



## DRUG MANAGEMENT AND POLICIES\*

This report contains information on the evolution of WHO's role in the field of drugs and outlines the programme of the new Division of Drug Management and Policies established at Headquarters.

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### 1. Introduction

More than sixty formal resolutions have been adopted by the World Health Assembly which call for the establishment of *international norms* for pharmaceutical and biological products and for the *exchange of information* through WHO on the quality, safety and efficacy of drugs among regulatory authorities.

Over the past decade, however, the remit of the Organization has been considerably extended as a result of a series of resolutions of the World Health Assembly establishing a correlation between the pharmaceutical supply system and the basic health needs of populations. This has resulted in the elaboration of the *essential drugs concept* as a basis for planning drug procurement in developing countries and, more recently, in the emphasis placed on the *rational use of drugs* as an inspiration for all governments seeking to optimize the use of available resources.

All countries also need to have access to reliable *independent sources of technical information* and to be able to obtain independent assurances regarding the quality, safety and efficacy of the products they import.

The governing bodies of WHO and its Member States have long recognized the importance of *traditional medicine* as a valuable health resource. They realize that if there is to be significant improvement in the health of the underserved populations of the world, there will have to be full utilization of available resources — both human and material. This is fundamental to the primary health care approach. In traditional medicine, WHO aims at exploiting those aspects of it that provide safe and effective remedies for use in primary health care.

Finally, the international drug control treaties have assigned to WHO the important functions, approved by the Health Assembly, of determining which *narcotic drugs and psychotropic substances* should be placed under international control and of recommending to the Secretary-General of the United Nations appropriate scheduling under these treaties. The Organization is also requested to promote the appropriate use of such drugs.

It is against this general background that the new Division, encompassing the different components of drug management and policies, has been established at Headquarters.

\*In this document the term "drug" includes:

- Substances and/or products used in man for prophylactic, diagnostic and therapeutic purposes of synthetic, biotechnological or natural origin (i. e. pharmaceuticals, biologicals — such as vaccines, sera, blood and its derivatives — as well as traditional medicines).
- Psychotropic substances and narcotic drugs as defined by the relevant international treaties.

## 2. Drug policies

The term "pharmaceutical supply system" is used to embrace all the activities within the industry, government and the health services directed to securing the procurement and distribution of drugs of assured quality, safety and efficacy to the patients in need of them. It bears upon:

- the development, manufacture and marketing of drug products;
- the regulation and control of these operations by competent national authorities; and
- the infrastructure through which the products are channelled and ultimately utilized within the public and private sector.

Wherever effective drug supply is compromised by lack of coordination or coherence in these activities, improvement is contingent upon the formulation of an integrated *national drug policy*. The determination of such a policy is a matter of national sovereignty. National drug policies include:

- legislation and regulatory control of drugs, including registration procedures and drug abuse control;
- quality assurance of drugs, either locally produced or imported;
- monitoring of marketed drugs, including utilization and adverse reactions surveillance;
- supply (procurement, local production, distribution, logistics);
- education and training;
- dissemination of information on the rational use of drugs, and
- drug research and development.

Few countries are self-sufficient to the extent that they can successfully implement such policies in isolation. Their implementation requires allocation of resources, an efficient *management system* and a core of technically competent and experienced administrators within the government ambit.

The formulation of national drug policies linked to health needs is particularly important for developing countries in order to improve the availability of essential drugs and to ensure the rational use of drugs.

### THE ESSENTIAL DRUGS CONCEPT

In order to make available to health services high-quality drugs at reduced prices, authorities in a few developing countries began in the early 1970s to draw up *restricted lists of drugs essential to meet major health needs*. The drugs were listed under generic names and manufacturers were invited to bid competitively to supply drugs of the required quality. Where large segments of the population could not afford pharmaceutical products at market prices, a need was perceived to *complement the commercial market by distributing essential drugs at low prices within the public sector*. The lower prices were to be achieved not by compromising quality but by reducing manufacturing costs through assurance of longer production runs and definite payment schedules, and by excluding marketing and distribution expenses. Since manufacturers of generic products do not normally provide prescribing information, health authorities would need to disseminate such information to health professions. It was also understood that the range of available drugs would be extended progressively as socioeconomic development led to more advanced health services.

This original concept of essential drugs was later developed further by the Health Assembly which, following a report on the importance of this approach in meeting the health needs of underserved populations, adopted a series of sequential resolutions requesting the Director-General, *inter alia*, to develop means by which the Organization can be of greater direct assistance to Member States in:

- the formulation of national drug policies;
- advising on the selection and procurement, at reasonable cost, of essential drugs of established quality corresponding to national health needs, and
- the education and training of scientific and technical manpower for research, production, evaluation, control and management of prophylactic and therapeutic substances.

Major new initiatives followed these resolutions of the Assembly, in particular:

- The publication of the *Model List of Essential Drugs*, which has been updated biennially. Throughout the list has been intended "as a contribution to solving the problems of those Member States whose health needs far exceed their resources and which may find it

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difficult to initiate such an endeavour on their own". It was emphasized that "a list of essential drugs does not imply that no other drugs are useful, but simply that in a given situation these drugs are the most needed for the health care of the majority of the population and, therefore, should be available at all times in adequate amounts in the proper dosage forms".

The List served as a stimulus to all countries to consider the available options for establishing cost-effective drug policies in the public sector. It has also highlighted the most serious lacunae among the drugs available to treat the major transmissible diseases endemic in developing countries and, in some measure, it has itself stimulated research and development of drugs for tropical diseases.

- The establishment of the *Action Programme on Essential Drugs* in 1981 as an operational programme concerned with support to Member States to ensure the regular supply of essential drugs with particular emphasis on primary health care (see section 7);
- A new emphasis on WHO's catalytic role in developing *training opportunities* for the different categories of personnel involved in all aspects of the provision of pharmaceutical services and their regulation.

### THE RATIONAL USE OF DRUGS

The manifest impact and potential of the essential drugs concept led to a call by the Health Assembly for the Organization to adopt a leadership role in promoting the rational use of drugs. The issues, as they relate both to flow of information and the role of marketing practices, were discussed in detail at a conference of experts, drawn from all interested parties, convened in Nairobi in 1985, and they have subsequently been incorporated in WHO's *Revised Drug Strategy* (WHA39.27).

This Strategy embodies all pre-existing activities and includes additional responsibilities, notably:

- preparing guidelines for national drug policies;
- preparing guiding principles for small national drug regulatory authorities;
- compiling model prescribing information to complement the WHO Model List of Essential Drugs;
- updating ethical criteria for medicinal drug promotion;

- examining the role of the pharmacist and clinical pharmacologist in promoting rational drug use;
- undertaking health systems research on socio-economic aspects of drug use;
- strengthening market intelligence, including information on prices of drugs and starting materials, and
- preparing a report on the world drug situation.

Accordingly, "Guidelines for Developing National Drug Policies" and a report on the "World Drug Situation" have been published recently.

Updated "Ethical Criteria for Medicinal Drug Promotion" were adopted by the Forty-first World Health Assembly in resolution WHA41.17.

### TRADITIONAL MEDICINE

In most developing countries, where coverage by health services is limited, it is to the traditional practitioner or to folk medicine that the majority of the population turn in sickness and treatment, in large part, is based on the use of medicinal plants.

The attention paid by health authorities and administrations to the use of *medicinal plants* has increased considerably, although for different reasons in different settings. In developing countries, this has largely resulted from a decision to take traditional forms of medicine more seriously and to explore the possibility of utilizing them in primary health care. In other countries, health authorities have been compelled to react to the great surge of public interest in the use of herbs and plants.

Medicinal plants have received extensive coverage in the press and lay publications, much of it uncritical and unverified and some even dangerous. Ensuring safety in the use of medicinal plants and remedies derived from them has obliged health authorities not only to come up with measures for control but also with programmes of public information and professional education.

A basic approach, therefore, has been to *bring together modern scientific medicine and proven useful traditional practices* at the primary health care level. The first step here is the formulation of relevant national policies and decisions on this question and, under certain circumstances, the elaboration of a legal framework of the practice of traditional medicine.

### 3. Drug legislation, regulation and registration

#### EVOLUTION OF REGULATORY REQUIREMENTS

Throughout the 1960s, when many countries were still instituting statutory systems of drug regulation, WHO provided an international forum for the discussion and elaboration of norms for the technical assessment of drug safety. Many basic recommendations on the pharmaceutical, toxicological and clinical aspects of drug evaluation were issued in the WHO Technical Report Series at that time.

WHO maintains a watching brief on the situation, as it relates both to pharmaceutical products, through its contacts with regulatory authorities and manufacturers, and through exchanges of view among members of its Expert Advisory Panels. Overall, however, the Organization is now less involved than formerly in the provision of didactic technical guidance for drug regulators. The broad scientific principles of drug assessment have long been established insofar as contemporary knowledge allows. The divergences now apparent in national policies and practices are without significant public health implications and they are unlikely to yield to further attempts to forge an international consensus. It is, nonetheless, necessary to remain alert to new developments that may impinge upon existing practices. The recent rapid evolution of biotechnology is a case in point, since fundamentally new approaches to the production of biotechnologically-derived substances establish a need for new approaches to their control.

The biennial *International Conferences of Drug Regulatory Authorities (ICDRA)*, held under the aegis of WHO, are intended to provide a forum for the discussion with a view to:

- promoting collaboration between national drug regulatory authorities;
- facilitating timely and adequate exchange of technical information;
- forging a consensus on matters of mutual interest; and
- discussing contemporaneous issues of international relevance in drug control.

Emphasis has now been directed, within the context of WHO's Revised Drug Strategy, to the needs of small national drug regulatory authorities who share with their larger counterparts a

basic responsibility to ensure that all products subject to their control comply with acceptable standards of quality, efficacy and safety. They differ insofar that a small authority has strictly limited capacity to engage in independent technical assessments of drug products. They are consequently largely dependent upon the provision of authoritative information generated abroad to furnish the required assurances in relation to imported pharmaceutical products and drug substances. This is available, in a *bilateral* context, through the WHO Certification Scheme and in a *multilateral* context through WHO's network of Information Officers.

Work is already in hand to develop guiding principles for small authorities that will provide the basis for a simplified product licensing system attuned to the Certification Scheme. If it is to be effective, however, this guidance will need to be supported by practical initiatives directed to providing the technical training and the data storage and retrieval facilities indispensable to an effective control operation. A document has been published in 1981 by the Organization on the "Basic Elements of Drug Legislation".

Technical support is being provided to developing countries in drafting drug legislation and in implementing regulatory control of essential drugs.

#### EXCHANGE OF INFORMATION ON REGULATORY DECISIONS

The exchange of regulatory information has become in recent years a very important activity. It confronts the Secretariat not only with an intensive operational responsibility but also with the technical challenge of placing national decisions into global perspective. Its importance is reflected in a series of some twenty resolutions from the governing bodies, one of which (WHA28.66) requests the Director-General, *inter alia*, to disseminate to Member states *evaluated* information on drugs. Direct relationships with all national regulatory authorities have been established through the creation, in 1980, of a network of formally-designated "Information Officers" and through the institution of the International Conferences of Drug Regulatory Authorities. A monthly newsletter is produced by WHO and circulated to

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competent national authorities in all Member States. A quarterly subscription journal, "WHO Drug Information", publishes summaries of the most important regulatory decisions.

The national "Information Officers", who were initially nominated at the invitation of the Director-General, are charged with providing information to WHO on the safety and efficacy of pharmaceutical preparations and with securing prompt transmission to national health authorities of new information on serious adverse effects. To date, 132 governments collaborate in this exchange of information.

### INTERNATIONAL NONPROPRIETARY NAMES (INN)

The selection of internationally-recognized nonproprietary names for pharmaceutical substances has become one of the most highly visible of WHO activities in the drug field. These names, sometimes called "generic" or "common" names, are vital in facilitating communication in medicine, as well as for providing a basis for the licensing, labeling and advertising of medicinal products all over the world.

Since it was first established in 1950 (WHA 3.11), the WHO programme on the selection of international nonproprietary names has published the names of roughly 5000 new products. Its role is to coordinate and harmonize the activities of existing national drug nomenclature commissions, which have come to accept a common set of conventions for devising generic names. Officially-assigned generic names now rarely differ from the INN, and some countries have disestablished their national commissions and automatically accept all recommended INNs.

The procedure for selecting INNs allows manufacturers to contest those names that are either identical or similar to their licensed trademarks. In contrast, trademark applications are disallowed, in accordance with present procedure, only when they are identical to an INN. A case for increased protection of INNs is now apparent as a result of competitive promotion of products no longer protected by patents. Rather than marketing these products under the generic name, many companies apply for a trademark derived from an INN. This practice endangers the principle that INNs are public property; it can frustrate the rational selection of further INNs for related substances, and it will ultimately compromise the safety of patients by promoting confusion in drug nomenclature.

Agreement is consequently needed both with manufacturers to discourage them from applying for trademarks that are derived from INNs and with national drug regulatory authorities to obtain their support in discouraging the use of such trademarks.

### BIOLOGICALS

WHO drafts *International Requirements for Biologicals* which, on adoption by the Expert Committee on Biological Standardization, may form the basis of national legislation if a health administration so desires. So far they have been adopted by more than 120 Member States.

With the assistance of the four International Laboratories for Biological Standards, WHO through the Expert Committee, establishes *International Reference Materials* to provide a means of assuring uniformity throughout the world in the designation of the potency, activity, or specificity of preparations that are used in the prophylaxis, therapy or diagnosis of human and some animal disease. The World Health Assembly recommended that Member States give official recognition to these materials. It is a measure of their value that some 11,000 ampoules were distributed in 1987 to some 80 countries.

### TRADITIONAL MEDICINE

That many traditional remedies are of therapeutic value is no longer open to doubt. However, their use as manufactured products should be governed by the same standards of safety and efficacy as are required for modern pharmaceutical products. Proof of safety should take precedence over establishing efficacy, and accuracy in labelling the constituents of medicinal plant remedies is critical for safety evaluation and drug control.

Where safe and simple medicinal plant remedies have been employed traditionally for a long time in the treatment of minor self-limiting conditions, establishing efficacy may not be so important, provided their composition is known.

However, where a medicinal plant remedy, traditional or otherwise, is to be marketed for the treatment of more serious conditions, the manufacturer should demonstrate both safety and efficacy before the product is licensed. A pre-market review is indispensable if the dangers of exaggerated claims and ineffective or unduly toxic medicaments are to be avoided.

## 4. Quality assurance

### PHARMACEUTICALS

The *International Pharmacopoeia* was established at a time when drug quality and safety were assured principally through the operation of pharmacopoeial standards and before the introduction of statutory product licensing procedures. With the development of national regulatory systems, the original aspiration that the Organization should seek to unify the various national pharmacopoeias has proved untenable, but the case for maintaining published compendia of pharmaceutical specifications by WHO has prevailed. Indeed, in recent years it has become more compelling as a result of increased trade in generic products and the circulation of products in export markets that are not registered in the country of origin.

These developments have led to a *reappraisal of the role of the International Pharmacopoeia* and priority has been accorded to developing monographs for substances contained within the WHO Model List of Essential Drugs.

Work has started on the compilation of monographs for final dosage forms and, as far as is practicable, reliance is being vested in classical methods of analysis that can be performed in a small, modestly-equipped laboratory which is recommended as a cost-effective investment in any country where no provision for quality control as yet exists (TRS 704).

Dependence upon costly *chemical reference substances* which are vital for purposes of comparison in many pharmacopoeial tests and which are offered free of charge to governments by a WHO Collaborating Centre located within the Swedish Cooperative of Pharmacies, is being reduced by the introduction of international standard infra-red spectra.

*Simplified (or basic) tests for drug substances* have also been developed to complement, but not to replace, pharmacopoeial standards. These provide a simple and readily applicable method for verifying the identity of a drug substance, using a limited range of widely available reagents. In some instances they also indicate whether gross degradation has occurred. Work is now in hand to develop analogous tests for the same substances in widely-available dosage forms.

The Action Programme on Essential Drugs is providing technical support at the country level for the purpose of improving quality assurance of locally manufactured or imported drugs.

### BIOLOGICALS

The various documents describing *International Requirements for Biological Substances* contain descriptions of procedures which taken together with the *International Reference Materials* provide the basis for the quality assurance of these products and are guidance for the manufacturer and the national authority of that manufacturer.

Monographs will be prepared for inclusion in the *International Pharmacopoeia* to provide, for the national authorities of importing countries, the standards with which the product must comply at any time within its period of use. These are not intended to be interpreted as manufacturers release specifications.

In addition to this largely advisory role WHO has specific objectives for certain *vaccines*. The Health Assembly agreed that WHO should jointly with UNICEF carry out all the technical functions necessary to assist governments in carrying out BCG vaccination programmes. At present on behalf of WHO the Statens Seruminstitut, Copenhagen, applies batch release procedures to all batches of vaccine intended for supply to the Expanded Programme on Immunization.

International certificates of vaccination against yellow fever are valid only if the vaccine manufacturer has been inspected and the facility its production methods and seed virus have been approved by WHO.

A special situation exists for *oral polio vaccine (OPV)* where WHO assumed the full responsibility for evaluating and approving a manufacturing facility and batches of the vaccine, in the manner of the exercise of control by a national control authority. Any laboratory wishing to prepare vaccine from the Sabin strains of polioviruses must be specifically approved by the Director-General on the advice of a special scientific committee.

The Organization is currently investigating the proficiency of laboratories world wide to determine the *potency* of oral polio vaccine and measles vaccines. The results of these studies will be used to define test procedures, dosage and the most suitable mechanism to assure conformity of procedures internationally.

WHO, through inspection of manufacturing facilities and random checks on vaccine lots,

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acts in an *advisory role* to UN Agencies on sources of vaccines meeting the WHO Requirements. Although it is not able to provide a similar service to Member States, it does arrange contacts with regulatory authorities or WHO Collaborating Laboratories which may be able to provide advice and help.

The WHO *guidelines for the national control of vaccines and sera* make it clear that the national authorities are responsible for the suitability of the biological substances used in the community and that national quality control facilities should be established before any manufacture of biologicals is contemplated. This important obligation of the national authorities is not always well recognized when schemes for the production of biologicals are initiated.

The success of the procedure for evaluating the acceptability in principle of vaccine proposed to UN Agencies for use in the Expanded Programme on Immunization has demonstrated a need for a wider scheme to include other products. It is apparent that Member States, appreciating the special nature of biologicals, are not necessarily prepared to accept the assurance of the national authority in the country of origin that products offered for sale conform to the international requirements. The necessary assurance could be provided by the drafting of guidelines for the procedures to be followed by a national authority licensing the product of a local manufacturer and a statement from a national authority that it fully complies with these guidelines. It is clear that this is an important and difficult area since current activities to evaluate vaccines for the Expanded Programme on Immunization have shown serious deficiencies in the expertise of some national authorities in complying with the guidelines and in the performance of the tests described in them.

In order to diminish the variation in assessments of the potency of a product by different countries a programme is under way to evaluate competence of national laboratories by inviting them to participate in *proficiency studies*. The immediate result will be to identify competent national laboratories able to assist neighbouring states by exchange of expertise and prepared to undertake the testing of products whose potency is in doubt. The long term aim is to promote regional self-sufficiency in matters relating to the potency of vaccines.

Not all the biologicals in the WHO Model List of Essential Drugs are the subject of international requirements. In order to provide additional assistance to the less developed countries monographs will be prepared for these bi-

ologicals. It is recognized that the tests necessary to confirm conformity with the monograph may not be available in these countries but the existence of the monograph will inform national authorities and strengthen licensing procedures.

## GOOD MANUFACTURING PRACTICES AND THE QUALITY OF PHARMACEUTICAL PRODUCTS MOVING IN INTERNATIONAL COMMERCE

The *Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce* and the associated recommendations for *Good Practices in the Manufacture and Quality Control of Drugs* have been made available since 1975. The Scheme extends and unifies various arrangements operated by the health authorities of some drug-exporting Member States which issue "free-sale" certificates on request to foreign importers in order to convey certain assurances about the quality of pharmaceutical products manufactured under their jurisdiction. It also confers an obligation on the authority in the exporting Member State to provide details of its inspection and control procedures and to institute relevant enquiries should a certified product be found to be of unacceptable quality.

Recently the Scheme has been extended in its scope to embrace pharmaceutical substances as well as finished dosage forms, to cover veterinary as well as human medicinal products, and to provide for exchange of the product information approved in the country of origin (resolution WHA41.18).

In technical terms, the importance of the Scheme stems from a realization that the quality of a pharmaceutical product cannot be adequately controlled solely by the analysis of samples of the finished dosage form. Rigorous standards of manufacture need to be maintained if consistent purity, stability and bioavailability are to be assured. It is a basic tenet of drug regulation that these standards should be codified by regulation and enforced by inspection. They touch upon every aspect of the manufacturing process from the design and maintenance of the premises, including provisions for sanitation and hygiene, to qualifications of personnel and requirements laid down for in-process quality control. A paramount advantage of the WHO Certification Scheme, over the pre-existing national free-sale certificates, is that the assurances regarding plant inspection are tied to an interna-

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tionally-accepted, normative definition of Good Manufacturing Practices.

Added emphasis to the need to improve the implementation of the Certification Scheme is given by resolution WHA41.18 which, *inter alia*, requests governments, pharmaceutical manufacturers and WHO to cooperate in detecting and preventing the export or smuggling of falsely-labelled, counterfeit or *substandard pharmaceutical preparations*. Drug quality has long been identified as a particularly acute problem when products are bought in the public sector through open tender. In these circumstances, any supplier may submit a bid in response to a published request. In the absence of rigorous certification of these bulk lots of drugs as they move in commerce around the world there is no "pedigree" to establish their true origin.

Much of the problem stems from an inadequate understanding of the objectives and operation of the Certification Scheme and sometimes from a lack of appreciation that it should be applied with at least the same rigour to generic as to branded products. An important priority, particularly now that the Scheme has been formally amended, is to prepare guidelines on its use, and subsequently to monitor the impact of this advice.

The existing document will now be revised in the light of amendments extending the scope of the Scheme adopted by the Forty-first World Health Assembly. This revised text will also be incorporated, together with detailed guidance on the use of the Scheme and extracts from Expert Committee reports on the use of pharmacopoeial analyses and the management of a national quality control laboratory, in a projected publication on guiding principles for small national drug regulatory authorities.

As many developing countries still lack even rudimentary quality control laboratory facilities, bilateral assistance has increased in recent years (e.g., from Federal Republic of Germany, France, Japan, Norway) providing support for analytical control laboratories and training of staff.

Several countries importing finished dosage forms and lacking their own quality control facilities now use regional and other quality control laboratories for their drug testing. Some drugs deteriorate when exposed to high temperature and humidity—antibiotics, vitamins and hormones being particularly susceptible to degradation. It is of great concern that drugs shipped to developing countries are often exposed to temperatures considerably above rec-

ommended storage temperatures for prolonged periods during shipment and local storage. The result may be loss of potency and even harmful side effects, which may not be recognized as such. WHO, in collaboration with UNICEF, are investigating the problem. WHO and UNICEF are jointly undertaking to review the stability of drugs during shipment to recipient countries. The outcome of this study will not only be of benefit to UNICEF, WHO and the recipient countries but will, hopefully, provide information useful to all parties involved in the supply of essential drugs.

### THE PRODUCTION OF DRUGS BY BIOTECHNOLOGY

Drugs especially vaccines have been produced for decades by methods involving biotechnology. Recently, however, powerful new tools have been developed which pose problems for the licensing authorities of producing and importing countries. Nevertheless the problems are not new in principle and can be encompassed within the existing framework.

Factors of special concern are those that affect the expression of foreign genes introduced into pro- and eukaryotic cells, the conditions required to maintain the efficient controlled expression of stable cloned DNA sequences, the elimination of agents used in the purification processes, as well as the limits for unwanted gene products, and biologically active extraneous components (such as DNA, proteins and adventitious agents, including retroviruses). WHO has drafted requirements for hepatitis B and interferons produced by recombinant DNA technology but, recognizing the need for a coherent international policy, WHO has commissioned a review of national and international action to control and license the products of recombinant DNA technology and is actively monitoring developments with the intention of drafting general guidelines.

### BLOOD AND BLOOD PRODUCTS

The setting up of an organization for the collection and fractionation of human blood and blood components calls for a great deal of expertise and considerable investment. Any country contemplating the establishment of such an organization should carry out a careful cost-benefit analysis to determine whether the investment is justified. The collection and distribution of whole blood, the separation of whole blood into components, and the fractionation

of plasma batches is a logical developmental sequence for a comprehensive organization. It is not always possible to be specific about the details of the procedures employed, the in-process controls, or the tests applied at each stage of production. This is particularly the case with whole blood and component cells. Although the general principle of fractionation of plasma is well established, there are in practice numerous variations in the details of the production steps.

The general prevalence of certain infectious diseases, such as various forms of *hepatitis*, *human immunodeficiency virus (HIV) infection*, and of *parasitic diseases*, differs so markedly in different geographical regions that each national authority must decide for itself whether the application of the most sensitive test on each blood donation is cost-effective and whether it is feasible to collect suitable source material.

Rapid technological developments in the measurement of biological activity of blood products and related substances require the establishment of international biological reference materials. The first two international reference materials (for anti-A and anti-B blood typing sera) were established in 1950, and a number of materials are currently under investigation for the preparation of new standards. Furthermore, the increased demand for the use of blood products is resulting in the extensive movement of such products between countries. Internationally accepted requirements are therefore necessary in order that countries without any regulations concerning blood products and related substances may refer to these requirements when importing such products. WHO has recently revised the international requirements, and is constantly monitoring the

situation with respect to developments related to infection with HIV.

### TRADITIONAL MEDICINE

A first step towards quality control would be to review on a national basis the utilization of *medicinal plants* in general and of medicaments derived from them. Such an examination might reveal opportunities for making greater use of safe and effective galenical preparations which might stimulate local cultivation and production and at the same time permit economies to be made, saving scarce foreign currency.

In any event, experience in the preparation and utilization of galenicals is a necessary prerequisite for clinical evaluation of traditional remedies, when these have been identified as meriting further study. Such evaluation may present many problems, particularly with compound medicines, containing several ingredients.

National inventories of medicinal plants are essential if sound programmes for their rational use and exploitation are to be developed. Such inventories, still to be made in many countries, need to describe the geographic and climatic distribution of medicinal plants, their source (collection from the wild, cultivation *in situ* or *ex situ* in botanic gardens, commercial plantations) and an indication of their relative abundance or scarcity.

For each plant there would be an account of its utilization (eg. folk medicine, traditional healers, pharmaceutical or food industries) and its place in commerce (eg. local use, internal trade, export). There would also be a description of its constituents, pharmacological properties, and therapeutic indications.

## 5. Drug safety and efficacy

### DRUG ASSESSMENT AND EXCHANGE OF INFORMATION ON LICENSED PRODUCTS

The pre-eminently pharmacopoeial approach to drug control was decisively changed by the thalidomide tragedy in the early 1960s. At a time when pharmaceutical innovation had gathered unprecedented momentum, pharmacopoeial quality standards and national poisons schedules were revealed as inadequate mechanisms for assuring drug safety and controlling trade in medicinal products. Henceforth, it became mandatory to accord more consideration to the biological activity of the

drug substance as a criterion of safety. Virtually at a stroke, governments found themselves obliged to engage directly in assessing the quality, efficacy and safety of products, in authorizing their marketing, in controlling their sale, in regulating their promotion and distribution, in monitoring their performance under routine conditions of use and, in a few instances, in setting up compensation schemes for drug-induced injury. In order to provide a regulatory framework for such control many governments simultaneously and independently created systems for formal licensing of individual products. Many of the products at issue, however,

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were widely available in international commerce and it was inevitable that new responsibilities would devolve upon WHO including the following:

- establish minimum basic requirements and recommend standard methods for the clinical and pharmacological evaluation of pharmaceutical preparations;
- secure regular exchange of information on the safety and efficacy of pharmaceutical preparations; and
- secure prompt transmission to national health authorities of new information on serious side effects of pharmaceutical preparations.

### COLLABORATION WITH THE UNITED NATIONS ON DRUG SAFETY

The mandate for the annual production of the *UN Consolidated List of Products whose Consumption and/or Sale have been banned withdrawn, severely restricted or not approved by governments* is provided by UN Assembly Resolutions (37/137 and 39/229). These cite concern regarding damage to health and the environment resulting from the export of products banned and/or permanently withdrawn in the country of origin. They emphasize the lack in many developing countries of the necessary information and expertise to keep up with developments in this field.

A memorandum of collaboration for the production of the list has been agreed upon which outlines the division of responsibilities between the organizations concerned and which charges WHO with responsibility for collecting, screening and processing information relating to regulatory measures taken by governments on pharmaceutical products.

### INTERNATIONAL DRUG MONITORING

During the early development of national drug monitoring programmes it was considered that WHO might assume an important coordinating role, not only in the exchange of drug regulatory decisions but also in the collation of reports of suspected adverse reactions. It was assumed that, by pooling data internationally, more secure early warning could be provided of unanticipated drug-related adverse effects. This aim has been partly compromised by the inevitable time-lags within the system and because of problems inherent in the interpretation of the data. However, collation of the data submitted by the 27 national centres par-

ticipating in the *WHO International Monitoring Programme* provides a useful working tool for the countries directly involved.

Since 1978, the operational activities of the Programme have been transferred within the Department of Drugs in Uppsala, Sweden, which has been sustained on funds allocated by the Ministry of Health. New mechanisms for more rapid selective transfer of relevant information are now being subjected to pilot testing. Some governments have imposed explicit statutory requirements on multinational drug companies to report adverse reactions to their products. In a broader context, WHO is maintaining a watching brief on developments in epidemiologically-based approaches to monitoring. Two needs are now apparent:

- to develop a more formal collaborative relationships with national centres that are developing epidemiological approaches to drug surveillance both with a view to advancing methodology and to training regulatory personnel in these approaches, and
- to provide a forum for epidemiologists working in regulatory authorities, in pharmaceutical companies and in universities to review the feasibility and reliability of alternative methods, to examine the prospects for increased international collaboration in the investigation of common problems, and to advise on the determination of research priorities and cost-effective deployment of resources.

### BIOLOGICALS

WHO needs to be better informed concerning clinical experience with biological products. National procedures for the reporting of adverse reactions do not necessarily include the available information on reactions to vaccines from different sources. This information is important, not only to the national authorities, but also to WHO since if an unsatisfactory vaccine complies with the international requirements these should be revised to exclude that product.

A consequence of the initiative for the Global Eradication of Poliomyelitis is a strengthening and an increased awareness of the Expanded Programme on Immunization with improved flow of information through the Regional Offices.

A data bank is being established to collate reports of adverse reactions to vaccines from different sources and to monitor their overall safety and efficacy.

## TRADITIONAL MEDICINE

It is often claimed, and is widely believed, that remedies of natural origin are harmless and carry no risk to the consumer. Nothing could be further from the truth, particularly where there is a risk of toxic plants being used by mistake or where "herbal preparations" are marketed with the addition of undeclared potent synthetic substances. In all countries, there is still a need to make readily available up-to-date and authoritative data on the beneficial properties and possible harmful effects of traditional remedies.

The problem is by no means simple, especially since most developing countries have not just a few but an abundance of medicinal plants that are used in their traditional forms of medicine. The planning of pharmacological and clinical studies to assess their safety and therapeutic efficacy, the decision to cultivate them commercially, and the development of policies for

their conservation all require some form of priority ranking or assessment of their relative values and importance.

Safety should be the overriding criterion in the selection of herbal medicines for human use, especially in the health service system.

Different procedures for screening, chemical analyses, clinical trials and regulatory measures should be applied to the various groups of products, namely:

- total plants or parts thereof;
- crude extracts; or
- pure phytochemicals.

Whereas a less stringent procedure could be applied to the first two groups of products, the same procedure applicable for synthetic drugs should be applied to the last group. In addition to the need for descriptive monographs on plant material, there is also occasionally the need for reference natural substances.

## 6. Narcotic drugs and psychotropic substances

Psychotropic and narcotic drugs under international control form about 10% of the total number of drugs on the market and some are used world wide.

They are used in medicine for the management of neuropsychiatric disorders and some have special indications. However, most of this class of drugs have *varying degrees of dependence liability* and abuse potential and are, therefore, likely to be abused. Internationally, they require close collaboration within the various offices under the Secretary-General of the United Nations, (e.g. INCB, UN Division of Narcotic Drugs) and WHO. They require also particular attention within the overall drug policies at national level.

One of the mechanisms used today to promote the rational use of psychoactive drugs is through establishing the benefit/risk ratio of a substance. Another very important element is through its proper use. This involves the manufacturers, distributors, officials in health services and members of the health care professions. The Executive Board, in resolution EB69.R9, has specifically requested the Director-General to promote activities in this direction.

### WHO'S RESPONSIBILITIES UNDER THE INTERNATIONAL DRUG CONTROL TREATIES

The following are the different components of these responsibilities:

- WHO inherited from the League of Nations a responsibility to recommend to the Secretary-General of the United Nations narcotic drugs which require international control and its level of control. The 1961 Single Convention on Narcotic Drugs (and its amending protocol of 1972) continued to lay that responsibility on WHO. In August 1976 the 1971 Convention on Psychotropic Substances came into force, which also requires WHO to recommend control of psychotropic substances. These recommendations apply primarily to single substances but also to combination products which contain those substances. The Organization has also recommended control of some so called "designer drugs" — i.e. analogues of controlled substances, having no therapeutic use. The abuse of such substances has recently produced significant public health and social problems in some parts of the world.

## DRUG MANAGEMENT AND POLICIES

- The basis for recommendations for the control of a substance by the Director-General is through evaluation of risk benefit ratio of a substance by an Expert Committee on Drug Dependence, or under certain circumstances by an informal group.
- The Expert Committee uses criteria for evaluation covering both benefit and risk issue involved. These criteria have been developed by WHO through Expert Committees or other groups. They include evaluation of psychopharmacological effects, dependence liability, therapeutic usefulness, public health and social problems. Efforts have been made to facilitate understanding of the effects of these drugs by the medical profession, e.g., through the publication of "Guidelines for the Clinical Evaluation of Psychotropic Drugs in Neuropsychiatric Disorders."
- Since the coming into force of the 1971 Convention, WHO has developed a set of guidelines for review of dependence-producing psychoactive substances for international control. The guidelines were commended by the UN Commission on Narcotic Drugs.
- All information collected by WHO including that from the United Nations Division of Narcotic Drugs, Interpol, pharmaceutical industry (IFPMA), and directly from countries is presented in a *Critical Review* document. A programme planning working group meets yearly to examine the Critical Review document for its completeness and makes recommendations for review of substances in future and on the programme as a whole. The WHO Expert Committee on Drug Dependence examines the Critical Review document and makes recommendations to the Director-General who forwards them to the Secretary-General of the United Nations. The UN Commission on Narcotic Drugs then decides on the WHO recommendations. WHO has evaluated about 160 substances in the last 12 years (the total number, including those re-evaluated, approaches 200). All recommendations for the control of these substances have been accepted by the UN Commission on Narcotic Drugs.
- Exemptions for combination products are provided for under the 1971 Convention which requires WHO, the UN Commission on Narcotic Drugs and countries to give an opinion. WHO was requested to develop guidelines for granting such exemptions. These guidelines were prepared and about 1000 preparations have so far been evaluated.

### GUIDELINES FOR IMPLEMENTATION OF THE TREATIES

It has also been recognized that countries require support from WHO and other UN agencies in their efforts to ratify a treaty and to obtain the maximum benefit from it. WHO has responded to resolution WHA 33.27 (1980) which had requested the Director-General:

"to promote the initiation and strengthening of national and international programmes for the assessment, scheduling, control and appropriate use of narcotic drugs and psychotropic substances, including those of plant origin and to support such programmes by the development of appropriate guidelines in consultation with the United Nations Division of Narcotic Drugs, INCB and other UN bodies concerned."

Accordingly, guidelines have been prepared in an effort to support WHO Member States in promoting the rational use of psychoactive drugs and in directing their administration to areas where action may be required.

### LIST OF ESSENTIAL PSYCHOACTIVE DRUGS

An updated list of "essential medicines in the management of neuropsychiatric disorders" has just been produced. In 1986 at Jilin, People's Republic of China, a WHO group reviewed the rational use of anxiolytics and hypnotics in medical practice. WHO has also published a book "Rational Use of Psychotropic Drugs with Special Emphasis on Tranquillizers in Non-Psychiatric Settings" (1987).

### TRADITIONAL MEDICINE

There are a large number of natural products which are used in traditional medicine for their psychotropic and other properties. WHO has a statutory responsibility to investigate and evaluate material of natural origin to enable the UN Commission on Narcotic Drugs to decide whether to restrict the availability of those which produce dependence or are likely to be abused. *Papaverum bracteatum* (white poppy), *Catha edulis* (Khat), are examples of such plants. A comprehensive review of existing knowledge regarding the psychopharmacological characteristic of natural substances including their liability to produce dependence was recommended by the Health Assembly in the above-mentioned resolution WHA 33.27.

## 7. Essential drugs

The Thirty-first World Health Assembly adopted in 1978 resolution WHA31.32, entitled "Action Programme on Essential Drugs", urging Member States to establish essential drug lists and adequate pharmaceutical supply systems, enact legislation, and collaborate with WHO and aid agencies in doing so. The Director-General was, in turn, requested to study ways of providing, upon request, support to Member States and to develop further dialogue with pharmaceutical industries to ensure their collaboration in meeting the health needs of underserved segments of the world's population. In 1979 resolution WHA32.41 called for the establishment of a special programme on essential drugs, including its administrative structure and to make provision for its initial financing, if necessary. The *Action Programme on Essential Drugs* was established in February 1981.

Some 100 countries have already adopted essential drugs lists and more than 40 developing countries are making great efforts to implement their programmes based on the WHO concept of essential drugs. The priorities and approaches may differ from country to country in accordance with each country's socio-economic situation, but the conceptual basis is the same. WHO provides a unique and common platform for a harmonized and collective search for suitable and feasible solutions to the problem of unavailability of the most essential drugs to the majority of the world's population.

The Alma-Ata Conference on Primary Health Care recognized that the supply of essential drugs is one of the eight components of primary health care. The Conference also recommended to governments that they give high priority to the utilization of traditional medicine in the incorporation of proven traditional remedies into national drug policies and regulations. In the ten years since Alma-Ata, decision makers in the health sector of many countries have taken the first steps, among them the identification of locally available plants or plants extracts that could usefully be added to national lists of drugs for use in primary health care and which could even replace some pharmaceutical preparations that need to be purchased and imported.

### APPROACHES

Most of the resources of the Programme are directed towards technical support at country

level. Governments in industrialized countries, in many cases with WHO coordination or collaboration, have also responded positively to the *WHO Revised Drug Strategy*. Most major bilateral development agencies have adopted the concept of essential drugs and support to developing countries has grown substantially over the last few years. It is no longer possible to estimate the financial resources mobilized in support of national essential drugs programmes but it is in excess of US\$ 500 million. WHO is often called upon to give technical support to bilateral programmes to ensure that the WHO principles and experience on essential drugs enter into planning and programming. Drug regulatory agencies and ministries of health in, for example, Denmark, Netherlands, Italy, Japan, Norway, Sweden, the United Kingdom and the United States of America are providing technical services to developing countries in improving drug regulation, quality assurance, good manufacturing practices, and training.

The work is divided into four major areas:

- country support;
- development activities and training;
- operational research; and
- management, monitoring, evaluation and administration of the programme.

The programme is implemented in accordance with relevant resolutions of the Health Assembly and its overall objectives are to support Member States in:

- planning and implementing national drug policies and essential drugs programmes and projects;
- ensuring regular supply and distribution of essential drugs;
- promoting the rational use of drugs;
- undertaking collaborative research on the results of the essential drugs programmes.

### COUNTRY SUPPORT

About 70% of the Programme's budget and 60% of its activities are focussed on support to country programmes. The approach used is to carry out a situation analysis, prepared jointly by nationals and WHO staff or consultants; then, a national seminar is organized where all interested parties are invited and where priori-

## DRUG MANAGEMENT AND POLICIES

ties are selected and constraints identified. Subsequently a country action plan is prepared with the help of WHO in which cost estimates, time schedules and defined responsibilities are included. Generally this document serves as the project document for funding. When funding is assured, implementation starts. An essential drugs management unit, headed by a programme coordinator and support staff is usually created. Staff from WHO Regional Offices and from Headquarters identifies appropriate consultants for specific technical areas, gives technical and administrative support, monitors progress, reports to donors and initiates evaluation of the programme. In many countries, particularly smaller ones, the essential drugs programme is part of the country's pharmaceutical and regulatory control services as trained manpower is scarce. In others, the essential drugs management unit is an operational unit which coordinates procurement and distribution of the drugs in the public sector and undertakes training of health personnel in their management and use.

In many countries direct technical support is being provided to streamline procedures of procurement, storage and distribution of essential drugs.

### DEVELOPMENT WORK AND TRAINING

The objective of the Programme is to provide training, guiding principles, methodologies and training materials which can be used or adapted for developing and implementing essential drugs programmes including the following aspects:

#### *Selection, estimation of quantities and use of essential drugs in countries*

Estimating drug requirements is a major problem in developing countries. Two methodologies have been developed: the patient morbidity-standard treatment method and the adjusted consumption method. Both methods are based on data concerning the actual (or projected) use of health services. Their purpose is to ensure that health services concerned have adequate drug supplies to treat their case load of patients. A practical manual for estimating drug requirements was published in 1988 along with a computer programme for calculating the needs. Training of trainers in these methodologies is now taking place including therapeutic schedules (or adaptation of existing ones) for primary health care.

#### *Supply of essential drugs (procurement, local production, distribution, logistics)*

Procurement of drugs as well as raw materials for local production continues to be a major

problem area in many countries. Fragmented procurement systems, irregular availability of foreign exchange, lack of credit and limited access to information about world market prices and sources of good quality drugs often result in higher prices than necessary.

WHO provides *information on prices and sources of supplies* to countries on request. UNICEF's indicative price list on essential drugs has provided many countries with information to bargain for better prices. Most price information has, however, been restricted to European suppliers.

A procurement fund of US\$ 23 million, jointly developed by WHO and UNICEF to provide credit for reimbursable procurement from UNIPAC, has been established. It is being managed by UNICEF with about US\$ 6 million so far received. A few countries have established revolving funds, but experience so far is limited.

UNICEF and WHO are currently working on the development of a large-scale procurement initiative for Africa as adopted by the Regional Committee for Africa in Bamako in September 1987. At the moment UNICEF is purchasing relatively small quantities of drugs in relation to the global market. The value of purchases during 1987 was US\$24.5 million, but a continuing increase is expected in purchasing volume in the coming years, particularly in relation to the possibilities which will be created by the *Bamako Initiative*. However, the long-term objective in the supply of pharmaceutical products must be to encourage the purchasing arms of the appropriate ministries to establish an efficient and effective purchasing and distribution mechanism from the point of definition of drug requirements through the establishment of quantities, bidding, purchasing and distribution with an appropriate quality assurance system enveloping the process. The major advantage that UNICEF has in the area of purchasing at this time is that it is able to purchase in quantities larger than many small countries are able to do and thus obtain lower prices.

There are no easy solutions to problems of foreign exchange. Many countries, however, spend more than needed on drug importation. Consolidated procurement, more precise estimation of requirements and careful selection of the drugs needed have the potential for making more drugs available to a greater number of people. Strong competition in the international generic market for essential drugs has kept their prices relatively low.

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*Local production* (see section 8)

*Distribution, logistics and essential drugs management*

The major requirement in establishing a successful distribution system is proper education and training of the personnel involved. These are pharmacists, dispensers, administrative staff, inspectors, accountants, store keepers, packers and transporters.

Most countries request assistance to develop more efficient management information systems for their procurement of essential drugs and inventory control system. Computer programmes which have been developed with WHO technical and financial support are already in operation in several Member States. Additional countries are requesting these programmes and an evaluation is planned for 1989.

*Quality assurance* (see section 4)

*Manpower development and needs: training, drug management and rational use* (see section 10)

*Legislation and regulatory control of essential drugs* (see section 3)

*Dissemination of information* (see section 9)

### ECONOMICS AND FINANCING OF ESSENTIAL DRUGS PROGRAMMES

WHO collaborates — and co-finances its country support — with UNICEF, the World Bank, UNIDO, bilateral aid agencies, nongovernmental organizations, professional associations and the pharmaceutical industry.

Financing of *drug supplies* remains a critical issue, and reliance on donor funding continues to be great in many countries. But, whereas in the past many countries were reluctant to impose a charge for drugs, this situation appears to be gradually changing under the pressure of the economic crisis. WHO has been assisting countries to find ways of generating additional resources for drug purchase. This assistance has taken the form of country visits to help design *cost recovery systems* (some in coordination with the World Bank) and the preparation of reports informing national decision-makers about various aspects of financing drug supplies. A conference on cost recovery was held in early 1988 at which representatives of different countries met to compare experiences with different types of cost recovery and drug financing schemes.

### OPERATIONAL RESEARCH

Support to operational research in developing countries (mainly in Asia and Africa) is pro-

vided to improve the availability and rational use of drugs. The research is divided into four main areas:

- utilization of drugs and epidemiology of prevalent diseases;
- supply, logistics, technology transfer;
- economics; and
- socio-cultural aspects.

Areas which need further research are financing supplies of essential drugs and health impact of essential drugs programmes.

A network of researchers in socio-economic and socio-cultural essential drug research has been established and a first meeting, supported by WHO, has been held in Nairobi in September 1988. There is a need to identify qualified researchers in developing countries; to create awareness in research institutions of the need for relevant research in the above topic; to establish research networks between developed and developing countries to ensure that research results are utilized by health care planners.

### MONITORING AND EVALUATION

The methodology for evaluation of essential drugs programmes developed in 1985 is being reviewed after having been tested in Papua New Guinea, Thailand and the United Republic of Tanzania. Monitoring, supervision and development of indicators are areas needing more attention.

### MANAGEMENT FUNCTIONS

Functions include planning, budgeting, fund raising, coordination, information, promotion, monitoring and evaluation.

An internal management survey was carried out in 1986-1987 and the recommendations are now being implemented. Each activity is classified according to type of work and subject area and is summarized (objectives, justification, cost estimates, administration) on a project sheet and computerized. It is used for planning and implementation, allocation and earmarking of resources, monitoring progress and balancing workload.

Considerable effort has been devoted to raising the necessary extrabudgetary funds, particularly in view of diminishing hopes for additional regular funds becoming available. In 1980-81, the Programme had approximately US\$400 000 in extrabudgetary resources. In 1988-89 these have increased to close to US\$20 million and are expected to reach US\$25 million in 1990-91. The regular budget has re-

## DRUG MANAGEMENT AND POLICIES

remained largely the same during this period; it is US\$1.3 million for 1988-1989. It was a few hundred thousand dollars less in 1980-81.

Fifteen donors contribute to the Programme. These are the governments of Canada, Denmark, Finland, France, Italy, Japan, Netherlands, Norway, Sweden, Switzerland and United Kingdom, and the UN High Commission for Refugees, UNICEF, Nigeria (Trust Fund from World Bank loan), and Interpharma (Switzerland).

The Programme works very closely with the official development assistant agencies, other UN agencies and NGOs, often jointly in country development and research work. Donors are regularly informed on development and progress of the Programme. A large part of the extrabudgetary funds are tied to specific countries where donors and the World Bank — and lately UNDP — have asked WHO to act as the

executing agency for the technical and administrative work. Other parts of the funds are untied money which also serve to support countries, development work, information and research activities, and manpower in Headquarters and Regional Offices. Denmark and the Netherlands support associate professional officers (APOs) in Regional Offices and national essential drugs programmes.

In June 1988 the second *Meeting of Interested Parties* took place. The purpose of the meeting was to review together and to inform donors on progress of the Programme's current and future activities. Representatives from sixteen developing countries participated and reported on their own activities as did UN agencies (UNICEF and the World Bank), NGOs (Christian Medical Commission, IFPMA, FIP, League of Red Cross and Red Crescent Societies, Médecins sans Frontières) and official development assistance agencies.

### 8. Transfer of technology

The practicability of building up, step by step, a viable pharmaceutical production industry, with the aim of achieving self-reliance in pharmaceutical supplies, depends on many factors. These include:

- population size and per capita income;
- the available technical manpower and supporting infrastructure;
- the geographical and climatic conditions;
- water and energy supplies; and
- the distribution network.

These are often major limiting factors and, in many cases, it is not possible to produce economically all the pharmaceutical products needed in one country. Ideally, therefore, cooperation between countries is desirable. Objective feasibility studies are needed before local production can be undertaken.

Some of the larger developing countries have maturing pharmaceutical industries producing bulk materials and finished products covering most domestic needs and increasingly including exports. Many of these countries are nearly self-sufficient in the production of finished drugs but almost completely dependent on imports of bulk raw materials. Many of the least developed countries have a few formulation plants but these, with notable exceptions, have been largely unsuccessful in producing drugs at an internationally competitive price.

Without supporting industries or trained staff, and with difficulty in securing a position in the local market, many operate at low capacity and the added value from the local production of generic drugs is low.

The larger middle-income countries are likely to move towards increased self-reliance at an acceptable cost. It is quite likely that some of the maturing industries will develop innovative drugs as a result of increased investment in research and development. Many smaller countries will need to find internal or external support for the rehabilitation or modernization of their existing formulation plants; otherwise they will be forced to continue subsidizing inefficient production.

Judging from present trends, however, the developing world's share of pharmaceutical production is likely to remain small, although an increasing number of developing countries will manufacture drugs as part of their overall development strategy, to keep costs low and save hard currency. How far they will succeed will depend greatly on the size of the market, their competitiveness, their willingness to seek the technology they need and the conditions of its transfer, local ability to adapt and develop technology, and the commitment of governments to their support. It will be a challenge for those countries to reconcile economic and health goals in the production of drugs and to ensure the production of low-cost good quality essential drugs.

Some developments in the past few years have created, and will probably continue to create, new opportunities for local production. The patents of a number of products have expired and those of some of the top products in the world market will expire before 1990; there is wider acceptance of generic drugs among the public; technology is increasingly available; market intelligence in raw materials has improved in developing countries. regional cooperation is developing.

It may be expected that the international pharmaceutical industry will try to maintain its position as a producer of drugs in, and exporter of drugs to, developing countries. The question of patents will continue to be debated, and the broader economic and political situation will determine the capacity of developing countries to formulate and manage their own drug policy.

International organizations such as UNCTAD, UNIDO, and WHO are taking an increasing part in providing technical support and information to developing countries.

### BIOLOGICALS

On request and if appropriate WHO will provide advice to countries contemplating the production of biologicals, indicating sources of specialist help and arranging independent tests of materials or the first production lots.

It is regrettable this advice is not always sought and inappropriate projects are initiated which fail to produce the desired material.

Closer contact between WHO and the funding agencies to assess realistically the prospects for proposed development schemes would be beneficial. This review should include the suitability of the proposed technology as well as the national capability to maintain production and assure the continuing safety and efficacy of the product after the donor agency has left. This process could avoid the current problems with some Member States when WHO consultants

refuse to accept as satisfactory projects established with international aid.

Present efforts to strengthen regional involvement in the potency assurance of the vaccines used in the Expanded Programme on Immunization are resulting in increasing awareness of the need for regional activities in the quality assessment of all biologicals. As this process accelerates the difficulties experienced in the past will diminish.

### TRADITIONAL MEDICINE

The application of modern scientific methods in the cultivation, selection, manufacturing and clinical trials of herbal medicines is the most appropriate way to transform traditional trade into modern industrial practice. In this connection, the Chinese model, along with other models that may be identified, could be considered by other countries when developing their own systems. Industrial production would require the adoption of appropriate agro-technology in order to obtain adequate quantities of medicinal plants of standard physical and chemical quality. There is thus a need for the large-scale cultivation of such plants and to devote attention to their genetic improvement.

At the Third UNIDO Consultation on the Pharmaceutical Industry in 1987 WHO and UNIDO, agreed to:

- assist developing countries in conducting pharmacological and clinical trials on plant-derived products to ensure regulatory requirements for safety and quality standards;
- conduct special educational programmes to publicize the proper use of plant-derived herbal medicine; and
- organize consultations at regional level on various facets of the medicinal plant industry, with special emphasis on quality standards and safety, with a view to promoting the wider use and acceptability of herbal medicines.

## 9. Dissemination of information

The following are examples of activities:

- *Provisional and cumulative lists of international nonproprietary names for pharmaceutical substances* have been issued in continuity as a service to Member States since 1962.
- The *International Pharmacopoeia*, first issued in 1951, is now in its third edition. Comple-

mentary information on the objectives and use of the Pharmacopoeia are featured in the biennial reports of the WHO Expert Committee on Pharmaceutical Specifications. Additional recommendations specifically applicable to biological products are contained in the reports of the WHO Expert Committee on Biological Standardization.

## DRUG MANAGEMENT AND POLICIES

- *Basic (or simplified) tests* for verifying the identity of pharmaceutical substances contained within the WHO Model List of Essential Drugs were published in 1987 and work is now in hand to develop analogous tests for widely available dosage forms.
- The *Model List of Essential Drugs* is updated in successive reports of the biennial meetings of the WHO Expert Committee on the Use of Essential Drugs. This will shortly be complemented by the first fascicule of complementary *Model Prescribing Information* which is intended to provide source material for adaptation by national authorities, particularly in developing countries, that wish to develop national drug formularies, drug compendia and similar material. It is intended to be illustrative rather than normative since it is not possible to develop information on a specific drug that is appropriate to circumstances prevailing in each country and also because some countries have already formally adopted product specific information that has a statutory connotation. Each section is reviewed in draft by individual internationally accredited experts, members of appropriate WHO Expert Advisory Panels, and by relevant nongovernmental organizations.
- A *monthly newsletter*, which at present is circulated only to national drug regulatory authorities, contains notifications received from Member States on the regulation of human and veterinary drugs and on medical devices, and provides information on the surveillance of marketed products.
- The *UN Consolidated List* of products whose consumption and/or sale have been banned, withdrawn, severely restricted or not approved by governments, which is updated annually, is distributed through the United Nations, New York. Because new material is added monthly to the data base, work is proceeding to meet a request from the UN General Assembly to offer the information on pharmaceutical products on-line from the computerized data base maintained in Geneva.
- The quarterly publication *WHO Drug Information* provides an overview of topics relating to drug development and regulation that are of current relevance and importance, and includes the lists of proposed and recommended International Nonproprietary Names (INNs). Its contents reflect, but do not present, WHO policies and activities and they embrace socioeconomic as well as technical matters. The objective is to bring issues that are of primary concern to drug regulatory authorities and pharmaceutical manufacturers to the attention of a wide audience of health professionals and policy-makers concerned with the rational use of drugs. In effect, the journal seeks to relate regulatory activity to therapeutic practice. It also aims to provide an open forum for debate. Invited contributions will portray a variety of viewpoints on matters of general policy with the aim of stimulating discussion, not only in its columns, but wherever relevant decisions have to be taken.
- The *Essential Drugs Monitor* is published in English, French and Spanish and provides information on activities in the essential drugs field. Its purpose is to share information and experience. It includes regular features on essential drugs programmes in different countries, news items, rational use of drugs, recent publications and on WHO activities.
- An *Essential Drugs Documentation and Distribution Centre* has been established and provides an information service and materials to health ministries, professionals and others. Continuous requests have resulted in thousands of documents being distributed annually to developing and developed countries. The Centre is also used as an education resource for professionals going to or working in developing countries.
- A *Market Intelligence System* on raw materials for the production of essential drugs has been established in accordance with a request of the World Health Assembly. Suppliers of raw materials, brokers and trading houses as well as purchasers of raw material provide information to a central computer system which, in turn, produces information on the range of transactions of about 60 different pharmaceutical raw materials. It is too early to determine the usefulness of this system, but it is assumed that if well operated it will enable formulating plants in developing countries to obtain raw materials at a lower prices than at present. It is intended later to transfer the system to an organization that will operate it on a fee for service basis.
- Information on *quality control of biologicals* is disseminated both through its publications in the Technical Report Series and documents containing the results of collaborative studies.
- *Psychoactive Drugs: Improving Prescribing Practices*: this book has been published with a view of promoting the rational use of psychoactive substances by physicians.

- A bibliography of all publications since 1947 on "WHO's Response to International Drug Treaty Obligations and Drug Dependence" has been issued recently.
- The *International Traditional Medicine Newsletter*, published by the Chicago Centre reports on the work of WHO Collaborating

Centres and on country experiences. It provides individuals and institutions with a means of keeping in touch with developments in the subject in other parts of the world. NAPRALERT which is the acronym for *Natural Product Alert* consists of a computerized database on the medicinal uses of natural products.

## 10. Education and training

The need for more opportunities for training personnel engaged in both drug licensing and analytical control is appreciated, not least by regulatory authorities themselves. The issue repeatedly attracts debate within the *International Conferences of Drug Regulatory Authorities* which have expressed the hope that WHO would maintain an information centre on ongoing and projected activities, but to monitor what is being accomplished and to promote equitable use of available resources.

The following are examples of activities:

A collaborative scheme has been developed by the International Federation of Pharmaceutical Manufacturers Associations, the World Federation of Proprietary Medicine Manufacturers and WHO. Since 1979, over 100 technicians employed in governmental quality control laboratories in developing countries have received extended periods of training in the laboratories of research-based manufacturing companies. Group training in quality control and in the principles of drug licensing have also been co-sponsored with several national authorities and nongovernmental organizations.

*Training in the production and quality control of biologicals* is an area of special difficulty. It can only be comprehensively achieved within the facility of a large producer. The large comprehensive national control laboratories accept WHO fellows for training but are unable to provide the necessary experience in many aspects of inprocess control, which are so essential for the production of most biological products.

Some *intercountry workshops on essential drugs* took place in 1986 and 1987. More than 20 national workshops were supported in 1986 and 1987, as well as five interregional seminars. Training material was developed by WHO in collaboration with the Management Sciences for Health, Boston, USA. It was then translated into French after evaluation and

improvement, and was sent to French-speaking countries in Africa for comment and possible use.

*Teaching and training materials in logistics and distribution of essential drugs* have been tested in workshops at regional and national levels and are now ready for wider application. Training of primary health care workers, including physicians, is expanding rapidly. Additional countries have developed training and teaching materials for this target group, using documentation and materials prepared and supplied by WHO.

A number of countries are beginning to review the curricula of their schools of pharmacy, medicine, etc., to include the essential drugs concept and to put more emphasis on the rational use of drugs. Workshops have been held for this purpose in Bangladesh, Bhutan, Democratic Yemen, Egypt, India, Nepal and the United Republic of Tanzania and Yemen. Educational material for patients on the correct use of drugs, with accompanying materials for the health worker, has been field-tested.

A network was formed in 1986, with support from WHO and the Mario Negri Foundation, Milan, to promote *clinical pharmacology* and collaboration among developed and developing countries. A second meeting of collaborators took place in 1988 in Zimbabwe. Clinical pharmacology was also an important topic in a course on *drug epidemiology* research held in Stockholm in May-June 1987 for 25 participants from eight developing countries. Identification of potential candidates for training in clinical pharmacology is part of the country situation analysis carried out.

*Psychoactive substances* require special attention at national level. The officials who provide statistics to International Narcotics Control Board (INCB) and the UN Division of Narcotic Drugs require special training. WHO

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has undertaken training activities in various regions of the world to familiarize various groups of professionals regarding national responsibilities of the treaties. In 12 such meetings, 800 trainees participated.

Collaboration has been developed with some countries on *training on rational use of psychoactive drugs*. For example, WHO and UNFDAC have worked closely with the authorities and the health professions in the People's Republic of China since 1980. A new Centre for Prevention of Drug Dependence has been established at the Beijing Medical University and professionals have been trained abroad in methods for drug analysis in body fluids and for the evaluation of dependence liability of both synthetic and natural substances. WHO has collaborated in the organization of four seminars on the rational use of psychotropic drugs for physicians and pharmacists in various universities in China. Similar collaboration has been developed with several countries, including Argentina, Barbados, Finland, Nigeria, Norway, Thailand, United Kingdom, United States of America and Union of Soviet Socialist Republics.

At the Fourth International Conference of Drug Regulatory Authorities co-sponsored by the

Ministry of Health and Welfare of Japan and WHO and held in Tokyo in 1986, a workshop was held on *traditional herbal medicines*. It was acknowledged that these medicines play an important part in health care in many countries, developed as well as developing. It was noted that truly traditional practices are more amenable to influence through education and training than to statutory control. The workshop also concentrated on the exploitation of traditional medicine through over-the-counter sales for labelled products on a commercial basis and addressed the need for legislation, quality, standards, and information.

*The selection and use of traditional remedies in primary health care* was the subject of an inter-regional workshop, held in Bangkok in 1985. The workshop was the first in a series intended to address problems of safety and efficacy of traditional remedies (including the related issues of standards, stability and dosage formulation). It was followed by satellite workshops at country level at which a number of single plant remedies were examined and selected for use in health services. Further workshops are planned for South East Asia and for countries of East, Central, Southern and West Africa.

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