitals in the United States showed that 41 per cent of 1,853 hospital pharmacies operated a manufacturing programme. The survey further demonstrated that 78 per cent of the sample group prepared galenical pharmaceuticals; 74 per cent of the products were not commercially available; 42 per cent were sterile solutions for topical use; 33 per cent were sterile pharmaceuticals such as collyria and ointments; and 30 per cent were small-volume injectable solutions. In addition, the same survey showed that hospital pharmacists were also active in the preparation of sterile products such as surgical irrigating fluid, large-volume injectable solutions and special sterile products for investigational use.

Most industrial-scale plants in developing countries are foreign owned. The establishment of equivalent plants, locally owned, probably by governments, is likely to be achieved by licensing. It seems probable that potential purchasers of plant and process know-how would be placed in a more reasonable negotiating position by the possession of basic design information provided by international agencies or the ITDG. Plant manufacturers in developed countries also have an interest in providing general process data where confidentiality agreements permit it.

Packaging of pharmaceuticals

Concern with packaging and storage methods for pharmaceuticals affects all distributors of pharmaceuticals at all levels of development.

When drugs are supplied from a developed country or by local manufacture in an advanced plant, attention will be centred upon the suitability of the packaging in severe climatic conditions with the possibility of poor handling. Most foreign companies producing drugs for tropical countries are aware of this problem. Small manufacturing facilities and hospital pharmacies must devise their own appropriate packaging systems which must satisfy local conditions and be cheap and simple to operate.

In 1973, a voluntary agency worker in one African country noted:

> "Working on a limited budget, conventional packaging materials for dispensing medicine are normally too costly. Envelopes or paper cartons are not adequate protection for drugs in a tropical climate. A relatively cheap alternative used for packing tablets and capsules is plastic sheeting, made into sachets using a heat-sealing machine. For solutions and mixtures, plastic bottles are used. Storage trials under tropical conditions need to be carried out to find the most acceptable. There may be possible reactions between the drug and the plastic. Medical staff are asked if possible to prescribe pre-packs which usually are a complete course of treatment or a month's supply. Pre-packing of tablets is at present done by hand using one person nearly full-time and three of the hospital out-patient interpreters on the non-clinic days. This job is very tedious and there is much scope for design of a simple mechanically operated tablet counting machine"

A similar comment from a relief agency in a still less developed country in eastern Asia notes that,

"because of the high humidity, rain and mode of life we found that it was not sufficient protection to place the tablets and capsules especially in envelopes".

Re-cleaned plastic vials from church organizations in the United States were satisfactory but were subject to customs requirements on the used plastic material.

"Plastic happens to be quite an industry but they have not yet produced medical vials. All in all, though, this method proved to be the most satisfactory since it protects the patient's medicine after the first dose, which we felt the plastic bag did not".

Another worker in a similar country in Africa remarks that:

"There are no locally made screw cap glass bottles. We used locally made beverage type bottles in the 200 ml to 1 litre range. The local plastics industry could produce containers for us, but we lack the sophistication for testing such containers with our products and we doubt that the plastic product would be of consistent quality. We package capsules and tablets mostly in bulk in sealed bags of 1000s and pack them in tins. We are not presently filling ointment tubes as the cost is high. Most of our products are dispensed from these bulk packages into paper or plastic containers for the patient at the time of use".

A 1974 report of a non-profit organization suggests a supply from the United Nations Children's Fund (UNICEF) of 20,000 1-litre bottles at an approximate cost of $10,000–$20,000 including freight.

In contrast to these comments is a report that

"in China – which is probably producing enough oral contraceptives for 20 million people – one form of the 'pill' is a small package of perforated paper strips on which the chemicals have been deposited. The monthly sheet contains 22 squares, each about one third the size of a postage stamp. The woman just tears off one of the bits of water-soluble paper and chews it for her daily dose. This 'paper pill' has great advantages, particularly on a mass scale. It saves pills, bottles, and the machinery for making them"[3].

A field worker in a less developed African country has reported on the problems of adequate labelling:

"A sample survey in the out-patients' department showed that over 50% of returning patients had taken one or more of their drugs wrongly. This perhaps is not surprising, as a large proportion of the patients are illiterate and only able to speak one or two of the many tribal languages".

Storage of pharmaceuticals

The problems of storage of pharmaceuticals apply to all types, whether imported or locally produced. The following examples illustrate how critical is correct storage. In a central Asian less developed country, a report notes:

"The typical (drugs) warehouse is a dank, decrepit room kept locked and sealed by a storekeeper who has assumed personal liability for the material entrusted to him in return for his salary. This arrangement has several shortcomings: since the storekeeper is never on the premises, he must first be located. If he is sick or on leave, no material can be taken out. Long delays are not uncommon. The storekeepers have very little experience or familiarity with the proper indentification, storage or handling of medical and technical supplies. Due to general disorganziation of its warehouses the government incurs substantial losses due to spoilage of medicines and food, damaged equipment, and materials which simply cannot be found".

A southern Asian government report on a visit to the government medical stores notes that a "deplorable state of affairs" was found, "resulting in near breakdown of their procedures–indenting, receiving, storing, record keeping

and supply of drugs to institutions". Several reports remark on the lack of stock cycling and its consequences. Problems with small local establishments are different but considerable. A field worker in West Africa reports that "the air-conditioned store is kept at a mean temperature of 70–75° F (21–24° C). Although a worthwhile investment, air-conditioning is still an expensive item. Other pharmacists from West Africa have found this less important". Another pharmacist processing pharmaceuticals in North Africa deals with the storage problem by the use of conservative expiry dates.

Quality control

Among the technologies needed by developing countries, the requirements of pharmaceutical products for stringent quality control are probably uniquely demanding.

WHO has been active in establishing internationally recognized standards of quality for pharmaceuticals and especially vaccines [4]. It has laid down desirable standards with respect to manufacturing personnel, premises, equipment, sanitation, manufacturing operations, labelling, packaging and quality control.

Unfortunately in many instances it is the difficulty of achieving these standards rather than ignorance of what is desirable that is the central problem. For example, the leader of a small African non-governmental processing unit notes that: "Problems of quality control are primarily due to lack of skilled workers. We would try to upgrade facilities if we had the expertise. Also our operation is small for supporting a good quality control facility." The latter feature is common to all process control facilities associated with production plants. The instrument costs, for example, on a small fermentor may be much greater than the cost of the vessel but will be fairly insignificant in relation to a 400,000-litre vessel for which they will be provided the same precise control. Regional, rather than local, quality-control laboratories may represent the most desirable goal, although once again this will frequently be a political and not a technical problem.

The same leader reports:

> "We are building up our range of equipment for the quality control laboratory (which is humidity controlled) but, even so, it will be a very modest laboratory for the foreseeable future. We plan to do aqueous and non-aqueous titrations, pH readings, other ordinary chemical and gravimetric tests, etc Our range of capabilities will stop short of spectrophotometric determinations, bio-assays, most chromatographic determinations, and all kinds of animal tests".

A more developed Asian country recently reported that:

> "This aspect (quality control) has been most neglected. Although private and public drugs are said to be tested for quality before they are shipped it is not known whether the drugs actually conform to standards when they arrive in the country. It is also not known whether the drugs retain their quality six months or for one year after they have been stored under the conditions of temperature and humidity prevailing in private and government drug stores . . . The establishment of a quality control laboratory for testing pharmaceuticals in this country is urgent and essential".

In commenting on the type of controls needed, the report notes:

> "In quality testing of drugs 70 per cent is chemical analysis, 20 per cent is microbiological analysis and 10 per cent is pharmacological. The quality control laboratory (under construction) will restrict itself to chemical testing for some years".

The field of quality control is one where labour-intensive methods could be used in place of expensive automation but, since this activity is the guarantee of standards of operation throughout manufacture and distribution, quite high technical proficiency and motivation are important.

Large versus small-scale production

Industrial producers in developed countries are governed by strictly commercial interests; the greatest gains will often be made by assisting them to view profit in new modes of operation or business which lead to cheaper drug supplies. Much has been made of the undoubted difference in costs between proprietary medicines and their exact generic equivalents. It may be that, with the increasing identification and general recognition of the few most basic drugs and the vast market represented by those who cannot afford proprietary drugs, companies will increasingly use the economies of large-scale operation to supply their proprietary products at generic prices, or to supply generic drugs very cheaply. They are likely to find that this policy will only work if a single "premier" product is marketed to all. The concept of separate cheap medicine for the poor is, as in the food field, likely to provoke a customer resistance that would prevent the opening up of a total market more profitable than the present one, which is limited to the comparatively rich. The initial marketing effort may be more laborious, with a narrower profit margin, and may require the use of new types of local pharmaceutical auxiliaries. Here, however, is an instance where the surplus of modestly educated people in many of the developing countries, if simply but adequately trained, could represent an asset not available elsewhere. Appropriate technology studies have a role to play in provoking discussion of such questions and the economies involved as much as in seeking small-scale production.

With respect to small-scale local production of generic medicines as alternatives to proprietary equivalents or mass-produced foreign generic products, it must certainly be borne in mind that a switch in transnational corporation policy of the kind mentioned above could destroy the commercial viability of a small-scale plant which was, in any case, profitable only in the artificial sense of saving foreign exchange.

The need to relate appropriate small-scale ventures to large-scale ones has been stressed in the Note by the secretariat. This is certainly valid for drugs. If countries have centralized facilities, these can be asked to devote part of their activity to the packaging of drug components into lots suitable for dispatch and local compounding. The gradual development of centralized facilities of inceasing complexity is not to be regarded as excluding local small-scale compounding, or vice versa. In the provision of drugs, appropriate technology means giving equal weight to centralized large-scale and localized small-scale operations.

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Appropriate technology in drug and pharmaceutical industries of India

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I. IDENTIFYING REAL PRODUCTION NEEDS

The purpose of the drug and pharmaceutical industry should be to deliver appropriate drugs to the population. One of the first steps is to identify the priority of essential drugs that are required to combat most of the prevailing diseases. Based on the pattern of diseases, such lists of essential drugs should be drawn up in co-operation with the industry, public health services and the medical profession. The best drugs needed for a particular treatment may not necessarily be cheap, and in many cases the choice of the drug may have to be dictated by the economic situation of the country. For example, while the present drug of choice for the treatment of leprosy is Rifampicin, its cost would be prohibitive for a developing country–over Rs 2,500 per year per patient, while the older drug Dapsone would cost only Rs 10–15. Similarly, this applies to the treatment with isoniazid and thiacetazone or para-aminosalicylic acid and the much more expensive isoniazid plus streptomycin, and the choice for treatment is obvious.

While identifying essential drugs, it must be borne in mind that reasonably good drugs for most of the major disease conditions are already available, and many newly introduced drugs have either no additional advantage or at the most only a marginal one over existing drugs. Each year perhaps one or two really better drugs emerge; others are introduced for other reasons–such as their patentability or greater profitability. Therefore, while drawing up a list of essential drugs, their superiority over known drugs should be carefully assessed, along with factors such as cost, patent position and the availability of the technology to produce them.

A list of essential drugs identified recently by a committee appointed by the Government of India is given in an annex. A number of variations of drugs included in this list have been introduced recently that have practically no major

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advantages over those listed. If, therefore, India could produce these drugs in sufficient quantity, most of its requirements would be met. With the addition of another eight to ten drugs to this list, some of the disease conditions which are prevalent in most developing countries would also be covered. There would be practically no problem with patents.

The World Health Organization (WHO) also has recently drawn up a list of essential drugs relevant to disease patterns in developing countries.[1]

Gaps in demand

As regards technological levels in the production of drugs and pharmaceuticals, most developing countries are far behind in their efforts to bring their production high enough to meet demand. While most of the world's population lives in developing countries, the developed countries account for 88 per cent of world production and 85 per cent of world consumption of pharmaceuticals. This leaves only 12 per cent of world production and 15 per cent of world consumption for the developing countries. Imports from developed countries to developing ones vary from country to country. For example, India imported Rs 470 million worth of pharmaceuticals in the 1976/77 fiscal year, as against a total consumption of Rs 7 billion, bringing the percentage of imports (by value) to total consumption to about 7 per cent. This is because India has a well-established pharmaceuticals industry that can meet its present requirements for the coverage of its established health services. However, these health services are accessible to barely 20 to 25 per cent of the population; the vast majority of 75 to 80 per cent must do without drugs. Even the quality of health service coverage to the small proportion of the population in India is hardly comparable to that in any developed country.

Figures of approximate percentage of imports to total consumption of pharmaceuticals by value for certain developing countries are as follows:

Country	*Year*	*Approximate percentage of imports to total consumption (by value)*
Algeria	1975	67
Egypt	1975	16
Liberia	1976	100
Mexico	1974	6
Nigeria	1976	70
Pakistan	1976	40
Philippines	1973	2
Turkey	1974	0.8
United Republic of Tanzania	1976	almost 100

Source: Country papers presented at the Consultation Meeting on Transfer of Technology and Technical Know-how between Developing Countries in the Field of Pharmaceutical Industries, held in Lucknow, India, 22 April–4 May 1976.

[1] WHO Technical Report Series, No. 615, 1977 (*The selection of essential drugs:* Report of a WHO Expert Committee), Geneva, Switzerland.

While these figures indicate the order of magnitude of reliance on imports, it is evident that, except for a few countries (such as India, Mexico, Philippines and Turkey) most of the developing countries rely substantially on imports.

The gap in demand for pharmaceuticals in developing countries can be considered as two levels:

Level I: Demand for pharmaceuticals governed by health-care facilities in existence;

Level II: Demand for pharmaceuticals for the entire population to control the major diseases.

The satisfaction of level II demand requires great efforts and substantial investment in health-care facilities which most of the developing countries can scarcely afford. Thus, the difference between level I and level II is the demand for the "have nots", that is, those who must do without basic health care and medical treatment for common diseases.

This difference is alarmingly large in developing countries. For instance, as has been noted, the level I demand in India covers barely 20 to 25 per cent of the population.

However, even for level I demand, which caters to a small fragment of the population (the "haves"), most developing countries must rely substantially on imports to meet the gap in demand, since domestic production is scanty. Even countries that produce some of their requirements, mainly by formulating imported bulk drugs, are still far from manufacturing the drugs themselves. For manufacturers of basic drugs, a developing country needs a sound industrial infrastructure and research facilities supplying raw materials, technical skills, machinery etc.; thus overall development of the pharmaceutical industry in any country is closely linked to the level of overall industrial development.

There is still, nevertheless, a strong case for developing countries to formulate most of their requirements after importing the bulk drugs, thus adding value and simulaneously saving foreign exchange, and creating nuciei for further development of the industry at a later stage. So far, only a few developing countries, among them India and Mexico, manufacture almost all of their bulk drugs and intermediates and have complete facilities for R and D.

International trade

As high-value, low-volume commodities, the transport costs of pharmaceuticals present no barriers to trade. The developed countries trade their pharmaceutical products freely but, the developing countries import only 3 per cent of the production of developed countries, and this amounts to about 20 per cent of the consumption of the developing countries, which thus constitute a very small market for the developed ones.

The Indian experience

It is laid down in the Constitution of India that "The State shall regard the level of nutrition and standard of living of its people and improvement of public health as among its primary duties".

Beginning with the first five-year plan (in 1951) health has been given considerable priority in order to implement the directive principles of state policy.

A beginning had already been made in the production of medicines by starting cinchona plantations in the States of Bengal and Madras (presently Tamil Nadu and West Bengal) in the early twentieth century. Factories were set up in their vicinity for the extraction and purification of quinine. During the Second World War, the local industry made further progress by producing a number of other products from locally available raw materials. Simultaneously, formulation activities based on imported bulk drugs were increasing considerably. The slow progress of the chemical industry in India also constrained the growth of the pharmaceutical industry.

In the early 1950s, various foreign companies began to found affiliates and subsidiaries in India. Some set up facilities for the manufacture of bulk drugs; most engaged in formulation activities based on imported bulk drugs. The entry of the transnational firms has offered stiff and healthy competition to the local industry. The Government of India itself set up two large public-sector units, Hindustan Antibiotics Ltd. in 1954 and Indian Drugs and Pharmaceuticals Ltd. in 1961, for the manufacture of bulk synthetic drugs and antibiotics, the production of some formulations of them, and the manufacture of surgical instruments.

Through a course of rapid growth, the pharmaceutical industry in India is now well established. It produces a wide range of drugs, including many sophisticated antibiotics, vitamins, hormones and synthetic drugs and has developed a wide-ranging capability in the production of bulk drugs and formulations. From a total product value of Rs 100 million in 1948, the Indian pharmaceutical industry was producing Rs 1.5 billion worth of bulk drugs and Rs 7 billion worth of formulations in 1976/77. Imports of bulk drugs in that year were Rs 470 million.

The breakdown of production of bulk drugs and formulations by various sectors of the industry in 1976–77 was as follows:

	(Rs million)	
	Bulk	*Formulation*
Public sector	480	470
Foreign sector (foreign equity exceeding 40 per cent)	630	2 920
Indian sector (including small-scale sector)	390	3 610
	1 500	7 000

There are now over 2,500 drug-producing units in India, of which 128 are in the organized sector, including 45 companies with foreign equity exceeding 40 per cent. With the rapid growth in demand and attempts by India to give coverage of basic health services, it is foreseen that the pharmaceutical industry in India is on the threshold of a rapid growth. The Government is tentatively planning a production level of Rs 5.5 billion worth of bulk drugs and Rs 19 billion worth of formulations by the fiscal year 1982/83. To achieve this target (which, however, will only increase the coverage of the population marginally),

the pharmaceutical industry must more than double its present size in barely five years.

II. TECHNO-ECONOMIC PROFILES

Bulk drugs can be classified into antibiotics and synthetics. The former are living organisms capable of combating disease (imparting pathogens), whereas the latter are complex chemicals capable of curing diseases because of their influences on the body or the materials in the cardio-vascular system and alimentary canal. Because of their differences, their methods of productions also differ considerably. The technologies generally used for the manufacture of both are briefly described in the following sections. Methods for manufacturing formulations are also given.

Antibiotics

Antibiotics, essentially special chemotherapeutic agents, are produced by special kinds of micro-organisms. These are chemical substances used for the treatment of infectious diseases or those caused by the proliferation of malignant cells. Antibiotics can broadly be divided into two groups, antibacterial and antifungal. Examples of antibacterial antibiotics are the penicillins, streptomycin and the tetracyclines; among the antifungals are nystatin and griseofulvin. In addition to the commercial antibiotics used for human therapy, there are several others which, although toxic to humans, may prove useful in the treatment of animal diseases or in combating insects, animal pests and plant diseases.

Antibiotics are produced commercially by biosynthesis, cultivating the suitable microbes under a suitable environment in an appropriate medium. The production is normally by fermentation, followed by chemical purification.

The strain of micro-organism used in industrial fermentation for the production of an antibiotic must be rigorously selected. It is well known that the productivity of an antibiotic during fermentation by a microbe is an interaction of its genetic potentiality and the environment within and outside the microbial cells. Augmentation of yield by altering genetic potentiality of a strain is a well-known technique, and results from the experiments with such micro-organisms in the area of mutation, microbial genetics and genetic control of secondary metabolites have given valuable information for the application to industrial strains. What was 100 of units (u) of penicillin per millilitre in the fermenter in late 1940 is now 30,000 to 40,000 u/ml of broth in the 1970s. Thus, increased yield in the fermenters has led to reduction of productions cost. It can be seen that strain improvement is an important activity in the field of antibiotics, one which has a bright future for further development.

Production on industrial scale is carried out in large vessels called fermenters. The process adopted is submerged aerobic fermentation under suitable conditions. The culture of appropriate strain is grown first in the inoculators containing sterilized medium. Seed mycelia of the first generation cultivated in the inoculator are then transferred to the second generation in seed

vessels. In some cases, such as that of the tetracyclines, the seed is grown directly in the shipping inoculator stage, and the seed multiplies within a period of 30 to 50 hours. A fermenter containing sterilized medium is then seeded with the mycelium culture grown in the seed vessel. Fermentation is continued for over a week or even longer. During fermentation, such parameters as pH, temperature, dissolved oxygen and carbon source, and nutrients such as nitrogen and phosphorus are continuously monitored and optimum conditions are maintained. In addition, a supply of sterile air and continuous agitation are prerequisites for achieving the desired results.

In the process of antibiotics fermentation, proper sterilization of vessels, the medium and all other inputs such as air and intermediate feeds must be ensured. The sterilization of the vessels and the medium is carried out by thermal processes using superheated steam, whereas the sterilization of air is done by passing compressed, modified air through suitable filters.

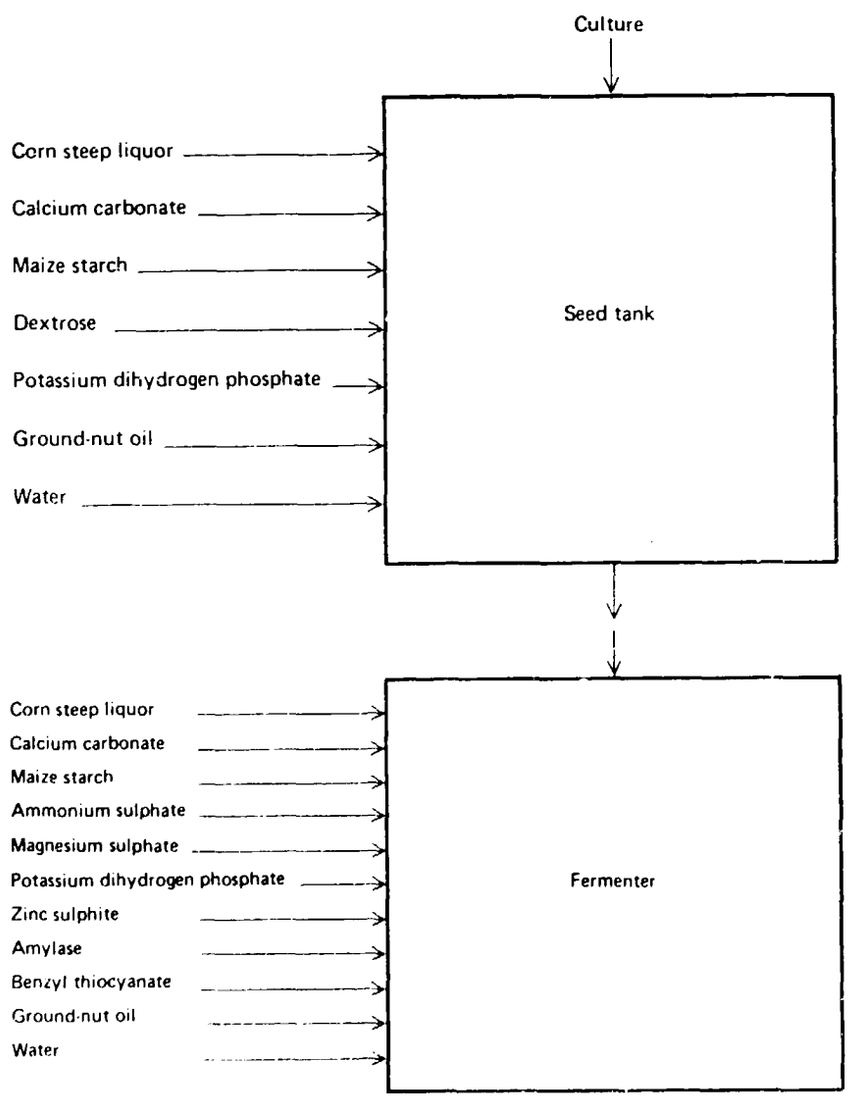


Figure IA. Flow chart for filtering, crystallizing and centrifuging in tetracycline production

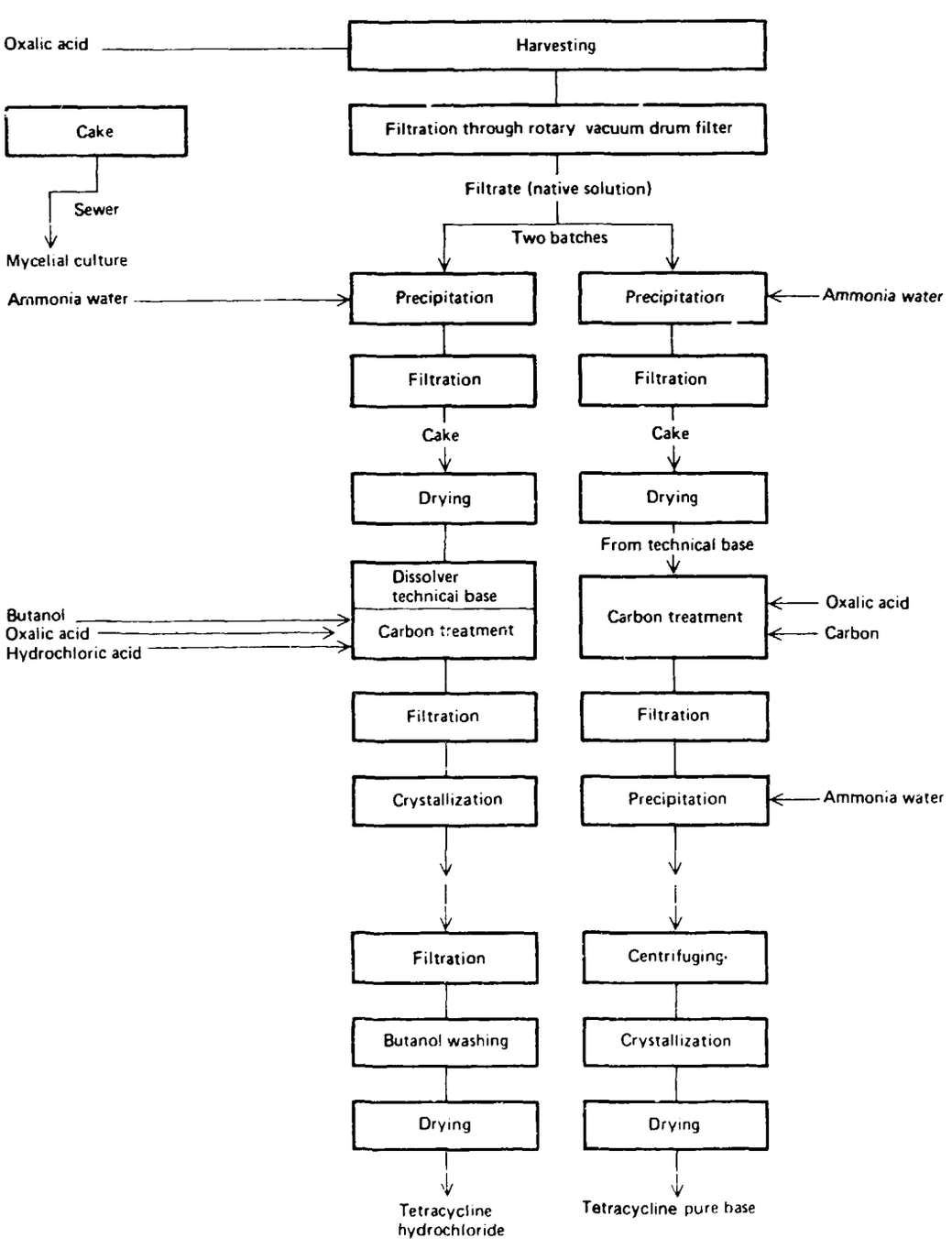
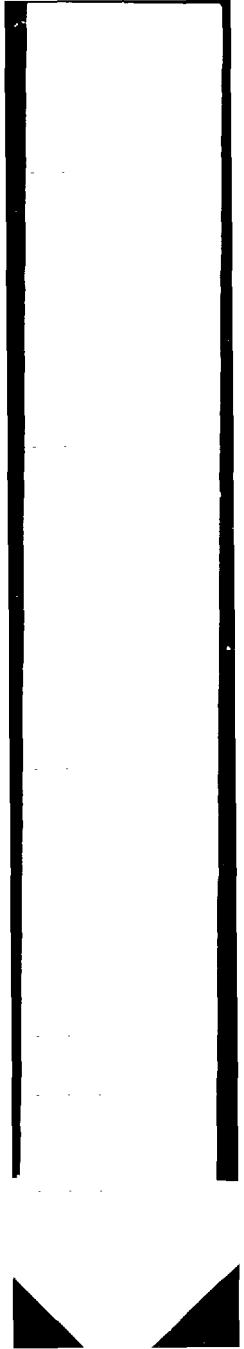
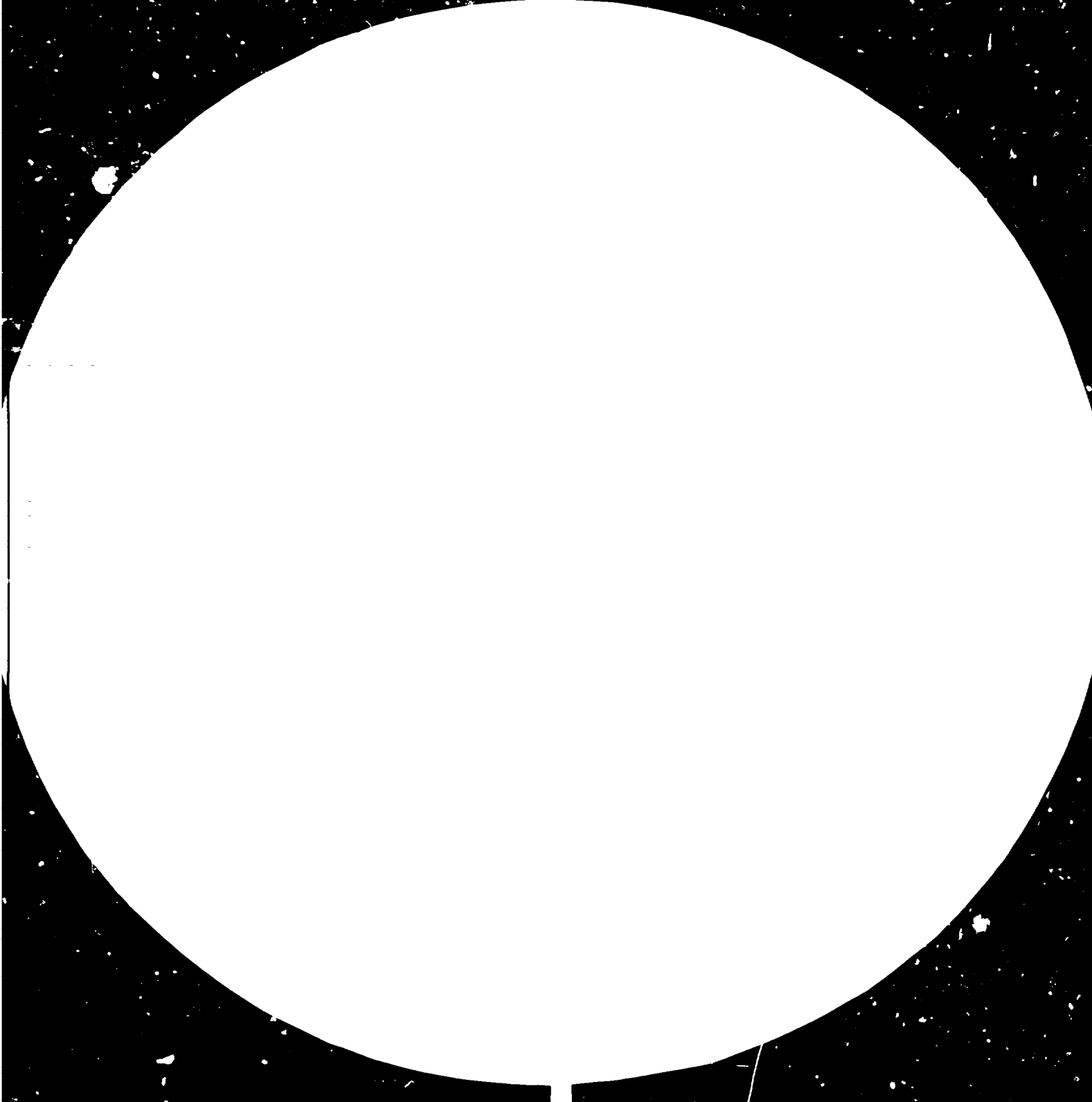
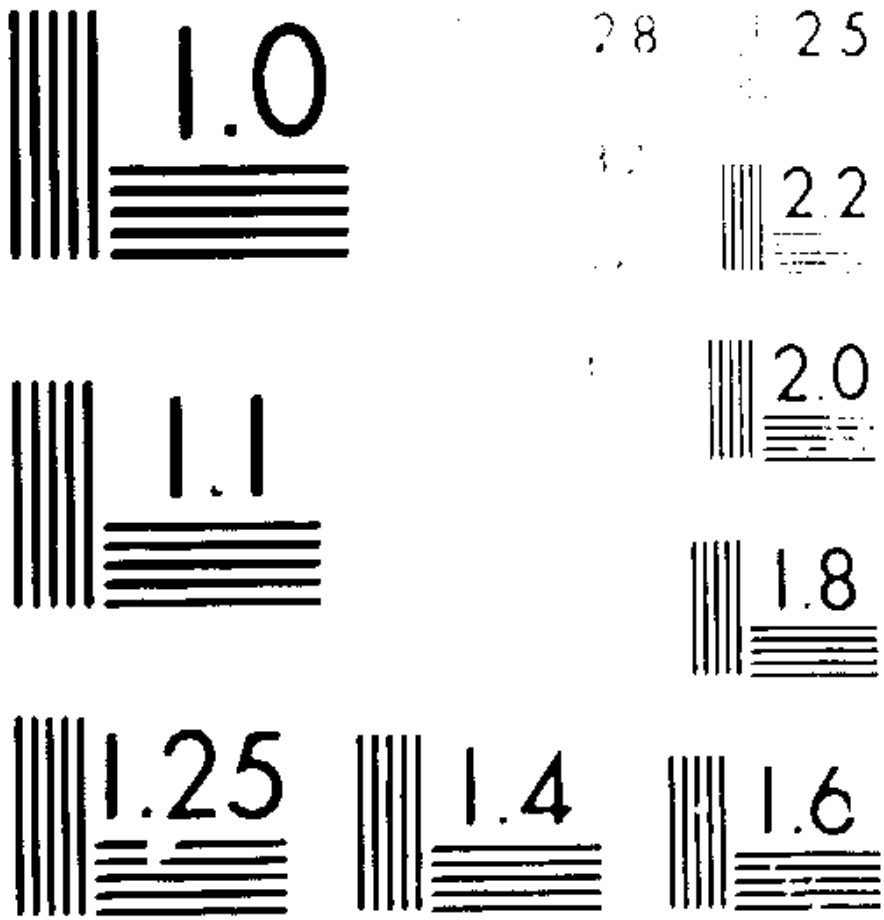


Figure IB. Flow chart for filtering, crystallizing and centrifuging in tetracycline production






2.8
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APPROPRIATE INDUSTRIAL TECHNOLOGY FOR DRUGS AND PHARMACEUTICALS

UNITED NATIONS INDUSTRIAL DEVELOPMENT ORGANIZATION
Vienna

Monographs on Appropriate Industrial Technology
No. 10

APPROPRIATE INDUSTRIAL TECHNOLOGY FOR DRUGS AND PHARMACEUTICALS

UNITED NATIONS
New York, 1980

EXPLANATORY NOTES

A full stop (.) is used to indicate decimals.

A comma (,) is used to distinguish thousands and millions.

A slash (/) is used to indicate "per", for example t/a = tonnes per annum.

A slash between dates (for example, 1979/80) indicates an academic, crop or fiscal year.

A dash between dates (for example, 1970–1979) indicates the full period, including the beginning and end years.

References to dollars ($) are to United States dollars.

References to rupees (Rs) are to Indian rupees. In October 1978 the value of the rupee in relation to the dollar was $1 = Rs 7.90.

The word billion means 1,000 million.

The word lakh means 100,000.

The following notes apply to tables:

Three dots (. . .) indicate that data are not available or are not separately reported.

A dash (–) indicates that the amount is nil or negligible.

A blank indicates that the item is not applicable.

Totals may not add precisely because of rounding.

In addition to the common abbreviations, symbols and terms and those accepted by the International System of Units (SI), the following have been used:

Economic and technical abbreviations and symbols

c.i.f.	cost, insurance, freight
EDTA	ethylene diamine tetraacetic acid
ft	foot (1 ft = 30.5 cm)
ft^2	square foot (1 ft^2 = 9.290 dm^2)
in.	inch (1 in. = 2.54 cm)
in^2.	square inch (1 in^2. = 6.45 cm^2)
INH	isoniazid
IR	infra-red
PAS	*p*-Aminosalicylic acid
psi	pound-force per square inch (1 psi = 6,895 Pa)
UV	ultraviolet

EXPLANATORY NOTES *(continued)*

Organizations

AHRTAG	Appropriate Health Resources and Technologies Action Group (London)
BNF	British National Formulary
BP	British Pharmacopoeia
BPC	British Pharmacopoeial Codex
CAEME	Camara Argentina de Espitialedades Medicinales
IP	Indian Pharmacopoeia
ITDG	Intermediate Technology Development Group Limited (London)
NFI	National Formulary of India
USP	United States Pharmacopoeia
WHO	World Health Organization

The concept of appropriate technology was viewed as being the technology mix contributing most to economic, social and environmental objectives, in relation to resource endowments and conditions of application in each country. Appropriate technology was stressed as being a dynamic and flexible concept, which must be responsive to varying conditions and changing situations in different countries.

It was considered that, with widely divergent conditions in developing countries, no single pattern of technology or technologies could be considered as being appropriate, and that a broad spectrum of technologies should be examined and applied. An important overall objective of appropriate technological choice would be the achievement of greater technological self-reliance and increased domestic technological capability, together with fulfilment of other developmental goals. It was noted that, in most developing countries, a major development objective was to provide adequate employment opportunities and fulfilment of basic socio-economic needs of the poorer communities, mostly resident in rural areas. At the same time, some developing countries were faced with considerable shortage of manpower resources; in some other cases, greater emphasis was essential in areas of urban concentration. The appropriate pattern of technological choice and application would need to be determined in the context of socio-economic objectives and a given set of circumstances. The selection and application of appropriate technology would, therefore, imply the use of both large-scale technologies and low-cost small-scale technologies dependent on objectives in a given set of circumstances.

Report of the Ministerial-level Meeting. International Forum on Appropriate Industrial Technology

CONTENTS

Annexes

Foreword

As part of its effort to foster the rapid industrialization of developing countries, the United Nations Industrial Development Organization (UNIDO), since its inception in 1967, has been concerned with the general problem of developing and transferring industrial technology. The Second General Conference of UNIDO, held at Lima, Peru, in March 1975, gave UNIDO the specific mandate to deal in depth with the subject of appropriate industrial technology. Accordingly, UNIDO has initiated a concerted effort to develop a set of measures to promote the choice and application of appropriate technology in developing countries.

Appropriate industrial technology should not be isolated from the general development objective of rapid and broad-based industrial growth. It is necessary to focus attention on basic industrial development strategies and derive from them the appropriate technology path that has to be taken.

The Lima target which, expressed in quantitative terms, is a 25 per cent share of world industrial production for the developing countries by the year 2000, has qualitative implications as well. These comprise three essential elements: fulfilling basic socio-economic needs, ensuring maximum development of human resources, and achieving greater social justice through more equitable income distribution. Rapid industrialization does not conflict with these aspirations; on the contrary, it is a prerequisite to realizing them. But, in questioning the basic aims of development, we also question the basic structure of industrial growth and the technology patterns it implies.

Furthermore, it is easy to see that the structure of industrial growth that should be envisaged and the corresponding structure of technology flows should be different from what they are today; a fresh approach is called for. This does not mean that the flow of technology to the modern sector and the application of advanced technologies are unnecessary. On the contrary, it is essential to upgrade the technology base in general, and it is obvious that to provide basic goods and services, there are sectors of industry where advanced or improved technology is clearly necessary. It would be difficult to envisage a situation where the dynamic influence of modern technology is no longer available for industrial growth and development in general. However, an examination of the basic aims of industrial development leads to the conclusion that there must be greater decentralization of industry and reorientation of the design and structure of production.

Such decentralized industry in the developing countries calls for technologies and policy measures that often have to be different from those designed for the production of items for a different environment, that of the developed countries. As a result, there is a two-fold, or dualistic, approach to

an industrial strategy. Morever, the two elements in such an industrial strategy need to be not only interrelated but also integrated.

In approaching the question of appropriate industrial technology from an examination of basic development needs, a mechanism is necessary to link and integrate appropriate industrial technology to the overall development process. Through such a process the concept of appropriate industrial technology could be placed in the mainstream of the industrial development effort.

It is hoped that these monographs will provide a basis for a better understanding of the concept and use of appropriate industrial technology and thereby contribute to increased co-operation between developing and developed countries and among the developing countries themselves.

It is also hoped that the various programmes of action contained in the monographs will be considered not only by the forthcoming meetings of the United Nations Conference of Science and Technology for Development and UNIDO III but also by interested persons working at the interface over the coming years.

Abd-El Rahman Khane
Executive Director

Preface

To focus attention on issues involved in choosing and applying appropriate technology, UNIDO organized the International Forum on Appropriate Industrial Technology. The Forum was held in two parts: a technical/official-level meeting from 20 to 24 November 1978 at New Delhi and a ministerial-level meeting from 28 to 30 November 1978 at Anand, India.

In response to a recommendation of the ministerial-level meeting, UNIDO, with the help of a generous contribution by the Swedish International Development Authority, is publishing this series of monographs based mainly on documents prepared for the technical/official-level meeting. There is a monograph for each of the thirteen Working Groups into which the meeting was divided: one on the conceptual and policy framework for appropriate industrial technology and twelve on the following industrial sectors:

Low-cost transport for rural areas
Paper products and small pulp mills
Agricultural machinery and implements
Energy for rural requirements
Textiles
Food storage and processing
Sugar
Oils and fats
Drugs and pharmaceuticals
Light industries and rural workshops
Construction and building materials
Basic industries

The monograph on the conceptual and policy framework for appropriate industrial technology also includes the basic part of the report of the ministerial-level meeting and some papers which were prepared for the Second Consultative Group on Appropriate Industrial Technology, which met at Vienna, 26-29 June 1978.

PART ONE

Issues and considerations

Note by the secretariat of UNIDO

INTRODUCTION

World sales of drugs in developed market economies are concentrated in the hands of transnational corporations. The table shows the increasing share in the production of drugs by developing countries from 1960 to 1980.

SHARE OF ECONOMIC GROUPS IN THE PRODUCTION OF PHARMACEUTICALS
(Percentage)

Economic grouping	*1960*	*1975*	*1980*
Developing countries of Africa, Asia and Latin America	8.4[a]	12.0[b]	14[c]
Developed market and centrally planned economies	91.6	88.0	86
Total	100.0	100.0	100
Value (billion dollars)	7.9	37.5	...

[a]Estimated distribution: Africa, 0.2; Asia, 3.4; Latin America, 4.8.
[b]Estimated distribution: Africa, 1.3; Asia, 4.4; Latin America, 6.3.
[c]Indicative only; estimates extrapolated on the basis of share increases during the period 1960–1975 would lead to shares ranging from 13.2 to 14.5 per cent.

This increase in production will involve much higher capital investment than normally envisaged, because, of 110 developing countries, only about 10 have formulation and bulk production plants, while some 50 have only formulation plants and the rest only import the finished products. Therefore, most of them now only carry out the final stages of manufacture, that is, formulating imported bulk drugs into finished preparations or repacking imported finished drugs. Backward integration of industries in these countries to go into more basic stages of manufacture will involve considerable capital investment without reflecting significantly on the value of output. Ancillary industries such as the production of packaging materials and associated engineering industries for making simple equipment must also be established. These measures will result in a considerable increase in the value added and reduce dependence on imports. With a simultaneous development of the chemical and chemical-based industries, where feasible, the developing countries will have more self-sustaining industries.

The trends from 1980 onwards are difficult to forecast because of political, social, economic and technological factors that are likely to play increasing roles

in the development of the pharmaceutical industry throughout the world. The growth of the industry will probably be more regulated to meet the urgent health needs of each country instead of the *laissez-faire* policy followed at present in many countries, especially as the right to health care will become widely established as a major socio-political goal. This development will also mean higher levels of government economic controls on prices, profits and foreign capital investment. To correct the present concentration of drug distribution in urban centres and make drugs available in the rural and more remote parts of developing countries, the trend will be towards public acquisition of the drug distribution systems. Smaller, dispersed plants will supplement the existing larger ones that operate in urban centres in the more advanced developing countries. Traditional medicine will also play a more important role in the health services, and greater attention will have to be paid by governments to the standardization and upgrading of products from this source.

I. OBJECTIVES

The major objectives in promoting pharmaceutical industries in developing countries are:

(a) To provide, in adequate quantities, products essential to health care at prices within reach of most of the population;

(b) To set up relatively independent drug industries that will allow developing countries more freedom to form health care policies relevant to their particular needs at minimal cost, using locally available raw materials and production facilities, and also utilizing the existing traditional forms of medicine;

(c) To contribute to the national economies of the developing countries;

(d) By taking steps appropriate to the stage of development of the industry in these countries, i.e., formulation of drugs in dosage forms, operation of multipurpose plants, production of bulk drugs of plant and animal origin or production of drugs from intermediates, to establish a self-sustaining industry. The industry can be designed for a variety of end-products, thus giving it a commercial and economic advantage over other industries. The technology for establishing such production is fairly well diffused and can be obtained relatively easily from small developed countries or advanced developing countries in forms adapted to the needs of developing countries;

(e) To have a catalytic effect on industrial development in general. The pharmaceutical industry usually spearheads the development of chemical and chemical-based industries, as well as the ancillary products and engineering industries required to supply their needs;

(f) To provide educational opportunities for young men and women in new disciplines of science and to provide employment for trained people.

II. FORMULATION UNITS

The choice and adaptation of appropriate technology in promoting the pharmaceutical industry in different groups of developing countries are

discussed in the first of the papers in Part Two. Even in developing countries that are fairly advanced, where products are made in economically sized units and located where the necessary infrastructure, such as the chemical and engineering industries, exists, it is possible for semi-industrial units dispersed over the rural and remoter parts of the country also to be set up to formulate basic drugs relevant to the region, to meet the local needs and to draw their requirements of raw materials from multipurpose factories located nearby. The size of these semi-industrial units, their capital cost and the testing facilities required to maintain quality are indicated in the paper. These units will supplement the major production plants and cater to the needs of the population of rural areas which now receive hardly any of the benefits of modern medicine.

The size of the formulation unit suggested in the paper is based on what the average control laboratory can cater to. If, however, it becomes necessary to set up smaller units, depending on demand, it will become necessary to link two or more formulation units to one control laboratory, provided the distances over which the samples must be moved are not too great. The use of raw materials and marketing of finished products in such cases will, however, have to await clearance of samples of each batch by the control laboratory.

It is necessary to ensure that the products turned out by these units have the required bio-availability and, for this purpose, assistance from other well established units or institutions within the country will be necessary. A small product-development laboratory (a research laboratory attached to the control laboratory) to work out any problems that may be encountered is also suggested in the paper.

While formulation facilities can be economical in small markets, and assist in developing skills to undertake backward integration into basic manufacture, economies of scale become very important in the production of antibiotics, drug intermediates and synthetic drugs. Many developing countries have already developed technological capability and adapted an improved technology to their specific needs and environments. Some have by their local R and D efforts improved the productivity of important processes. In such cases, however, there is also a well developed chemical industry, including a petrochemical industry, to supply the basic chemicals and integrate development of chemical-based industries such as dyes, plastics, synthetic fibres, pesticides, rubber chemicals and surfactants, which makes the production of common chemical intermediates feasible, thereby linking the gaps between the chemical industry and intermediates for drugs, dyes and the like.

In developing countries, a large proportion of the population depends on the indigenous systems of medicine. To improve their usefulness, such systems must be standardized and upgraded after proper screening. In addition to improving the reliability of the products, it will be necessary to weed out many useless preparations. The methods to be adopted by different countries will not be the same, but some indications to developing countries as to how they can improve these systems of medicine and make them more effective are suggested in the paper.

III. MEASURES

The following are the principal measures to be taken to achieve the objectives:

(a) Establishment of a national list of drugs as a basis for rational development of the pharmaceutical industry in relation to the health needs of the population;

(b) Improvment and strengthening of the scientific base for development and production of the traditional medicine and household remedies;

(c) Development of repacking and formulation plants;

(d) Development of manufacturing plants for sanitation products, in particular water-treatment agents, pesticides and disinfectants;

(e) Formation of an intrasectoral framework to advance the development and production of bulk drugs, including immunologicals and antibiotics, as well as their related basic materials such as intermediates, biologicals, plant products, chemical precursors and various nutrient media;

(f) Study and establishment of standards for tropical conditions, chemical engineering plant facilities and layout structures. Dosage forms also should be designed to withstand the high temperature and humidity conditions in tropical countries;

(g) Development of manufacturing plants for dosage packaging (for example pharmaceutical glass) and various other types of packaging materials;

(h) Establishment of a comprehensive quality assurance system, including specifications of standards and procedures, training of specialized personnel, information training to all persons concerned, in-plant quality assurance systems, inspection and auditing and verification methods relating to the total materials and products stream including the storage, administration and use of drugs. A system of registration that takes into account both the usefulness of a drug and its associated risks should be established. This could be done on a regional basis for smaller countries that cannot afford the elaborate facilities needed;

(i) Establishment of regulations relating to domestic and foreign corporate ventures and the importation of foreign drugs, intermediates and know-how;

(j) Establishment of model manufacturing units in less developed countries and in the rural areas of more advanced developing countries. These units will formulate selected indigenous drugs, household remedies, antiseptics, infusions and other simple formulations, depending on the common ailments prevalent in the area;

(k) Establishment of multipurpose plants to produce drugs from intermediates for a group of model manufacturing units;

(l) Establishment of units for the extraction of active ingredients of plant products that can be cultivated in developing countries instead of the present practice of exporting them as crude drugs. This will improve the value added of the products exported to developed countries and give the developing countries the necessary foreign exchange reserves to import intermediates and other

substances required for the manufacture of drugs to combat diseases common in the area.

The measures above reflect the main elements of the alternative technological development strategies for establishing a pharmaceutical industry, taking into account the development requirements of a particular country.

IV. ROLE OF INTERNATIONAL CO-OPERATION

In the pharmaceutical industry there is a high rate of obsolescence of products, not only owing to the development of new and improved products or cheaper substitutes, but also because over a period of time, the users become sensitized to certain drugs or the micro-organisms against which the drug action is directed develop resistance to it. In these circumstances, efforts to update the technology used and products manufactured by the larger units and government research institutions, which can afford the expenditure involved on R and D, are essential. Large manufacturing units in developed countries which have established modern research laboratories and spend a considerable portion of their sales revenue on R and D are the main source of information on both improved processes and strains and new drugs; they will hold a commanding position in this regard for quite some time. Association with such units and maintenance of the flow of information is therefore essential.

In less-developed countries, both special experience in management methods and technical expertise in operating pharmaceutical units are lacking. Manufacturing operations must be carried out under hygienic and often sterile conditions, with scrupulous attention to quality, and personnel must be trained to work in such an environment. The developing countries should therefore seek assistance in this regard from international companies. Training facilities for managerial personnel and technical staff at the factory level are therefore essential, and international co-operation in this regard will be most useful to developing countries.

For dissemination of scientific information to the medical profession on the action of newly introduced drugs, toxic effects, treatment of toxic effects and precautions necessary, based on experience encountered during clinical trials and those reported from time to time, the developing countries essentially depend on their foreign collaborators. A flow of information from the international firms concerned is essential in this respect.

International collaboration therefore still plays an important role in this industry, and for developing countries to obtain greater benefits from such collaboration, guidance is necessary. Governments can also establish certain guidelines in regulating collaboration arrangements to obtain the maximum benefits in this regard.

Report of the Working Group

I. DEVELOPING A PHARMACEUTICAL INDUSTRY

Most of the developing countries are at present dependent almost entirely on imports for their requirements of drugs and pharmaceuticals. The technological range and sophistication and high capital intensity of the industry make it nearly impossible for these countries to establish a conventional pharmaceuticals industry in the near future. On the other hand; governments must ensure that adequate supplies of drugs essential to the health of the population are available to the largest segment of it. For this, drugs would have to be progressively manufactured within the developing countries themselves with a view to achieving a measure of self-sufficiency in this key area. A beginning can be made by adopting appropriate technological alternatives by which the benefits of modern drug technology are available to larger segments of the population of the less developed countries, especially to people in rural and remote areas.

Simultaneously, the production of drugs used in traditional and local systems of medicine should be encouraged and integrated with the general programme of medical care. These would, however, need to be standardized and further developed. The cultivation of medicinal plants in the developing countries should be encouraged, and, where possible, facilities for extraction should be established to isolate the active principles for domestic and export markets.

If appropriate technology is selected and adopted for the development of a pharmaceutical industry it would be possible to establish sound structural linkages with auxiliary industries such as packaging materials and engineering goods industries.

Small-scale pharmaceutical units

The pharmaceutical industry should be considered from the standpoint of the country's health requirements, rather than as a commercial proposition. Despite the existence of more than 3,000 drug manufacturing units in India, for instance, the basic requirements of the rural population have not yet been met. The fact that there is a well-established pharmaceutical industry in any developing country does not by itself guarantee that the drug requirements of the most vulnerable sections of the population will be met. Small manufacturing

units and hospital pharmacies should therefore be set up in the rural and remote areas to produce the common drugs and simple household remedies needed in those areas.

Such small manufacturing units could provide employment opportunities for young people and increase the familiarity of the local population with drug manufacture. Such a strategy would also help developing countries to produce more sophisticated drugs in due course. Developing countries without a pharmaceutical industry could begin with units of this kind, which also include small infusion plants. They could become growth nuclei and progressively develop into an organized pharmaceutical industry even in the least-developed countries. Advantage should be taken of the offers of some countries to provide simple bulk drugs and equipment at minimum cost for establishing and operating such model manufacturing units. See the paper "Medicine for the rural population in India" in part two of this monograph for details of the equipment required and its approximate cost in India.

Many of the products that can be manufactured in such small-scale units are listed in the pharmacopoeia and formularies for treatment of common ailments and can be produced in the form of tablets, capsules, ointments, syrup and other liquid preparations. The background paper mentioned above presents such a formulary, developed after interviews with a large number of physicians serving in the rural areas either under the Indian Medical Association or through social organizations. A plan for small pharmaceutical units is also included. Each unit is initially supposed to serve 2 million people and to produce medicaments at an average cost of one rupee ($0.12) per person per year.

It is, however, essential that the formulary should be reduced to a small list of products required in the rural areas by a large majority of the population. This list could vary from area to area within the same country, as well as from country to country, according to local requirements and conditions. Once the products have been identified, it would be possible to manufacture them in small factories near the local hospitals. Small formulations units could be as economic as the high-value, small-sized manufacturing units. For hospital supplies and other bulk requirements, standard formulations and packaging lists should be prepared and products could then be manufactured on a contract basis by manufacturing units within the country. This system has been developed successfully in Brazil and Peru and has resulted in considerable savings on essential drugs.

In Sri Lanka, the State Pharmaceutical Company, which is government owned, invites tenders for the products listed in the formulary approved by the National Formulary Committee. After purchase these are distributed to the central drug stores, which in turn distribute them to the smaller stores in the outlying districts.

Zambia imports but also has its own small formulation units. The Government gives preference to local production; mark-ups as high as 12 per cent over the cost of overseas supplies are charged. The medicines are then passed to the medical stores and from there to the provincial medical stores and district hospitals. In this way a fairly wide distribution is achieved. The medicines are supplied free of charge by hospitals. In addition, there is commercial distribution through drug stores, wholesalers, retail shops,

supermarkets and grocery shops. What restricts supply is not poor distribution but insufficient production.

Packaging

Packaging is an important and integral part of the total technology of drug production. Sufficient information on packaging technologies suitable for different climatic conditions and distribution methods and systems is available. However, packaging institutes should be established in those developing countries which still do not have such institutes. Information on the kind of help that the existing institutes could provide in packaging pharmaceuticals for rural areas could be collected by UNIDO and be made available to interested developing countries.

Training

The developing countries generally lack special experience in management methods and technical expertise in operating pharmaceutical units. Drug-manufacturing operations must be carried out under hygienic and often sterile conditions, with scrupulous attention to quality. Personnel engaged in pharmaceutical units must be adequately trained in both management methods and production operations. Training facilities for managerial personnel and technical staff at the shop-floor level are therefore essential. International co-operation in this regard would be most useful.

Integrated training centres should be set up on a regional and sub-regional basis to provide training in management, pharmaceutical manufacturing, quality control and packing. These centres should be equipped with small research and development (R and D) and pilot-plant facilities to help solve the specific problems.

Drug research

In view of the rapid obsolescence of drugs and the special requirements of the developing countries, particularly for drugs to treat communicable and tropical diseases, it may be necessary to establish drug centres or institutes in the developing countries as joint or regional ventures.

These institutes should be able to make clinical evaluations of drugs. The development of new drugs to fight tropical diseases is often delayed because of the lack of facilities for their clinical evaluation in developed countries, where such diseases do not exist. The research centres should also undertake the evaluation and standardization of traditional remedies and plant products.

Regional co-operative centres

In would be helpful for the development of the pharmaceutical sector in developing countries if regional co-operative pharmaceutical centres, each

serving a group of countries, were established. Work of this kind has already been initiated by UNIDO and the United Nations Conference on Trade and Development.

These centres could also provide the following services:

Information on available sources of technology
Assistance in arranging for technological training
Market intelligence
Regional market and national resources surveys
Management training
Product information

Information

The developing countries depend on their foreign collaborators for the supply of scientific information to the medical and pharmaceutical professions on the action of newly introduced drugs, their toxic effects and their treatment, and the necessary precautions. This information is based on experiences encountered during clinical trials and those reported from time to time. A flow of information in this respect from independent sources is also highly essential. International collaboration therefore still plays an important role in this industry.

Role of international co-operation

The pharmaceutical industry is characterized by a high rate of obsolescence of its products, not only owing to the the discovery and development of new ones or of less costly substitutes, but also because, over a period of time, users become immunized to certain drugs or, what is equally important, the micro-organisms against which the drug action is directed tend to develop a resistance to the drug. In either case the drug loses its efficacy and becomes obsolete. Therefore, sustained efforts to improve and modify the technology used and to manufacture new products are needed. This is possible only with the assistance of large pharmaceutical companies and government research institutions that can afford the R and D expenditures involved.

The development of process technology for pharmaceuticals and basic drugs requires a great deal of research. It is therefore necessary for the developing countries to establish strong R and D capabilities in this field to keep abreast of global developments.

II. PROGRAMMES OF ACTION

The programme of action at the national level should include the following elements:

(a) An industrial policy that clearly outlines the short- and long-term plans

for the development of a pharmaceutical industry and a production plan based on a list of drugs to be taken up for priority production;

(b) The establishment of a drug control organization with a testing laboratory. The cost of such an elementary control laboratory is estimated to be $25,000;

(c) Carrying out of feasibility studies of small pharmaceutical formulation units. Adequate fiscal and other incentives to the private sector to establish such units in rural and remote areas. In the conditions prevailing in most developing countries, a lead will have to be given in this aspect by governments themselves. The capital cost of establishing a small pharmaceutical manufacturing unit would be approximately $200,000. An infusion unit could cost an additional $300,000;

(d) An organization for the collection, cultivation and processing of domestic medicinal plants;

(e) Research on the standardization and preparation of products used in traditional systems of medicine;

The programme of action at the international level should include the following elements:

(a) Regional pharmaceutical centres set up on a co-operative basis until separate national centres can be established. These centres would provide training in scientific management and production methods. Some of the existing organizations in more developed countries could be developed into regional or subregional centres. These centres could have small R and D outfits to undertake studies of certain types of operational problems;

(b) Examination of the offers made by developed countries to supply at cost bulk drugs to be formulated in the proposed small manufacturing units with a view to promoting the establishment of such units in selected developing countries on a trial basis;

(c) Assistance of the major pharmaceutical firms and research institutions in the developed countries in updating the technologies used in developing countries and also in developing new products suitable to the local conditions in and the needs of developing countries;

(d) Suitable forums for the exchange of the technological experience of developing countries in establishing pharmaceutical industries;

(e) Institutes that can make clinical evaluation of new drugs in developing countries. They should be established on a regional or subregional basis and should also undertake to standardize traditional remedies and phytochemical products.

III. RECOMMENDATIONS

1. Each developing country should accept a commitment to establish a strong local pharmaceutical industry including adequate capabilities for repacking and formulation. The goal should be to offer as wide a range of drugs as may be required by the medical profession. However, in order to utilize

limited resources and to assist in establishing a local industry, it is essential to develop a national list of drugs. Local production of such drugs would bring the benefits of technological advances in the manufacture of pharmaceuticals to the people who do not yet have access to them. The criteria for selecting drugs for local production may include the following:

(a) The drug is widely used or required by the health authorities to treat prevalent diseases;

(b) Its efficacy and safety in the treatment of diseases has been demonstrated;

(c) The cost per treatment is low enough for the population to afford;

(d) There are other special advantages of local manufacture as opposed to imports (lower costs of transport, availability of raw materials, saving of foreign exchange etc.);

(e) A feasibility study of the project should indicate that economic production could be ultimately attained including the meeting of regional and interregional demands;

(f) The manufacturing process is appropriate to the conditions prevailing in the country;

(g) The know-how for manufacture is available for production.

2. The scientific base for the development and production of preparations based on traditional systems of medicine and household remedies should be improved and strengthened.

3. An intrasectoral framework to promote the development and production of bulk drugs, including immunologicals and antibiotics as well as their related basic materials such as intermediates, chemical precursors and various nutrient media should be established.

4. Arrangements should be made for the collection of suitable animal by-products from modern abattoirs for medicinal purposes.

5. Standards for chemical and pharmaceutical engineering plants and layouts for structures for tropical conditions should be studied and elaborated.

6. Dosage forms and packages should be designed to withstand the high temperature and humidity conditions encountered in tropical countries.

7. Ancillary industries for pharmaceutical packaging materials, pharmaceutical machinery, auxiliary materials and suitable refrigerated transport facilities should be developed.

8. A comprehensive quality assurance (QA) system, including the specification of standards and procedures particularly suited for local conditions should be established. This programme should also include the training of specialists in in-plant QA systems and in inspection, auditing and verification methods relating to the materials and products stream.

9. Special consideration should be given to the storage conditions, distribution and usage of drugs.

10. A system of registration of new drugs should be established. Such a system could be set up on a regional basis for smaller countries that cannot individually afford the elaborate facilities needed.

11. Guidelines relating to the transfer of technology to produce drugs and intermediates should be drawn up.

12. Small model pharmaceutical units for formulation in less developed countries and in the rural and remote areas of more advanced developing countries should be established. These would include selected drugs of the traditional systems of medicine, household remedies, antiseptics, infusions for rehydration, and other simple preparations: tablets, capsules, ointments, syrups to treat ailments common in the area. These units should not attempt to produce high-potency drugs. The location of such units would depend entirely on government policy on the dispersal of industries. Infusion plants in local settings such as hospital pharmacies would be useful and could help the rural population and prevent loss of life from dehydration. These manufacturing units should also produce sanitation products such as water treatment agents and disinfectants. Such small pharmaceutical manufacturing units could, in specific cases, become nuclei for future expansion.

13. Multipurpose plants to produce drugs from intermediates should be established in developing countries wherever feasible.

14. The cultivation of medicinal plants in developing countries should be encouraged, and where possible, facilities should be established for the extraction of active ingredients of plant products for domestic or export markets instead of the present practice of exporting them as crude drugs to developed countries.

PART TWO

Selected background papers

Choice and adaptation of appropriate technology for the production of pharmaceuticals in developing countries

*B. Shah**

To meet the requirements of a country's medical and health services, its pharmaceutical industry needs to produce drugs of adequate quality in sufficient quantities and at reasonable prices. Developed countries are flooded with innumerable preparations; it is not possible for any developing country to market all of them within its limited resources. It is recommended, therefore, that each developing country establish a national list of drugs to meet the needs of the majority of its population. The drugs included in such a list would differ from country to country depending on many conditions, such as the pattern of prescription, common diseases, type of health services, available personnel, financial resources and genetic, demographic and environmental factors.

CHOICE OF TECHNOLOGY FOR DIFFERENT GROUPS OF COUNTRIES

After the preparation of a national list, the manufacturing method chosen will depend on the development stage of the country's industry and its technical base. The developing countries have been broadly classified into five groups, depending on their stage of development, as follows:

Group	*Description*
I	No manufacturing facilities and dependent on imported, finished pharmaceuticals
II	Packaging of formulated drugs and production of simple formulations
III	Formulation of a broad range of drugs in dosage form; production of simple drugs from intermediates
IV	Production of a broad range of drugs from intermediates and manufacture of some intermediates from local raw materials
V	Manufacture of intermediates and production of the plant and equipment required

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GROUP I COUNTRIES

Group I countries not only have no manufacturing facilities for pharmaceuticals, they also have limited public health services and poor distribution channels. The steps they should take are:

(a) Establish procurement procedures for the items in the national list of drugs to take advantage of bulk purchasing;

(b) Develop quality-control facilities to ensure the quality of the drugs purchased (see annex I for a list of control and formulation equipment);

(c) Establish units for repackaging formulated drugs which will help build auxiliary industries for producing packaging materials and standardize their production (see annex II for list of packaging materials);

(d) Set up units to produce infusion solutions and simple formulations on a semi-industrial scale (see annex I for the necessary equipment).

GROUP II COUNTRIES

Group II countries already package formulated drugs and produce simple formulations. The steps they should take are:

(a) Establish formulation units to convert bulk drugs into dosage forms such as tablets, capsules, liquid preparations, ointments and infusion solutions (see annex I);

(b) Establish facilities to control quality from the raw material to the finished product (see annex I);

(c) Set up the requisite organization to monitor drug stability. When products fail to meet specifications they should be recalled from the market.

To achieve these steps, it is essential to train industrial pharmacists to set up and operate semi-industrial units and to establish test facilities. This is a very important part of the infrastructure. UNIDO has been assisting in this area by providing training at certain universities. For example, over the last five years, trainees from 82 nations have participated in courses at the University of Ghent, Belgium, obtaining the expertise to begin the production of simple preparations, set up and operate small infusion-producing installations and introduce semi-industrial formulation facilities for tablets, capsules, ointments, ampoules and the like. Several of the more advanced developing countries have similar facilities and are co-operating with less advanced ones in this field.

Semi-industrial plants need no elaborate equipment. The technical assistance and equipment for them are not difficult to acquire within the developing countries themselves. Such units should also undertake production of simple antiseptic solutions to help prevent the spread of infection. The infusion solutions referred to above are essential for treating severe cases of dehydration caused by diarrhoea; unless they are administered immediately, lives are lost. It would cost more to import such solutions, which contain nearly 95 per cent water, than to produce them locally at hospital pharmacies. A list of equipment required for making such infusions and simple formulations is given in annex I. The ancillary products required to formulate drugs are given in annex III.

Types of formulations

The various ingredients involved in making simple formulations are described below.

Tablets

Various types of tablet are made, such as plain, chewable, sugar-coated, press-coated, layered, film-coated and sustained-release.

The tablet form offers several advantages:

Ease of dispensing and administering

Ease of packaging and shipping

Accuracy of dosage

Preservation of drug activity

In addition to the active drug or drugs, the other ingredients in tablets are diluents, binders, lubricants and disintegrating, colouring and flavouring agents:

(a) Diluents. Many synthetic and natural drugs are highly potent; only extremely small quantities are required per dose. In order to be able to make a tablet for administering such small quantities, certain inert materials called diluents are included. Some examples are lactose, starch, sucrose, mannitol, dicalcium phosphate, calcium sulphate and micro crystalline cellulose;

(b) Binders. Substances that keep the components of the tablets together in the tablet form after compression are known as binders. Examples of common binders are gum acacia, gum tragacanth, gelatin, starch paste, sodium carboxymethylcellulose, ethylcellulose, polyvinyl pyrrolidone and sodium alginate;

(c) Lubricants. These are substances that prevent adhesion of the powder to the punches during compression and ensure smooth ejection of the tablets from the dies. Some commonly used lubricants are talcum powder, liquid paraffin and stearic acid and its salts;

(d) Disintegrating agents. Substances that help break up tablets after administration to the patient are called disintegrating agents. Some commonly used ones are cornstarch, gum guar, methylcellulose, sodium carboxymethylcellulose, micro crystalline cellulose and alginates. The pharmacopoeias prescribe a limit of 15 minutes for the disintegration of common tablets after administration;

(e) Colouring agents. Colour, in addition to making tablets look more attractive to patients, also helps to distinguish different medicines. Only certified food and drug colours are normally used;

(f) Flavouring agents. To make tablets more palatable, various flavouring agents are incorporated into them.

All ingredients must be tested for their compatibility both with each other and with the active drug or drugs.

Capsules

Capsules are solid dosage forms in which the drugs are enclosed in hard or soft shells of gelatin. (The gelatin shells themselves are also called capsules.) As a dosage form, capsules have advantages over tablets in that:

(a) They retain drug potency without complex formulation techniques;

(b) They give more protection from the atmosphere by holding each dosage in a sealed container;

(c) They mask the taste and odour of the active drug;

(d) They disintegrate in the stomach in less than five minutes, thus making the drugs available for quick absorption.

Capsules are largely used to market single active drugs such as antibiotics. However, mixtures of drugs, either as made or in granules, are also marketed in capsule form (for example, vitamins). Capsules come in a variety of sizes. The choice of size depends on the bulk density of the mixture for a single dose. The colouring of capsules is adopted extensively as a method of identification for proprietary products. In damp conditions, capsules tend to stick together, so it is recommended that they be stored in a dry and cool place.

The general process for manufacturing hard gelatin capsules containing drugs involves four operations: preparing the powder mixture, and filling, sealing and cleaning of the capsules.

The drug for capsules is blended in a blender, with a diluent if necessary, and with a little lubricant to ensure free flow of the powder while filling the capsule. The blended material is then filled in semi-automatic or automatic machines that are now available even in several developing countries. The machine first separates the top and bottom parts of the empty capsule, delivers an accurate weight of the blend in the bottom part and then replaces the top part.

Sealing is achived in a machine that applies a solution of gelatin at the joint of the top and bottom parts of the filled capsule. Such machines are easily available. Self-locking capsules, however, do not need sealing. Some of the pharmaceutical houses also print their capsules to identify their products. This can be done before or after filling.

Liquid preparations

Liquid preparations have these major advantages:

(a) Ease of handling when the active drug is a liquid;

(b) Flexible administration, as with small or large doses, as required by the physician;

(c) Quick action–the drug is available for absorption immediately after administration;

(d) Ease of formulation–liquid preparations can be sweetened or flavoured to facilitate their administration, particularly for children and old people.

Parallel with these advantages, however, there are certain disadvantages:

(a) For single doses, liquids are bulkier than equivalent solid dosage forms, resulting in higher costs;

(b) Deterioration of drugs such as antibiotics, vitamins and hormones is much faster in the liquid form than in solid dosage forms.

Liquid dosage forms are mainly of three types: solutions, emulsions and suspensions.

Solutions

Solutions are made by dissolving a drug or drugs in a compatible solvent. The product should be a homogeneous, clear mixture, free from suspended particles. Water, alcohol, sugar syrup, glycerin and sorbitol (70 per cent) are the most common solvents.

Apart from the active drugs und diluents, other ingredients involved are sweetening, colouring and flavouring agents as described in the discussion of tablets. Also, preservatives are added to prevent the growth of moulds and bacteria to which liquid preparations are susceptible. Commonly used preservatives are alcohol, hydroxybenzoates and sorbic acid.

Emulsions

Emulsions are two-phase systems prepared by combining two immiscible liquids, one of which is uniformly dispersed in the other. In order to keep this emulsion stable for a considerable time, emulsifying agents, such as benzalkonium chloride, glyceryl monostearate and gum acacia are added. The last of these is the most commonly used natural emulsifying agent.

Suspensions

Like an emulsion, suspension is a two-phase system, but it involves a solid phase finely suspended in a liquid phase. In order to keep the solid well suspended, certain chemicals are used, among them sodium carboxymethylcellulose, methylcellulose, polyacrylic acid and sodium alginate. The natural suspending agents include gum acacia and gum tragacanth.

Ointments

Ointments are soft, semi-solid preparations usually containing medicinal agents intended for application to the skin or eyes. All ointments should be sterile.

While it is not possible to give full manufacturing details here, the general method of ointment manufacture involves three types of material besides the active drug or drugs:

(a) Diluents or bases constitute the major portion of ointments and influence the absorption of the drugs through the skin. Various types of bases are used, for example:

(i) Oleagenous bases consisting of mineral, animal or vegetable oils, among them soft paraffin, liquid paraffin, lard, olive oil and cottonseed oil;

(ii) Absorption bases, for example hydrophilic substances such as wool fat (lanolin);

(iii) Washable bases are water soluble and are easily removable from the skin by washing with water. Common examples are the polyethylene glycols. They are compatible with a wide range of active drugs;

(iv) Emulsion bases are of two types. In one, water is the internal phase and oil the outer (W/O–water-in-oil emulsion); the other contains oil in the inner phase and water in the outer (O/W–oil-in-water emulsion). An example of a W/O emulsion is hydrous wool fat; stearic acid soap is an example of an O/W emulsion. Agents that help in forming emulsions for both the oil and water phase are called emulsifying agents. Sodium lauryl sulphate is an example;

(v) Emulsifying waxes are waxes that form O/W emulsions when fused with water. Examples are cetyl alcohol, stearyl alcohol and glyceryl monostearates;

(vi) Silicon bases include products that contain silicon compounds such as bentonite;

(b) Antioxidants are sometimes added to ointments to prevent oxidative deterioration. Their selection depends on factors such as toxicity, irritancy, potency, compatability, odour, discolouration, stability and solubility. Common antioxidants are butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA) and propyl gallate.

(c) Preservatives are added to ointments to prevent contamination, deterioration and spoilage by bacteria or fungi. The most common are esters of *p*-hydroxy benzoic acid (methyl ester or propyl ester) and sorbic acid.

Infusions and other parenterals

Popularly known as injections, parenteral preparations, including infusions, are sterile pharmaceutical dosage forms that can be administered intravenously or intramuscularly. Pharmacopoeias recognize four main types of parenteral products:

(a) Solutions of medicaments ready for injection. This is the most common form (such as glucose, saline) and are commonly known as infusions;

(b) Dry solid medicaments that make up into solutions by the addition of suitable solvents just before administration. These are mostly antibiotic preparations such as penicillin;

(c) Suspensions of solid medicaments ready for injection. These are mostly drugs in colloidal or micronized form such as hydrocortisone;

(d) Dry, solid medicaments that yield suspensions upon addition of suitable vehicles such as procaine penicillin.

Parenteral preparations offer the following advantages over the other dosage forms:

(a) They are the only way certain drugs can be absorbed in active form as with streptomycin and neomycin;

(b) They offer more predictable absorption because they are independent of the vagaries of the gastro-intestinal system;

(c) Their effective dose can be more accurately selected and the desired blood concentrations obtained quickly;

(d) They permit immediate action in emergencies, for example for unconscious or unco-operative patients. This is usually achieved by intravenous injection;

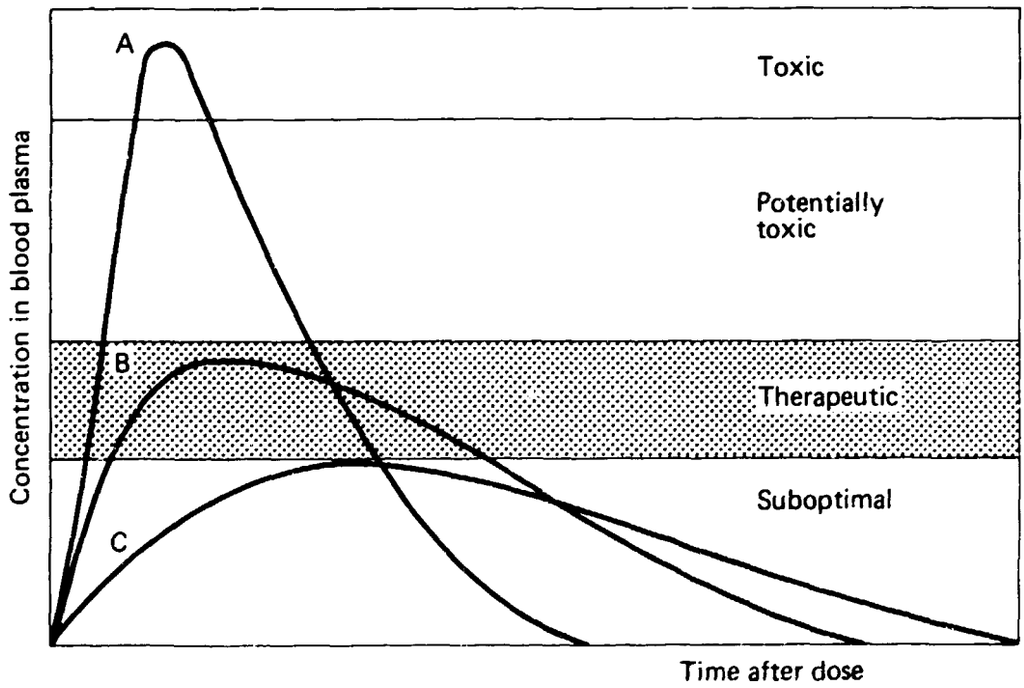
(e) The intravenous parenteral route offers the only method of rapidly increasing blood volume in cases of dehydration;

(f) They are the only possible method of administering drugs when patients are unable to take or retain drugs orally;

(g) The intramuscular and the subcutaneous parenteral routes can be used to prolong absorption of a drug, especially where sustained release is needed.

Supplies to primary health centres in rural areas

To improve supplies to the primary centres at reasonable cost, hospital pharmacies must be established to undertake simple formulations, infusions and the like. The selection should be made with special reference to the diseases prevalent in the area. A formulary of drug preparations commonly required in rural hospitals will have to be prepared, based on the national list of drugs. The facilities needed for organizing such production are:



Types of variation of bio-availability of drug formulations, depending on the nature of auxiliary ingredients, particle size and method of formulation. All three drug formulations, A, B and C, release the same total dose into the bloodstream, but drug A is released so quickly that it reaches toxic levels, while drug C is released so slowly that it never reaches the level at which it has any effect. Only drug B is medically useful

(a) Small infusion installations that could initially serve the needs of a group of hospital pharmacies;

(b) Semi-industrial formulation facilities for producing tablets, ampoules, ointments, antiseptics (such as sodium hypochlorite, potassium permanganate, chloramine and cresol) and solutions. These semi-industrial facilities would supply local needs. Their production would entail no transport difficulties and could therefore be distributed on regional and local bases;

(c) Quality control (chemical and bacteriological) laboratories connected with the hospital pharmacies or semi-industrial units.

These hospital pharmacies or semi-industrial plants would have the great advantage that locally trained industrial pharmacists could undertake the work very easily. Development of the human skills needed to carry out the operations involved under hygienic and aseptic conditions and operate testing facilities, however, needs special emphasis and can be achieved only by proper training. Essential technical help should be available to these units and other institutions within the country, especially to ensure that the preparations they produce have the necessary bio-availability. A given quantity of active ingredient can produce differing results if not properly formulated, as illustrated in the figure.

Proper supply and storage of immunologicals is also necessary. These are heat-sensitive products that lose their effectiveness with time. Their storage therefore needs special attention; otherwise the rural population receives hardly any benefit from them for prevention and treatment of epidemics. In a later stage, rural centres can undertake the work of preparing individual doses from bulk shipments under sterile conditions.

Other preventive measures at the rural centres include supply of water-treatment chemicals, pesticides and disinfectants. These could also be formulated locally in a separate unit to meet local requirements.

GROUP III COUNTRIES

Group III countries formulate a broad range of bulk drugs in dosage form and have also begun to produce simple bulk drugs from intermediates. The steps to be taken by them are:

(a) Establish multipurpose plants to produce the bulk drugs required for health programmes by manufacturing products, using production processes involving similar chemical reactions;

(b) Set up units for extracting active ingredients from indigenous medicinal plants, growing wild or cultivated;

(c) Set up centres to utilize slaughterhouse by-products, for example, extracting active ingredients from animal glands and organs and production of surgical catgut;

(d) Set up units to produce immunologicals both for prophylaxis and treatment.

Multipurpose plants

The advantage of multipurpose plants in countries where demands are limited is that the facilities can be utilized throughout the year by changing from one product to another. Demand for each product will always vary from season to season and from year to year, depending on epidemics etc.

Groups of simple bulk drugs can be made from intermediates in one multipurpose plant designed to carry out similar processes and operations. Among the major synthetic drugs are, for example, the sulpha drugs. They are chemically similar and are usually produced with the same type of equipment, starting from the same or similar chemical intermediates.

A list of equipment for a multipurpose plant that can be used to produce a large number of bulk drugs starting from late intermediates is presented in annex IV. To withstand corrosive reactions, the reaction kettle should preferably be glass-lined, but many reactions can be carried out in stainless-steel equipment, using only small, all-glass equipment for the final corrosive stages, thus reducing capital outlay. By changing intermediates and varying the reactants and reaction conditions, it is possible to use such equipment to produce, at the rate of about 200 t/a, the following drugs: aspirin, lidocaine, isoniazid, nicotinamide, methyl salicylate, paracetamol, phenacetin and phenylbutazone, the demands for which vary with market conditions.

It is also possible to set up such multipurpose plants to meet the demands of groups of semi-industrial formulation units or hospital pharmacies. They have the advantage of low overheads and few distribution problems compared to large manufacturing units set up in urban centres.

Botanical extraction units

The design of extraction units for recovering active ingredients from plants depends on the kind of plants available and of the products to be obtained from their extracts. Many developing countries now export crude herbs to developed countries and in turn import the active principles. Even exporting semi-processed products would improve export earnings.

Later, as experience is gained, the active ingredients could be isolated within the country of origin and be used for medical treatment as well as for export. In such cases, the value added increases many times. It would be an important step in redeploying industry from developed to developing countries and would help to improve the share of industrial production of developing countries.

In recent years greater attention has been given to plant products because plants synthesize complicated molecules from simple ones by means of highly specific reaction mechanisms that would be either too difficult or too costly to duplicate by classical chemical methods. In the case of steroid hormones, the partial synthesis of finished hormones starting from the very closely related naturally ocurring product diosgenin is more economic than total synthesis. Therefore, collection of wild or cultivated *Dioscorea* root for extraction of diosgenin is undertaken on a large scale, and plantations have been developed in many developing countries with suitable climatic and soil conditions. *Dioscorea* root grows wild on the Mexican and Himalayan mountains. Its collection for the extraction of diosgenin has however, depleted the lower and more accessible

ranges. One solution, therefore, is scientific cultivation of *Dioscorea* tubers and other plant genera such as *Solanum*, whose berries contain solasodine. Extraction of hecogenin from sisal waste can also form a starting point for the synthesis of steroid hormones. Another example of partial synthesis is that of vitamin A, starting from the citral present in lemon-grass oil. Guatemala, India and other subtropical countries have suitable climatic and soil conditions for cultivation and offer great scope to supply plant materials.

There are also certain phytochemicals that it is more advantageous to extract as active ingredients of plant products than to obtain by synthesis. Some of these can exist in different steric forms, and their chemical synthesis, therefore, yields a mixture of isomers that is very difficult to separate. The products thus obtained by synthesis may be toxic and have different therapeutic properties. In plants, these reactions take place at normal biological temperatures and pressures, so that the type and quantity of the substances produced will be those that they need for their own metabolism and hence are normally free from toxic ingredients. In view of these factors, there is great demand for certain plant products in the world despite the advances in chemical technology and the appearance of cheaper synthetic substitutes.

Some of the drugs extracted from plants obtained either by cultivation or collection from the wild are the following:

(a) Strychnine and brucine. The dried ripe seeds of *Strychnos nux vomica* yield two important alkoloids, strychnine and brucine. Although strychnine is a very powerful central nervous system stimulant and has been used therapeutically, it has now been replaced by other, safer drugs. These are produced in large quantities (mainly for export), from seeds collected in the forests of India, Israel and other countries;

(b) Atropine, hyoscyamine and scopolamine. These drugs are mydriatic alkaloids obtained from *Solanum* sp. Scopolamine is additionally used as a sedative and a tranquillizing depressant to the central nervous system. As a first stage, the extraction of crude extracts can be undertaken in the developing countries where the plants grow wild, for export to developed countries;

(c) Quinine. The *cinchona* tree is cultivated over large areas in India as in Darjeeling, the Nilgiris and also in Indonesia. The factories attached to these plantations in India alone have a total quinine production capacity of 61 t/a. The output is very much greater in Indonesia. Efforts can still be made to increase production of quinine salts to meet the growing demand from foreign markets. Although the use of quinine as an antimalarial drug has decreased, it is used increasingly for the production of quinine, which is used against cardiac ailments such as auricular fibrillation and ventricular tachycardia, and as a bitter in aerated waters and non-alcoholic beverages;

(d) Reserpine. Reserpine from *Rauvolfia vomitoria* roots is a tranquillizer that induces sedation without somnolence. It is used in psychiatry for the treatment of schizophrenia and paranoia. Its wide use in drugs against hypertension is well known. *R. vomitoria* is cultivated in Africa and in India, in Darjeeling, Kerala and other places. Extraction prior to isolation of reserpine is fairly simple;

(e) Emetine. Plantations have been established in Darjeeling, India, to

produce ipecac at the rate of 20 t/a of dry roots and are largely meeting the requirements for the production of emetine. Emetine is extracted at two factories (in Bombay and Calcutta) with a combined capacity of 590 kg/a. It is principally used in the treatment of amoebic dysentery and in small quantities in expectorants, emetics and the like;

(f) Digitalis glycosides. In India, two units for extraction of digoxin, a cardiac drug, from locally grown *Digitalis* leaves have been set up in Bombay. In this case, the cultivation of *Digitalis* and the application of modern extraction technology were necessary for its manufacture. In particular, it has been grown successfully on slopes near tea plantations but not considered suitable for the cultivation of tea. Although developing countries may not be in a position to isolate the active principle, they can make crude extracts for export to countries that produce cardiac preparations;

(g) Caffeine. In regions where tea is extensively grown, caffeine can be easily extracted from tea wastes and tea prunings with such solvents as benzene, chloromethanes or chloroethanes. Although caffeine is made synthetically in large factories in developing countries, natural caffeine is preferred in certain drug preparations. As an ingredient of aerated soft drinks, it fetches a high price. Several extraction units exist in India near the tea-growing centres of Assam and Kerala. Coffee husk is another source for caffeine extraction. Caffeine is also a by-product of the production of decaffeinated coffee;

(h) Ephedrine. This drug can be extracted from *Ephedra* shrubs, which grow wild in the arid Himalayas in Afghanistan and Pakistan. It has many uses in the production of cough syrups and antiasthmatic preparations. Here, also, there is competition from synthetic ephedrine, but the natural alkaloid enjoys certain preference;

(i) Schillarin. The bulbs of squill *(Scilla)* grow wild in many subtropical regions and need only be converted into a crude extract to supply countries that make a cardiac drug that is very effective for patients who do not respond to digoxin;

(j) Other extracts. Multipurpose plants for the extraction of the active ingredients of senna (laxative), belladonna (for colic), podophyllum (for cancer) and the like are also possible. All of the active ingredients of some of these plant products are already being extracted in India and some other countries. A new unit in India will, in addition, isolate the active constituents.

Utilization of slaughterhouse by-products

The production of sera and vaccines from slaughterhouse by-products is linked with the upgrading of abattoirs in large cities and the setting up of primary extraction centres in their immediate vicinity. The by-products must be collected frozen and preferably processed immediately after slaughter.

For example, in the production of insulin, which is essential for controlling diabetes, the pancreatic glands are removed from cattle carcasses immediately after slaughter and frozen below −10°C. Insulin is isolated by repeated extraction of the pancreas with cold acidulated alcohol in special mincing equipment. The extract is filtered to remove biological matter, and the insulin-alcohol solution is concentrated initially in a special rising-film

evaporator and later at reduced pressure in a vacuum still. Chilling the alcoholic concentrate leads to the separation of residual fat, which is removed by filtration. The insulin is salted out from the filtrate as the crystalline hydrochloride, called salt cake, which is then dissolved in water. Crystalline insulin is precipitated by adjustment of the pH to the isoelectric point of insulin.

Many active ingredients of glands and organs of slaughtered animals, such as epinephrine and other hormones, pancreatin, pepsin and other enzymes, and liver extracts, can be similarly recovered. Catgut required for surgery and other uses can be produced from sheep intestines. Many intermediary products such as cholesterol can be obtained from the spinal cord or wool fat. Cholesterol can be used for the synthesis of steroid hormones and vitamin D_3. Bile can also be used to produce the bile acids required for synthesis of hormones and the like. Most of these raw materials are wasted but at the same time there are heavy demands for the limited output of such products produced in the developed and a few of the developing countries.

Biologicals such as the sera, vaccines, antitoxins and toxoids necessary for both prophylaxis and treatment can be produced by public health laboratories with simple equipment. The list includes vaccines against smallpox and cholera, anti-tetanus serum and toxoid, anti-diptheria serum and toxoid, anti-rabies vaccine, triple antigen and oral polio vaccine.

GROUP IV COUNTRIES

Group IV countries are those that already produce a broad range of bulk drugs from intermediates and manufacture some intermediates, using local raw materials. The steps to be taken by them are:

(a) Set up units for the production of antibiotics by fermentation;

(b) Set up plants for intermediates that also cover the needs of other chemical-based industries.

The steps involve both a significantly more sophisticated technology, for example the production of antibiotics, and an infrastructure of a developed chemical industry capable of manufacturing intermediates for drug production.

Antibiotics

Unlike synthetic drugs, antibiotics are made with the help of micro-organisms using fermentation technology. However, chloramphenicol and some of the newer, semi-synthetic penicillins such as ampicillin are produced industrially by chemical methods. Despite their complete lack of chemical similarity, they all exhibit antibiotic activity, that is, they can interfere with the metabolic processes of specific micro-organisms in that the growth of these organisms is either retarded or suppressed. Again, unlike the production of synthetic drugs, which needs a large number of chemicals and a complicated series of chemical reactions, the production of antibiotics needs mainly nutrient media and certain solvents. It is therefore easier to produce antibiotics than synthetic drugs in developing countries, provided the technology and equipment for their manufacture are available and that workers are trained to maintain

strict hygienic and sterile conditions. The raw materials required for the manufacture of antibiotics are shown in annex V.

The large-scale production of antibiotics by fermentation involves growing the antibiotic-producing organism in a liquid medium. The correct pure strain of the micro-organism is chosen and then grown from the master culture in a series of intermediate transfers from laboratory shake flasks to seed tanks of increasing size and finally to the fermentor. Each vessel contains a liquid medium with sufficient nutrients for the optimum growth of the organism. Transfer of the growth from a smaller to a larger tank is carried out at 5 to 10 per cent of the volume of the larger vessel. All transfers are made under aseptic conditions and, in fact, there are facilities not only for steam sterilization of the vessels, but also all outlets from the tanks are continuously exposed to flowing steam so as to prevent contamination of the broth by other organisms. The plant equipment is made of iron or, preferably, of stainless steel, and the tanks are equipped with mechanical agitators and dip tubes for aeration of the broth, so as to obtain uniform growth of the micro-organism. Aeration is carried out with compressed air, which is first sterilized by filtration through suitable cartridge filters. Strict temperature control at all stages of the fermentation is maintained. The pH is also controlled between narrow ranges by addition of acids or buffer salts. The fermentor has sampling devices so that the progress of the fermentation can be monitored with suitable analytical procedures. These depend on the type of fermentation being carried out.

Once analytical assay has indicated the antibiotic concentration in the broth has reached an optimum, the batch is harvested. Usually the antibiotic is in solution, so the broth is filtered to separate it from the mycelia, which are discarded. The filtrate is then solvent extracted to isolate the antibiotic prior to final purification. Purification procedures depend on the nature of the antibiotic.

Chemical intermediates for synthetic drugs

For the basic production of drugs from locally available raw materials, integrated development of all the chemical raw materials for the chemical-based industries is necessary. In developing countries, the development and production of chemical intermediates means a series of exercises in import substitution, which has to be progressively achieved.

This step can be undertaken as more and more basic chemicals become available and the expansion of a chemical-based industry makes it possible to set up economical units for the production of intermediates. Many co-products will be involved in such manufacture, and they will have to find proper uses in allied industries. This is therefore a continuous process, akin to solving a gigantic jigsaw puzzle; it involves not only development of a drug industry but also of dyes, plastics, fibres, synthetic rubber, pesticides and the like.

The basic raw materials involved are the chemicals based on alcohol, coal and petroleum. Not only must these resources exist, but there must also be production units for making alcohol-based and coal-based chemicals and petrochemical reformers and crackers. Such developments are not possible when these resources are lacking or if the country is too small to undertake such projects. The problem can only be solved by regional co-operation between countries that have these resources and the setting up of regional units located at

the most convenient centres, whose production can then be shared by the countries within the region. The exchange of chemical intermediates produced where natural facilities exist between developing countries can also be examined as an alternative.

The problem is not so acute in the production of antibiotics, plant products and those based on animal by-products. The nutrients required by the antibiotics industry are mainly agricultural products, and their supply depends on overall agricultural production. The other raw materials such as solvents, precursors and filter aids are not difficult to import from other producing countries at reasonable prices. Similarly, plant products are based on local resources and, with the required climatic and soil conditions, can be cultivated or, if they grow naturally, collected from wild sources. Animal by-products need proper organization of abbatoirs and the collection and storage of glands, organs and the like under proper conditions to prevent the deterioration of active ingredients before they are extracted. If proper attention is given, these products can be undertaken by developing countries more easily than setting out to make chemical intermediates for the production of synthetic drugs from basic raw materials.

GROUP V COUNTRIES

Group V countries manufacture the intermediates required for the pharmaceutical industry and also produce the plant and equipment required. They also undertake local research in order to develop new products and improve manufacturing processes. The steps to be taken by them are:

(a) Expand the range of intermediates and the volume of production to be able to meet other developing countries' requirements;

(b) Expand the production of chemical plant equipment and machinery both for production of dosage forms and of drugs from basic chemicals;

(c) Undertake R and D to develop new processes and screen new products.

Countries at this stage have reached near self-sufficiency with regard to basic raw materials, range of therapeutic groups, developmental and process research and effective distribution. Developing countries arrive at this level (which is comparable to international standards in production technology and the quality of products) only after many years of experience with international collaboration. Although they have not reached a stage where they can be self-sustaining with regard to the discovery of new products they have achieved a strong technical base and the capacity to produce different chemical intermediates (and thereby improved their negotiating power). They can select the processes best suited to their conditions and have the capacity to absorb any new technology and improve on it with their local R and D facilities.

Their capacity to produce machinery and equipment depends on how well the co-ordinated development of other engineering industries has taken place. Just as the manufacture of basic drugs using primary raw materials depends mainly on the level that the chemical industry has attained in the country, the ability to build capital goods to produce drugs depends on the level that the engineering industries have achieved.

The manufacture in a developing country of the two types of machinery and equipment needed depends on there being adequate demand from associated chemical and chemical-based industries, that is, equally rapid development, especially in the fields of dyes, drugs, pesticides, fertilizers and petrochemicals. The type of equipment can be classified under four main categories (see annexes I and IV):

Pharmaceutical processing and packaging machinery

Laboratory and research instruments

Chemical plant and machinery, including specialized equipment for services and utilities

Process-control instruments

Each category includes a large variety of equipment and instrumentation. It is necessary to have a further breakdown of the different categories into individual types according to the expansion envisaged in the industries, their present status and future needs. This depends in turn on the development of consultancy, process engineering and design, and project management in the country.

After arriving at the probable requirements, other considerations include:

Plant location

Process and know-how selection

Finance planning

Detail process engineering and design for equipment and plant

Procurement of materials and planning for equipment fabrication

Manpower planning, recruitment and training

Installation of equipment

Test run and start-up of plant

Regular routine production

Such activities, however, need capable engineers with experience in a variety of design and development activities.

A list of the raw materials required for the manufacture of drugs is in annex VI.

PATENT PROTECTION AND RELATED NEGOTIATIONS

Patent protection plays a significant part in sustaining industrial development in countries that have strong patent laws covering both user and process patents. Usually in developing countries, however, there are only process patents, and in some countries there are none at all. In others, patent protection is prohibited for drugs, while still others have made the patent laws so weak in the field of food and drugs that, even if patents are granted, they are endorsed with a "licence of right" and limited with a clause for compulsory licensing. The period of validity of the licence is also much reduced.

In all of these cases, what is sustaining industrial development is access to unpatented rather than patented know-how. If a country has a technical base

adequate to unravel unpatented know-how and has access to intermediates. permission to use a patent is very easy to acquire, and if fees are paid at all in such circumstances, they are nominal.

Thus, countries that develop a strong technological base and have access to chemical intermediates are in a stronger position to negotiate to obtain the unpatented know-how to establish production. They also have the wherewithal to absorb the new technology and improve on it with local R and D facilities.

It is only the less-developed countries that do not have the appropriate background to be in a position to understand, and compare foreign know-how and are therefore unable to negotiate effectively. They often negotiate weakly and grant excessive concessions owing to inadequate information on other agreements and the lack of ability of those who negotiate, who usually are non-technical people and are therefore unaware of the technical aspects. Shortage of capital or foreign exchange and lack of managerial skills to organize and operate plants lead to projects being set up for production of non-priority items and where production is undertaken from stages which only increase the dependence on foreign suppliers of intermediate products.

Countries in this category can, however, be helped by international organizations such as UNIDO. Assistance is available on the selection of products, the type of technology best suited to the country, improved utilization of local raw materials; how to negotiate better terms and conditions for acquisition of appropriate technology. UNIDO can also help promote technical co-operation between developing countries in areas where the technology is more easily adaptable and where prevailing local conditions are similar.

The following are some guidelines that would be of help in negotiations for acquisition of technology:

(a) For drugs on which patents have expired, the cost of purchasing technology and manufacturing know-how (often expressed in terms of technical fees and royalties on sales) should be at a reasonable rate, appropriate to the product concerned in view of the patent expiry date;

(b) For drugs on which patents have not expired; the cost of buying the technology and manufacturing know-how may be higher; but nearness to the end of the patent life should be taken into account;

(c) When only the supplying of know-how for formulation is involved, such payments should be reasonable and appropriate for the information supplied;

(d) When further stages of manufacture are undertaken within the country, higher payments are admissible;

(e) The package of terms and conditions should admit different scales of royalties, taking into account the technology involved;

(f) The transfer of technology and manufacturing know-how should be as complete as possible in the sense that the developing country should be entitled to existing and new information on the medical effectiveness of the drug and improvements in the manufacturing process made by the licensor;

(g) Personnel of the developing country should be trained to manage and operate the production facility and to undertake product information, distribution and product R and D;

(h) The technology transfered should be adapted as and when required to suit local conditions by the supplier of technology, collaborating with the expertise of the developing country;

(i) When the drug is manufactured from a late intermediate, the supplier of technology should ensure that the required quantity of the intermediate shall be made available at reasonable prices;

(j) In recognition of the desire by many developing countries to develop exports, the inclusion of such export markets should be considered by both parties when negotiating each technology transfer arrangement. (It is recognized that, in several countries, the restrictions on procurement of key ingredients such as intermediates from particular suppliers need not apply. This will depend on the technological competence of the firm concerned and would, in any case, be a matter of discussion between the interested parties.);

(k) The supplier of technology should assist the developing country in undertaking the production of late intermediates within the country in a phased programme, so that all or as many stages of production as possible are undertaken within the country.[1]

PROMOTION OF DRUGS UNDER INDIGENOUS SYSTEMS OF MEDICINE

In developing countries, much of the population depends on indigenous systems of medicine. It would go a long way to meet the medical needs of these countries if some of the medicines used under these systems were standardized and upgraded after proper screening.

In addition to determining the efficacy of the products for the purposes for which they are prescribed, it is also necessary to weed out many useless preparations now offered to the public. The methods to be adopted by different countries will not be the same but some indication to developing countries as to how best they can improve these systems of medicine and make them more effective are the following:

(a) A system to screen and select the useful preparations should be established. Following this a formulary should be laid down to ensure that what is dispensed is of uniform standard and gives the required therapeutic response. Some 444 preparations have been listed in a national formulary for indigenous drugs in India, for example;

(b) Uniform standards of education concerning these systems of medicine should be evolved and a central register of practitioners should be maintained. A minimum standard of education should be laid down for those who practise the system;

(c) A post-graduate institute or department financed by the government should be established to specialize in different branches of these systems of medicine;

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[1]Report of the Second Panel Meeting of Industrial Experts on the Pharmaceutical Industry (ID/WG.267/4/Rev. 1), p. 7.

(d) A central council for research in indigenous systems should be established as an autonomous body engaged in intensive research in the various fields. The council should conduct research on drugs literature and clinics and make a survey of medicinal plants throughout the country;

(e) Herbarium sheets should be established to identify the herbs required for cultivated and experimental gardens. Folklore claims should be examined scientifically. Books containing simple remedies for common ailments should be prepared and published;

(f) Pharmacopoeial laboratories for indigenous medicine should be established to work out standards and develop tests for the single drugs and compound preparations used in these systems of medicine. A museum of medicinal plants should be set up to facilitate identification of drugs used in indigenous systems of medicine;

(g) State governments should establish their own pharmacopoeias of indigenous medicines to meet the requirements of drugs for their dispensaries and hospitals. Private pharmacies should also be encouraged;

(h) Incorporating certain modern drugs into indigenous formulations has also helped bring about improved preparations. This has the advantage of reducing the toxic effects of the ingredients and making the preparations less costly. Such useful preparations can also be incorporated in the national formulary.

Traditional medicines are extensively used in developing countries because they are cheap and within the reach of everyone, which cannot be said about most modern medicines; traditional medicine will therefore play an important part in the health services of many of these countries. How to improve the use of the locally available substances of natural origin is already receiving the attention of the governments of many developing countries.

Annex I

LIST OF EQUIPMENT REQUIRED FOR A DRUG FORMULATION UNIT[a]

Tablet department

Capacity: 1.5 billion tablets/a = 6.25 million tablets (2.5 t)/d (2 shifts)
Average tablet weight, 350 mg

Floor area: 485 m²

Equipment

Granulation

Scales
Platform, 1 t
Platform, 300 kg
Two-pan, 10 kg
Chemical, 10 kg

Powder sifter
Comminution mill, jacketed
Comminution mill, simple

Mixers
Hobart-type, with stirrer, 500 litre
Extra bowls for above (3)
Hobart-type with stirrer, 100 litre
Extra bowls for above
Steam-operated kettle, stainless-steel, 50 litre
Steam-operated kettle, stainless-steel, 100 litre
Mortar and pestle, 5 kg and 10 kg
Cabinet dryer, thermostatically controlled, 110° C, steam-operated, 48 trays (2)
Fluid-bed dryer, 120 kg
Fluid-bed dryer, 60 kg
Extra vessels for above (3)
Drying room (50 m²), thermostatically controlled, with 6 trolleys of 48 trays

Lubrication

Powder sifter, 50 kg
Granulator (2)
Hobart mixer, 500 litre
Platform scales, 10 and 500 kg

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[a]I. A. Modi, *Project Profile for a Drug Formulation Unit*, Cadilla Laboratories, Ahmedabad, India.

Compression

Press coat, 900 series
Rota press, 45-station, 8,000 tablets/min
Rotary tablet machine, 37-station, (2) 2,500 tablets/min
Rotary tablet machine, 27-station, (2) 1,500 tablets/min
Rotary tablet machine, 16-station, (2) 500 tablets/min
Single-stroke compression machine, 90 tablets/min
Hardness tester (4)
Vernier calipers (2)
Disintegration-time unit (2)
Chemical balance
Chilsonator, 250 kg/h
Tablet-dedusting unit (4)

Coating (1.5 million tablets per day)

Coating pan, 60 in. (1.5 m)
Coating pan, 72 in. (1.83 m)
Jacketed kettles (2), 20 litre
Colloid mill
Polishing pan, with drive

Dryer

Cabinet-type, 48 trays (2)
Two-pan balance, 10 kg
Two-balance, 1 kg
Chemical balance

Capsule department

Capacity: 240 million capsules/a = 1 million (300 kg)/d (2 shifts)
Average capsule weight, 300 mg

Floor area: 255 m²

Equipment

Platform balance, 330 kg
Two-pan balance, 10 kg
One-pan balance, 1 kg
Mixer, 2 × 210 litre
Doubler conc. mixer, 100 litre
Mortar and pestle, 5 kg
Chilsonator, 40 kg/h
Dryers, specially designed (2)
Vacuum dryer, 40 trays
Automatic capsule-filling machine (2), 500 capsules/min
Extra accessories for filling other sizes
Semi-automatic capsule-filling machine, 300 capsules/min
Extra accessories for other sizes
Empty capsule loader (2)
Capsule-inspection unit with belt (1 for pencillin, 1 other)
Capsule-printing machine
Chemical balance (3)
Humidity recorder (6)
Capsule-polishing unit (1 for pencillin, 1 other)

Liquid department

Capacity: 1.8 million litres/a = 7,500 litres/d (shifts) 60-ml and 120-ml packages 94,000 units/d (2 shifts)

Floor area: 890 m²

Equipment

Scales
Platform, 500 kg
Two-pan, 10 kg
One-pan, 1 kg

Mixers
Stainless steel, with stirrer
2 × 5,000 litres
2 × 1,500 litres
2 × 500 litres
Jacketed, with stirrer
2,000 litres
1,000 litres
Hobart-type, 500 litres
Colloid mill (2)
pH meter
Viscometer
Pump, 1,500 litres/h
Filter press, 2,000 litres/h
Eight-head filling unit, 48,000 units shift
Automatic capping unit
Automatic labelling unit
Automatic carton-opening machine
Conveyor belts with checking units, 2 m × 7 m
Automatic gravity filling machine for viscous liquids such as malt
Kettle, stainless steel, 500 litres

Ointment department

Capacity: 60,000 kg/a = 250 kg/d (2 shifts)
Floor area: 200 m²

Equipment

Cleaning and sterilization
Isopropyl alcohol sterilizer for tubes
Powder sterilizer, UV, cabinet, 5 kg

Manufacturing
Scales
Platform, 200 kg
Two-pan, 10 kg
One-pan, 1 kg
Chemical (sterile and non-sterile)

Preparation

Jacketed mixing tank with stirrer, 200 kg, sterile and non-sterile

Mills

Triple roll, stainless-steel
Ball, 50 kg
Edge-runner, 25 kg
Jacketed colloid
Oven (for ophthalmic preparations), 200°C, 48 trays
Autoclave, double-door

Filling and crimping

Automatic tube-filling and crimping machine, 4,000 tubes/h
Chemical balance, one-pan

Parenteral department (including infusions)

Capacity: 300,000 litres/a = 1,250 litres/d (2 shifts)
Floor area: 305 m²

Equipment

Washing

Automatic rotary-type, high-speed washing machine for ampoules and vials
Demineralization plant, 300 litres/h
Distillation plant, 500 litres/h
Rubber-stopper washing machine, 100 kg

Sterilization

Double-door autoclave with thermo-recorder, 24,000-vials capacity
Double-door dry-heat sterilizer (2), 20,000-vials capacity
Storage tank with constant temperature for distilled water (2), 1,000 litres

Manufacturing

Scales

Platform, 100 kg
Two-pan, 10 kg
One-pan, 200 g
Stainless-steel tank, jacketed, with stirrer, (3), 200 litre
Stainless-steel tank, jacketed with stirrer, (3), 100 litre
Stainless-steel pressure vessel, 2 × 100 litre
Stainless-steel pressure vessel, 50 litre
Membrane filtering units: column type (2)
    193 mm (2)
    141 mm (2)
Vacuum pump, high-capacity
Air compressor

Filling and sealing

Automatic multihead vial-filling and rubber stoppering unit with sealing unit
Three-head ampoule-filling and sealing machine (2)
Laminar-flow unit (3)

Leak test

Vacuum-operated vessel
Inspection unit for physical checking (10)

Powder and granules section

Capacity: 60 t/a = 250 kg (12,500 bottles)/d (2 shifts)
Floor area: 165 m²

Equipment (2 each, 1 for penicillin, 1 other)
Mixer, 210 litre
Dryer, 48 trays
Automatic bottle-filling machine
Conveyor belt
Semi-automatic capping machine
Granulator

Quality-control department

Chemical analysis
Balance (3)
Melting-point apparatus (2)
Hot-air oven (3)
Vacuum oven, with pump
Distilled-water unit
Muffle furnace
Oxygen flask with platinum baskets (2)
Platinum dishes and crucibles (6)
Glassware
Water-baths, electric (3)
Gas plant
Miscellaneous

Instrument analysis
Gas chromatograph
IR spectrophotometer
UV spectrophotometer
Fluorimeter
pH meter (2)
Refractometer
Paper chromatographic equipment
Thin-layer chromatographic equipment
Air-permeability apparatus for surface area
Polarimeter
Viscometer (3)
(Redwood, Ostwals and Brookfield, 1 each)
Tablet-disintegration machines (2)
Tablet dissolution-rate machine
Tablet-hardness tester
Tablet friability-test machine

Tablet-inspection belt
Karl Fischer moisture-determination apparatus
Flame photometer
Vernier calipers (2)
Micrometers (2)
Potentiometric titration unit

Microbiological analysis

Aseptic cabinet for sterility testing
Hot-air ovens (2)
Incubators (to maintain temperature from 0°–50°C) (4)
Autoclaves (sterilizer) (2)
Microscope with camera lucida
Projection microscope
Refrigerated high-speed centrifuge machine, 20,000 rev/min
Zone reader
Refrigerators (3)
Culture counter

Pharmacological analysis

Automatic temperature-recording machine for pyrogen test
Kymograph for test for depressor substances
Galvanized cages for rabbits, cats and guinea-pigs
Polypropylene or galvanized cages for mice
Animals:
  Rabbits for pyrogens (36)
  Cats for depressor test (6)
  Mice for toxicity (200)
  Guinea-pigs for toxicity (50)

R and D department (formulation)

Floor area: 150 m^2

Equipment

Tablet-compression machine, single-stroke
Rotary tablet machine, 16-station
Mixer
Granulator
Coating pan
Oven, small size, 40°–200°C
Capsule-filling machine, 200 capsules/min
Balance, 5 kg
Chemical balance, single-pan, 200 g
Triple-roller mill, small
Colloid mill, small
Jacketed vessel and stirrer, 5 litre
Ball mill, 2 kg
Tube-filling machine, semi-automatic
Tube-crimping machine, semi-automatic
Liquid-filling machine, 1–30 ml
Capping machine for vials and bottles

Mini-bottle and vial washing machine
Autoclave, small
Ampoule-sealing machine
Incubators (3), 30°C, 45°C and 60°C
Refrigerator, small
Humidity- and temperature-control cabinet
Library books and periodicals

Packaging department

Floor area: 750 m^2

Equipment

Strip-packaging machines (6 tablets) (6)
Conveyor belts (12), 5 m
Automatic tablet counting and filling machines (2)
Automatic capsule counting and filling machine
Automatic capping machines (2)
Tin-sealing machine
Gumming machines (2)
Automatic carton openers (3)
Automatic label- and carton-printing machines (2)
Automatic printing and labelling machines for vials and ampoules (3)
Heat sealers for plastic bags (3)

Maintenance and common utility services department

Floor area: 375 m^2

Equipment

Lathe, 165 mm × 600 mm
Lathe, 300 mm × 200 mm
Drilling machine (2), 2 in.
Bench grinder, 150 mm
Flexible grinder, medium
Portable drill machines (2), 13 mm and 38 mm
Portable blower, small
Electric welding machine, 12 kVA, 3-phase, oil-cooled
Gas welding set, standard
Air compressor, 20 hp (15 kW), 3-phase, 60 ft^2/min (28 litres/sec), 150 psi (10 bar)
Vacuum pump, 10 hp (7.5 kW), 3-phase, 177 ft^2/min (84 litres/sec), ultimate vacuum 0.005 (0.7 Pa)
Gas plant, 141.5 m^3/h
Boiler, 2 t
Water-treatment plant:
  Demineralizing, 1,000 litres/h
  Softening, 10,000 litres/h
  Distilling, 500 litres/h
Air-conditioning plants (3), 80 refrigeration

Annex II

LIST OF PACKAGING MATERIALS FOR PHARMACEUTICALS

Type of formulation	*Containers*	*Closures*	*Outer packaging*	*Shipping*
Sterile antibiotics, powders in vials	USP Type III vials (20 mm), 5, 10 and 20 ml	Rubber stoppers Aluminium seals	Labels Printed carrier cartons	Corrugated boxes Gummed tape
Parenteral solutions	USP Type I vials (11 mm), 5, 10 and 20 ml	Gum-rubber stoppers Aluminium seals Aluminium dust caps	Labels Printed individual cartons Inserts Carrier cartons	Corrugated boxes Gummed tape
	USP Type I glass ampoules, amber or white flint), 1, 2, 5, 10 and 25 ml	End-sealing by jet flame	Labels Carrier trays (paper or plastic) Carrier labels Inserts	Corrugated boxes Gummed tape
Sterile transfusion solutions	Neutral glass infusion bottles or special plastic bottles, 500 ml	Rubber plugs Aluminium caps Aluminium dust caps	Labels Individual cartons (printed) with corrugated liners Dispensers Inserts	Seven-ply corrugated boxes with cushion liners Gummed tape
Elixirs, syrups and suspensions; ophthalmic or solutions etc.	White or amber bottles, 10, 25, 50, 100, 250, 500 and 1,000 ml	Bakelite or metal caps with paper wads Pilfer-proof closures	Labels Individual cartons (printed) with corrugated liners Inserts	Seven-ply corrugated boxes with cushion liners Gummed tape
	Polyethylene squeeze bottles, 10 and 20 ml (printed)	Polyethylene screw caps Dust caps	Individual printed cartons Inserts	Corrugated carrier boxes Gummed tape
	"Drop-talners" with droppers	Bakelite screw caps	Labels Individual printed cartons Inserts	Corrugated carrier boxes Gummed tape

Type of formulation	*Containers*	*Closures*	*Outer packaging*	*Shipping*
Tablets, capsules, suppositories etc.	White or amber bottles	Cork or polyethylene plugs Pilfer-proof caps with silica-gel bags	Labels Printed individual cartons Inserts	Seven-ply corrugated boxes with cushion liners Gummed tape
	Polystyrene containers with polyethylene bags	Polystyrene screw caps with silica-gel bags	Printed carrier cartons (paper or plastic)	Corrugated paper boxes Gummed tape
	Printed, laminated paper; plastic or aluminium foil laminates in rolls	Heat sealing	Catch covers (printed) Inserts Carrier cartons	Corrugated paper boxes Gummed tape
	Plastic tablet dispensers (printed)		Carrier cartons (printed) Inserts	Corrugated paper boxes Gummed tape
Ointments, creams and pastes	Printed collapsible tubes (inside lacquered aluminium or tinned steel)	Bakelite or polyethylene screw caps with wads	Individual cartons Inserts Carrier cartons Carrier labels	Corrugated boxes Gummed tape
	Glass jars (amber)	Bakelite or polyethylene screw caps with wads	Individual cartons Inserts Carrier cartons Carrier labels	Corrugated boxes Gummed tape
Powders for suspension powders, granules etc.	Amber or white bottles	Rubber wads Bakelite screw caps Pilfer-proof seals	Labels Individual cartons Inserts Printed carrier cartons	Corrugated boxes Gummed tape
	Polyethylene squeeze bottles	Plastic plugs Polyethylene screw caps	Labels Individual cartons Inserts Printed carrier cartons	Corrugated boxes Gummed tape
	Polyethylene laminated paper bags, pouches etc. (printed)	Heat sealing	Inserts Printed carrier cartons	Corrugated boxes Gummed tape
Tinctures, extracts, and infusions	Amber bottles, 500 ml	Pilfer-proof caps	Labels Cellophane wrap	Wooden boxes Signod straps
Nutritional products (foods, biscuits)	Bags made of polyethylene or other laminates	Heat sealing	Inserts Printed carrier cartons	Corrugated boxes Gummed tape

LIST OF PACKAGING MATERIALS FOR PHARMACEUTICALS
(continued)

Type of formulation	*Containers*	*Closures*	*Outer packaging*	*Shipping*
	Printed tins or printed composite containers	Metal lids Paper wads		Corrugated boxes with liners Gummed tape
	Printed waxed paper or laminated aluminium foil wraps	Adhesive wrap sealing		Corrugated boxes Gummed tape
Aerosols and sprays (pressure packs)	Printed container made of tinplated steel, extruded, seamless, aluminium, coated glass or synthetic plastics with polyethylene dip tubes	Spray valves with polyethylene actuators and pistons	Inserts Printed carrier cartons	Corrugated boxes Gummed tape

Annex III

LIST OF ANCILLARY PRODUCTS REQUIRED TO FORMULATE DRUGS

Diluents
- Lactose
- Starch
- Sucrose
- Mannitol
- Dicalcium phosphate
- Calcium sulphate
- Microcrystalline cellulose

Binders
- Gum acacia
- Gum tragacanth
- Gelatin
- Starch paste
- Sodium carboxymethylcellulose
- Methylcellulose
- Ethylcellulose
- Polyvinyl pyrolidene
- Sodium alginate

Lubricants
- Talcum powder
- Liquid paraffin
- Stearic acid
- Calcium stearate
- Magnesium stearate

Colouring agents
- Certified food and drug colours only

Flavouring agents

Capsules
- Hard gelatin
- Soft gelatin
- Seamless

Emulsifying agents
- Benzalkonium chloride
- Glyceryl monostearate
- Gum acacia

Suspending agents
- Sodium carboxymethylcellulose
- Methylcellulose
- Carbopal polyacrylic acid
- Sodium alginate
- Gum acacia
- Gum tragacanth

Preservatives
- Alcohol
- Hydroxy benzoates
- Sorbic acid

Annex IV

LIST OF EQUIPMENT FOR A MULTIPURPOSE PLANT[a]

Process equipment

	Quantity
Glass-lined reactors, 1,000 litres; jacketed, with anchor agitator, condenser and 500-litre receiver	2
Stainless-steel reactors, jacketed, with stirrer, 100-litre steel receiver (500 litres)	2
Steel distillation units, 1,000 litres, with receiver (500 litres)	3
Cast-iron reactor, jacketed, anchor-type stirrer, steel receiver (500 litres)	1
Stainless-steel 316 centrifuges, 1,000-mm diameter	2
Steel rubber-lined centrifuge, 1,000-mm diameter	1
Steam-heated dryers, 72 aluminium trays (80 cm × 80 cm × 3 cm)	2
Vacuum steam-heated tray dryers with trays as above	2
Stainless-steel crystallizers with jacket and anchor-type stirrer, 5,000 litres	3
Pressure leaf-filter, stainless-steel	1

Services equipment

Water-ring pump, 80 m^3/h	1
Air compressors with receiver, 30 ft^3/min (14 litres/sec) 30 psi (2 bar), with receiver	2
Steam-generating plant, 600 kg/h with water softener and accessories	1
Refrigeration plant for chilled water, 20 refrigeration tonnes with cooling tower	1
Water-circulation pumps	6
Demineralized water plant	
Electrical distribution panel, with circuit breakers	

Laboratory equipment

Balances	2	pH meter	1
Vacuum pump	1	Glassware (1 set)	
Muffle furnace	1	Miscellaneous instruments	
Electric oven	1		

[a]Multipurpose basic pharmaceutical plant project proposal, Sarabhai International, Baroda, India.

Annex V

RAW MATERIALS REQUIRED FOR THE MANUFACTURE OF ANTIBIOTICS

Carbohydrates
- Starch
- Dextrin
- Dextrose
- Cane sugar

Protein sources
- Soya flour
- Corn-steep liquor (50%)
- Ground-nut meal

Salts
- Ammonium sulphate
- Sodium sulphate
- Ammonium chloride
- Manganese suphate
- Zinc sulphate
- Sodium biphosphate
- Sodium chloride
- Potassium acetate
- Potassium dihydrophosphate

Acids
- Sulphuric
- Nitric
- Hydrochloric
- Oxalic
- Ethylenediaminetetraacetic

Alkalis
- Calcium carbonate
- Sodium hydroxide
- Potassium hydroxide
- Calcium oxide

Gases
- Ammonia
- Chlorine
- Nitrogen
- Carbon dioxide

Solvents
- Butanol
- Butyl acetate
- Methanol
- Isopropanol
- Octanol

Quaternary ammonium compounds

Filter aid
- Dicalite/Hyflosupercel

Decolourizing agent
- Active carbon

Resins (replenishment)

Antifoamers
- Wax emulsion
- Vegetable oils

Miscellaneous
- Formaldehyde (30%)
- Potassium phenylacetate
- Phenylacetamide and phenylacetic acid

Annex VI

RAW MATERIALS REQUIRED FOR THE MANUFACTURE OF DRUGS

Raw materials	*Drug or intermediate for which it is used*
Acetanilid	Sulpha drugs
Acetaldehyde	Sulpha drugs
	Indomethacin
Acetic acid	Phenacetin
	Chloroquin
	Sulpha drugs
Acetic anhydride	Chloramphenicol
	Sulfacetamide
	Paracetamol
	Acetazolamide
	Thiacetazone
	Acetylsalicylic acid
	Vitamin B_1
	Phenacetin
Acetoacetic ester	Amidopyrine
	Noramidopyrine methanesulfonate
	4-Diethylamino-1-methylbutylamine
Acetonitrile	Sulpha drugs
Acetone	Vitamins A, B and C
	Ephedrine
	Amodiaquin
Acetophenone	*p*-Nitroacetophenone
Acetone semicarbazone	Nitrofurazone
Acetoin	Sulphamethoxazole
Acetylacetone	Sulfamethoxazole
Acetylaminophenol (paracetamol)	Amodiaquin
Acetyl chloride	Vitamin A
Activated carbon	All
Acrolein	Folic acid
Acrylonitrile	Vitamin B_{12}, sulpha drugs
Adipic acid	Iodipamide
Alcohol (absolute)	All
Aluminium metal	Chloramphenicol
Allyl bromide	Secobarbital
Aluminium chloride (anhydrous)	Chloramphenicol
	Prenylamine
Amino chlorobenzophenone	Chlordiazepoxide
	Diazepam
D-2-Aminobutanol	Ethambutol
4-Amino-2,6-dimethylpyrimidine	Sulfisomidine
Aminohydantoin sulphate	Nitrofurantoin

Raw materials	*Drug or intermediate for which it is used*
o-Aminophenol	Di-iodohydroxyquinoline
m-Aminophenol	*p*-Aminosalicylic acid (PAS) and esters
	Paracetamol
	Diloxanide
2-Aminopyridine	Mepyramine
2-Aminopyrimidine	Sulphadiazine
	Sulphadimidine
2-Aminothiazole	Sulphathiazole derivatives
Ammonium thiocyanate	Acetazolamide
	Thiacetazone
	Vitamin B_1
Ammonia gas	All
Ammonium sulphate	Antibiotics
Alanine	Vitamin B_6
Aniline	Acetanilid
p-Anisidine	Indomethacin
Anthranilic acid	Methaqualone
Anisaldehyde	Mepyramine
Beet molasses	Vitamin B_{12}
Benzene	Vitamins
	Analgesics
	Sulpha drugs
	Thiacetazone
Benzaldehyde	Chloramphenicol
	Noramidopyrine methanesulfonate
Benzoic acid and salts	Diazepam
	Chlordiazepoxide
Bromine	Chloramphenicol
	Diphenhydramine
Benzyl chloride	Chloramphenicol
	Bephenium hydroxynaphthoate
	Benzyl cyanide
	Phenobarbitone
Benzyl cyanide	Pethidine
	Phenobarbitone
	Phenylacetic acid
	Phenformin
2-Benzylpyridine	Pheniramine maleate
Boric acid	Anti-dysentery drugs
2-Bromopentane	Barbiturates
Butyl acetate	Penicillin
n-Butyl alcohol	Penicillin
	Tetracyclines
	Vitamins B_1 and B_2
t-Butyl alcohol	Hydrochlorothiazide
n-Butylamine	Tolbutamide, methyldopa
2-Butene-1,4-diol	Vitamin B_6
Diethyl butylmalonate	Phenylbutazone
Butyl oxide	Ephedrine
n-Butyl bromide	Phenylbutazone, oxyphenbutazone

Raw materials	*Drug or intermediate for which it is used*
Calcium cyanamide	Sulfamethoxazole
Calcium oxide	Antibiotics
Calcium carbonate	Antibiotics
Carbon disulfide	Tolbutamide
m-Chloraniline	Amodiaquin
	Chloroquin
	Hydrochlorothiazide
Chloral hydrate	Diloxanide
Chloracetyl chloride	Lidocaine hydrochloride
p-Chlorobenzoic acid	Analgesics
	Indomethacin
p-Chlorobenzene sulphonamide	Chlorpropamide
2-Chloroethanol	Metronidazole
1-Chloro-2-diamethylaminoethane	Chlorpheniramine maleate
Chlorofluoroethane	Acetylaminophenol (paracetamol)
	Diaminodiphenylsulphone
	Halothane
2-Chlorophenothiazine	Chlorpromazine
p-Chlorophenol	Clofibrate
2-Chloropropyl-dimethylamine hydrochloride	Chlorpromazine
Chlorosulphonic acid	Sulpha drugs, diaminodiphenylsulphone hydrochlorothiazide
	Furosemide
	Chlorpropamide
5-Chloro-2,4-disulphonamidoaniline	Chlorothiazide
Cholesterol	Ethisterone
	Spiranolactone
Citric acid	Tetracyclines
	Citrates
Cinnamaldehyde	Prenylamine lactate
Cobalt nitrate	Vitamin B_{12}
Corn-steep liquor	Antibiotics
Copper powder	Chlorpromazine
Cotton-seed flour	Amphotericin B
	Tetracyclines
Cyanoacetic acid	Theophylline
Cyanoacetic ester	Folic acid
	Sulphadimethoxazine
Cyanoacetamide	Ethionamide
Defoamers	Antibiotics
7-Dihydrocholestrol	Vitamin D
Dibutyl ether	Ephedrine
2,4-Dichlorobenzoic acid	Furosemide
Dichloromethyl acetate	Chloramphenicol
4,7-Dichloroquinoline	Amodiaquin
2,5-Dichloronitrobenzene	Chlorpromazine
Dicyandiamide	Sulphaguanidine
	Sulphadimidine
	Phenobarbitone
	Phenformin

Raw materials	*Drug or intermediate for which it is used*
Diethylamine	Diethylcarbamazine
	Lidocaine hydrochloride
	Amodiaquin
	Nikethamide
	Diethylaminoethanol
Diethanolamine	Pethidine
2-Diethylaminoethanol	Procaine hydrochloride
	4-Diethylamino-1-methylbutylamine
4-Diethylamino-1-methylbutylamine	Chloroquine
Diethyl carbonate	Furazolidone
Diethylethoxymethylene ester	Chloroquine
	Amodiaquin
Diethyl malonate	Phenylbutazone
	Diethylethoxymethylene malonic ester
	Vitamin B_2
Diethylmethylamine	Pethidine, ethionamide
Diethyl oxalate	Phenobarbitone
	Vitamin B_2
	Ethionamide
Dimethylamine	Chloramphenicol
	Bephenium hydroxynapthoate
3,4-Dimethylaniline	Anthistamines
2,6-Dimethylaniline	Antihistamines
	Sulphadimethoxazine
Dimethylaminochloroethane hydrochloride	Mepyramine
Dimethyl formamide	Antibiotrics
	Steroids
1-Dimethylamino-2-chloropropane hydrochloride	Promethazine and salts
Dimethyl sulphate	Vitamin B_1
	Noramidopyrine methanesulfonate
	Aminopyrine
	Diloxanide
Dimethyl sulphoxide	Vitamin A
	Diloxanide
Dinitrobenzal chloride	Vitamin D
Diphenyl oxide	Chloroquin
	Amodiaquin
Diphenylamine	
Diosgenin	Steroids
Ergosterol	Vitamin D
Epichlorhydrin	Xanthinol nicotinate
Ether	Vitamins and analgesics
2-Ethoxyethanol	Tetracyclines
Ethyl acetate	Vitamins
Ethyl bromide	Phenobarbitone
	Vitamin A
	Ethambutol
Ethylene dichloride	Chloramphenicol
	Isoniazid (INH)

Raw materials	*Drug or intermediate for which it is used*
Ethylene dichloride *(continued)*	Diethylcarbamazine
	Bephenium hydroxynaphthoate
	Chloroquin
	Amodiaquin
Ethylene diamine	Ethylene diamine tetraacetic acid (EDTA)
	Caffeine and thiophylline
Ethylene diamine tetraacetic acid (EDTA)	Antibiotics
2-Ethylhexanol	Antibiotics
Ethyl orthoformate	Diethylethoxymethylene malonate
Ethyl chloroformate	Vitamin B_6
Ethylene oxide	Chloroamphenicol
	4-Diethylamino-1-methylbutylamine
	Furazolidone
	Vitamin B_1
Ethylene chlorohydroin	Diethylaminoethanol
Ethyl palmitate	Vitamin A
Ethylisopropyl malonate	Amylobarbitone
Ethylmethyl ketone	Ethionamide
	Vitamins
Filter aids	All
Formamide	Hydrochlorothiazide and other chlorothiazides
Formaldehyde (30%)	Streptomycin
	Chloramphenicol
	Amodiaquin
	Tetracycline
	Isoniazid
Formic acid	*p*-Aminosalicylic acid and esters
	Diethylcarbamazine
	Vitamin B_1
	Hydrochlorothiazide
Fumaronitrile	Vitamin B_6
Furfurylamine	Furosemide
Gelatin	Vitamin A
	Gelatin capsules
Glucose (dextrose)	Vitamin C
	Calcium gluconate
	Antibiotics
L-Glutamic acid hydrochloride	Folic acid
Guanidine nitrate	Folic acid
Guanidine carbonate	Sulpha drugs
Hexamethylene tetramine	Chloramphenicol
Hydrazine hydrate	Isoniazid
	Thiacetazone
	Nitrofurantoin
Hydrazine sulphate	Acetazolamide and others
Hydrobromic acid	Methyldopa

Raw materials	*Drug or intermediate for which it is used*
Hydrogen peroxide (30%)	Tolbutamide
Hydroxyethylhydrazine	Furazolidone
p-Hydroxynapthoic acid	Bephenium hydroxynaphthoate
3-Hydroxymethylpyridazine	Pyrazinamide
Hydroxylamine hydrochloride	Hydroxy urea
	Sulfadimethazine
8-Hydroxyquinoline	Halogenated oxyquinolines
Hydroquinone	Vitamin A
Hexane	Soya-flour vitamins
Iodine	Iodochloro- and dichlorohydroxyquinoline
Isoamyl formate	Imipramine
Isopropyl alcohol	Chloramphenicol, tetracyclines
Isopropyl ether	Vitamins
Isophytol	Vitamin E
Ketoacetal	Vitamin A
Lard oil	Antibiotics
Lithium metal	Vitamin A
Lactic acid	Calcium lactate
	Calcium sodium lactate
Levulinic acid	Indomethacin
Maleic acid	Pheniramine maleate
	Chlorpheniramine maleate
Magnesium metal	Vitamin A
Malonic ester	Riboflavin
	Amylobarbitone and other barbiturates
Methoxypyridoxin	Vitamin B_6
Methyl alcohol	Streptomycin
	Chloramphenicol
	Vitamin A
	Vitamin C
	Ephedrine
	Pethidine
	Vitamin D
	Chloroquine
Methylamine (40%)	Ephedrine
	Caffeine
	Thiophylline
n-Methylalanine	Vitamin A
Methylbenzene sulphonate	Amidopyrin
	Noramidopyrine methanesulfonate
2-Methylimidazole	Metronidazole
Methyldichloroacetate	Chloramphenicol
	Vitamin A
Methyl acrolein	Sulphamerazine
Methylaminophenol	*p*-Aminosalicylic acid and esters
b-Methylaminoethanol	Xanthinol nicotinate
Methylene chloride	Vitamin A

Raw materials	*Drug or intermediate for which it is used*
Methylethylpyridine	Vitamin A
Methyl formate	Chloramphenicol
Methylisobutyl ketone	Tetracycline
	p-Aminosalicylic acid and esters
	Tolbutamide
	Chlorpropamide
Methylaminochloroacetate	Vitamin A
Methylcyanoacetate	Sulphadimethoxazine
Methylene dichloride	Antibiotics
Methylethyl ketone	Vitamins
	Ethionamide
b-Methylnapthalene	Vitamin K
2-Methyl-1, 3-propanediol	Meprobamate
Monochlorobenzene	Chloramphenicol
Monochloracetic acid	Analgesics
	Vasodilators
	Xylocaine
Monoethanolamine	Piperazine salts
Nickel catalyst	Vitamin C
	4-Diethylamino-1-methylbutylamine
Nickel alloy (Raney nickel)	Several synthetic drugs
p-Nitroacetophenone	Chloramphenicol
Nitrobenzene	Phenyl butazone
p-Nitrobenzoyl chloride	Folic acid
5-Nitrofurfuryl diacetate	Furazolidone
	Nitrofurazone
Nitromethane	Antihypertensives
Nitroethane	Methyldopa
Nitropropane	Methyldopa
Nitrogen gas	Methyldopa
o-Nitrophenol	Iodochloro- and Diiodohydroxyquinoline
p-Nitrotoluene	Thiacetazone
	Procain hydrochloride
	Imipramine
p-Nitrobenzoic acid	Procaine hydrochloride
m-Nitrobenzoic acid	Iodipamide
Novaldiamine	Chloroquin phosphate
1-Octanol	Vitamin B_{12}
Oxalic acid	Vitamin B_2
	Diethyl oxalate
	Tetracyclines
Oil (maize, peanut or soya)	Antibiotics
Palladinized charcoal	Vitamin A
Palladium chloride	Chloramphenicol
Palmitoyl chloride	Vitamin A
Pancrea[illegible] (animal gland)	Insulin
Paraformaldehyde	Vitamins
Phenol	Acetylaminophenol (paracetamol)
	Salicyclic acid

Raw materials	*Drug or intermediate for which it is used*
	Iodochloro- and Diiodohydroxyquinoline
	Bephenium hydroxynaphthoate
	Chloroquin
Phenothiazine	Promethiazine and salts
Phenoxyacetic acid	Penicillin V
Phenylacetylcarbinol	Ephedrine
Phenylacetamide	Penicillin
o-Phenylenediamine	Thiabendazole
Phenylacetic acid and its potassium salt	Penicillin
a-Phenylglycine	Ampicillin
b-Phenylethylamine	Phenformin
	Diethylcarbamazine
Phosgene	Phenobarbitone
Phosphoric acid	Antimalarials
Phosphorus oxychloride	Chloroquin
Phosphorus pentasulphide	Vitamin B_1
Phosphorus pentoxide	Nikethamide
	Ethionamide
Phosphorus trichloride	Methaquolone hydrochloride
Phosphorus pentachloride	Ethionamide
Phytyl bromide	Vitamin E
Phenyl acetone	Phenylamine
Phenylhydrazine	Sulpha drugs
b-Picoline	Nicotinic acid
	Nicotinamide
	Nikethamide
Piperazine hexahydrate	Diethylcarbamazine
	Piperazine salts
Piperidine	Ethionamide
Potassium acetate	Antibiotics
	Ethionamide
Potassium borohydride	Vitamin A
	Chloramphenicol
Potassium hydroxide	Antibiotics
	Vitamin B_2
	Synthetics
Potassium carbonate	*p*-Aminosalicylic acid and esters
	Penicillin
Potassium dihydrogen phosphate	Antibiotics
Potassium permanganate	Pyrazinamide
	Nicotinic acid
Potassium cyanate	Tolbutamide
	Chlorpropamide
Potassium cyanide	Vitamin B_{12}
Potassium thiocyanate	Tolbutamide
	Chlorpropamide
Potassium ferricyanide	Antibiotics
Procaine hydrochloride	Penicillin
Propargyl bromide	Vitamin A
n-Propylamine	Chlorpropamide
	Probencid

Raw materials	*Drug or intermediate for which it is used*
Pyridine	Sulpha drugs
Pyrazine monocarboxylic acid	Pyrazinamide
Quaternary ammonium compounds	Penicillin and other antibiotics
Quaternary ammonium compounds	Tetracyclines
Quinoline	Hydroxyquinolines
Resins	Streptomycin and other antibiotics
Salicylic acid	Acetylsalicylic acid
	Sodium salicylate
Silicones	Antibiotics
Sodamide	Pethidine
Sodium borohydride	Vitamins
Sodium benzoate	Vitamin A
Sodium bromide	Analgesics
Sodium citrate	Antibiotics
Sodium acetate	Chloramphenicol
Sodium cyanide	Phenobarbitone
	Vitamin B_{12}
	Phenylbutazone
	Diloxanide
Sodium diethyldithiocarbamate	Vitamin A
Sodium ferrocyanide	Tetracycline
Sodium hydrosulphite	Antibiotics
Sodium metal	Metamizol
	Folic acid
	Phenobarbitone
	Vitamin B_1
	4-Diethylamino-1-methylbutylamine
	Aminopyrine
Sodium methoxide	Vitamin A
	Phenylbutazone
	Sulpha drugs
	Analgesics
Sodium sulphide	Analgesics
Sodium metabisulphite	Vitamins
Sorbitol	Vitamin C
Sodium hydroxide	All
Sodium carbonate	All
Sodium nitrate	Vitamin B_{12}
	Folic acid
Sodium nitrite	Chloramphenicol
	Phenacetin
	Noramidopyrine methanesulfonate
Sodium phosphate	Antibiotics
Soya flour	Antibiotics
Sulphuric acid	All
Stearyl alcohol	Vitamin C
Stannic chloride	Analgesics
Sulphur	Anti-TB drugs

Raw materials	*Drug or intermediate for which it is used*
Tartaric acid	Chloramphenicol, sulpha drugs
Thiosemicarbazide	Anti-TB drugs
Toluene	Analgesics
o-Toluidine	Methaquolone
Trichloroethylene	Chloramphenicol
	Emetine
	Bephenium hydroxynapthoate
	Phenylbutazone
p-Toluenesulphonamide	Tolbutamide
Trimethylquinol	Vitamin E
Thionyl chloride	Procaine hydrochloride
	Pethidine
	Hydrochlorthiazide
	4-Diethylamino-1-methylbutylamine
Thiazole-4-carboximide	Thiobendazole
Triethylamine	Tetracycline
	Vitamin B
L-Tyrosine	Anti-convulsants (L-dopa)
Urea	Chloramphenicol
	Vitamin B_2
Urethane	Meprobamate
Vanillin	Methyldopa
	Anti-hypertensives
Wax emulsion	Antibiotics
o-Xylene	Chloramphenicol
	Vitamin B_2
	Phenylbutazone
m-Xylidine	Xylocaine
Zinc dust	Phenylbutazone
	Chloramphenicol
Zinc chloride	Vitamins

Provision of drugs by appropriate technology

*P. Dunnill**

INTRODUCTION

History suggests that sanitation and vaccination should be given the highest priority in achieving good health for the greatest number of people at the lowest cost. However, there are situations where only the use of drugs can be effective. The problem is that, in contrast to other factors influencing good health, such as food, water, shelter and drainage, which can generally be provided by local, simple and small-scale operations, given the vital input of proper information, many key pharmaceuticals are the products of intrinsically complex processes. Therefore, finding ways by which communities other than fully developed ones can be better provided for is particularly difficult.

With no other products are technical decisions so influenced by powerful commercial, ethical and social pressures as with drugs. For this reason a brief analysis is given of the ways in which government policies influence the provision of drugs, particularly to poor rural communities.

Technical factors shaping policy

For the present purpose drugs may be divided into two classes: *(a)* the traditional local remedies, many of which are complex mixtures of plant origin; *(b)* the modern drugs, which are mostly well-defined chemicals derived from the petrochemical or fermentation industries. A few traditional materials have, in refined forms become important drugs in all countries; examples are quinine, caffeine and ergot. Some of the remaining traditional remedies are comparable to modern cough and indigestion mixtures in that they give comfort but are not life saving. Greater claims are made for others, but their effects, which may depend on the method of administration, are unproven. Without discounting the eventual emergence of further key drugs from traditional local remedies, present needs can only be met with the aid of a small number of modern drugs. The desire to utilize local resources at times seems to be so great that it is put before sound medicine.

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The problem of providing modern drugs to a local community, often an isolated rural one in a developing country, can be considered in three parts:

(a) Provision of chemicals from which the drugs are compounded at the lowest possible cost;

(b) Compounding of the drug as a tablet, capsule, injectable etc. from the chemicals at the lowest possible cost;

(c) The provision of the drug to an individual patient with the maximum regard to local circumstances.

Production of basic chemicals, fermentation and compounding

Few developing countries have the ability to produce the range of basic chemicals needed for their key drug requirements. Some, like India, are approaching this capability. The best that many others can expect in the next decade is the ability to manufacture selected basic chemicals from local raw materials. Coal and oil are obviously being used in this way, but the production of solvents by fermentation in countries rich in sugar and starch resources is also important; it saves foreign currency even if it is not strictly economic.

Where imports are essential, it is evident that only by being better technically and economically informed about world chemical supplies and by exerting a greater degree of central government control will developing countries obtain imported chemicals at the lowest possible cost.

All countries will progress from the straight purchase of the chemicals which constitute the active ingredients of drugs to the purchase of simpler and cheaper chemicals from which the ingredients can be made. Their sources of information are the local subsidiaries of foreign companies, international agencies such as UNIDO and independent consultants. Organizations like Indian Drugs and Pharmaceuticals Ltd. (IDPL) and ITDG have a role in providing information about the use of local raw materials and small-scale production of basic chemicals.

Making basic chemicals is not simple. Many countries that have made considerable progress in the production of basic chemicals, for example Egypt, have nonetheless experienced difficulties in preparing them in the exceptional quality needed for pharmaceuticals. Quality control of the chemical steps by which the active ingredients of a drug are prepared is crucial, and the requirement for expensive analytical equipment cannot be avoided.

On the other hand, drugs produced by fermentation, expecially the antibiotics, are at first sight attractive for local production in developing countries since the principal starting material may be any number of low-cost carbohydrates such as molasses or corn-steep liquor. However, even here the quality must often be raised. Much greater problems are presented by the sophistication of the production process and by the need to obtain special strains of micro-organisms which produce high product yields. Government involvement may be essential in negotiating for these strains or initiating strain selection in local research institutes and in being prepared to underwrite an unprofitable phase of production. Independent organizations and individuals

can help by collecting basic process design information which will aid countries either in setting up their own plants or, more likely, in negotiating from a position of greater knowledge for foreign plants and know-how.

Given that a government can restrict advertising and promotion so that such overheads are eliminated, it seems quite possible that antibiotic production could be profitable on a smaller scale than is now practised in developed countries. However, the technology cannot be simplified beyond a certain level, and regional rather than local production seems appropriate.

If antibiotic fermentation is technically too advanced, a carbohydrate-rich country could begin by producing food yeast with technology closely allied to that of brewing to provide B vitamins. However, one ambitious programme to combat vitamin deficiency by this means failed on the grounds of consumer resistance to a product of low appeal. Nevertheless, a modest local programme closely linked with health clinics where a yeast product would be given with conviction and authority could be better accepted.

The compounding of drugs in appropriate forms is a field where much more radical change could occur. This step is generally done in large factories in the commercial companies of developed countries, where even small local companies could commonly process one million tablets a year. However there is ample evidence that factory-scale operation is not essential. Hospital preparation of drugs is still practised in a surprisingly large number of institutions. For example, in the United States of America in the late 1960s, 41 per cent of hospitals surveyed operated "manufacturing programmes". Though drug compounding in the local pharmacy has lost its place in many developed countries, the procedures for sound practice are recorded in the literature, and the approach is still used in developing countries with respect to simple remedies.

There appear to be no insuperable technical reasons why the hand compounding or very small machine compounding of drugs should not be the means of reducing costs and shifting the centre of gravity of manufacturing towards the local community. Quality control at this level would entail maintenance of clean mechanical handling equipment in regulated conditions with regular checking of chemical quality by a regional regulatory laboratory.

Quality control is clearly a sensitive issue, one on which physicians, conventionally trained pharmacists and industrial producers have strong views, and it is an area where government involvement is essential. International agencies can also play a role if they adopt a strictly practical approach. Inter-governmental co-operation may also reduce costs, but this development demands particularly close and harmonious relations.

The pharmaceutical auxiliary

The third requirement in providing drugs is a suitable method of transfer to the patient. It is increasingly accepted that rural communities most at risk will not have access to fully trained physicians in the foreseeable future, and that local people must be trained as medical auxiliaries to diagnose the more obvious local diseases, referring only intractable cases to regional hospitals. It therefore seems sensible to consider making the compounding of drugs from bulk

ingredients the responsibility of local people. The intention would be to train them locally to avoid the inevitable tendency of people trained in urban centres to gravitate back to them.

Pharmaceutical auxiliaries will need training and operation manuals in local languages and guidance on small-scale equipment, some of it hand-operated, including tablet punches and counters, blenders, mixers and dryers. At present, neither suitable manuals nor consumer guides specifically concerned with equipment are available.

The training of pharmaceutical auxiliaries to compound, package, label and prescribe a very limited number of drugs appears to be the only means of bringing modern life-saving drugs to rural communities. Even in India, which has over 2,000 drug manufacturing companies, with less than half the market foreign controlled, the population cannot be effectively served by conventional means. The country requires its larger firms to provide to small companies, for formulation, a proportion of drug ingredients which they manufacture. By analogy, governments can elect to ensure supply of even smaller quantities of material to rural centres for manual or very small-scale mechanical manufacture.

The provision of drugs at a rural level seems less likely to compete with powerful commercial interests than is the case in urban areas, since the rural market is commercially less attractive. It is fragmented, and its inhabitants are unable to afford drugs in the normal way. From experience of missionary and similar hospitals, patients do not show resistance to non-brand-name drugs, a common problem in commercial pharmacies.

Other technologies needed for drug production

The adequate handling of drugs by rural centres requires a number of other appropriate technologies. The assumption that chemical and biological quality is maintained after dispatch of ingredients from a central store depends not only on good stock recycling but also on adequate, low-cost, cool or cold storage. Adequate packaging of drugs is of great importance, especially in tropical conditions. Organizations in developing countries often find, for example, that a lack of suitable local glass bottles restricts preparation of even simple formulations. While strip packaging of individual tablets or capsules is expensive, the preparation of sachets of tablets by hand-sealing plastic sheets is already used, and refinement of this method to make it more reliable and convenient would be valuable. Since misuse is a major problem, ITDG and others have operated pilot schemes examining the use of pictorial labels to aid the correct self-administration of drugs.

Current objectives on drug provision

Having concluded that small-scale compounding could make a contribution and that pharmaceutical auxiliaries could provide a means of delivery, ITDG is seeking to assist such developments. The Ministry of Overseas Development of the United Kingdom has recently funded a project to survey small-scale

pharmaceutical equipment together with a survey of the litarature on how such equipment is or has been used. ITDG is also exploring with the Appropriate Health Resources and Technologies Action Group (AHRTAG) the issues involved in training pharmaceutical auxiliaries.

It is hoped that the resulting catalogue of equipment and bibliography of uses will be of wide interest, but ITDG is particularly concerned to see a specific practical outcome. It is therefore interested in collaborating with individual governments or local organizations who are prepared to establish pilot projects. With such pilot projects many of the problems of supply of bulk materials to the rural centre can be circumvented by special measures so that the central issue of local compounding can be tested. The total investment in such pilot studies will be very small, so that modifications after initial experience should not be as great a problem as it could be with major capital investments.

Government actions influencing the provision of drugs

This section deals only with those aspects of government policy which relate directly to the local compounding of drugs from constituents imported in bulk and with the employment of rural pharmaceutical auxiliaries.

The objective of government policy in this case will be to obtain bulk materials at the lowest cost possible and to transfer them in smaller unit amounts to rural centres with minimal loss of drug activity. These centres will provide guidance on compounding, some equipment and regulatory checks on the use of material supplied. The bulk purchase of drugs by non-profit agencies, governments and even groups of governments is becoming well established. Similar approaches are applied to raw drug components and containers.

The efficient importation of bulk drug components is crucial. Delays in customs clearance and transit will lead to deterioration much more rapidly than for many other commodities. Special warehousing and careful stock recycling are imperative and a central facility for re-packaging into smaller units is required. The technology required is conventional but the organizational problems can be formidable.

Delivery to rural areas is often difficult and the work initiated by ITDG/AHRTAG and others, which is supported by the World Health Organization (WHO), on vaccine transportation is relevant. It is hoped that current projects of ITDG on small-scale equipment and ITDG with ARHTAG on pharmaceutical auxiliaries will help to provide a basis for advice to local rural health centres. Close co-operation with governments will be essential to ensure that this information is made available in a useful form and in the local language.

These are some of the social, political and economic factors influencing the provision of basic drugs:

(a) Need to co-ordinate national chemical or drug buying to obtain favourable bulk purchase terms;

(b) Desirability of persuading companies to produce and package basic but low-profit drugs while allowing them to manufacture some trivial but high-profit drugs and cosmetics;

(c) Need to rely heavily on foreign company technical expertise while seeking to change the balance of drug production and packaging;

(d) Shortage of servicing facilities for equipment and analytical instruments used in drug production and compounding;

(e) Migration of entrepreneurs and skilled persons away from rural areas;

(f) Need to persuade doctors to prescribe from limited lists mostly of generic drugs;

(g) Resistance of conventionally trained doctors and pharmacists and of local folk doctors to the introduction of rural health auxiliaries;

(h) Existence of powerful fashions in medicines, for example, the use of multivitamins;

(i) Lack of experience in the use of potent synthetic drugs by rural communities and problems of prescribing to largely illiterate communities;

(j) Tendency of universities and medical and pharmacy schools to reinforce conventional approaches;

(k) Conflict of interest of middle-class urban patients and poor rural ones in terms of drug imports, packaging and health care.

TECHNOLOGY APPROPRIATE TO DIFFERENT TYPES OF COUNTRIES

Common features in many developing countries are their limited supply of capital for investment and their under-employed population. Both suggest that small, local and labour-intensive organizations are more appropriate than very large, capital-intensive and highly automated ones. However, the manufacture of pharmaceuticals provides a very severe test of this viewpoint.

Many of the most useful drugs, such as the antibiotics are complex chemicals produced by methods requiring very precise control. They are potent in action, may have to be taken by injection, and their quality control requires a degree of sophistication which is not easily attained. Stocks of pharmaceuticals must be available for rapid prescription, and medication may have to continue for extended periods. The product must also remain in an essentially unchanged state for a relatively long time after production.

Governments may accept locally produced hospital buildings of rather limited quality rather than have none for their communities; they may even accept, for the treatment of illness, the use of rather crude local remedies which have been long established. However, they are not likely to accept modern pharmaceuticals of a quality lower than those known to be produced in the most advanced facilities.

On occasions, even high-technology pharmaceuticals have been withdrawn because they were perceived to be inferior. One developing country banned the use of an imported vaccine against a common disease which was frequently fatal there. In the country of production, the vaccine had been withdrawn because it very occasionally caused encephalitis, and the disease against which it was used was mild. A government will naturally feel that what is not good enough for a so-called developed country is not good enough for its own community.

Concerning the degree of under-employment in developing countries, it is necessary to ask first whether an abundance of labour is of value in the

controlled production of complex substances such as pharmaceuticals. The answer is that it probably is not. A. E. Humphrey of the University of Pennsylvania has encouraged the development of fermentors even more highly instrumented than those used in current antibiotics production because, in his experience, the employment of operators of limited training or motivation to measure and control important parameters leads to serious errors. These errors tend to grow with the number of personnel responsible for control. Taken in isolation, this consideration argues for large, centralized production facilities with highly trained staff and fairly sophisticated instrumentation. Most of the pharmaceuticals manufactured in developing countries are indeed produced in this way by foreign-owned companies. The past record suggests that this approach has not provided adequate amounts of pharmaceuticals for those sectors of the community most in need.

The options open for the manufacture of raw materials and pharmaceuticals, and their packaging, storage and quality control depend on the general level of industrialization. It is estimated that three quarters of the total drug manufacturing operations in developing countries takes place in 12 countries; the vast majority of others have either few or no drug manufacturing facilities.

Manufacture of pharmaceutical raw materials

The precursors of many modern drugs are fine chemicals which are converted in pharmaceutical processing into tablets, capsules, injectables and other preparations suitable for administration in therapy. The variety of fine chemicals required is large, and their quality must be as high as that of the preparations into which they are to be formulated. In these circumstances, few developing countries will be in a position to manufacture the necessary range of fine chemicals.

The production of drugs directly from local natural products has been the subject of considerable interest in both the developing and developed countries. UNIDO has, as one of its pharmaceutical programmes, the utilization of extracts from medicinal plants and of slaughterhouse wastes as raw materials for pharmaceuticals.

The production of drugs from local natural products is also one of the most difficult aspects of pharmaceuticals supply to assess. Aside from the few well-known natural drugs and precursors that have been examined in detail in developed countries, there is a vast number of natural materials for which healing properties are claimed but on which little controlled study has been done. The extraordinary range of curative properties claimed for some materials might seem unrealistic in the light of accepted practice in developed countries, but it must be admitted that the natural materials are complex mixtures unlike most modern drugs. Increased production of those natural drugs and precursors of defined value and their complete processing in the country of origin is certainly to be encouraged. This would avoid loss of foreign exchange in repurchasing the final, more expensive product from a foreign manufacturing country. It may even provide a source of high-value pharmaceutical exports.

The controlled testing of the curative properties of local traditional drugs is perhaps desirable in view of their widely established use. However, the task

involves great expense. It also seems likely that the chances for the successful production of new drugs with definite curative value will be small. The advanced pharmaceutical companies of the world do not lightly dismiss promising sources of important new drugs. While the complexity and variability of the natural materials could account for some failure to recognize important materials, this only further emphasizes the difficulty and expense in assessing their potential. It would, however, be hypocritical to suggest that people of other countries should abandon the use of natural materials of "unproven" value in view of the equivalent use, for example, of digestive aids in developed countries.

It would be useful to have local assessments of those natural materials which, though not as accepted as caffeine, ergot, quinine or senna, do seem to have fairly definite benefits. (At present there appears to be a tendency to produce large lists of natural materials with no classification of the confidence in their efficacy.)

The need for assessments is illustrated by the position in India. In 1970/71, India exported drugs valued at Rs 48 million ($5,720,000 at 1975 exchange rates). To this export, psyllium- and senna-based products alone contributed Rs 33 million ($3,960,000). In the same year, crude drugs, alkaloids and other derivatives from vegetables worth Rs 14 million ($1,661,000) were imported. This indicates the extent to which imports might be substituted. Surveying the prospects for medicinal plants, Kempanna cites the rejuvenation of cinchona plantations (for quinine) through improved planting systems, better management practices and optimizing extraction techniques, as the kind of approach that is applicable to sources of drugs of proven value [1]. He notes that, of 200 tonnes of caffeine available from 8,000 tonnes of tea wastes per annum, only 80 tonnes are produced. Huge quantities of tea waste are apparently disposed of by burning. The demand for diosgenin as a precursor of steroid hormones has led to the finding of several *Dioscorea* species rich in this material.

The annual turnover in pharmaceuticals in India was Rs 2,000 million ($237.6 million) in 1972, but only 1.6 per cent of this was spent on research. About 98 per cent of research expenditure went for chemistry and the clinical aspects of pharmaceuticals; the remainder was spent on studies of the cultivation of suitable plants. However, a co-ordinated national programme has since begun to isolate improved plants and preserve collections as forests and jungles disappear. Kempanna concludes by arguing the need for careful planning to integrate the cultivation of medicinal plants with food crops, better marketing to eliminate speculation and better quality control [1]. Agricultural polytechnics (the proposed Krishi Vigyan Kendras) represent local agencies for spreading the necessary technical knowledge.

The preparation of vaccines and the production of antibiotics from micro-organisms by fermentation can be considered as the biological equivalent of fine chemicals manufacture. The technology demanded, particularly for vaccine preparation, is even more advanced than that for fine chemicals. In developed countries, the preparation of vaccines does not involve large-scale operation; but the degree of expertise and the exceptional quality-control requirements would seem to make this field too difficult to approach by any but the most advanced technology. In one less-developed country in Central Asia, a

vaccines and sera institute is already functioning under the financial auspices of a public health institute. An enlarged, independent institute is under construction with an estimated capital development cost of about $3.3 million. This is a relatively large project for the country concerned.

Fermentation is operated on an extremely large scale (up to 500 m^3). There is therefore ample scope for scale reduction. However, while the fermentative stage does not present the hazards of live-virus handling faced in some vaccine operations, the technology is still very demanding. For example, in penicillin fermentation, if the culture is contaminated at any point over a period of six to eight days, not only may the contaminating organism utilize nutrient and synthesize unacceptable substances, but enzymes may be produced which totally degrade the penicillin. In these eight days, with a vessel of 120 m^3, a volume of sterile air of 1.38 million m^3 will be required for growth, and 43,000 kWh of electrical energy will be required for agitation. The surface finish and sealing of the whole fermentor and ancillary fittings must be such that effective sterilization can be achieved and maintained during the same prolonged period. Construction is normally of stainless steel, requiring specialist fabrication, but recently a 3,000-litre plastic fermentor vessel has been tested (for other applications) where the agitation as well as the aeration for respiration is brought about by compressed air. Following this work, a 20,000-litre vessel of glass-reinforced plastic inside standard concrete pipe sections is planned.

The production and extraction of some other antibiotics produced by fermentation is not quite as difficult. However, given that for all antibiotic production some well-trained and experienced staff are required, there is little incentive to operate a small-scale facility. The question of how small a scale is technically worth while will require a detailed analysis. The assessment of economic feasibility will be unique to each case. Nevertheless, the developing countries currently face great difficulties in ensuring adequate supplies. A physician working in a less-developed country in Africa states that antibiotics account for up to 30 per cent of the annual budget. For example, Perlman, reviewing the fermentation industries, notes that penicillin G wholesale prices rose 50 per cent in 1973/74 [2]. In these circumstances, countries with adequate capital resources may be expected to set up medium-sized fermentation and production facilities.

Manufacture of pharmaceuticals from raw materials

The manufacture of pharmaceuticals from fine chemicals and the formulation of the final drug represent an area where greater use could be made of local industry. The scale of manufacture in operation in different developing countries ranges from very small (with less than ten employees) to the industrial level. Problems such as quality control are common to all scales, but the manufacturing problems are rather different. Very small-scale manufacture may involve just those compounding operations that are undertaken in hospital pharmacies.

Typical of equipment and output of such compounding units is the following description of a modest non-governmental compounding facility in a least-developed country in Africa:

"The facility processes about one 40-litre batch of liquids per working day. The tablet machine works all day most days. About one million capsules are produced annually. One trained worker from Europe and one university-trained African pharmacist control operations and two dependable and experienced secondary-level local men do most of the manufacturing work. Others assist in packaging, cleaning etc. The plant is in fact under-utilized and production could be greatly increased with little or no additional outlay for plant."

The organization supplies only its own hospitals and clinics.

Because none of the equipment is large, space requirements are small and the rooms organized according to the following functions:

Quarantine storage for incoming raw materials and batch samples

Raw-material storage

Weighing and batching

Mixing, granulating, drying

Compressing (tabletting)

Packaging

Capsuling

Ointment and suppository processing

Liquids processing

Washing-up facilities

Quality control laboratory

Office

In four rooms there will be humidity control.

Liquids are made up in 40-litre and 100-litre stainless-steel kettles. Ingredients are stirred in using small, propeller-type electric-powered stirrers; various types of small restaurant-type electric mixers are used for making pastes for suspensions. Bottling is carried out with the aid of a hand-operated self-metering filler and a hand-operated capping machine.

For tabletting, wet and dry granulation and direct compression techniques are employed. It is hoped to acquire a drum-type blender and a small oscillating granulator for powder blending. At present large stainless steel sieves are used and the material is processed by hand. Drying of granules is accomplished in a home-made cabinet with a capacity of about 25 kg. Compression is by a single punch machine.

For ointments, either the ingredients are stirred in after melting the base or a small mill is used when required.

A small capsule-filling device has an output of 12,000 to 15,000 capsules per shift with one operator.

The range of preparations possible with such limited equipment is illustrated by the following:

Analgesic balm ointment

Antist tablets (chlorpheniramine maleate), 4 mg

Baby aspirin, 75 mg tablets

Benzyl benzoate application

Calcium gluconate, tablets

Carbarsone tablets, 250 mg
Cherry cough syrup
Chloramphenicol syrup
Chloroquine syrup
Chlorpromazine, 25 mg tablets
Citrazine syrup (piperazine citrate syrup)
Codeine cough mixture (children's use)
Codeine cough syrup (adult use)
Diaminodiphenylsulfone (DDS), 5, 10 and 25 mg tablets
Diazepam, 5 mg and 10 mg tablets
Diethylcarbamazine citrate (Hetrazan), 50 mg tablets
Diphenhydramine expectorant
Elixir terpin hydrate with codeine
Folic acid, 5 mg tablets
Gripe water
Icthyol ointment
Kaolin and pectin
Neomycin wound powder
Paracetamol, 500 mg tablets
Paracetamol elixir
Phenobarbital and atropine tablets
Phenobarbital elixir
Prednisolone di-iodoquine cream
Promethazine, 25 mg tablets
Promethazine syrup
Scabex (gamma benzene hexachloride) ointment
Sim San (benzalkonium chloride)
Streptoguanine powder
Streptoguanine tablets
Sulfadur (sulfamethoxy pyridazine) suspension
Sulfanilamide ointment
Triple sulfa suspension
Vitamul (multiple vitamin) syrup
Whitfield's ointment

The borderline between such small-scale maufacture and the compounding of pharmaceuticals in what are not primarily manufacturing establishments is ill defined. The potential of compounding in hospitals, clinics and pharmacies is, however, so important that it is worthwhile examining what can be done to encourage and improve it. Two extreme examples illustrate this.

A report dealing with drug availability in a less-developed country in Central Asia notes that:

> "The pharmacy network of about 600 outlets, together with the bazaar merchants and others who sell drugs, represents a major, under-utilized group of health workers already active in every community of any size. The Ministry of Health, by exercising simple regulatory authority, may well be able to improve the availability and quality of health care through simplification of drugs sold generically".

Statistical data on manufacturing or bulk compounding in hospitals in the United States showed that 41 per cent of 1,853 hospital pharmacies operated a manufacturing programme. The survey further demonstrated that 78 per cent of the sample group prepared galenical pharmaceuticals; 74 per cent of the products were not commercially available; 42 per cent were sterile solutions for topical use; 33 per cent were sterile pharmaceuticals such as collyria and ointments; and 30 per cent were small-volume injectable solutions. In addition, the same survey showed that hospital pharmacists were also active in the preparation of sterile products such as surgical irrigating fluid, large-volume injectable solutions and special sterile products for investigational use.

Most industrial-scale plants in developing countries are foreign owned. The establishment of equivalent plants, locally owned, probably by governments, is likely to be achieved by licensing. It seems probable that potential purchasers of plant and process know-how would be placed in a more reasonable negotiating position by the possession of basic design information provided by international agencies or the ITDG. Plant manufacturers in developed countries also have an interest in providing general process data where confidentiality agreements permit it.

Packaging of pharmaceuticals

Concern with packaging and storage methods for pharmaceuticals affects all distributors of pharmaceuticals at all levels of development.

When drugs are supplied from a developed country or by local manufacture in an advanced plant, attention will be centred upon the suitability of the packaging in severe climatic conditions with the possibility of poor handling. Most foreign companies producing drugs for tropical countries are aware of this problem. Small manufacturing facilities and hospital pharmacies must devise their own appropriate packaging systems which must satisfy local conditions and be cheap and simple to operate.

In 1973, a voluntary agency worker in one African country noted:

> "Working on a limited budget, conventional packaging materials for dispensing medicine are normally too costly. Envelopes or paper cartons are not adequate protection for drugs in a tropical climate. A relatively cheap alternative used for packing tablets and capsules is plastic sheeting, made into sachets using a heat-sealing machine. For solutions and mixtures, plastic bottles are used. Storage trials under tropical conditions need to be carried out to find the most acceptable. There may be possible reactions between the drug and the plastic. Medical staff are asked if possible to prescribe pre-packs which usually are a complete course of treatment or a month's supply. Pre-packing of tablets is at present done by hand using one person nearly full-time and three of the hospital out-patient interpreters on the non-clinic days. This job is very tedious and there is much scope for design of a simple mechanically operated tablet counting machine"

A similar comment from a relief agency in a still less developed country in eastern Asia notes that,

"because of the high humidity, rain and mode of life we found that it was not sufficient protection to place the tablets and capsules especially in envelopes".

Re-cleaned plastic vials from church organizations in the United States were satisfactory but were subject to customs requirements on the used plastic material.

"Plastic happens to be quite an industry but they have not yet produced medical vials. All in all, though, this method proved to be the most satisfactory since it protects the patient's medicine after the first dose, which we felt the plastic bag did not".

Another worker in a similar country in Africa remarks that:

"There are no locally made screw cap glass bottles. We used locally made beverage type bottles in the 200 ml to 1 litre range. The local plastics industry could produce containers for us, but we lack the sophistication for testing such containers with our products and we doubt that the plastic product would be of consistent quality. We package capsules and tablets mostly in bulk in sealed bags of 1000s and pack them in tins. We are not presently filling ointment tubes as the cost is high. Most of our products are dispensed from these bulk packages into paper or plastic containers for the patient at the time of use".

A 1974 report of a non-profit organization suggests a supply from the United Nations Children's Fund (UNICEF) of 20,000 1-litre bottles at an approximate cost of $10,000–$20,000 including freight.

In contrast to these comments is a report that

"in China – which is probably producing enough oral contraceptives for 20 million people – one form of the 'pill' is a small package of perforated paper strips on which the chemicals have been deposited. The monthly sheet contains 22 squares, each about one third the size of a postage stamp. The woman just tears off one of the bits of water-soluble paper and chews it for her daily dose. This 'paper pill' has great advantages, particularly on a mass scale. It saves pills, bottles, and the machinery for making them"[3].

A field worker in a less developed African country has reported on the problems of adequate labelling:

"A sample survey in the out-patients' department showed that over 50% of returning patients had taken one or more of their drugs wrongly. This perhaps is not surprising, as a large proportion of the patients are illiterate and only able to speak one or two of the many tribal languages".

Storage of pharmaceuticals

The problems of storage of pharmaceuticals apply to all types, whether imported or locally produced. The following examples illustrate how critical is correct storage. In a central Asian less developed country, a report notes:

"The typical (drugs) warehouse is a dank, decrepit room kept locked and sealed by a storekeeper who has assumed personal liability for the material entrusted to him in return for his salary. This arrangement has several shortcomings: since the storekeeper is never on the premises, he must first be located. If he is sick or on leave, no material can be taken out. Long delays are not uncommon. The storekeepers have very little experience or familiarity with the proper indentification, storage or handling of medical and technical supplies. Due to general disorganziation of its warehouses the government incurs substantial losses due to spoilage of medicines and food, damaged equipment, and materials which simply cannot be found".

A southern Asian government report on a visit to the government medical stores notes that a "deplorable state of affairs" was found, "resulting in near breakdown of their procedures–indenting, receiving, storing, record keeping

and supply of drugs to institutions". Several reports remark on the lack of stock cycling and its consequences. Problems with small local establishments are different but considerable. A field worker in West Africa reports that "the air-conditioned store is kept at a mean temperature of 70–75° F (21–24° C). Although a worthwhile investment, air-conditioning is still an expensive item. Other pharmacists from West Africa have found this less important". Another pharmacist processing pharmaceuticals in North Africa deals with the storage problem by the use of conservative expiry dates.

Quality control

Among the technologies needed by developing countries, the requirements of pharmaceutical products for stringent quality control are probably uniquely demanding.

WHO has been active in establishing internationally recognized standards of quality for pharmaceuticals and especially vaccines [4]. It has laid down desirable standards with respect to manufacturing personnel, premises, equipment, sanitation, manufacturing operations, labelling, packaging and quality control.

Unfortunately in many instances it is the difficulty of achieving these standards rather than ignorance of what is desirable that is the central problem. For example, the leader of a small African non-governmental processing unit notes that: "Problems of quality control are primarily due to lack of skilled workers. We would try to upgrade facilities if we had the expertise. Also our operation is small for supporting a good quality control facility." The latter feature is common to all process control facilities associated with production plants. The instrument costs, for example, on a small fermentor may be much greater than the cost of the vessel but will be fairly insignificant in relation to a 400,000-litre vessel for which they will be provided the same precise control. Regional, rather than local, quality-control laboratories may represent the most desirable goal, although once again this will frequently be a political and not a technical problem.

The same leader reports:

> "We are building up our range of equipment for the quality control laboratory (which is humidity controlled) but, even so, it will be a very modest laboratory for the foreseeable future. We plan to do aqueous and non-aqueous titrations, pH readings, other ordinary chemical and gravimetric tests, etc Our range of capabilities will stop short of spectrophotometric determinations, bio-assays, most chromatographic determinations, and all kinds of animal tests".

A more developed Asian country recently reported that:

> "This aspect (quality control) has been most neglected. Although private and public drugs are said to be tested for quality before they are shipped it is not known whether the drugs actually conform to standards when they arrive in the country. It is also not known whether the drugs retain their quality six months or for one year after they have been stored under the conditions of temperature and humidity prevailing in private and government drug stores . . . The establishment of a quality control laboratory for testing pharmaceuticals in this country is urgent and essential".

In commenting on the type of controls needed, the report notes:

> "In quality testing of drugs 70 per cent is chemical analysis, 20 per cent is microbiological analysis and 10 per cent is pharmacological. The quality control laboratory (under construction) will restrict itself to chemical testing for some years".

The field of quality control is one where labour-intensive methods could be used in place of expensive automation but, since this activity is the guarantee of standards of operation throughout manufacture and distribution, quite high technical proficiency and motivation are important.

Large versus small-scale production

Industrial producers in developed countries are governed by strictly commercial interests; the greatest gains will often be made by assisting them to view profit in new modes of operation or business which lead to cheaper drug supplies. Much has been made of the undoubted difference in costs between proprietary medicines and their exact generic equivalents. It may be that, with the increasing identification and general recognition of the few most basic drugs and the vast market represented by those who cannot afford proprietary drugs, companies will increasingly use the economies of large-scale operation to supply their proprietary products at generic prices, or to supply generic drugs very cheaply. They are likely to find that this policy will only work if a single "premier" product is marketed to all. The concept of separate cheap medicine for the poor is, as in the food field, likely to provoke a customer resistance that would prevent the opening up of a total market more profitable than the present one, which is limited to the comparatively rich. The initial marketing effort may be more laborious, with a narrower profit margin, and may require the use of new types of local pharmaceutical auxiliaries. Here, however, is an instance where the surplus of modestly educated people in many of the developing countries, if simply but adequately trained, could represent an asset not available elsewhere. Appropriate technology studies have a role to play in provoking discussion of such questions and the economies involved as much as in seeking small-scale production.

With respect to small-scale local production of generic medicines as alternatives to proprietary equivalents or mass-produced foreign generic products, it must certainly be borne in mind that a switch in transnational corporation policy of the kind mentioned above could destroy the commercial viability of a small-scale plant which was, in any case, profitable only in the artificial sense of saving foreign exchange.

The need to relate appropriate small-scale ventures to large-scale ones has been stressed in the Note by the secretariat. This is certainly valid for drugs. If countries have centralized facilities, these can be asked to devote part of their activity to the packaging of drug components into lots suitable for dispatch and local compounding. The gradual development of centralized facilities of inceasing complexity is not to be regarded as excluding local small-scale compounding, or vice versa. In the provision of drugs, appropriate technology means giving equal weight to centralized large-scale and localized small-scale operations.

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Appropriate technology in drug and pharmaceutical industries of India

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I. IDENTIFYING REAL PRODUCTION NEEDS

The purpose of the drug and pharmaceutical industry should be to deliver appropriate drugs to the population. One of the first steps is to identify the priority of essential drugs that are required to combat most of the prevailing diseases. Based on the pattern of diseases, such lists of essential drugs should be drawn up in co-operation with the industry, public health services and the medical profession. The best drugs needed for a particular treatment may not necessarily be cheap, and in many cases the choice of the drug may have to be dictated by the economic situation of the country. For example, while the present drug of choice for the treatment of leprosy is Rifampicin, its cost would be prohibitive for a developing country–over Rs 2,500 per year per patient, while the older drug Dapsone would cost only Rs 10–15. Similarly, this applies to the treatment with isoniazid and thiacetazone or para-aminosalicylic acid and the much more expensive isoniazid plus streptomycin, and the choice for treatment is obvious.

While identifying essential drugs, it must be borne in mind that reasonably good drugs for most of the major disease conditions are already available, and many newly introduced drugs have either no additional advantage or at the most only a marginal one over existing drugs. Each year perhaps one or two really better drugs emerge; others are introduced for other reasons–such as their patentability or greater profitability. Therefore, while drawing up a list of essential drugs, their superiority over known drugs should be carefully assessed, along with factors such as cost, patent position and the availability of the technology to produce them.

A list of essential drugs identified recently by a committee appointed by the Government of India is given in an annex. A number of variations of drugs included in this list have been introduced recently that have practically no major

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advantages over those listed. If, therefore, India could produce these drugs in sufficient quantity, most of its requirements would be met. With the addition of another eight to ten drugs to this list, some of the disease conditions which are prevalent in most developing countries would also be covered. There would be practically no problem with patents.

The World Health Organization (WHO) also has recently drawn up a list of essential drugs relevant to disease patterns in developing countries.[1]

Gaps in demand

As regards technological levels in the production of drugs and pharmaceuticals, most developing countries are far behind in their efforts to bring their production high enough to meet demand. While most of the world's population lives in developing countries, the developed countries account for 88 per cent of world production and 85 per cent of world consumption of pharmaceuticals. This leaves only 12 per cent of world production and 15 per cent of world consumption for the developing countries. Imports from developed countries to developing ones vary from country to country. For example, India imported Rs 470 million worth of pharmaceuticals in the 1976/77 fiscal year, as against a total consumption of Rs 7 billion, bringing the percentage of imports (by value) to total consumption to about 7 per cent. This is because India has a well-established pharmaceuticals industry that can meet its present requirements for the coverage of its established health services. However, these health services are accessible to barely 20 to 25 per cent of the population; the vast majority of 75 to 80 per cent must do without drugs. Even the quality of health service coverage to the small proportion of the population in India is hardly comparable to that in any developed country.

Figures of approximate percentage of imports to total consumption of pharmaceuticals by value for certain developing countries are as follows:

Country	*Year*	*Approximate percentage of imports to total consumption (by value)*
Algeria	1975	67
Egypt	1975	16
Liberia	1976	100
Mexico	1974	6
Nigeria	1976	70
Pakistan	1976	40
Philippines	1973	2
Turkey	1974	0.8
United Republic of Tanzania	1976	almost 100

Source: Country papers presented at the Consultation Meeting on Transfer of Technology and Technical Know-how between Developing Countries in the Field of Pharmaceutical Industries, held in Lucknow, India, 22 April–4 May 1976.

[1] WHO Technical Report Series, No. 615, 1977 (*The selection of essential drugs:* Report of a WHO Expert Committee), Geneva, Switzerland.

While these figures indicate the order of magnitude of reliance on imports, it is evident that, except for a few countries (such as India, Mexico, Philippines and Turkey) most of the developing countries rely substantially on imports.

The gap in demand for pharmaceuticals in developing countries can be considered as two levels:

Level I: Demand for pharmaceuticals governed by health-care facilities in existence;

Level II: Demand for pharmaceuticals for the entire population to control the major diseases.

The satisfaction of level II demand requires great efforts and substantial investment in health-care facilities which most of the developing countries can scarcely afford. Thus, the difference between level I and level II is the demand for the "have nots", that is, those who must do without basic health care and medical treatment for common diseases.

This difference is alarmingly large in developing countries. For instance, as has been noted, the level I demand in India covers barely 20 to 25 per cent of the population.

However, even for level I demand, which caters to a small fragment of the population (the "haves"), most developing countries must rely substantially on imports to meet the gap in demand, since domestic production is scanty. Even countries that produce some of their requirements, mainly by formulating imported bulk drugs, are still far from manufacturing the drugs themselves. For manufacturers of basic drugs, a developing country needs a sound industrial infrastructure and research facilities supplying raw materials, technical skills, machinery etc.; thus overall development of the pharmaceutical industry in any country is closely linked to the level of overall industrial development.

There is still, nevertheless, a strong case for developing countries to formulate most of their requirements after importing the bulk drugs, thus adding value and simulaneously saving foreign exchange, and creating nuciei for further development of the industry at a later stage. So far, only a few developing countries, among them India and Mexico, manufacture almost all of their bulk drugs and intermediates and have complete facilities for R and D.

International trade

As high-value, low-volume commodities, the transport costs of pharmaceuticals present no barriers to trade. The developed countries trade their pharmaceutical products freely but, the developing countries import only 3 per cent of the production of developed countries, and this amounts to about 20 per cent of the consumption of the developing countries, which thus constitute a very small market for the developed ones.

The Indian experience

It is laid down in the Constitution of India that "The State shall regard the level of nutrition and standard of living of its people and improvement of public health as among its primary duties".

Beginning with the first five-year plan (in 1951) health has been given considerable priority in order to implement the directive principles of state policy.

A beginning had already been made in the production of medicines by starting cinchona plantations in the States of Bengal and Madras (presently Tamil Nadu and West Bengal) in the early twentieth century. Factories were set up in their vicinity for the extraction and purification of quinine. During the Second World War, the local industry made further progress by producing a number of other products from locally available raw materials. Simultaneously, formulation activities based on imported bulk drugs were increasing considerably. The slow progress of the chemical industry in India also constrained the growth of the pharmaceutical industry.

In the early 1950s, various foreign companies began to found affiliates and subsidiaries in India. Some set up facilities for the manufacture of bulk drugs; most engaged in formulation activities based on imported bulk drugs. The entry of the transnational firms has offered stiff and healthy competition to the local industry. The Government of India itself set up two large public-sector units, Hindustan Antibiotics Ltd. in 1954 and Indian Drugs and Pharmaceuticals Ltd. in 1961, for the manufacture of bulk synthetic drugs and antibiotics, the production of some formulations of them, and the manufacture of surgical instruments.

Through a course of rapid growth, the pharmaceutical industry in India is now well established. It produces a wide range of drugs, including many sophisticated antibiotics, vitamins, hormones and synthetic drugs and has developed a wide-ranging capability in the production of bulk drugs and formulations. From a total product value of Rs 100 million in 1948, the Indian pharmaceutical industry was producing Rs 1.5 billion worth of bulk drugs and Rs 7 billion worth of formulations in 1976/77. Imports of bulk drugs in that year were Rs 470 million.

The breakdown of production of bulk drugs and formulations by various sectors of the industry in 1976–77 was as follows:

	(Rs million)	
	Bulk	*Formulation*
Public sector	480	470
Foreign sector (foreign equity exceeding 40 per cent)	630	2 920
Indian sector (including small-scale sector)	390	3 610
	1 500	7 000

There are now over 2,500 drug-producing units in India, of which 128 are in the organized sector, including 45 companies with foreign equity exceeding 40 per cent. With the rapid growth in demand and attempts by India to give coverage of basic health services, it is foreseen that the pharmaceutical industry in India is on the threshold of a rapid growth. The Government is tentatively planning a production level of Rs 5.5 billion worth of bulk drugs and Rs 19 billion worth of formulations by the fiscal year 1982/83. To achieve this target (which, however, will only increase the coverage of the population marginally),

the pharmaceutical industry must more than double its present size in barely five years.

II. TECHNO-ECONOMIC PROFILES

Bulk drugs can be classified into antibiotics and synthetics. The former are living organisms capable of combating disease (imparting pathogens), whereas the latter are complex chemicals capable of curing diseases because of their influences on the body or the materials in the cardio-vascular system and alimentary canal. Because of their differences, their methods of productions also differ considerably. The technologies generally used for the manufacture of both are briefly described in the following sections. Methods for manufacturing formulations are also given.

Antibiotics

Antibiotics, essentially special chemotherapeutic agents, are produced by special kinds of micro-organisms. These are chemical substances used for the treatment of infectious diseases or those caused by the proliferation of malignant cells. Antibiotics can broadly be divided into two groups, antibacterial and antifungal. Examples of antibacterial antibiotics are the penicillins, streptomycin and the tetracyclines; among the antifungals are nystatin and griseofulvin. In addition to the commercial antibiotics used for human therapy, there are several others which, although toxic to humans, may prove useful in the treatment of animal diseases or in combating insects, animal pests and plant diseases.

Antibiotics are produced commercially by biosynthesis, cultivating the suitable microbes under a suitable environment in an appropriate medium. The production is normally by fermentation, followed by chemical purification.

The strain of micro-organism used in industrial fermentation for the production of an antibiotic must be rigorously selected. It is well known that the productivity of an antibiotic during fermentation by a microbe is an interaction of its genetic potentiality and the environment within and outside the microbial cells. Augmentation of yield by altering genetic potentiality of a strain is a well-known technique, and results from the experiments with such micro-organisms in the area of mutation, microbial genetics and genetic control of secondary metabolites have given valuable information for the application to industrial strains. What was 100 of units (u) of penicillin per millilitre in the fermenter in late 1940 is now 30,000 to 40,000 u/ml of broth in the 1970s. Thus, increased yield in the fermenters has led to reduction of productions cost. It can be seen that strain improvement is an important activity in the field of antibiotics, one which has a bright future for further development.

Production on industrial scale is carried out in large vessels called fermenters. The process adopted is submerged aerobic fermentation under suitable conditions. The culture of appropriate strain is grown first in the inoculators containing sterilized medium. Seed mycelia of the first generation cultivated in the inoculator are then transferred to the second generation in seed

vessels. In some cases, such as that of the tetracyclines, the seed is grown directly in the shipping inoculator stage, and the seed multiplies within a period of 30 to 50 hours. A fermenter containing sterilized medium is then seeded with the mycelium culture grown in the seed vessel. Fermentation is continued for over a week or even longer. During fermentation, such parameters as pH, temperature, dissolved oxygen and carbon source, and nutrients such as nitrogen and phosphorus are continuously monitored and optimum conditions are maintained. In addition, a supply of sterile air and continuous agitation are prerequisites for achieving the desired results.

In the process of antibiotics fermentation, proper sterilization of vessels, the medium and all other inputs such as air and intermediate feeds must be ensured. The sterilization of the vessels and the medium is carried out by thermal processes using superheated steam, whereas the sterilization of air is done by passing compressed, modified air through suitable filters.

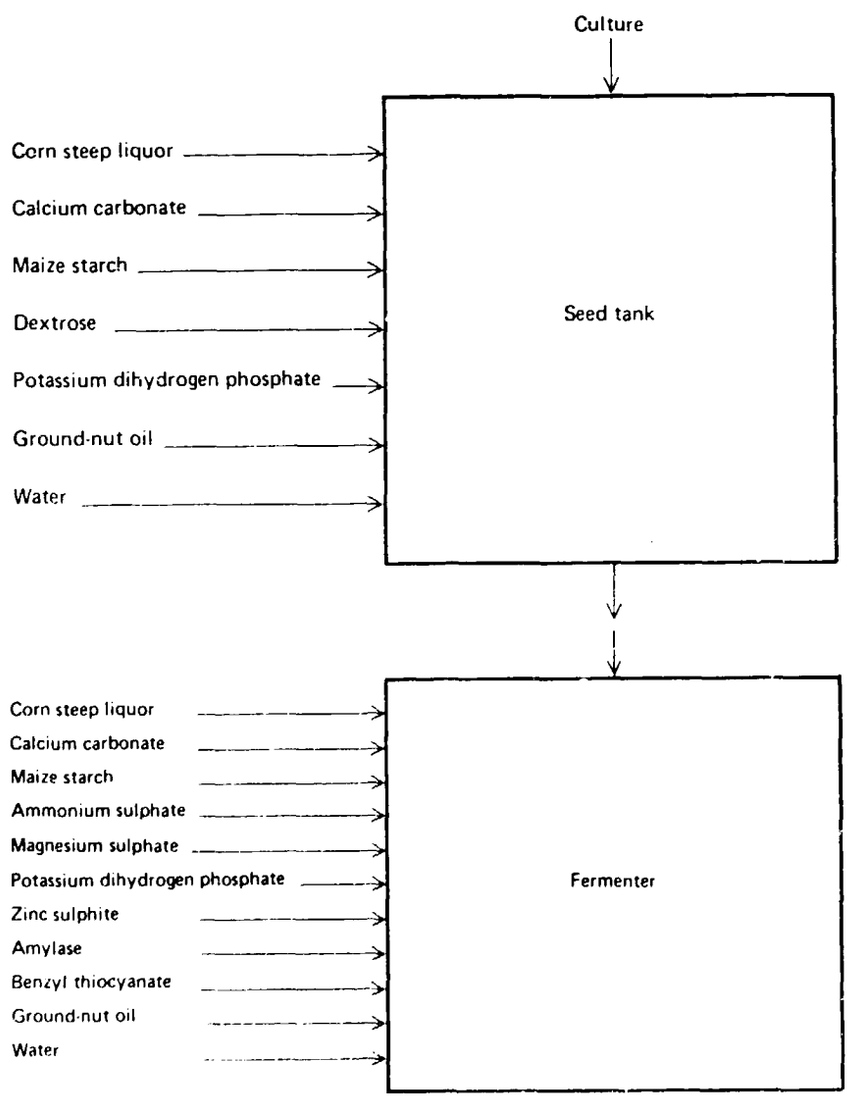

Figure IA. Flow chart for filtering, crystallizing and centrifuging in tetracycline production

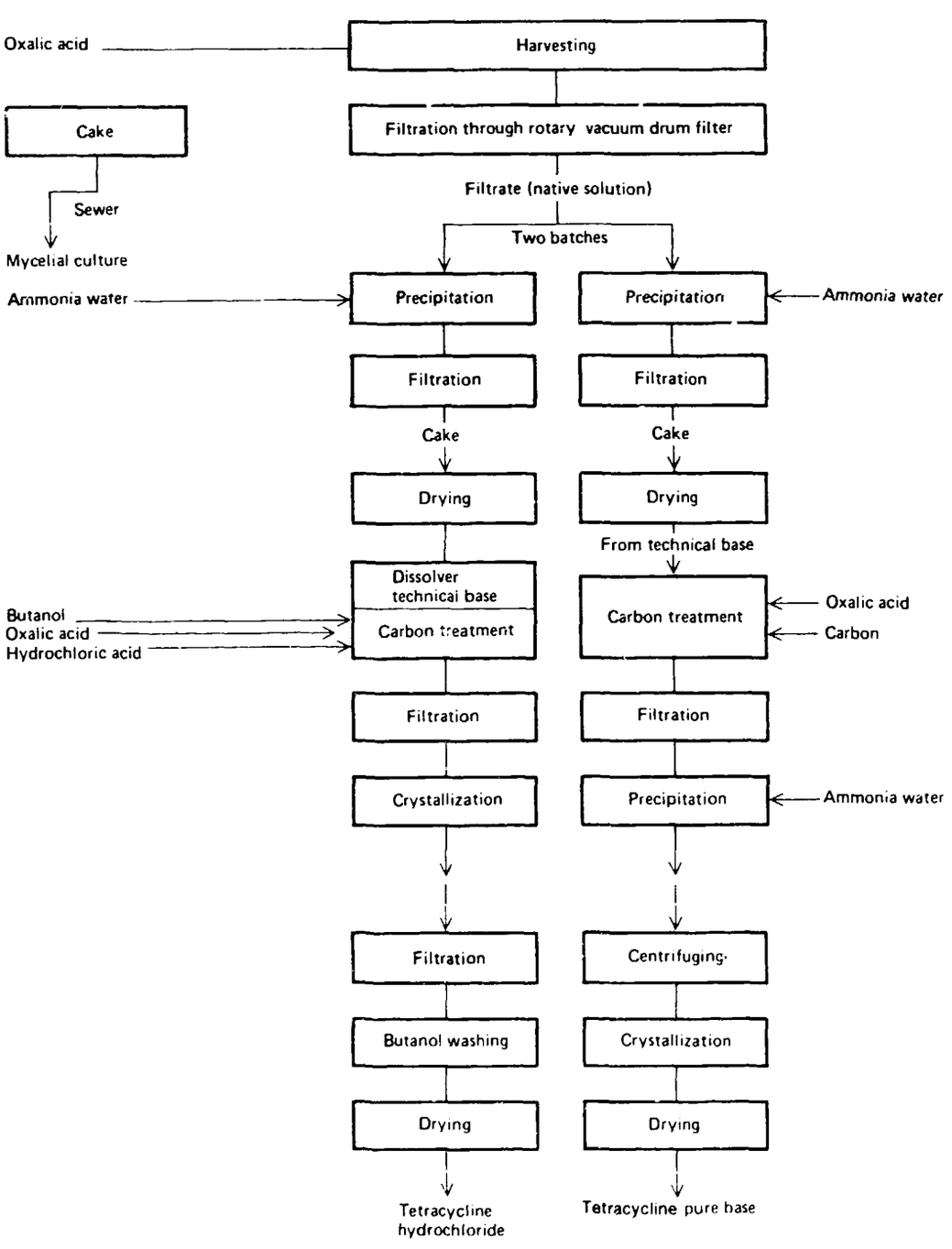

Figure IB. Flow chart for filtering, crystallizing and centrifuging in tetracycline production