WORLD HEALTH ORGANIZATION
ORGANISATION MONDIALE DE LA SANTÉ

EB47/13

28 November 1970

EXECUTIVE BOARD

Forty-seventh Session

Provisional agenda item 2.5

ESTABLISHMENT OF PHARMACEUTICAL PRODUCTION IN DEVELOPING COUNTRIES

Report by the Director-General

In its resolution WHA22.54[1] the Twenty-second World Health Assembly requested the Director-General to report to the Executive Board and the World Health Assembly on the course to be taken to further co-operation between the United Nations Industrial Development Organization (UNIDO) and WHO in the establishment of pharmaceutical production in developing countries.

1. GENERAL CONSIDERATIONS

1.1 Differences in the development of therapeutic practices in countries of the world are mentioned in the preamble to the resolution. Uniformity cannot be expected or achieved because the organization of medical care, the medical infrastructure, and epidemiological and many other factors differ from country to country. The consumption of pharmaceutical preparations is especially influenced by, for example, the prevalence of infectious and other diseases, the numbers of physicians, pharmacists, nurses, and hospitals and last, but not least, the availability of the preparations. In the less developed areas additional factors come into play: for example the cost of drug treatment, the ease with which drugs can be administered and, in tropical climates, the stability of drugs.

1.2 In developing countries of low economic potential where patients are unable to pay for treatment and government funds are insufficient to provide adequate care for everyone who requires drug treatment, the amount of money that needs to be spent to ensure effective drug treatment for a single patient is of critical importance, since the drug that provides the least costly treatment per person permits treatment for the greatest number of patients.

1.3 Ease of drug administration has little influence on consumption as long as a sufficient number of physicians, nurses and hospital beds are available for patients who, for example, need long-term treatment by a drug that has to be injected, or as long as drug effects must be controlled by a continuous surveillance of the composition of body fluids. But where adequate daily treatment of patients cannot be provided, or patients only receive intermittent hospital care, have to be treated at out-patient clinics or dispensaries, or live at some distance from medical centres, drugs that can be given orally will be the drugs of choice even if they are not as satisfactory as injectable drugs.

1.4 Drugs that deteriorate quickly in tropical climates will have to be excluded from use unless the necessary technical conditions for the maintenance of their activity can be provided.

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[1] Off. Rec. Wld Hlth Org., 176.

1.5 When local pharmaceutical production is planned the effect of such factors on drug requirements must be considered. Early exploration, analysis and evaluation of such factors are a prerequisite for a realistic decision on what drugs should be produced and for the integration of the new pharmaceutical industry into the development of public health services in general.

1.6 In the preamble of the resolution WHA22.54[1] the widespread use of various traditional medicines is considered. Traditional medicines play and will continue to play a role where modern treatment is not available and, in particular, because of the very low physician/population ratio which prevails in many areas. It has been stated that "large numbers of the world's people, probably more than half, have no access to medical care at all."[2]

1.7 Though the role of traditional medicines is likely to change as the medical infrastructure develops they are at present to be found almost everywhere and are occasionally produced on a semi-industrial or industrial scale, although as a rule not in accordance with accepted modern pharmaceutical standards.

1.8 In consideration of some of the factors mentioned above, the United Nations Industrial Development Organization (UNIDO) requested the co-operation of WHO in its efforts to assist countries in the establishment of pharmaceutical production.

2. BASIS OF CO-OPERATION BETWEEN UNIDO AND WHO

2.1 UNIDO was established by the General Assembly in 1966 for the purpose of encouraging the more rapid industrialization of developing countries.

2.2 UNIDO's mandate includes both operational and research activities; its principal organ is a forty-five-member Industrial Development Board, which normally meets once a year, and which has been entrusted with the task of ensuring co-ordination within the United Nations system of organizations at the intergovernmental level. For this purpose it reviews at each session a consolidated report of the activities of the United Nations system relating to industrial development, to which WHO regularly contributes.

2.3 Arising out of the Athens Conference on Industrialization, 1967, a recommendation had been made that greater attention should be paid to the development of national or sub-regional pharmaceutical industries. In 1969 UNIDO proposed in its programme that an Expert Working Group on the Development of Pharmaceutical Industry should be held. UNIDO asked WHO to provide assistance on the health aspects of pharmaceutical industry development.

2.4 WHO participated in the UNIDO Expert Working Group meeting which was held at Budapest in May 1969 and contributed three papers: "Therapeutic Needs and Production of Drugs"; "Considerations of Drug Efficacy and Safety"; and "Quality Control in Pharmaceutical Manufacturing". The recommendations of the meeting in relation to the establishment of pharmaceutical industries include the following:

"In order to prepare a suitable plan for the introduction of pharmaceutical industry sectors in a developing country, the following should be assessed:

- Data on the general economic and hygienic standards of the country;

- Demographic data, such as the population of the country, average life expectancy, population structure and increases, and general attitudes of the population concerning medical treatment and pharmaceuticals;

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[1] Off. Rec. Wld Hlth Org., 176.

[2] J. Bryant (1969) Health and the developing world, Cornell University Press, Ithaca and London.

- Local patterns of medical treatment and its costs;

- The existence and prevalence of diseases and common ailments, especially those of an infectious and epidemic nature;

- Medical care available, the number of practising physicians, nurses, hospital beds, pharmacies, pharmacists, technicians in the medical area and scientific personnel in sciences related to medicine;

- The size and the nature of the existing local pharmaceutical market, the traditional supply and distribution system, price levels and pricing structures;

- Laws regarding the importation and distribution of pharmaceuticals, company policies and industrial laws, taxation, custom duties and protection of industrial property;

- Local availability of trained and/or trainable manpower for assignments in the pharmaceutical industry;

- Availability of packaging materials for pharmaceutical preparations and the development potential of this area;

- The present and projected demand for pharmaceuticals, classified in therapeutic categories;

- Potential export possibilities and regional and interregional co-operative plans;

- Therapeutic and prophylactic requirements of food-animal and work-animal populations;

- General attitudes towards foreign assistance or investments, and incentives and protection policies, if any;

- Industrial feasibility of the manufacture of selected pharmaceuticals. (Such an assessment should be undertaken jointly by WHO, FAO and UNIDO, and should be carried out not only by pharmaceutical, veterinary, medical, financial and economic advisers of the organizations, but also by specialists resident in the respective developing countries or regions.)

- Data on human therapeutic requirements, treatment patterns, and treatment costs. These can be obtained from:

  (a) Physicians and veterinarians familiar with the local situation;

  (b) Statistical data on drug imports;

  (c) Indicated demand of drug consumption obtained, for example, from local sickness boards or from records of local hospitals and military pharmacies;

  (d) Representative samples of medical prescriptions by hospital physicians and general practitioners.

2.5 Under the aegis of the health authorities, a detailed analytical evaluation of such information should be undertaken by therapeutic and clinical pharmacological experts with a view to evaluating demands for pharmaceutical preparations and drugs essential for sound medical care in the region under study, with estimates of annual consumption and, where possible, standard treatment costs per patient per day.

2.6 From the above assessments an up-to-date evaluation can be made of products essential to sound medical care which could potentially be produced in the country or region."[1]

3. AREAS OF RESPONSIBILITY OF WHO

3.1 There are three important areas in which WHO has a responsibility and can assist in the planning of pharmaceutical industries:

(i) Assessment of the therapeutic needs of countries for which pharmaceutical industries are contemplated;

(ii) Assessment of the efficacy and safety of the drugs so produced;

(iii) Control of their pharmaceutical quality.

3.2 In relation to the assessment of therapeutic needs, the necessary data can be extracted from publications and reports or collected by consultants (physicians, preferably clinical pharmacologists) in co-operation with local medical and pharmaceutical specialists.

3.3 The efficacy, safety and pharmaceutical quality of pharmaceutical preparations are the concern of the local manufacturer. He may wish to make use of the principles for the biological evaluation of drugs and for their efficacy and safety that have been worked out by WHO experts and advisers.[2] Such principles and criteria must be observed by every manufacturer, including those who restrict their activities to the compounding or repackaging of pharmaceutical products and are not normally involved in the biological evaluation of new drugs, because the choice of drugs and the conditions of drug application in developing countries often differ widely from those in developed countries. Specific efficacy and safety problems are likely to arise since local factors - such as nutritional habits, malnutrition or genetic disorders - may lead to adverse reactions not observed in the countries where the drugs are developed.

3.4 Manufacturers may furthermore consider that the desired pharmaceutical quality of finished preparations must be built into the product from the very beginning of manufacture. Principles of good practices in the manufacture and quality control of drugs have been established and published by WHO.[3]

3.5 Serious doubts have recently arisen about the therapeutic equivalence of various proprietary forms of certain generic products. Since industries in developing countries tend to prefer generic products because of their lower cost, they should be aware of this problem and be prepared to evaluate products for their therapeutic equivalence whenever possible.

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[1] "Establishment of Pharmaceutical Industries in Developing Countries". Report and Proceedings of Expert Working Group Meeting, Budapest 5-9 May 1969; United Nations, New York, 1970; ID/35.

[2] Principles for Pre-Clinical Testing of Drug Safety: Report of a WHO Scientific Group (Wld Hlth Org. techn. Rep. Ser., 1967, 341); Principles for the Testing of Drugs for Teratogenicity: Report of a WHO Scientific Group (Wld Hlth Org. techn. Rep. Ser., 1967, 364); Principles for the Clinical Evaluation of Drugs: Report of a WHO Scientific Group (Wld Hlth Org. techn. Rep. Ser., 1968, 403); WHO Expert Committee on Specifications for Pharmaceutical Preparations: Twenty-second Report (Wld Hlth Org. techn. Rep. Ser., 1969, No. 418); Principles for the Testing and Evaluation of Drugs for Carcinogenicity: Report of a WHO Scientific Group (Wld Hlth Org. techn. Rep. Ser., 1969, 426).

[3] Off. Rec.Wld Hlth Org., 176, Annex 12.

3.6 In pursuance of such co-operation, WHO may be asked to deal with problems in relation to research into or production of traditional medicines.[1] Any request of this kind should be given individual attention and all the factors involved - such as efficacy, safety, pharmaceutical quality, and the economic aspects - should be carefully considered. To enable WHO to assist UNIDO in subjects of this kind, basic considerations referring to the characteristics, status and cost of traditional medicines and to fundamentals of scientific research in this field have been outlined with the assistance of consultants in the attached document.[2]

4. CURRENT AND FUTURE UNIDO/WHO ACTIVITIES

4.1 Co-operation between UNIDO and WHO is carried out on the following lines:

1. WHO co-operates with UNIDO in the planning of pharmaceutical industrial projects as appropriate (in relation to the composition of exploratory teams of consultants; the briefing of consultants on the medical infrastructure and therapeutic requirements of an area; problems of efficacy and safety; good practices in the manufacture and quality control of drugs; comments on consultant reports and UNIDO Project Data Sheets)

2. WHO provides assistance to UNIDO:

   (a) in planning the production of natural products as a source of active medicinal ingredients;

   (b) in providing information on the manufacture of pharmaceutical products.

3. WHO participates in meetings dealing with pharmaceutical production convened by UNIDO.

4.2 Co-operation between UNIDO and WHO could be further extended, inter alia, by:

(a) Gathering information through WHO Member States on the therapeutic needs of countries and of local problems related to efficacy, safety and quality of drugs.

(b) Strengthening and developing participation by WHO in the assessment of such therapeutic needs at an early stage in UNIDO's planning of pharmaceutical projects; and

(c) Within the limits of available resources, increasing the number of fellowships for the training of specialists in drug therapy and production and of consultations on relevant problems, and providing more information on therapeutic and pharmaceutical requirements through publications.

4.3 Such extended co-operation would also establish a feedback system whereby WHO would collect valuable information on the experience gained in different countries.

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[1] See also the preamble of Resolution WHA22.54, Off. Rec. Wld Hlth Org., 176.

[2] See: Annex.

ANNEX

TRADITIONAL MEDICINES

A note on their characteristics, status and costs, with special reference to research

Traditional medicines are to be found everywhere in the world. Their use is based on expectation and experience handed on from generation to generation. The contribution of traditional medicines to drug treatment differs from country to country though, as a rule, they are used most widely where medical services and thus modern drug treatment does not yet reach everyone who needs them.

1. CHARACTERISTICS OF "TRADITIONAL MEDICINES"

1.1 The term "Traditional Medicines" refers to medicines that consist of naturally occurring materials, which have as a rule been developed empirically and are produced by methods that do not necessarily meet modern pharmaceutical standards. They are generally administered on the basis of an assumption of past empirical findings and of subsequent practice by traditional practitioners who do not possess qualifications in modern medicine.

1.2 The ingredients of traditional medicines are obtained from plants, animals and minerals. For some medicines the nature of the ingredients and the methods used in processing them are kept secret, whereas for others reliable botanical, pharmacognostic and galenical information is available. The harvesting and processing of traditional medicines can be associated with certain customs and rituals; examples of these are harvesting at particular times of the day, under various astrological signs, or by persons meeting certain conditions. Processing includes the separation or isolation of certain parts or constituents of the raw materials; drying, pressing, extracting, boiling, burning, compounding and other procedures may also be involved. The operations range from primitive gathering and drying of wild plants to highly sophisticated methods of cultivation of plants containing active principles in the desired quality and concentration.

1.3 Knowledge of traditional medicines is generally passed from generation to generation by word of mouth or in simple herbals. There is considerable variation in the administration of traditional medicines and the uses to which they are put from region to region. In certain parts of the world, however, especially in some Asian countries, systematized lists of ingredients, details of the manufacture of preparations, and of administration and dosage have been recorded. Information about traditional medicines is provided through publications or by the relevant teaching institutions, for example, in the Ayurvedic and Unani systems. In spite of recent progress in the pharmaceutical and medical sciences in the prophylaxis, diagnosis and treatment of diseases such systems have continued in a more or less unchanged form for many generations.

1.4 The professions concerned with prescribing, preparing, distributing and administering traditional medicines vary widely.

In certain parts of Western Africa one person, the "Guérisseur" or healer prepares and administers the medicaments himself to each patient according to experience and knowledge he has obtained himself or has inherited from his father. The healer keeps secret the details of his medications and special ceremonies generally accompany their administration. More recently these healers have formed associations to safeguard the interests of their profession. They have, however, no schools or other means to achieve uniform instruction.

In some areas, in addition to these professional healers, medicaments are prepared by certain people who dispense them through drug dealers on public markets. In these cases the patient consults a dealer and receives a remedy corresponding to his symptoms, without any ceremony. This practice is declining in importance because accidents in recent years have alerted the consumers. However, the simple medicinal plants used to prepare infusions or decoctions are still found in the markets.

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In Africa, no industrialization of the production of traditional medicines has taken place so far.

In India, Pakistan and some other Asian countries, the prescription of traditional medicines by the Ayurvedic, Unani or similar systems is the task of Veds, Hakims and other learned healers. The students of these ancient medical systems undergo training and examinations before they are allowed to practice.

The medicaments are often produced on a semi-industrial or industrial scale, but in a manner not corresponding to modern pharmaceutical standards. They are distributed through the markets or by special pharmacies.

In Latin America traditional medicines are distributed in the main by "curanderos", who are frequently women. They practise either in the villages or in the markets of the larger cities wherever their work is tolerated. They either collect the medicinal plants themselves, or have people working for them. No ceremonies are connected with the administration of their medicines. Their knowledge is derived from inheritance and experience. These systems have to be regarded as being more or less socially accepted forms of traditional medicine.

1.5 Classifications of the symptoms of diseases, and of diseases indicative for the administration of traditional medicines vary with the types or systems of traditional medicine and can only partly be correlated with the modern concepts of diseases.[1] Such classifications do not include for example, most of the important infectious diseases, although the communicable diseases are a cause of major concern, especially in those countries where traditional medicine plays an important role. These differences in classification stem mainly from the lack of medical education of traditional healers in the causal relationship between pathological processes and drug action.

1.6 In some countries traditional medicines are subject to drug control legislation. Such legislation can introduce statutory safeguards to ensure their conformity with official requirements, e.g. safeguards for manufacturing under hygienic conditions, for labelling and advertising, and in relation to distribution and retail sale. However, since neither scientific specifications for quality control, nor reliable information about efficacy and safety of traditional medicines are available, the contribution of such legislation to consumer protection cannot be evaluated.

1.7 It is worth mentioning that some medicinal plants which have long been in use - often in traditional medicine - are included in modern pharmacopoeias. In the Second Edition of the International Pharmacopoeia[2] monographs are included for, inter alia, ergot, stramonium herb, ipecacuanha root, digitalis leaf. Some drugs widely used in modern medicine were originally isolated from such medicinal plants as, for example, ergotamine, ergometrine, atropine, emetine, digitoxin, digoxin, lanatosides, tubocurarine, reserpine, etc.

However, it must be recognized that only a few traditional medicines have been taken over directly into modern therapy because most of the active natural products were not used for specific diseases. Moreover, the modern use of drugs isolated from traditional medicines could occur only when scientific methods for isolation, determination of the chemical structure, and tests for purity and quality control were developed and when experimental methods were introduced for toxicological evaluation (safety) and for controlled clinical trials (efficacy).

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[1] International Classification of Diseases, 1965 Revision, Geneva, World Health Organization.

[2] World Health Organization (1967) Specifications for the quality control of pharmaceutical preparations - second edition of the International Pharmacopoeia, Geneva.

Annex

In modern therapy only defined substances isolated from medicinal plants are used; however, the vegetable drug itself and pharmaceutical preparations therefrom may maintain their place in therapy in some countries, for example, for economic reasons.

2. STATUS AND COSTS OF TRADITIONAL MEDICINES

2.1 The efficacy and safety of traditional medicines are not evaluated in accordance with principles as established by national or international groups of experts or authorities in these fields.[1] This situation does not allow an acceptable comparison of the therapeutic value of traditional medicines with that of drugs which have been shown to fulfil these requirements.

2.2 Where modern drugs are not available, traditional medicines have, and may continue to have a function. Apart from their humanitarian value, in appropriate cases traditional medicines may provide pharmaco-dynamic or psychosomatic benefit for the diseased. However, as the general level of education and that of medical education rise and as the per capita income increases and therefore allows for larger contributions to health care, the role of traditional medicines is likely to evolve in relation to modern methods of treatment.

2.3 The proposition that medical care through traditional medicines is less costly than modern drug treatment and therefore better suited for populations living in economically under developed areas must certainly be considered. It cannot, however, be supported by facts, firstly because the individual expenditure for traditional medicines is difficult to assess since fees for the healer and costs for his medicines are usually combined, and secondly because the possible benefit derived from the empirical use of traditional medicines cannot be quantified and therefore not be balanced against cost. It is therefore difficult to make a meaningful comparison between the costs of modern drug treatment and the expenditure for traditional medicines.

3. TRADITIONAL MEDICINES AND DRUG RESEARCH

3.1 It has been suggested that the efficacy of traditional medicines could be improved by the addition of modern drugs. The incorporation of substances of proven therapeutic activity into traditional medicines, however, might lead to unforeseeable interactions between them. Such interactions might result in unpredictable and hazardous changes in the biological effects, especially if the constituents of traditional medicines are not known. Therefore a warning should be given not to incorporate substances of proven biological activity into traditional mixtures; even their simultaneous administration may be dangerous.

The only possible way of integrating traditional medicines into modern drug treatment would be as a result of scientific investigation and the addition of products so obtained to the arsenal of modern therapeutics.

3.2 There are rational ways of benefiting from experience gained in the pursuit of traditional medicine. Drug manufacturers and research institutions are conducting drug research on the basis of direct contacts with traditional healers or by systematic exploration of plant and other material used in traditional medicine. This type of drug research orients itself

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[1] For example: Principles for the Pre-Clinical Testing of Drug Safety: Report of a WHO Scientific Group (Wld Hlth Org. techn. Rep. Ser., 1967, 341); Principles for the Clinical Evaluation of Drugs: Report of a WHO Scientific Group (Wld Hlth Org. techn. Rep. Ser., 1968, 403) etc.

along the principles which are generally accepted and laid down inter alia in a series of WHO technical reports.[1] It consists of the identification and, if possible, isolation of the active material, its biological or chemical assay, its evaluation for therapeutic purposes through animal and clinical experimentation, and does not differ in its fundamentals from any other form of drug research. As far as the necessary manpower, facilities, and equipment are concerned, costs are equal to or may even be higher than, those of drug research on synthetic substances; they may reach dimensions which exceed by far the economic potential of a developing country or group of countries. The time needed for the study of one product from the beginning of research to registration as an approved drug, is estimated to be more than five years. As a rule, the probability of any product being able to pass successfully all the steps of evaluation, and of becoming a useful drug, would seem to be low considering the high standard of efficacy and safety of comparable drugs already on the market.

Where established and legally accepted systems of traditional medicine exist it would be of interest to investigate ways of shortening the process of development, or decreasing costs and thereby increasing the probability of a positive result. Theoretically such possibilities exist. Where the treatment of diseases by traditional methods is legalized, the efficacy of available medicines can be reliably tested in controlled clinical trials if all the conditions are fulfilled which are required to make them meaningful. Should such a trial yield a positive result, support is likely to be forthcoming from governmental or private enterprises for further thorough investigation of the material in question. Expenditures for research of this type can usually be kept low by the rational use of already existing local facilities and infrastructures.

3.3 Countries that can support research programmes for the development of materials of potential therapeutic interest from local natural resources, including traditional medicines, may consider doing so, but the expectation of developing useful materials should be weighed against the costs of such research and the utilization of funds to the best interest of the population in supplying them with medical care.

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[1] Principles for Pre-Clinical Testing of Drug Safety: Report of a WHO Scientific Group (Wld Hlth Org. techn. Rep. Ser., 1967, 341); Principles for the Testing of Drugs for Teratogenicity: Report of a WHO Scientific Group (Wld Hlth Org. techn. Rep. Ser., 1967, 364); Principles for the Clinical Evaluation of Drugs: Report of a WHO Scientific Group (Wld Hlth Org. techn. Rep. Ser., 1968, 403); WHO Expert Committee on Specifications for Pharmaceutical Preparations; Twenty-second Report (Wld Hlth Org. techn. Rep. Ser., 1969, No. 418); Principles for the Testing and Evaluation of Drugs for Carcinogenicity: Report of a WHO Scientific Group (Wld Hlth Org. techn. Rep. Ser., 1969, 426).