I. INTRODUCTION

The Twenty-second World Health Assembly in resolution WHA22.41 requested the Director-General "to examine possible ways of providing advice to governments in developing machinery for evaluating the therapeutic safety and efficacy of drugs and to report to the Executive Board and the Twenty-fourth World Health Assembly". The Director-General reported to the Executive Board at its Forty-seventh Session and the present report takes into account the views expressed during the Board's discussion.

The report first deals with drug control regulations; then it sets out guidelines for the organization of a national regulatory agency; finally it gives an indication of the possible role of WHO in this connexion.

II. DRUG CONTROL REGULATIONS

During the last decades the production and use of drugs have increased in all parts of the world. There has been greater awareness on the part of physicians, national health administrations and the public that the specificity, potency, and growing variety of drugs now available aggravate the difficulty of ensuring optimum results without undue risk and that efficient control must be exercised over the efficacy, safety and pharmaceutical quality of drugs as well as over information on their indications and use.

To this end regulations, varying widely in scope and form, have been developed by governments, together with the machinery required for their implementation. Although the structure of such machinery varies from country to country the principles on which it is based are similar.

Regulations should be designed mainly to cover the following characteristics of drugs: (a) efficacy and safety for the recommended indications for use; (b) pharmaceutical quality; (c) information on drugs. Such regulations, and any procedures intended to control drugs should be incorporated in national health legislation. Such legislation is a necessary first step in the establishment of a drug control administration. Legislation ensures consistent administration, and also that the position of the government authorities and their procedures are clearly defined to all concerned.

1. Efficacy and safety

Efficacy and safety are two facets of a single problem and must be considered together. Approval or rejection of a particular drug should be based upon an estimate of the anticipated benefit relative to the potential risk. Since the permissible risks in the administration of a drug to a patient with, for example, cancer or a massive systemic infection are very different from those in the use of a mild analgesic or a drug to relieve the symptoms of coryza, the benefit/risk equation must be evaluated separately for each recommended indication.

1 Off. Rec. Wld Hlth Org., 176
General principles for therapeutic investigations to demonstrate, scientifically, the efficacy and safety of a drug have been developed by WHO scientific groups. They constitute a valuable basis for regulations controlling such investigations. These regulations, however, should be flexible, to allow for the full development of professional expertise.

The results of pre-clinical and clinical investigations on a given drug, evaluated by the scientists who have planned or performed them, together with any relevant conclusions and recommendations, must be submitted to the governmental authority concerned for consideration and appropriate action. These results should prove, with reasonable certainty, the efficacy and safety of the drug for the recommended indication, notwithstanding the fact that further experience of its adverse and therapeutic potential may be obtained after it has come into use.

Comparison of the efficacy of different drugs for a specific indication may be difficult. However, new drugs that are clearly less effective than those already on the market should not be accepted when this lower degree of efficacy is not counter-balanced by advantages. Governments of countries that import drugs, or that manufacture drugs developed elsewhere, should bear in mind the fact that differences in nutritional state, climatic and other environmental conditions, as well as genetic factors can influence the efficacy and safety of drugs. But, where such differences are not to be expected and where the therapeutic requirements are similar, arrangements between governments or groups of governments for the mutual acceptance of drugs are advisable.

Government authorities should dispose of adequately trained personnel to deal with these studies. However, as it is unlikely that any such authority would be able to employ specialists in all branches of the sciences concerned, it should be prepared to seek outside help from professional experts in the various fields of therapy and prophylaxis.

The considerations outlined above relate to the requirements that may be imposed on producers of drugs when approval is requested either for the sale of new drugs or for the maintenance on sale of established drugs. However, the responsibilities of governments with respect to a particular drug, whether new or established, are not fully discharged when the drug has been accepted. After a drug has been used in general medical practice for some time, complementary information accumulates on its efficacy and safety from both scientific research and clinical uses. This information may persuade the regulating authority to modify the terms of the original approval.

It may be advisable to promote regulations to impose requirements on manufacturers or institutions undertaking drug research, before studies on human subjects are undertaken. These requirements could include presentation of details about the composition of the drug and available data about its pharmacological and toxicological properties in animals, the qualifications of the investigator and identification of the institution in which the work is to be done, an outline of the proposed procedures in human subjects and a statement that the informed consent of the participants has been obtained. A further important requirement should be that the protocols and results of these initial trials be reported fully to the government authorities concerned.

In approving a drug, these authorities will decide whether it should be freely available to the public or subject to different degrees of limitation. The regulations on distribution, which would be attached as a condition of the individual approval, may depend upon the territory concerned, the availability of professional and technical personnel, or hospital facilities, etc., and the needs of the public. Where more than one government department in a country is concerned with regulations on the distribution and use of drugs, there should be co-ordination under the direction of the national health authority.

2. Pharmaceutical quality control

The quality of a drug is primarily defined in terms of identity, strength and conformity to specifications. Specifications for quality control are to be found in national or international pharmacopoeias, in similar compendia, or in documents submitted by manufacturers to the government; these specifications ensure the standards of drug quality. Another important aspect of pharmaceutical quality control is production control. Requirements for "Good Practices in the Manufacture and Quality Control of Drugs" were recommended by the Twenty-second World Health Assembly in its resolution WHA22.50.1

3. Information on drugs

Governments should accept responsibility for ensuring that all information and publicity provided by the manufacturer is consistent with the terms under which a drug was approved for use. All such information material should contain the essential facts concerning indications, forms of administration, dosages, contra-indications, and adverse reactions, as agreed upon when a drug is accepted. Any anticipated changes in this material should, as a rule, be reported to the government in advance. In certain cases, e.g. new indications, government agreement should be obtained before any changes are instituted. The physician also needs critical comparative drug evaluation from independent sources. In order to ensure such evaluation, health authorities and medical organizations should be encouraged to provide information on drugs.

Information designed for the general public requires special consideration; in particular no information or advertising should be directed to the general public that: (a) induces consumption of drugs through fear; (b) stimulates unnecessary self-medication; or (c) recommends treatment where medical attention is necessary. The Twenty-first World Health Assembly in resolution WHA21.412 emphasized the need for Member States to enforce the application of ethical and scientific criteria for pharmaceutical advertising.

WHO transmits to governments decisions by any health authority to prohibit or limit the availability of drugs if such decisions have been taken as a result of serious adverse reactions or because of lack of substantial evidence of effectiveness in relation to toxicity and the purpose for which the drugs are used.3 Additional information on drugs may be produced by the monitoring of adverse drug reactions at national and international levels.4 Such information will become more widely available as monitoring systems develop. National authorities should disseminate to the physician, if appropriate, the information derived from the above warning mechanisms.

4. Cost of drugs

The cost of drug consumption, like other forms of expenditure on medical care, is increasing year by year. Authorities who have to meet drug cost will feel a growing need to assure themselves that this expenditure is justified. The cost of a drug should be in proportion to such aspects as need, efficacy, and safety. If official action is to be taken in this field it should, therefore, be decided upon by the appropriate government department, in conformity with those departments that have expertise in prophylactic and therapeutic requirements.

1 Off. Rec. Wld Hlth Org., 176, Annex 12
2 Handbook of Resolutions and Decisions, 10th ed., p. 113, resolution WHA21.41
3 Handbook of Resolutions and Decisions, 10th ed., p. 111, resolution WHA16.36,
Off. Rec. Wld Hlth Org., 184, resolution WHA23.48
Wld Hlth Org., 184, Annex 8 (WHO Pilot Research Project for International Drug Monitoring, Report
by the Director-General). A WHO international group of experts defined drug monitoring as "the
systematic reporting, recording and evaluation of adverse reactions to drugs generally available
In summary, governments have a responsibility to ensure that all drugs on the market are efficacious and safe, that the pharmaceutical quality of the drug is satisfactory and that the information provided by the manufacturer for each drug is correct with regard to indications, directions for use, contra-indications, and adverse reactions. These tasks should be performed without undue delay. Health authorities could also undertake other responsibilities in this area, such as those of controlling clinical trials of drugs and collecting and disseminating drug information.

III. GUIDELINES FOR THE ORGANIZATION OF A NATIONAL REGULATORY AGENCY

1. General considerations

A regulatory agency should fulfil the main functions described, as well as other related functions that may be desired. Some countries have already taken steps to establish such an agency. In others it has yet to be developed; this may be a difficult and time-consuming task, but the ultimate goal should be an adequate organization of this kind to some individual countries or groups of countries.

Some countries may wish to extend the facilities and effectiveness of the drug regulatory agencies they possess; others may wish to establish such agencies. The realization of such plans depends on the availability of funds, accommodation, equipment, and manpower. It should be stressed that, because of the serious consequences to human health that may result from any decision made by a drug regulatory agency, the professional quality, impartiality, and dedication of the staff is the primary consideration for its contribution to public health. Further, the agency should be able to perform the services mentioned without undue delay, which would seriously interfere with the availability of new drugs.

The first priority in the establishment, extension, and maintenance of a drug regulatory agency should be the education and training of specialists in the fields of efficacy and safety of drugs and their quality control including the surveillance of manufacturing. Education and training can be achieved on an individual basis or in groups, and by exchange of professional experience on a national and international basis by written information, symposia and scientific meetings, with emphasis on the development of working methods and the exchange of results of regulatory activities.

2. Registration of drugs

The regulatory agencies should be aware of all available drugs. Therefore they require a complete record of drugs. For drugs manufactured by the industry and sold as pharmaceutical preparations, this should be effected by registration. At the time of registration the efficacy and safety of the drug should be evaluated. It should be possible to withdraw registration of a drug if sufficient new evidence has accumulated to invalidate the earlier decision.

Drugs are also compounded according to pharmacopoeias and other official formularies, and in some countries these do not need to be registered. It is important that some criteria of efficacy and safety be applied when these drugs are accepted or included in official compendia; therefore the evaluation of this type of drug should be made by the same regulatory agencies as above.

Some patients may, for various reasons, such as a rare disease or allergy to certain drugs, need efficacious and safe drugs that are not available in the two groups mentioned. Means should exist for such patients to obtain the necessary drugs.

Regulatory agencies which register or approve for the first time the drugs available in their country may find it difficult to evaluate all the drugs already marketed for their efficacy, safety and pharmaceutical quality within a short period. Such circumstances may
call for provision of transitional dispositions. However, ultimately no drugs should be registered or approved that do not meet the full requirements of efficacy and safety.

The calculation of the selling price of drugs might also be considered by the regulatory agencies.

3. Technical structure of national regulatory agencies

The regulatory agency should be adequately staffed with specialists in pharmacology, toxicology, therapeutics, and pharmaceutical quality control. For effective execution of the work it will be necessary to have access to laboratory facilities. The pharmacological and toxicological evaluations will, to a large extent, be based on the documentation submitted by the manufacturer, but the agency should also have the facilities to undertake independent control studies, particularly for pharmaceutical quality control. All these activities of the regulatory agency should preferably be located together in a single institute or unit. The experts on drug therapy who are in this unit should have access to and work in close co-operation with clinical departments. They should be physicians trained in clinical pharmacology1 or clinicians with special training in therapeutics.

4. Administrative structure of national regulatory agencies

The responsibility for making decisions must rest with the government. The government department best suited for this purpose is the department of health. Decisions may however be made either by the department or by any other agency to which such powers are delegated. It is important to ensure the independent status of the decision-making body with regard to the industry, whether the latter be private or public. There should be adequate machinery for deciding controversial issues by some appellate authority.

5. Use of advisory bodies

It is impossible to have expert advice in all disciplines concerned within the governmental structure. Therefore it is necessary in all countries to utilize the services of competent non-governmental experts drawn from universities, medical and other scientific institutions, and the industry. Such services should be used freely when deemed desirable. Standing advisory committees of such experts will, for many purposes, play a more useful role in this connexion than will ad hoc committees, although the latter may be required in special cases.

IV. POSSIBLE ROLE OF WHO

In order to support Member States in the implementation of the activities described above, WHO is using the following means of co-operation and assistance:

(a) the provision of fellowships for the training of personnel of different professional categories;

(b) the organization of regional or inter-regional seminars on drug quality control;

(c) the inter-governmental drug information system established under resolutions WHA16.362 and WHA23.483;

(d) information provided by the monitoring of adverse drug reactions (which will be extended in the future to cover a progressively larger number of countries);

2 Handbook of Resolutions and Decisions, 10th ed., p. 111.
(e) the data contained in the technical reports and other publications of WHO on specific problems of therapy as well as on principles for the testing and evaluation of drugs for their efficacy and safety.

Having regard to what is at present available, to the need that has been stressed for the development of adequately qualified staff for drug regulatory agencies, and the request made to the Director-General in resolution WHA22.41,1 "to examine possible ways of providing advice to governments in developing machinery for evaluating the therapeutic safety and efficacy of drugs", the following are possible ways in which WHO could make further contributions to improvements in this field:

(a) organization of:

   (i) workshops, seminars and symposia, for government officials dealing with the registration of drugs, on principles for pre-clinical and clinical evaluation and on surveillance of drugs on the market;

   (ii) scientific meetings for the development of methodology for the study of drug action in man.

(b) assistance in the establishment of teaching and research centres, for the training of clinical pharmacologists and for investigations in clinical pharmacology.

(c) improvement of the international reporting system which transmits substantive decisions taken in respect of particular drugs and concerning the efficacy and safety of drugs. (Suggestions to that effect have been made in the Director-General's letter of 11 August 1970 to Member States).

In order to avoid unnecessary duplication of effort, and where facilities are likely to be limited for some time, co-operation between governments with similar needs and able to work together on a region-wise basis may be a fruitful way to make use of scarce resources. While it is incumbent upon the governments themselves to appreciate the desirability of such a course of action, WHO would stand ready to assist in any possible way.

1 Off. Rec. Wld Hlth Org., 176