The rational use of drugs

Report of the Conference of Experts
Nairobi, 25–29 November 1985

World Health Organization
Geneva
For reasons of economy, and in order not to delay its distribution unnecessarily, this report has been photo-offset from typescript and has not received such detailed editorial revision as other WHO publications.

The World Health Organization is a specialized agency of the United Nations with primary responsibility for international health matters and public health. Through this organization, which was created in 1948, the health professions of some 160 countries exchange their knowledge and experience with the aim of making possible the attainment by all citizens of the world by the year 2000 of a level of health that will permit them to lead a socially and economically productive life.

By means of direct technical cooperation with its Member States, and by stimulating such cooperation among them, WHO promotes the development of comprehensive health services, the prevention and control of diseases, the improvement of environmental conditions, the development of health manpower, the coordination and development of biomedical and health services research, and the planning and implementation of health programmes.

These broad fields of endeavour encompass a wide variety of activities, such as developing systems of primary health care that reach the whole population of Member countries, promoting the health of mothers and children, combating malnutrition, controlling malaria and other communicable diseases including tuberculosis and leprosy, having achieved the eradication of smallpox, promoting mass immunization against a number of preventable diseases; improving mental health; providing safe water supplies, and training health personnel of all categories.

Progress towards better health throughout the world also demands international cooperation in such matters as establishing international standards for biological substances, pesticides and pharmaceuticals; formulating environmental health criteria; recommending international nonproprietary names for drugs; administering the International Health Regulations; revising the International Classification of Diseases, Injuries and Causes of Death; and collecting and disseminating health statistical information.

Further information on many aspects of WHO's work is presented in the Organization's publications.
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PREFACE

In 1984 the World Health Assembly requested the Director-General of the World Health Organization to arrange a meeting of experts of the concerned parties, including governments, pharmaceutical industries, and patients' and consumers' organizations, to discuss ways of ensuring the rational use of drugs, in particular through improved knowledge and flow of information, and to discuss the role of marketing practices in this respect, especially in developing countries.

The meeting, named "Conference of Experts on the Rational Use of Drugs", was held in Nairobi, Kenya, from 25 to 29 November 1985.

In 1986 the Health Assembly requested the Director-General to publish the report of the conference and to ensure its wide dissemination.
PART 1

DIRECTOR-GENERAL'S SUMMING UP OF THE ISSUES, THE PROCEEDINGS AND THE POTENTIAL IMPLICATIONS FOR WHO'S PROGRAMME
POTENTIAL IMPLICATIONS FOR WHO'S PROGRAMME

Introduction

1. I should like to start by thanking you all for your contributions and
for keeping the climate of the Conference highly constructive. I cannot
possibly incorporate all your comments in my report, nor can I do full
justice to the many proposals you made, all within the time at our
disposal. All I can do is give you an impressionistic picture of the
proceedings. However, I can assure you that copious notes of the discussion
have been taken and that I shall use these in preparing a full report to the
World Health Assembly next May. As I see it now that report will consist of
an executive summary dealing with the issues I shall now try to outline, as
well as a more detailed account of the proceedings. I shall be consulting
the Executive Board's Ad Hoc Committee on Drug Policies at the end of
January on the report before finalizing it for the Assembly.

2. I think the Conference has been very useful in identifying the problems
in all their complexity and in permitting you who come from such different
backgrounds to exchange views. Yes, in spite of the number of participants
and wide spectrum of expertise and experience there has been a dialogue, and
I believe this has resulted in a better understanding – a better mutual
understanding – of the different situations each of you are facing and the
different solutions you have found or are trying to find. It became clear,
to me at least, that many of you are facing quite different problems and
therefore see matters in quite different perspectives. As I said in my
opening statement, we must not allow the problems and solutions of one group
of countries to be transferred to another group of countries for which they
are not necessarily relevant.

3. At the same time, I could discern a number of issues on which there
appeared to be a high degree of agreement, even if there were different
viewpoints about how best to deal with them. Again, these viewpoints
naturally tended to reflect the background of those who expressed them. So
I shall dwell on those issues and will point out where there is agreement,
where there is a lesser degree of agreement and where there is none at all.
I shall, of course, bring all the issues to the attention of the World
Health Assembly.

4. There seemed to be general agreement on the importance of governments
displaying the political will to formulate and implement national drug
policies incorporating an appropriate drug information system. I also
sensed strong support for strengthening national drug regulatory mechanisms
or setting them up where they do not exist. The importance of ensuring good
quality drugs for all at the lowest possible cost was also stressed again
and again, particularly for developing countries. Nobody contested the need
to ensure ethical drug advertising, although there were differing opinions
about the best ways of doing that. The importance of rational prescribing
was agreed upon by all. The need to improve drug distribution systems was
generally acknowledged. And there was universal support for the development
and implementation of national essential drugs programmes. I shall take those up one by one.

5. But before doing so I would add that there was a general understanding of WHO's international as opposed to supranational role. WHO is a cooperative of Member States and it is they who decide on its policy. Some years ago they agreed to carry out individually what they had decided collectively. That is the key to appreciating the respective roles of governments and of WHO in the field of drugs as in all other fields. Policies can be defined in WHO but cannot be imposed by WHO. Once governments have adopted these policies in WHO they are expected morally and otherwise to implement them domestically and in their relationships with other countries, or, if they do not wish to do so, to adopt other policies collectively.

National drug policies

6. And now to national drug policies. The Conference expressed overwhelming support for the suggestion that governments should formulate and implement national drug policies as an integral part of national health policy for attaining the goal of health for all by the year 2000, which, I would remind you, was inspired by the principle of social equity. The aim of such a drug policy should be to ensure the constant availability of and access to efficacious drugs of acceptable quality and safety to all in need wherever they live and whatever their socioeconomic status, including dwellers in urban slums and rural areas. By implication, such drugs must be really required to improve or maintain the health of the people concerned and to combat the diseases from which they suffer. The concept of essential drugs, as has been decided by the World Health Assembly unanimously, is thus universally applicable, although the interpretation of what is essential is a national responsibility and each country will decide in the light of its health problems, socioeconomic circumstances and managerial capacities. WHO's model list of essential drugs - a "common core" of basic needs which has universal relevance and applicability - should be used more widely by interested countries and WHO should take the necessary steps to ensure that it is widely available, not only in WHO's official languages but also in additional local languages.

7. The wide variation in health problems, socioeconomic circumstances and managerial capacities in the countries of the world makes it inevitable that there will be wide variation in national drug lists. In some countries, to ensure social justice it will be necessary, if only for economic reasons, to start by ensuring that the whole population has access to those drugs that are absolutely vital to carry out the national health policy, with emphasis on primary health care in community health facilities. Then would come the other essential drugs for the first referral level and central hospitals. Even in the most affluent countries, individual medical practitioners use their own limited lists of drugs, in some countries there are limited lists for general practitioners decided by governments, in others only drugs on the list are reimbursed but patients can buy other drugs at their own expense, many hospitals have hospital formularies, and differential pricing and taxation can ensure greater use of some drugs and lesser use of others.
The harmonization of such lists is important to permit rational use by consumers, who are entitled to access to different practitioners and hospitals; the extent and manner of ensuring such harmonization should form part of the national drug policy and is a national responsibility.

8. It can be seen that the concept of essential drugs enshrined in the national drug policy conforms to WHO's definition of appropriate technology for health - that is, it is scientifically, socially and economically sound. Scientifically sound implies that it is of proved efficacy. Socially sound implies that it is acceptable both to those on whom it is used and to those who use it. And economically sound implies that it can be afforded by individuals, the community and the country as a whole.

9. I think the discussion and the field trip demonstrated the need for continuing health systems research to ensure that the drugs available meet health needs, are constantly available in sufficient quantities, and are properly prescribed and used by patients. That would of course include social and economic studies, as a number of you pointed out.

10. So far, the accent has been on national responsibility. At the international level, WHO should widely disseminate guidelines for national drug policies. The outline of such guidelines was endorsed by the Thirty-fifth World Health Assembly. They were subsequently elaborated further. They should now be speedily updated and disseminated to all governments.

Drug information

11. You emphasized that national drug policies should include as an essential component an appropriate information system to satisfy the need for impartial, objective information on drugs - for prescribers, patients and policy makers. One comment was that information should precede the availability of drugs. Another was that a drug is a chemical entity plus information. The international standardization of drug information was proposed but the problem of relevance for different societies appears to be formidable.

12. The quantity of information is no less important than its quality. There is too much information on drugs and too little on people's health problems for which they may or may not need drugs. It is also important to stress what is not known.

13. What kind of information is required? Prescribers need information that can help them to choose between different treatments, as well as detailed information about a particular treatment once it has been selected. Just as important, they need information on what to tell patients about treatment, including drug therapy. There was support for convening a group of people with the relevant experience to study this question. To choose between different treatments, prescribers need information on efficacy - i.e., does the drug do what it is stated it can do; effectiveness - does the drug improve the patient's health; and medical indication - is the drug optimally effective in the given circumstances.
Information is also badly needed on the cost of drugs, since this might well be the decisive factor concerning choice.

14. Who should provide such information? Governments have the ultimate responsibility, but a number of countries have found it useful to have multidisciplinary, widely representative, consultative groups to advise them.

15. A useful way for governments to provide information to prescribers is to prepare national drug formularies or at least national drug data sheets. You felt that WHO should prepare model data sheets and formularies for preparations on WHO's model list of essential drugs but that the ultimate responsibility for preparing them and distributing them free of charge rests with governments. Much more attention should be given to presenting information attractively and ensuring that it reaches those who deal with patients. You considered national drug bulletins a useful medium for disseminating information to prescribers and international collaboration in this area of potential benefit. WHO's drug bulletin will be enhanced as outlined in the discussion document.

16. It was pointed out that some prestigious journals are offering governments space for objective information on drugs free of charge. Others should be encouraged to follow suit, and if possible given financial incentives. Drug regulatory authorities and WHO should regularly provide information to editors in the form of bulletins, monographs, etc. Editors have responsibility for the provision of ethical information.

17. Experimentation is taking place with computerized drug information systems in a number of developed countries, aimed at providing a telecommunication service to prescribers. These may eventually become more widely available once experience is gained and, if the volume is kept reasonable, software packages are made available for microcomputers. In that event, they may soon be useful in a number of developing countries too, or at least in some parts of them.

18. There was general approval of the measures to improve drug information to the public. The important role of doctors, nurses and pharmacists was stressed. General information should be provided on measures for health promotion and disease prevention and on the uses and limitations of drugs, in addition to specific information on particular drugs. Mothers in particular should be stimulated to demand adequate standards of care. Drug education should become part of general health education. WHO should be more active in providing popularized drug information. Some suggestions were made to issue publications on such matters as drugs in pregnancy and during childhood, as well as on contraceptive measures. One of you pointed out that there is a contradiction between popular demand for drugs on the one hand and non-compliance in their use on the other. Again, social studies are required to ascertain how best to inform the public in different sociocultural settings. It was suggested that WHO arrange for a consultation of experts aimed at issuing guidelines.
19. I sensed that you approved of measures to make the decisions of national drug regulatory authorities more widely known, including reasons for restricting or rejecting drugs.

**National drug regulatory authorities**

20. You were unanimous in stressing the importance of national drug regulatory authorities in every country, no matter what its stage of socioeconomic development. To start off, some countries may have to content themselves with simple mechanisms, but if they do, it should be clear that proper drug registration has to be instituted as early as possible. When considering registration the benefit of the drug has to be compared with its risks. Some form of inspection and enforcement is essential. Yet, many of you felt that too bureaucratic an approach should be avoided and that the advice should be sought of a wide range of disciplines in the health service and the teaching institutions. Some of you felt that regulation should be restricted to quality, safety and efficacy, with greater emphasis on education than on regulation. Others, however, felt that, particularly in developing countries, the regulatory authorities should distinguish between what is essential, what is less essential and what is not essential in registering drugs, in order to keep the national drug list at a size that is commensurate with the country's socioeconomic and managerial capacities. WHO's essential drugs concept would seem to be highly relevant for this purpose.

21. A number of suggestions were made for strengthening the regulatory capacity of developing countries. These included that more advanced regulatory authorities in developing countries should be asked to support less advanced ones, and that developed countries should support the developing ones in strengthening their drug regulatory mechanisms. WHO's role should be coordinating and catalytic, encouraging bilateral and multilateral arrangements. It should be very active in providing information, with no supranational overtones. External support should always have an educational component to promote national self-reliance in drug regulation and WHO should provide fellowships in this field. You also agreed that the International Conference of Drug Regulatory Authorities should be extended to cover additional developing countries and that simultaneous interpretation should be provided to permit all countries to participate.

22. It appears that international norms for drug labelling are hardly possible. Rather, it was suggested, guidelines should be prepared on good labelling practice within countries and for drugs moving in international commerce.

23. However, guidelines such as these are only part of the story. You all seemed to favour the idea that WHO should convene a group to produce WHO guidelines on minimum requirements for drug regulation. These guidelines should be in the form of points to be considered in setting up drug regulatory mechanisms. In the final analysis, once more, establishing such mechanisms is a government responsibility.
24. You also all seemed to favour enlarging WHO's Certification Scheme, and a number of you spelled out in which ways it should be broadened in scope and more developing countries encouraged to use it. You suggested that WHO convene a group of experts to prepare this broader scheme.

Costs

25. You all seemed to agree on the importance of reducing costs, and on the expedient of using market forces to that end. Yet invitations by developing countries for open international competitive tenders have their problems too. To be effective, they have to be accompanied by quality control and people have to be trained in the techniques of inviting tenders so that the country can become self-reliant in drug procurement. Then problems arise with payment, particularly due to lack of foreign currency, leading sometimes to cancellation of the order and urgent purchases of smaller quantities by air freight. It was pointed out that in the final analysis the resources available for drugs dictate the scope of drugs available. I am afraid you did not suggest concrete solutions to these problems, although identifying them is in itself a useful precursor to finding solutions. One of you pleaded with bilateral agencies to dissociate financial loans or gifts from the need to purchase in the country of the so-called donor, since this could negate the advantages of international competition.

26. An interesting remark was that cheaper procurement would hinder the development of local production. But another comment was that the competition of local production helps to bring about cheaper bids from foreign companies.

27. I was particularly touched by the statement that many developing countries have no markets, so that it is difficult to talk of market forces there. This brought a plea to UNICEF for access to UNIPAC for both drugs and raw materials, and I was happy to hear the assurances of UNICEF's representative on those scores.

28. As for total or partial cost recovery from patients, viewpoints differed widely. Some of you felt that for people in least developed countries that was out of the question. Others felt that even a symbolic payment would encourage lighter use of drugs and greater respect for them. One suggestion was for graded payment in accordance with ability to pay. Then of course practices range widely in many countries with respect to pre-payment when well or payment when ill.

29. Finally, WHO was asked to act as a clearing house on drug costs. In view of the unanimous agreement about WHO's international and not supranational role, I presume this means an information clearing house.

Research

30. Two kinds of research were identified - research to improve essential drug systems and research to develop new drugs. I have already referred to the first kind. You seemed to have varying viewpoints about drug research
and development, and in particular about its funding. Governments, foundations, WHO and industry are all involved in that.

31. It is still difficult to know how much money is required to generate new drugs. The need to recuperate funds for research from the sale of drugs was stated by some of you. Yet others claimed that those funds should be recuperated from people in developed countries since they are the main beneficiaries of most drug research. In my humble opinion the only way to even start to sort out this question is to collect relevant and coherent facts; they are very difficult to get hold of.

32. Finally, a proposal was made that WHO should establish a special programme of assessment of health care technology including the rational use of drugs.

Production

33. I would repeat my comment about the need for relevant and coherent information with respect to local production too. One or two of you were categorical that all developing countries should set up local production facilities, even if they have to start by packaging alone. Others were more cautious, pointing for example to the problem of raw materials and their transfer pricing, and in general to the situation that sometimes arises whereby local production costs more than procurement from abroad. At the same time, it employs local labour and saves some foreign currency. I should point out that the Thirty-fifth World Health Assembly, when it endorsed the main lines of a national drug policy, advocated technical and economic feasibility studies before embarking on local production. I repeat that in my opinion we have to collect more facts before we can be more rational on this matter.

Right to prescribe, distribute and sell drugs

34. I think you realized the need for flexibility concerning the right to prescribe, distribute and sell drugs, depending on the availability of manpower in the country concerned. Some countries with adequate numbers of doctors and pharmacists can be highly restrictive. Others have to be more permissive, particularly in rural areas, allowing non-professional health workers to prescribe certain drugs; without that there would be no primary health care in the community. Again this illustrates the importance of national decisions. At the international level only general principles can be enunciated.

Prescription practices

35. Again, you all seemed to realize the importance of improving prescription practices. You indicated that the means to do so are better information, proper training and continuing training throughout the health worker's career, from the most senior medical prescriber to the humble non-professional village health worker. At the same time, it was pointed out that only if there is constant availability of the right drug is it possible to prescribe rationally and train people to do so. Another comment
was that, within limits, the fewer the drugs any one prescriber has to select from, the greater the likelihood that she or he will prescribe rationally.

36. Obviously rational consumption is an essential partner of rational prescribing. I have already referred to the education of consumers, not only with respect to individual drugs when they are patients, but also to their education in health care in general and the proper place of drugs in that. The often negative influence of the mass media on rational drug use was mentioned, and a plea was made to hold dialogues and seminars with them to improve the situation.

Promotion

37. All of you spoke in favour of the application of ethical criteria in drug promotion, whether by sales representatives, by advertising, by the provision of free samples or by means of symposia sponsored by industry. But many of you differed in your concepts on the scope of these criteria and the manner of their application.

38. There was a general feeling that the pharmaceutical industry has major responsibility for complying with established criteria and avoiding different standards in different countries. But opinion differed as to the best way of ensuring compliance by industry. Some of you felt that voluntary compliance, with a degree of independent advice, was the best method. Others felt that governments should ensure compliance, and should be active in denouncing infringements. Also, the role of the health professions was mentioned in resisting spurious advertisements, and people in general were advised to be vigilant, whether as individuals or in associations such as consumer groups.

39. On one point there seemed to be general agreement, and that is that there is no place for supranational regulation of drug promotion by WHO. At the same time, a plea was made for WHO leadership in preparing appropriate guidelines. I presume that what was meant was the updating and expansion of the criteria for drug advertising approved by the Twenty-first World Health Assembly in 1968, so that these could be adapted by governments to national circumstances and used by them and by industry. I shall certainly bring that proposal before the World Health Assembly.

Legislation

40. Many of the issues you discussed and I have briefly mentioned require appropriate legislation if they are to be put into effect. Once more you stressed that such legislation has to be national in character, since it has to be tailor-made to the circumstances in each country. At the same time, some of you asked WHO to provide information on points to be considered when formulating national drug legislation as well as on drug legislation in different countries. There was also a plea for WHO to provide advisory services on the formulation of drug legislation on the request of any of its Member States. An opposing view was that WHO should not get involved in that. Well, I must point out that such support is part of WHO's
constitutional mandate, and I would remind you again of the synergism between collective policy and individual national policy that I mentioned before.

**National essential drug programmes**

41. I understand that there is unanimous support for the further development and implementation of national essential drug programmes along the lines described in the working papers and in WHO's Technical Reports Series, so I shall not dwell any further on that highly important point. I think the field trip demonstrated just how important these programmes are, and at the same time how much remains to be done to improve them in countries where they exist and to introduce them where they do not yet exist. Many of you have thanked the Government of Kenya through our Chairman for having made that demonstration possible, and I should like to take this opportunity of expressing the gratitude of WHO as a whole to the Government of Kenya for having acted as a pioneer and showing what it is possible to achieve when the political will is there.

**Education and training**

42. There was unanimous agreement on the importance of adequate education and training for all categories of health personnel as a prerequisite of rational drug use. This should continue throughout their career. The subjects to be learned include drug regulation; product approval; quality control; drug information, including the interpretation of information; new areas of drug development; the economics of drug development, distribution and availability; the concept of essential drugs; research on essential drugs, their proper use and related managerial issues; and the assessment of health care technology, including drugs. A new type of subject emphasized was training health workers how to communicate information to people.

43. Among the kinds of people to be trained you mentioned prescribing physicians; pharmacists; nurses; non-professional primary health care workers; drug regulators; clinical pharmacologists, particularly those concerned with primary health care; deans and leaders of health institutions; medical representatives; policy makers; and consumers. You also pointed to a number of learning mechanisms. These included tripartite seminars provided by the academic community, government and industry; bilateral training schemes, possibly on a regional basis with faculty going out to the host developing country; designation of academic institutions as undergraduate or postgraduate training centres; provision of fellowships; seminars, including those for senior people such as deans and leaders of health institutions; regional training programmes; use of local radio; development of appropriate training curricula; provision of distance learning material for prescribers and pharmacists; preparation of guidelines for prescribers and pharmacists concerning the education of consumers; and distribution of essential books, including those on drug regulation.
44. You all felt that WHO had a major role in stimulating and coordinating education and training on drugs. One of you even suggested that WHO should establish an action programme on training in current drug concepts so as to make more people in more countries aware of them.

Responsibilities

45. In my humble opinion this Conference has at least had the effect of stimulating dialogue among experts with widely different viewpoints and of bringing home to you the importance of cooperation rather than confrontation. Many of you were anxious to spell out the respective responsibilities of all those concerned with making drug use more rational in the ways you have indicated. These include governments; the pharmaceutical industry; prescribers; universities and other teaching institutions and professional nongovernmental organizations; the public, patients and consumer groups; the mass media; and, last but I hope not least, WHO.

46. Here is a list of the main responsibilities you have identified for governments:

- Establishing national drug policies; instituting or reinforcing essential drug programmes and taking steps to convince health personnel and the public of their usefulness; ensuring the objectivity and completeness of drug information in the country; ensuring relevant, good quality information to the public on health matters, including drug matters; setting up or strengthening drug regulatory authorities so as to ensure adequate registration of drugs of acceptable quality and safety; safeguarding international nonproprietary names of drugs; ensuring improved training of health workers in health care, including drug therapy; taking measures to ensure that drugs cost as little as possible but yet are of acceptable quality and are constantly available; making more use of open competitive tenders for generic drugs to reduce costs in developing countries; studying ways of cost recovery; deciding who shall have the right to prescribe, distribute and sell drugs; establishing lists of drugs permitted for sale over the counter; establishing up-to-date ethical criteria for drug promotion and supervising compliance with them; enacting appropriate drug legislation and ways of enforcing it; taking measures to improve prescription practices; improving distribution systems as necessary; and studying the technical and economic feasibility and extent of local production where that does not exist or exists only to a limited extent.

47. The list is long, but the responsibilities of government are heavy.

48. And here are the responsibilities you have identified for the pharmaceutical industry:

- Providing complete and unbiased information on pharmaceutical products to all concerned - governments, prescribers and consumers; observing good manufacturing practices; complying with established drug promotional criteria and avoiding double standards in different countries; responding
to the need of developing countries for low-cost drugs of acceptable quality; and developing badly needed new drugs in neglected fields, particularly to solve the health problems of developing countries.

49. As for prescribers, they have responsibility for:

Prescribing rationally in conformity with health, as well as social and economic, criteria; providing appropriate information on health care in general, and drug therapy in particular, to patients and the public at large (dispensing pharmacists have the same responsibility); and insisting on being provided only with information that tells the truth, the whole truth and nothing but the truth.

50. Universities and other teaching institutions, and professional nongovernmental organizations, have responsibility for:

Improving the training of different categories of health workers in health care in general and in the rational use of drugs, incorporating the use of appropriate curricula and modern educational technology; introducing the concept of essential drugs in the training of health personnel; providing continuing education for health care providers; ensuring that symposia on drugs comply with acceptable educational norms; and providing general education on proper health care and drug therapy also to those not training as health workers.

51. The public, patients and consumer groups have the following responsibilities:

Improving the relevance and quality of information for the public; sharing responsibility with governments and nongovernmental organizations for the education of consumers on drug matters; maintaining vigilance and demanding compliance with established criteria for drug advertising, and drawing the attention of the health authorities to suspected infringements; and supporting essential drugs programmes.

52. The mass media's responsibilities are:

Providing relevant and balanced information on health matters, including drug therapy; sharing in public education on the proper use of drug therapy; giving favourable publicity to those complying with ethical criteria for drug advertising and unfavourable publicity to those not complying.

53. And now for WHO. What responsibilities devolve on it?

Preparing guidelines for national drug policies; accelerating the promotion of national essential drug programmes; supporting countries in carrying out technical and economic feasibility studies on local production; providing complete and unbiased information on drugs at the international level, such as by issuing model data sheets and formularies on drugs in the WHO model list of essential drugs, extending the scope of the
Drug information bulletin and publishing it more frequently, and publishing monographs on selected drug issues; making available learning material for improved training of health workers in rational drug use and helping countries to use it; reinforcing national drug regulation, such as by providing relevant information to countries, coordinating bilateral support for strengthening national drug regulatory mechanisms and facilitating related training; enlarging the Certification Scheme on the Quality of Drugs Moving in International Commerce; issuing guidelines on minimum requirements for drug regulation and expanding the work of the International Conferences of Drug Regulatory Authorities; supporting developing countries, together with UNICEF and possibly the World Bank, in procuring drugs internationally at the lowest possible cost; defining ethical criteria for drug promotion; providing governments with information on national drug legislation and helping them to formulate such legislation on request; stimulating technical and socioeconomic research on drugs and drug practices and publishing the results; fulfilling the role of lead agency in the implementation of the United Nations General Assembly resolution on the dissemination of information on drugs that have been banned, withdrawn, severely restricted or not approved by governments on grounds of safety; and studying with other appropriate bodies ways of providing information to combat the criminal offence of counterfeiting.

WHO's revised drug strategy

54. That too is a long list. What implications do I see for WHO's programmes?

I shall be bringing to the World Health Assembly a strategy for strengthening WHO's activities in support of the action required to make drug use more rational throughout the world. This strategy will include:

- intensifying further the promotion of national drug policies and the Action Programme on Essential Drugs;
- supporting the setting up by governments of drug regulatory systems;
- enlarging the scope and use of the WHO Certification Scheme on the Quality of Pharmaceutical Products moving in International Commerce;
- enhancing information collation, analysis and dissemination;
- training in rational drug use;
- defining ethical criteria for drug promotion; and
- research.

I shall take them up one by one.
55. National drug policies and Action Programme on Essential Drugs

Guidelines will be published on national drug policies. To prepare them, a consultation of experts will be convened. The Action Programme on Essential Drugs will be promoted in all relevant forums with a view to intensifying it so that it is carried out by all interested countries and that the infrastructure of these countries is capable of delivering such programmes. Related training curricula and schemes will be developed and put into effect.

56. National drug regulatory systems

A group of experts will be convened to prepare WHO guidelines on minimum requirements for drug regulation. This group would also look into the matter of preparing guidelines on good labelling practices. Measures will be taken to facilitate support by developed national drug regulatory authorities to less developed ones and WHO will ensure that appropriate information is available to countries desirous of setting up or strengthening such authorities. Countries will also be provided with information on national drug legislation that is relevant to their circumstances and they will be supported in formulating such legislation on request.

57. WHO Certification Scheme

The Scheme will be enlarged to include your recommendations. A group of experts will be convened to prepare the enlarged scheme. Measures will be taken to promote its widespread use among all countries concerned.

58. Information

The area of information will include not only the exchange of information received from countries but also such activities as the assessment of the world drug situation from time to time; issuing model drug formularies and data sheets on drugs on WHO's model list of essential drugs; analytical reviews of specific topics; widening the scope of information disseminated through the Drug information bulletin, newsletters and the like and ensuring its penetration to wider audiences; as well as intensification of information to the public. For public information, booklets will be prepared on such topics as drug use and pregnancy, drug therapy in children, contraceptives and the like. Greater thought will have to be given to communications with patients, and possibly a group of experts convened to suggest the social studies required, or, if the subject is already ripe, to prepare a publication on what to tell patients and how to tell it.

59. Training

Training curricula and schemes in pharmacology and the rational use of drugs will be developed for various categories of health care providers — doctors, nurses, pharmacists and others. Such schemes will have to take account of the need to reduce the volume of learning material and
concentrate on principles, to explain the concept of essential drugs and to facilitate the capacity to discriminate between essential and non-essential and between proved assertions and unproved assertions. A group of experts will be convened to prepare such schemes.

60. Ethical criteria for drug promotion

The ethical criteria established by the Twenty-first World Health Assembly will be reviewed and updated by a group of experts, and appropriate guidelines will be prepared accordingly.

61. Research

I have listened with great interest and sympathy to the proposals a number of you made concerning the establishment of a special programme on health care technology assessment in general and drug assessment in particular, and I shall certainly bring it to the attention of the Health Assembly for its consideration.

62. Wide involvement

The WHO strategy will also include ways of involving all those concerned. WHO Secretariat obviously cannot do all of this on its own, so experts in various fields will have to be consulted, governments encouraged to undertake the activities concerning them, contacts maintained with industry with respect to their new responsibilities, dialogues held with prescribers, universities and technical nongovernmental organizations involved in training programmes, consumer groups integrated into broader measures for social control of drug systems, particularly through the provision of valid information to the public, and contacts established increasingly with the mass media.

63. Resources

The strategy will obviously have to be costed and ways of covering costs identified. You realize that very considerable additional resources will be required. If they are not obtained, the whole strategy will be jeopardized. Quite apart from financial resources, appropriate human resources will have to be found and that may not be at all easy. I shall, of course, bring all of this before the Thirty-ninth World Health Assembly in May 1986. It may be necessary to appeal to the developed countries for voluntary funding since WHO's regular budget is fully committed until the end of 1987.

64. Report to the Thirty-ninth World Health Assembly

As I started by saying, this report is somewhat impressionistic and you may not have found in it everything you wanted. I shall, I repeat, prepare a fuller report for next year's World Health Assembly and shall be consulting the Executive Board's Ad Hoc Committee on Drug Policies before finalizing it. Most of the members of that Committee are participating in this Conference, including our Chairman, Dr Koinange, and our Moderator,
Mr Grímsson, so the Committee's review will be undertaken on the basis of first-hand information on the Conference's proceedings. The report to the Health Assembly will be accompanied by the working papers. I promise you that it will be couched in more definitive language than the "coulds" and "mighties" that some of you criticized. That language was only used to present the issues for your consideration. WHO is not only not supranational vis-à-vis its Member States; it is not dictatorial vis-à-vis its experts! Now that you have made your comments and proposals, we will be able to adopt a firmer style. As soon as the report is ready, which will be some time in the latter half of March 1986, I will send each of you a copy. That is the least I can do to thank you for your contributions.
PART 2

SUMMARY OF THE DEBATE
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INTRODUCTION

1. In resolution WHA37.33, the Thirty-seventh World Health Assembly requested the Director-General "to arrange in 1985 a meeting of experts of the concerned parties, including governments, pharmaceutical industries, and patients' and consumers' organizations, to discuss the means and methods of ensuring the rational use of drugs, in particular through improved knowledge and flow of information, and to discuss the role of marketing practices in this respect, especially in developing countries". In response to that resolution the Director-General convened a Conference of Experts on the Rational Use of Drugs in Nairobi, Kenya, from 25 to 29 November 1985. The Conference was attended by 92 participants drawn from the parties concerned but appearing as individual experts and not as representatives of those parties. Opening addresses were made at a public ceremony by Mr P.C.J.O. Nyakiamo, Minister of Health of Kenya, and Dr H. Mahler, Director-General of WHO (see Part 3).

INTRODUCTORY STATEMENT BY THE DIRECTOR-GENERAL

2. The Conference then took place in closed session. Dr W. Koinange (Kenya) was unanimously elected Chairman of the Conference, Mr A. Grímsson and Dr B. Westerholm moderators. More than 200 interventions were made by participants. At the first meeting the Director-General, in an introductory statement reminded participants that they were there as experts and not as representatives of any of the concerned parties. After describing the acrimonious atmosphere in which the Conference had been prepared, he said that its aim was to ensure that people, particularly in the developing countries, should have access to the drugs they need; it was not intended to be an international battleground in which the pharmaceutical industry and consumers were to vent their differences. He asked participants to consider the rational use of drugs particularly from the perspective of the situation in the developing countries, and of the underprivileged in the urban slums and the rural areas, and not to consider their problems in the perspective of those of the affluent countries and the urban elite of the developing countries. Describing the working papers, the Director-General pointed out that they contain many suggestions for making drug use more rational. Those suggestions, he proposed, should be the main focus of the Conference's discussions, and he begged participants to consider them seriously and with sincerity, leaving behind past quarrels and preconceived ideas and presenting proposals for improving the situation. Some proposals, he said, such as the assumption of greater responsibility by governments, are feasible; others, such as the assumption by WHO of supranational powers, are not. The full text of the Director-General's statement appears in Part 3 of this publication.

3. In the general discussion that followed the Director-General's statement, a participant suggested that the rational use of drugs should be taken to consist of appropriate prescribing, marketing, and use, in accordance with national regulations and practices, of drugs approved by national authorities on the ground of safety, quality, and efficacy, the existence of an effective infrastructure and of sufficient affordable drugs of quality to meet needs being implied. Another participant considered the
rational use of drugs to form an essential element of primary health care. In the view of yet another, the irrational use of drugs arises from socioeconomic inequality; until such inequality is eliminated, the rational use of drugs cannot be achieved. A participant said that in his country the health programme had placed great emphasis on prevention and education; but mothers whose children suffer from malaria or diarrhoea are not interested in hearing about prevention, they want drugs to treat the children. Another participant thought that throughout the discussions the different stages of development in the developing countries should be borne in mind.

4. The Conference decided to concentrate on a list of issues arising from the background documents. These include a number of national case studies (see Part 4, pages 215-272), some of which were described by participants from the countries concerned.

5. One participant strongly recommended identifying the respective responsibilities of concerned parties regarding each of the issues. She submitted specific proposals for these, and the matter was kept in mind throughout the proceedings.

NATIONAL DRUG POLICIES

Nature and content

6. It was generally agreed by the participants that countries, if they have not done so already, should formulate and implement a national policy for the rational use of drugs as part of their national health policy and their strategy for health for all by the year 2000. The view was expressed that such a policy follows logically on the essential drugs policy already adopted by WHO. A participant claimed that those few developing countries which have so far succeeded in achieving a rational use of drugs are those which have established a national drug policy.

7. The aim of a national drug policy, it was held, is to ensure that drugs of acceptable quality, safety, and efficacy are available at affordable cost to all who need them where and when they need them, to combat the diseases prevalent in the country and to improve or maintain the health of its inhabitants. It was emphasized that such a national drug policy needs a political will on the part of governments, together with a strong commitment to formulating the policy and carrying it through, and governments would have to make sure that the resources are available to meet the need for drugs in the country. This requires the coordinated action of the sectors involved, such as planning, finance, industry, trade, communications, and education. Controls are required to exclude the marketing of pharmaceutical products of unacceptable quality, safety, and efficacy, and to ensure that promotion of those products meets ethical criteria. Thus, in order to develop a national drug policy and coordinate all the activities required for its implementation, a strong health infrastructure is needed. Such an infrastructure will vary according to the social and economic conditions of each individual country. Participants said that the policy must be linked with those conditions and that, if social justice is not actively sought, no national drug policy will succeed. Other participants felt that a national
drug policy must cover traditional medicine, as well as scientific medicine, preventive medicine as well as curative medicine, and veterinary medicine too. It also needs the cooperation of both developed and developing countries and WHO. As regards the infrastructure, other participants stressed the need for a research infrastructure with adequate resources to deal with the changing patterns of disease and health care and social priorities in countries; in that respect mention was made of the emergence of AIDS as a major new medical problem calling for research, and other problems are sure to follow.

8. It is necessary, it was held, in a national drug policy to identify the therapeutic needs of the country and to select the drugs and estimate the quantities required for each need. A drug supply system has to be set up, covering procurement, storage, inventory control, distribution, and training. Prescribers and consumers have to be educated to use the drugs properly. Quality control has to be ensured. Provision has to be made for monitoring adverse reactions. The technical and economic feasibility of formulating and producing drugs locally has to be considered. An appropriate information system has to be set up to provide objective information on drugs and ethical criteria for promoting drug use must be defined. Appropriate legislation has to be enacted. The manpower requirements for a national drug policy have to be estimated and personnel trained. And a financial master plan has to be drawn up.

9. Many participants considered that, because of the excessively large number of drugs on the market in so many countries, a rational first step in a national drug policy is to reduce the number of drugs to the really essential ones, stopping the import or manufacture of those that do not really help the patient. Moreover, reduction of the number simplifies the task of drug regulatory authorities, provides economies, and makes it easier to teach prescribers to use drugs rationally. This view, however, was opposed by other participants on the ground that restriction of drugs already exists, in the sense that no individual prescriber or hospital uses more than a limited number of drugs that they themselves have selected; an argument that was countered by a participant who said that different hospitals and different prescribers have their own different lists of drugs and the sum total is excessive. For that participant treatment needs to be standardized so that hospitals and prescribers all use the same range of drugs. It was further argued against limitation that it deprives patients of the best possible treatment, prevents therapeutic progress, does not offer the cost savings claimed for it (since inadequately treated patients need lengthier treatment), is a major disincentive to pharmaceutical research, and prevents the quite frequent and important discovery of new indications for existing drugs. Some participants felt that the limiting factors should be the quality, safety, and efficacy of the drugs, freedom of choice being left to prescribers. The different views were brought up later in the Conference during the discussion on essential drugs programmes.

10. At the international level, it was felt that WHO should disseminate guidelines on national drug policies. An outline of such guidelines was endorsed by the Thirty-fifth World Health Assembly and they have been further elaborated since; they should, it was felt, be brought up to date
and dispatched to governments. It was also recommended that WHO should ensure the closer coordination of the work of the United Nations agencies in relation to drug policies: with UNICEF in drug procurement and prices and supplies, with UNCTAD in trade and technology aspects, with UNIDO in production, and with the United Nations Centre on Transnational Corporations (UNCTC) in the relationships between development and those corporations in the field of drugs.

Legislation

11. A national drug policy, it was agreed, finds expression in national legislation, which needs to be adapted to the circumstances of countries. Thus, as various participants pointed out, in some countries nurses or other community health workers would have to be authorized to prescribe and dispense medicines because they are the only health workers in the area. There was general agreement that legislation should be developed within countries and that governments with existing legislation that have not already done so should review it and bring it up to date, taking into account the extent to which it can be enforced. WHO should, it was felt, disseminate information on national legislation and the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce and prepare monographs on specific issues. It should also prepare guiding principles in the form of points for consideration by governments when formulating drug legislation and, on request, provide guidance to countries in formulating, adapting, and updating legislation. One participant said that there is no difficulty in developing the necessary legislation in the developing countries; help could be given not only by WHO but also by countries that have a more developed legislation. Another participant doubted whether WHO should become involved in helping countries to formulate national drug legislation; the preparation of general guidelines is, he thought, a legitimate WHO activity, but to go beyond that may invite the suspicion that WHO is attempting to establish supranational control. The Director-General explained that to help governments to formulate legislation at their request falls squarely within the Organization's constitutional mandate, illustrating the application of collectively agreed policy to individual national policy.

12. Much information is already available on drug legislation. Mention was made of the quarterly International Digest of Health Legislation, published by WHO, as a valuable source of information. Attention was also drawn to the working paper entitled "Review of national health legislation on drug marketing" (Part 4, pages 152-192). It was stated that the Pan American Health Organization (PAHO) was making efforts to introduce uniform criteria in Latin America for drug legislation, information, and marketing, with a view to establishment by countries of an essential drugs programme and local manufacture of drugs.

Drug regulatory authority

13. It was considered that the first step in implementing a national drug policy is to set up a drug regulatory authority if one does not already exist, although one participant sounded a note of warning that this would
give rise to an expensive and cumbersome bureaucracy; others refuted this contention. WHO should prepare guidelines on the minimum requirements for such an authority, it was suggested, along the lines of those it had prepared for national laboratories for quality control. An expert committee could be convened to establish such minimum requirements.

14. A participant expressed the view that the task of a drug regulatory authority should be limited to ensuring the quality, safety, and efficacy of drugs, the stress in countries being placed on the education of prescribers rather than on coercive measures. A number of participants warned of the danger of over-regulation, which might be counterproductive by slowing down the supply of drugs. But other participants argued that, in view of the vast and in their opinion excessive number of drugs on the market, the authority should seek to limit the entry of drugs to essential drugs only and to encourage the local production of such drugs. It was advocated that drug regulatory authorities should meet regularly, in regions as happens in the Nordic countries, or in the International Conference of Drug Regulatory Authorities, which meets periodically. That conference, it was suggested, should meet more frequently and its members should keep in contact during the intervals between meetings; and more countries should become members because of the valuable exchange of information that takes place during the meetings. To attract more participants, it was suggested that part of the proceedings should be conducted at a less sophisticated level suitable for new regulatory authorities. A participant thought that a drug regulatory authority should consist of professionals from many disciplines with managerial skills and that, to avoid friction with government departments, it should also be in charge of drug management as a whole in countries.

Drug information

15. To achieve a rational use of drugs it is not enough to create a health infrastructure; the people most intimately concerned, the prescribers and consumers of drugs, must receive the information they need to use drugs rationally. How drug information can be made more objective and more accessible to prescribers and consumers was the subject of much discussion at the Conference. It was pointed out that a great deal of information already exists. In France a database has been established and provides physicians and pharmacists with information on 3000 pharmaceutical substances and 8000 brand products. In Italy the Ministry of Health produces a drug information bulletin distributed to physicians and pharmacists that contains monographs on drugs and advice on prescribing and utilization. In the United States of America, a drug bulletin is issued by the Food and Drug Administration, and a National Council on Patient Information and Education brings together representatives of the government, health organizations, the pharmaceutical industry, and consumer organizations and, inter alia, produces small cards that are distributed to employers and to employees with their pay checks and list questions patients should ask in relation to the drugs they take. PAHO is having the cards translated into Spanish for use in the education of health workers in Latin America. The drug regulatory authority in the United States sends

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information on its regulatory decisions to its sister authorities throughout the world. In Australia an adverse drug reaction bulletin informs doctors about reports of adverse reactions and receives information from them on such reactions. Other countries also produce and disseminate quantities of information, as do international organizations, including WHO.

16. Nevertheless, it was pointed out, much of the information does not reach those for whom it is intended. One of the participants thought that if there is too much information, as in many developed countries, prescribers and consumers do not read it. Another said that information is all too often presented in an unpalatable and offputting style, a criticism that is also applicable to much of the information provided by WHO; if official and other sources of information were to take a leaf out of the pharmaceutical industry's book and present information in the glossy and attractive way utilized for drug promotional material, the information would be more easily assimilated. It was observed by a participant that drugs and information together form an inseparable entity. Another recommended that information should precede the introduction of any drug on the market. A participant suggested that all information on drugs should be in a standardized form; as it is, it varies confusingly throughout the world.

17. A suggestion was made that national consensus groups should be set up consisting of representatives of government, the pharmaceutical industry, the academic community, professional organizations, prescribers, and consumer associations, to monitor the information provided by governments, the industry, and the consumer associations. This suggestion was rejected by a number of participants as unworkable and as implying the surrender of government responsibility to outside groups; their preference was for monitoring by experts and decisions by government. Other participants, however, said that consensus groups of that kind function perfectly satisfactorily in their countries in an advisory capacity to the governments. This is so, for example, in Sri Lanka. In France groups with different sorts of participants reach consensus together. It was argued in favour of national consensus groups that they offer an opportunity to influential people not directly involved with drugs to learn about an important subject; moreover, those directly involved in the groups are much more committed to the concept of rational use.

18. It was felt that WHO should act as a clearing-house for information and take steps to see that it is properly circulated, as by reinforcing channels of communication with its Member States through its regional offices.

19. There was general agreement on the value of national drug formularies or, at least, national drug data sheets. Some participants held that they should be prepared for essential drugs only, otherwise they merely encourage prescribers to prescribe inessential drugs. In some countries, it was pointed out, data sheets must be attached to the pharmaceutical industry's promotional material, to health service information bulletins, and to lists of drugs for which reimbursement of the cost is permitted. WHO, it was felt, should intensify its preparation and dissemination of data sheets for essential drugs for doctors, pharmacists, nurses, and non-professional health workers. It should also actively support governments in the
preparation and bringing up to date of drug formularies and data sheets. One participant suggested that it should organize symposia and workshops to enable developing countries to become self-reliant in the production of data sheets. Governments should distribute formularies and data sheets free of cost, since if they have to be bought prescribers may not buy them.

20. One participant placed the responsibility for clear and unbiased information on governments, the pharmaceutical industry, professional organizations, teaching institutions, the medical and pharmaceutical press, the mass media, and prescribers. The primary source of information, it was pointed out, is the industry, and in some countries its sales representatives are the only available source of information. Such a source, it was claimed, is inevitably biased, since the industry's aim is to sell its own products and sales representatives will not compare their own firm's products with those of other firms in any way that may indicate the possible superiority of the latter. In general, drug regulatory authorities require very detailed information on drugs before approving them for marketing, but only in a few countries do they consider the usefulness of the drug under consideration as compared with others in the same therapeutic category. It was suggested that governments and professional organizations and journals should make better use of their opportunities to disseminate complete and unbiased information on drugs, ensuring that the information conforms with approved product monographs and comes from reliable national or international sources. The information should also as far as possible contain a comparison of the drug's value with that of other drugs in the same therapeutic group, since what prescribers need is information on the best drug for a particular patient. They then need detailed information on how exactly to use the drug and with what precautions, and on what they should tell the patient about it.

21. A participant said that in the United States of America a column in the Journal of the American Medical Association is devoted to information from the Food and Drug Administration, and other journals have asked the Administration for the same service. It was suggested that governments might help medical journals defray the cost of such a column, which would probably be widely read by prescribers, but care should be taken that financial support should not lead to undue government influence over the content. Another participant thought that all those providing information should look more at health problems and therapeutic groups than at individual drugs, placing emphasis on the evaluation of the groups and comparison of their member drugs so as to help regulatory authorities in their work and prescribers in the selection of the most suitable drug. A key element is post-marketing surveillance, the monitoring of the drugs on the market so that the authorities are informed of any untoward events associated with them. It was noted that there are, for example, 28 regional drug monitoring centres in France from which prescribers can obtain information and to which they can send information about adverse reactions.

22. A distinction was made between the information to be given to prescribers and that to be given to patients and the public. Doctors, the main but not the only prescribers, need detailed information to help them select from among various treatments, and use properly the drug selected;
they therefore need information on efficacy, effectiveness, and medical indication—in other words, on whether the drug does what it is said to do, improves the patient's health, and is optimally effective in the given circumstances. Such information doctors can generally obtain from drug regulatory authorities, professional journals, drug bulletins, the publications of the industry, and so on. They are not told what they should say to patients, nor have they been trained in the art of explaining in simple language why they prescribe certain drugs, how the patients should take them, or what the effects of the drug are likely to be. Part of medical education, the Conference held, should be devoted to that subject. A participant, returning to the question of the presentation of information to the doctor, said that it is much too frequently in small print and offputting in style, and given in great slabs. Ideally it should be given in small doses in drug bulletins or otherwise. The same participant mentioned a meeting held in Madrid in May 1985 that discussed the role of drug bulletins in the world and decided to form an international society of drug bulletins. Another suggestion was that editors of medical journals should be brought together to consider how best to publish objective information on drugs that would be read by prescribers. Yet another was that a panel of experts should review medical journals, provide recommendations on the publication of information on drugs, and perhaps too decide whether the information appearing in advertisements and elsewhere in journals complies with national legislation or the voluntary code on marketing practices of the International Federation of Pharmaceutical Manufacturers Associations (IFPMA).

23. Some countries possess computerized drug information systems or other reference systems that are accessible to prescribers. That in France has been mentioned above. In Italy each drug dosage form has been codified and the code placed on a magnetic ticket attached to the drug package. When the drug is sold the ticket is read by a detector connected to a computer located in each health service centre. The network of computers provides a continuous flow of information on drug consumption by therapeutic group, geographical area, and individual doctor. Such a system enables the Ministry of Health to take appropriate action on drugs and so facilitate rational use. It was suggested by a participant that such a system need not necessarily be restricted to developed countries but, because of advances in technology and the falling cost of equipment, could be installed and operated in developing countries also.

24. One of the observations made was that the information needed by prescribers varies according to the cultural conditions in countries. WHO should, it was felt, convene an expert committee to consider the kinds of information needed. It might also consider ways in which prescribers should communicate with patients in different circumstances. A participant noted that doctors, because of the information they receive and the gaps in their education, frequently show a predilection for brand names, a predilection that adds to the cost of drugs. It has been found in his country that a visit to the quality control laboratory convinces them that generic drugs are perfectly acceptable in the place of drugs with brand names, and much less expensive. A suggestion put forward was that WHO should devise a WHO
label or symbol for generic drugs; such a label would carry as much prestige as a brand name.

25. The Conference felt that pharmacists should assume a greater role in providing complete and unbiased information, but it was also stated that, because of the greater profit they make out of selling more expensive brand products, they tend to favour them rather than generic drugs, regardless of whether they are any better than cheaper ones. Also, for the same profit motive, it was held, they tend to sell over-the-counter drugs to the public rather than suggest that drug treatment is unnecessary. In this context it was noted that the sale of over-the-counter drugs is increasing rapidly in many countries and it was suggested that measures to control those drugs need to be studied.

26. Participants considered that pharmacists should be educated to provide unbiased information, and it was suggested that they should be given financial incentives to counteract the temptation to profit-making. This suggestion met with opposition, on the ground that financial incentives would involve increased expenditure, which all countries, developed and developing alike, are seeking to curtail. Nor, it was said, is it easy to see how such an incentive system could work.

27. Information to consumers, it was held, should be presented clearly and simply in the inserts in drug packages as well as in the instructions given to consumers by prescribers. The role of the mass media was discussed. Some participants advocated using them extensively to inform the public, one participant stressing the value of women's magazines for that purpose. It was also suggested that WHO should encourage and perhaps sponsor meetings with media representatives to study ways of presenting information to the public and to inculcate in the media a greater sense of responsibility for the information they publish.

28. Other participants, however, felt that, because of the tendency of the mass media to distortion and sensationalism, they should be used as little as possible, if at all, and if used, used with caution and in cooperation with professional bodies to ensure that the information they provide is objective and free from exaggeration. A reference was made to a declaration by the International Pharmaceutical Federation in 1984 at Budapest that it is necessary that information on drugs should be provided by professionals, not by people who are not in a position to furnish objective information. In that respect, a participant noted that medical and nursing associations do not communicate enough with the public and should do much more and be trained for that purpose.

29. Among the other comments on information to the public, it was suggested that WHO should play a more active part in information to special groups such as the elderly and women (in relation to pregnancy and contraceptives). As part of its programme of health education it should provide information on measures for health promotion and disease prevention and on the uses as well as the limitations of drugs, in addition to specific information on particular drugs. Mothers in particular, it was held, should be encouraged to demand adequate standards of health care for their family.
WHO should also, some participants said, lay stress on traditional medicines; but one participant, noting the rise of obscurantism in recent years in relation to health and "nature cures", emphasized the need to ensure that traditional medicines are safe and effective. In relation to those suggestions, it was pointed out that WHO has a Special Programme of Research, Development and Research Training in Human Reproduction and a unit concerned solely with traditional medicine. A suggestion was that information and learning materials should be included in the UNICEF drug kits sent to countries, to provide health centre staff with information on the drugs contained in the kits and enable them to pass on the information to consumers and the public.

30. Information on drugs, it was felt, should include indications, contraindications, dosage, adverse reactions, the long-term effects, and the reasons for withdrawals from the market. It was recommended that the national regulatory authorities should publish in extenso the reasons for regulatory decisions; designate a WHO liaison or information officer responsible for the transfer and utilization of information in accordance with the relevant World Health Assembly resolutions; ensure that WHO is notified of the withdrawal of drugs by manufacturers and the reasons for the withdrawal; and, in compliance with United Nations General Assembly resolution 37/137, inform WHO inter alia about locally manufactured drugs that are available for export but have not been approved for the home market. WHO should ensure that developing countries have ready access to reliable information through the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce and through the distribution of national compendia containing approved information on drugs to other regulatory authorities. The information should cover the uses and limitations of drugs and measures for disease prevention and health promotion as well as specific information on particular drugs. A participant recommended that national regulatory authorities should keep in direct touch with each other and supply each other with information on the decisions they take.

31. The Conference considered that WHO should disseminate information more systematically. It should publish its Drug information bulletin more frequently and include in it more detailed information on regulatory decisions in countries, on teaching and learning materials, and on the economic and financial aspects of drug regulation; and it should add book reviews and a question-and-answer section. One participant, citing the wide circulation and success of Dr David Werner's Where there is no doctor, maintained that an essential books list is as important for information as an essential drugs list is for drugs. Another stressed the need to provide information in the local language or languages. It was suggested that WHO should actively support countries that wish to draw up national formularies or national data sheets by producing monographs on selected therapeutic groups based on wide consultation; and it should organize meetings to seek agreement on important issues. International collaborative mechanisms, it was suggested, might provide national regulatory authorities possessing limited resources with an information base for drug assessment, thus releasing national resources for other purposes. But such collaboration, it was emphasized, should in no circumstances develop into supranational
control of drugs. Many speakers voiced their approval of the biennial International Conference of Drug Regulatory Authorities as a source of information and a mechanism for bringing drug regulatory authorities together, and again expressed the wish that it should increase its membership and expand its agenda. The WHO designation of international nonproprietary names (INNs) was generally approved, and countries were urged to adopt them and reject applications for trademarks similar to INNs or for drugs without INNs. If brand-name drugs are accepted, it was suggested, the INN should be prominently displayed on the package.

32. It was felt that WHO should continue to cooperate closely with the United Nations in the implementation of United Nations General Assembly resolution 37/137 concerning the dissemination of information on drugs that have been banned, withdrawn, severely restricted or not approved by governments on grounds of safety. WHO is, according to that resolution, a lead agency. But it should not, participants considered, confine its role to that of a postbox; it should analyse and elaborate on the information received for the benefit of the countries to which it is circulated.

33. A participant said that more knowledge is required of how decisions about drugs are made and on how information is assimilated. Research with a social science approach may produce results that will affect the information given to prescribers and consumers as well as the training of health workers. Thus it is not known why doctors prescribe as they do, how many drugs they use, how they respond to new information, why the public demands drugs, what effect drug advertising or the price of a drug has, or whether cultural attitudes play a part in drug consumption; and yet knowledge about such matters will affect not only information but also every aspect of drug management. Similarly, compliance with treatment is often very poor, but not enough is known about the reasons for non-compliance, although it may be damaging to the patient and expensive to the community. Equally poorly understood is the mystic significance that drugs have for many people, that desire to take medicine (a participant quoted from Sir William Osler) which is perhaps the greatest feature that distinguishes man from animals.

34. Another participant, agreeing that non-compliance is widespread, said that a study published in Yugoslavia in 1985 attributes it in the first place to lack of knowledge and of proper information. The patient thinks that the doctor gives a prescription routinely, sometimes without a proper examination; the pharmacist fails to provide the instructions needed on the package; most patients stop taking the drug or drugs when they feel better, some try another doctor to see if he prescribes the same drugs; and so on. The study also notes the economic cost of non-compliance. It calls upon doctors and pharmacists to fulfil their responsibility for providing information to patients and recommends the inclusion of information on the utilization of drugs in health education and general educational programmes, with use of the mass media.

35. A number of other points were raised in the Conference in relation to information. It was repeated that there is too much information on drugs in developed countries, with the result that prescribers tend to throw much or all of the material containing it, unread, into the waste-paper basket. At
the same time there is too little information on people's health problems for which they may or may not need drugs. In the developing countries there is too little information on drugs, and too much of what there is is promotional and biased. Participants criticized the information received in countries, even from WHO, as inadequate and often not adapted to the circumstances in countries. A participant mentioned the problem of identifying foreign drugs and suggested that WHO should prepare a foreign drug dictionary for wide dissemination. Opinions were widespread that WHO should increase the number of expert committees, workshops, and seminars to produce guidelines on the many aspects of information and the teaching of the rational use of drugs. A participant thought that the number of issues raised even in regard to information is so great and their importance so manifest that it is desirable that WHO should follow up the Conference with others and a whole series of meetings, symposia, and publications to deal with them properly. Another participant considered that, if national regulatory authorities wish to compete seriously with the pharmaceutical industry in the field of information, governments must provide them with greater financial support, more facilities, and more personnel.

**DRUG MARKETING**

Constituent elements

36. Drug marketing is not synonymous with drug promotion but covers the whole range of activities from the manufacture or purchase of drugs to their consumption, including registration, quality and safety assurance, labelling, packaging, pricing, storage, distribution, and right to prescribe, as well as promotion. The Conference agreed that governments are responsible for ensuring that the drugs available in the country are of acceptable quality, safety, and efficacy and that for that purpose drug marketing needs to be regulated. Some participants maintained that the pharmaceutical industry's marketing practices, particularly its drug promotional activities, all too often lead to a demand for inessential drugs that do not meet health needs. A study in one country that was mentioned showed that a third of the drugs consumed - oral antibiotics, hormones, vitamins, analgesics, tranquillizers, etc., many of which are habit-forming or create drug resistance - fall within the category of overconsumption and are promoted aggressively by the industry, bringing with them increased prices, over-prescription, and dependence on brand names. A participant suggested that, to expose the marketing methods employed by the pharmaceutical industry, WHO should buy large quantities of books such as *Bitter pills* by Melrose or *Drug disinformation* by Medawar and send them to the drug regulatory authorities in developing countries, who are ill acquainted with marketing practices. It was also suggested that WHO should produce clear guidelines on drug marketing, based on the principle that all drugs, both in the public and in the private sector, should have full regard for the needs of public health. A participant observed that UNCTAD, UNIDO, and UNCTC have all produced studies of marketing; their conclusions should have been reflected in the background papers of the Conference.

37. It was agreed that an essential step in dealing with the marketing of drugs is to set up a drug registration system, and that countries unable to
establish one immediately should at least start by devising simple administrative procedures to identify and list marketed drugs, with the intention of instituting proper drug registration as soon as possible. It was advocated that WHO should elaborate a basic multipurpose model for developing countries with limited capacity in this field, complementary to the WHO Certification Scheme for the Quality of Pharmaceutical Products Moving in International Commerce and providing for the identification of priority needs, the rationalization of procurement, quality assurance, and the establishment of information standards with which all promotional activities must comply. A participant suggested that WHO should produce a document containing points to consider in establishing a drug registration system and a list of references that would help developing countries. It was also suggested that WHO should produce monographs on specific marketing issues and, one participant thought, encourage governments to establish permanent technical committees on drug marketing.

38. It was again urged that, at least in developing countries, the number of drugs allowed on the market should be restricted so as to simplify registration and other marketing activities. A participant opposing restriction cited the case of a contraceptive product developed in Japan in 1950, which had to face stiff competition from more than 40 other products with the same ingredients but different formulations and brand names. The competition involved the manufacturer in intensive research to improve the dosage and formulation and the compliance of patients, and it led to improvement of the product and a lower price. Now that product is the one in current use.

39. It was generally felt that international norms for labelling deserve study by WHO to ensure that labels are both clear and comprehensive. A participant found it logical and desirable that drug packages should clearly identify the name of the drug, both brand and nonproprietary, the dosage form, the strength, and the route of administration. It should also identify the manufacturer, the batch number, and the date of expiry and provide storage instructions, since all that information is needed for those concerned with handling the package up to the moment when it is opened. It might also indicate clearly if the product is intended for free sale or for prescription only, as is indicated in Mexico by the use of coloured bands. But the situation is more complicated after the package is opened. If it is the patient who opens it he needs clear instructions on the dosage, quantity, and frequency, on side effects, on whether the drug should be taken before or after food, and so on, and the instructions have to be understandable by a large number of patients whose educational standards vary considerably. If the pharmacist opens the package he needs more sophisticated information. The doctor needs still more detailed information but in many cases he does not even see the package. Another participant considered that it would be sufficient if WHO disseminated examples of acceptable labels, leaving countries to select those they preferred. Thus they would not spend scarce resources on the study of labels that could be better employed elsewhere. It was finally realized that practices vary so much from country to country that it is difficult to imagine any guidelines going beyond basic product description that would have universal
applicability. Labels should therefore be adapted to a country's individual needs.

Drug costs

40. Expenditure on health, according to the World Bank, has either remained the same or declined in real terms in the past decade in the developing countries, and the Bank estimates that expenditure up to the year 2000 will be of the order of US$ 3–4 per capita in the low income countries, of which 20–25% will be for drugs. This implies an average per capita drug expenditure in these countries of the order of between 60 US cents and US$ 1.

41. Opinion was divided on the question of the cost of drugs. On the one hand, it was held that the research-based drug firms, which sell the majority of the drugs marketed in the world, fix exorbitant prices that bring them large profits and impose a heavy burden on health budgets, especially in the developing countries. On the other hand, it was argued that the cost of research and development for a new drug is so high that it must be reflected in the price. Some participants claimed that most research and development costs are for drugs that are of limited value to the developing countries, so that in paying high prices for drugs in general these countries are paying more than their due for research that mainly benefits the developed countries. Many of the drugs manufactured, it was also held, are little more than variants of drugs already in existence and, if not harmful, are certainly not essential; and vast sums are invested in product differentiation and in sales promotion through advertising, sales representatives, and incentives to prescribers, with a consequent effect on prices. A participant drew attention to the variation in prices for drugs, even in nearby countries; according to a UNCTC report entitled "Transnational corporations in the pharmaceutical industry in developing countries", 1000 capsules of a drug in one Caribbean island cost US$ 106 and in a neighbouring island US$ 262. Such price discrepancies are widespread and inadmissible, he declared.

42. Other participants maintained that drugs throughout this century have revolutionized the treatment of disease because of the research put into them. To reduce the price of drugs would be to reduce the amount of research carried out and put a brake on medical progress.

43. It became clear during the discussion that not enough is known about how much money is required to develop and market a new drug or how pharmaceutical firms fix prices, and WHO was asked to study the subject. A participant described the favourable effect on prices of the system in Sweden whereby a government agency controls practically all the wholesale dealers and pharmacists in the country and negotiates prices with the pharmaceutical industry. In negotiating the price for variants of drugs it insists that it should be at least 10% less than that of products already on the market. In Sweden, too, the pharmacies are run on a non-profit-making basis.
Local manufacture

44. A number of participants considered that the cost of drugs should come within a comprehensive scheme for drug regulation that would limit the number of drugs imported or manufactured locally, the regulatory authority negotiating the price with the manufacturer. Because of the high cost of imported drugs, some saw the solution in local manufacture. It was agreed that, as well as providing employment, local manufacture would reduce the price of drugs and compel non-local manufacturers to reduce their prices too. A participant maintained that local manufacture is essential in all developing countries to ensure the rational use of drugs. Local manufacture, it was held, can concentrate on the drugs really needed in the country. Mention was made of oral rehydration salts in a Latin American country, which government laboratories manufacture because the pharmaceutical industry is not interested; with the paradoxical result that the poor in government hospitals are being successfully treated with oral salts while the rich in private hospitals are still receiving more expensive and less successful treatment by drip injection.

45. Other participants pointed out that many if not most developing countries lack the manufacturing skill and facilities for producing drugs and would inevitably have to depend on imported raw materials and intermediate products that are themselves extremely expensive. It is therefore far from sure, they held, that locally manufactured drugs would be cheaper, especially as they would be required to meet competitors' standards for quality, safety, and efficacy and, unless advertising were controlled, the formidable promotional efforts of the pharmaceutical industry. In relation to the importation of raw materials and intermediate products, a participant claimed that they are in the hands of a cartel, have to be procured through brokers, and are correspondingly expensive. WHO could perhaps, this participant suggested, help countries that wished to embark on local manufacture to purchase raw materials and intermediate products directly from producers at a reasonable price. Another participant said that many developing countries do not have the foreign exchange to import all the drugs they need, but they have the potential to manufacture some of them and the raw materials as well, often derived from traditional herbal medicines; a programme is needed to enable such developing countries to use their own raw materials to produce the drugs they need. In that respect, a participant mentioned what appeared to him to be a propaganda offensive by the transnational pharmaceutical industry against local manufacture in an African country that had recently become independent. Another participant warned against the assumption that local manufacture of drugs would solve all the problems of drugs in developing countries. In one large country in Asia, for example, the local drug production is enormous, yet there is a falling production of essential drugs and instead an increasing production, presumably for commercial reasons, of irrational combinations and useless drugs. Yet another participant stated that in most of the developing countries the full-scale manufacture of drugs will be out of the question for economic and technical reasons, and they will have to import the drugs they need.
46. Nevertheless, the view was put forward again and again by some participants that developing countries must strive to attain self-reliance in drug production, self-reliance being a goal towards which both developed and developing countries strive. Only then, these participants maintained, can developing countries obtain the drugs they need and perhaps finance the research that is required for their individual circumstances. It was suggested that countries wishing to go ahead with the local production of drugs should, as advocated by the Thirty-fifth World Health Assembly, first carry out a study of its technical and economic feasibility and also look at the possibility of technical and economic cooperation with other developing countries. Bilateral or multilateral agreements with other countries should also be encouraged.

47. It was pointed out that for some six years a working group in UNIDO has been collecting data on the possibility of local drug production. A participant expressed the hope that countries embarking on such local production should make sure that the manufacturers produce the drugs really required. WHO, it was held, should provide support for the preparation of lists of drugs suitable for local manufacture and for calculation of the amounts required. It should also, one participant thought, promote single-ingredient drugs instead of multiple-ingredient drugs, most of whose extra ingredients add nothing to their safety and efficacy.

Tenders

48. If drugs have to be imported - and it was pointed out that all countries, both developed and developing, import drugs - how can they be imported at the lowest possible price, at least for the public sector? A suggestion that met with considerable support was that countries should make greater use of international open tender, preferably as part of a national essential drugs programme. A participant wondered whether an international drugs market might be established, along the lines of the commodities markets in London and elsewhere. Another suggested that WHO should act as a broker for its Member States. It was pointed out, however, that many developing countries lack the information that would enable them to estimate the quantities of drugs required for a specific period, the funds to pay for bulk quantities, and the storage space to keep them for any length of time. Some countries, it was observed, have to make emergency imports of drugs because they have not the currency to pay for large quantities or underestimate the demand; and the price is disproportionately high. Developing countries are also often compelled to accept tenders from developed countries because those countries provide credit; developing countries from which they could obtain the drugs on possibly more advantageous terms cannot provide the credit and so their tender is rejected. Again, a condition of technical assistance provided by some countries that export drugs is that the importing country should buy the drugs they want from them; this prevents the importing countries from taking advantage of lower terms quoted elsewhere. Another criticism of the tender system was that local agents of the successful tenderer, even if they do nothing, receive a commission, which adds to the price of the drugs.
49. It was pointed out that the tenderers too sometimes have grievances. Some countries do not give the manufacturers sufficient advance notice, and a company cannot, for example, hold 100 million tablets of chloroquine on the off chance that a country may wish to purchase them and the company win the tender. Some countries have also cancelled tenders abruptly, leaving the manufacturers with uncovered losses.

50. A participant raised the question of the lack of foreign exchange to import drugs that is so often a major problem in developing countries. Hidden costs in risk premiums may affect the drug prices quoted, since suppliers may charge for the delay if they have to wait a long time for payment and are unwilling to accept payment in the local currency. WHO and UNICEF have looked for ways of initially financing a revolving fund to solve that problem, but for a revolving fund to be self-sustaining the country must be able to forecast drug consumption, eliminate leakages of stock through pilferage and otherwise — which amounts to as much as 40% in some countries, according to the World Bank — and collect the sums paid for the drugs, no easy task in many developing countries whose administrations are weak. They must also be able to convert the local currency into foreign currency and augment the fund when required to cover delays and defaults and meet an increased demand for drugs. A revolving fund established and guaranteed by WHO, UNICEF, or the World Bank might reduce the risk premiums and so the cost of imported drugs. Such a fund should preferably be set up for a group of countries, thus making it more likely that the foreign currency will be available; and part or all of the disbursement might be taken in local currency by, say, WHO or UNICEF.

51. It was generally agreed that, whether a revolving fund is established or not, groups of developing countries uniting to invite tenders would have the effect of bringing down the price for individual countries. It was also clear to the Conference that developing countries need to know more about tendering and marketing rules and practices and about methods of estimating needs and obtaining funds for the purchase of drugs. Essential drugs are basically generic drugs, and the international generic drugs market is highly competitive. Developing countries have not been able to take advantage of that market, not only for the reasons given but also because they have been unable to identify substitutes and alternatives if they lack the funds for first-choice drugs. In that respect INNs have been of invaluable help. They also lack market knowledge — how to run tenders, how to procure drugs at reasonable prices, how to expand traditional supply services, where to find credit terms and so on. WHO and other international organizations such as the World Bank, it was felt, have an important role to play in informing developing countries about such methods and practices, as well as about current prices of drugs and price trends, and countries should call upon their services more frequently. It was pointed out that UNICEF publishes drug prices, dispatches drug kits of essential drugs under a neutral label, and on request suggests sources and examines export guarantees and other financial options.
Charging for drugs

52. The question of levying a charge for drugs was considered by the Conference. Many countries supply drugs free of charge for the public health sector. Some doubt was expressed about the desirability of this practice, on the ground that something given for nothing tends to be undervalued, the patient is likely to be more careless about using it properly, and since it is free there may be an inflated demand for it. A charge based on the ability of people to pay, it was argued, would help towards financing the cost of drugs and perhaps of the health services, and it was maintained by one participant that even a symbolic charge would impress people with the need to use drugs carefully.

53. A number of methods of recovering the whole or part of the cost of drugs were mentioned, such as differential pricing with two- or three-tiered price mechanisms, charges for all drugs except those needed for severe and chronic diseases, charges for all but essential drugs, and various kinds of reimbursement. Participants pointed out, however, that in many countries political considerations make it difficult or impossible to levy a charge on drugs if previously they have been free of cost, even if the economic situation makes it desirable. The solution to that problem, according to another participant, is to begin with a very small charge, justifying it by some small improvement in the health service or a new programme. The paradoxical effect of subsidizing prices in one African country was noted by a participant; bringing the price of drugs within the range the population could afford has increased the demand to such an extent that the authorities are criticized even by people who previously could not afford any drugs at all, because there are not enough drugs to satisfy the new demand. Mention was made of a system in the Gambia, where the village health services are given a three-month supply of drugs free of charge and they regenerate the funds required to replenish the stocks by selling the drugs and using other sources. Another participant said that the recovery of cost from the poor should not become another way of subsidizing the rich.

54. It was recommended that WHO should prepare a study of cost recovery and of other methods of helping developing countries to meet the cost of drugs. A meeting of experts might be convened for that purpose.

Prescribing and selling

55. The right to prescribe, distribute, and sell drugs depends, the Conference agreed, on a country's circumstances, and prescribers are of key importance. In many if not most developing countries qualified medical practitioners are rarely to be found in the rural areas; pharmacists, nurses, and other health personnel therefore have to be authorized to prescribe and dispense, perhaps from a short list of the drugs available where they work. Similarly, in remote areas where there are no pharmacies it may be necessary to permit village shops or cooperatives, possibly under the guidance of the local health centre, to sell drugs. Here again, it was pointed out, there is the danger that, if there is no limited list of essential drugs, the shopkeeper will offer for preference to his client heavily promoted brand products because the profit margin is greater.
56. Governments should also, it was felt, establish lists of drugs authorized for sale over the counter and specify those persons, if any, other than pharmacists who should be authorized to sell them. The need for this step is the more urgent, it was pointed out, because sales of over-the-counter drugs are increasing enormously throughout the world. It should however be borne in mind, a participant said, that there is lost effort in authorizing health personnel or others to prescribe and training them to prescribe properly if the drugs are not available, as they often are not.

**Drug promotion**

57. The role of sales representatives was viewed differently by different participants. Some regard them as aggressive promoters of the products of their firm, making unscrupulous use of free samples and other inducements to cajole prescribers into accepting drugs about whose comparative value they know nothing. The use of the free samples that sales representatives distribute liberally was objected to, on the ground that some prescribers sell them to add to their income, some give them to patients who later cannot continue with them because the drug is not generally available or is too expensive, and some throw them away. One participant spoke of doctors in some developing countries setting up practice with free samples as their stock in trade, while pharmacy graduates opening shop in the same area have to fall back on the sale of cosmetics because the doctors dispense the drugs. The net result in all cases is to add to the price of the drugs, with no corresponding benefit to the consumers.

58. Other participants saw the sales representatives as valuable counsellors to prescribers, providing them with person-to-person information on new drugs and receiving in return information on side effects and adverse reactions that benefits the manufacturers, the consumers, and the community. Their role is of special importance, it was said, in countries where there is a dearth of information about drugs.

59. Many participants were opposed to the retention of sales representatives in countries. If they are retained, they held, they should be properly qualified and properly trained and their activities should be strictly regulated. A participant said that in the Federal Republic of Germany sales representatives, if they are not doctors, dentists, veterinarians, or pharmacists, receive 1000 hours of training in the relevant fields and have to undergo a state examination before they can practise. In his view they are therefore particularly qualified to advise about drugs.

60. The participants considered in general that there should be ethical criteria for advertising drugs along the lines of those laid down in resolution WHA21.41 of the Twenty-first World Health Assembly. The criteria should include the obligation to use for both prescription and over-the-counter drugs only such information as is approved by the national regulatory authorities; restriction of the advertising of prescription drugs to professional journals; and punishment for non-compliance with the criteria, as for example revocation of the licence to market a drug or
drugs. According to one participant the regulation of advertising and other forms of drug promotion should form part of national legislation on drugs or, if that is not feasible, of agreements with the pharmaceutical industry, health professionals, patients, and consumers. Another participant saw drug promotion by advertising and other means as coming entirely within the process of drug registration, subject therefore to the control of the drug registration authorities.

61. Doubt was expressed about the desirability of using the mass media for advertising drugs. It was said that such advertisement encourages the public to indulge in self-medication, which is already too widely spread, especially in many countries where people can obtain any drug they want in pharmacies or shops. A participant expressed the view that the excessive volume of drug advertising is attributable to the excessive number of drugs on the market; reduce the number of drugs and the amount of advertising will automatically diminish. If the mass media are used, participants suggested, advertising should not be permitted for prescription drugs, for the treatment of conditions that can only be treated by a doctor, or in a form that may cause fear or distress, that claims infallibility, or that suggests that the drug is recommended by the medical profession. A participant felt that drug advertising should be limited to press releases by the health authorities drawing the attention of the public to the dangers of self-medication and overconsumption and the risks of and contraindications to drugs.

62. The major responsibility for ensuring that ethical criteria for advertising are observed, it was held, lies with the pharmaceutical industry. The IFPMA voluntary code of marketing practices lays down that pharmaceutical products should have full regard to the needs of public health, base claims on valid scientific evidence, and provide scientific information with scrupulous regard for the truth. It has failed in these aims, it was claimed, since thousands of drugs are found in the market that do not meet the criteria laid down; and the third International Conference of Drug Regulatory Authorities had looked at the IFPMA code and had come to the conclusion that it has not been effective. It was pointed out that legislation or a voluntary code that stipulates, for example, that the INN should be recorded on a package could hardly be said to be observed if the brand name is in huge letters and the INN barely visible. A participant also pointed out other grave drawbacks in the IFPMA code: it does not apply to over-the-counter drugs, there are no sanctions and no monitoring, and the member associations cover only 50 countries, as against WHO's 166 Member States.

63. The IFPMA code was defended by other participants, who pointed out that the member companies belonging to the 50 member associations mentioned cover about 80% of the world pharmaceutical market and that the code's provisions bear a marked resemblance to those of resolution WHA21.41. A breach of the code when committed is referred to a national member association, which takes it up with the chief executive of the company accused of the breach. Some member associations have brought independent advisers into the review procedure. Within IFPMA the final say lies with the president's committee, which consists of the president and vice-presidents and will be reinforced
by three independent advisers. In the view of some participants, voluntary regulation is more reliable, more effective, and cheaper than external regulation.

64. Whatever the value of the pharmaceutical industry's voluntary code, it was considered that governments should ensure that the industry fulfils its responsibilities, that the health profession should insist on properly screened information, and that the public should report infringements. WHO should bring up to date and expand the advertising criteria approved by the World Health Assembly in 1968 so that they can be adapted to present conditions. A participant urged governments to enact legislation on all forms of drug promotion and recommended that WHO should prepare guidelines for such legislation, guidelines that would carry the moral force associated with WHO. WHO should also call upon the industry to withdraw from the market products that do not meet adequate standards of safety and efficacy or may have harmful effects on patients or epidemiologically. In addition, it was stated, the WHO health technology assessment programme should be correspondingly strengthened, with special emphasis on the situation in the developing countries.

65. If advertising and sales promotion are not regulated by legislation, some participants thought, they should be regulated by voluntary agreements or arrangements between all the parties concerned, including consumers. In such systems panels of experts should screen drug advertisements, as they do in some countries, and the use of INNs should be encouraged since, as a participant pointed out, they introduce much-needed clarity into drug nomenclature.

Prescribing practices

66. Several participants stated that prescribing practices, as studies have shown for many countries, are frequently illogical, irrational, even dangerous. Many prescriptions are inappropriate, many are given unnecessarily, many contain too many drugs, prescription drugs are bought over the counter without a prescription, and patients who cannot afford to buy all the drugs prescribed buy a proportion only, indicating a failure on the part of the prescriber as well as on that of the consumer. Doctors are often confronted with a demand by the patient for a specific drug, and to keep the patient and safeguard their living they are compelled to comply with the demand, regardless of the value of the drug for the patient's condition. In the developing countries, too, doctors often do not have the diagnostic facilities to diagnose the disease from which their patients suffer, and health staff authorized to prescribe are insufficiently informed to make the diagnosis; they consequently in both cases prescribe a number of different drugs on the same prescription form in the hope that one will be effective, but with little awareness of the effect on the patient of the combination. Indeed, one participant suggested that adverse reactions are often not drug-induced but doctor-induced or pharmacist-induced.

67. In the light of such practices, which were described by a number of participants, it was observed that few if any prescribers in the course of their education have received instruction on prescribing practices and,
because they do not themselves in general pay for the drugs they prescribe, they are poorly informed about either the effect of the cost of the drug on the patient and on treatment or the economic effect in the community. It was consequently considered desirable that doctors and other prescribers should be instructed during their training on good prescribing practices and receive continuing education through refresher courses or otherwise. Prescribers should also, it was felt, particularly outside hospitals, be provided with trustworthy information on therapeutic indications and on the selection of drugs from within the same therapeutic category. Mention was made of hospital drug committees that meet monthly or more frequently in Malaysia, with all heads of services present and the hospital pharmacists as secretary, to discuss proper drug management.

68. Some participants argued that, if prescribing is limited to essential drugs, the task of the prescriber will be easier, the cost to the community less, and prescribers less exposed to the promotional activities of the pharmaceutical industry and its sales representatives. The first step in controlling prescribing practices is therefore to establish a limited list of essential drugs.

69. Since better information admittedly does not necessarily ensure better prescribing, it was considered that governments and professional organizations should take steps to ensure that prescribers meet acceptable prescribing standards. WHO should therefore produce guidelines on rational prescribing for selected therapeutic groups such as antibiotics. One participant noted that WHO programmes such as those in diarrhoeal diseases and acute respiratory infections help to rationalize prescribing practices and should be developed and given wide publicity.

70. In the field of prescribing practice, as in the field of drug consumption by patients, more research was seen to be needed. The Conference recommended that field research should be carried out in different settings in both developed and developing countries. WHO should analyse the results of such research and make them widely known in its Member States.

Distribution system

71. The Conference acknowledged that the distribution of drugs in the developing countries is often defective, the drugs being available in the urban areas or, rather, in the prosperous parts of the urban areas and absent or little available in the rural areas and urban slums. When available, drugs tend to be concentrated in the hospitals and are not distributed to the health centres and village dispensaries; or, because of the ignorance or inefficiency of the distributors, the wrong drugs are dispatched to the peripheral areas and there kept till expiry and destroyed, while elsewhere where they are needed they are in short supply or lacking. It was agreed that the first step in creating a good distribution system is to decide what drugs are needed, estimate the quantities required for all sectors of the population, and determine where they should go. The Conference was informed of the work of UNIPAC, the division of UNICEF that prepares sealed drug kits for dispatch to the health centres in developing
countries, and participants had the opportunity to observe for themselves how a system of sealed drug kits works in Kenya, generally abolishing pilferage and bypassing the hospitals. Attention was also drawn to the case studies on drug control and distribution in Bangladesh, Hungary, Kenya, Mexico, Norway, and the United Kingdom of Great Britain and Northern Ireland (Part 4, pages 215-272), and some of them were explained by participants from the countries concerned. A participant described the system in the Gambia, where the Government, in collaboration with a few United States pharmaceutical firms, reviewed and overhauled the entire drug supply system from procurement, tendering, storage, distribution, and sale to stock level accounting. This participant maintained that the system has been put in difficulty by the attitude of a number of doctors, who not only prescribe but also sell drugs and form a powerful lobby. In that country too foreign exchange is in short supply, and the Government has had to base its orders for drugs not on the needs of the country but on the foreign currency available.

72. Participants considered that developing countries should when necessary take steps to improve physical conditions for the importation, storage, inventory control, and distribution of drugs, providing storage warehouses, controlling distribution through authorized sources, putting an end to or reducing pilfering (as by the sealed kit system), and reducing spoilage, for example by speeding up customs clearance, ensuring proper transport conditions, and seeing that pharmacies and other drug outlets store drugs properly. Other steps recommended, depending on the circumstances, were direct distribution from central warehouses to community health centres, appropriate use of middlemen, both public and private, and the creation of adequate logistic and information systems incorporating an information feedback on the quantities of drugs required and the stocks remaining. One participant expressed the view that the main problem in developing countries is logistics, the effective distribution of drugs to where they are needed, and in solving that problem the pharmaceutical industry, on the basis of its extensive knowledge of the difficulties, would be prepared to help developing countries by providing training for the personnel needed.

73. There was general agreement in the Conference that a responsible person with the necessary managerial capacity should be in charge of storage and distribution, one participant going further and suggesting that the whole field of drug regulation and distribution should be under one managership. Another participant noted that those in charge of distribution are often not but should be properly remunerated, their responsibilities being as a rule far greater than those of most health professionals. WHO could help with training in the managerial skills required, it was suggested, and provide governments with information on experience in other countries, cooperating with them on request in introducing the necessary measures. A participant described the situation in Malaysia, where there is inventory control by computerization over central and regional medical stores providing information on drug stocks, drug utilization, and drug requirements. Other participants considered computerization to be now within the technical and financial reach of most developing countries.
74. The majority of the participants accepted the concept of national essential drugs programmes adapted to conditions and disease patterns within the countries. Some participants, however, considered that if such programmes entailed limitation of the number of drugs, that might endanger research on and the development of the new drugs needed in the world, and others again maintained that differential pricing, subsidies, and other measures could achieve the aims of such a programme without entailing a ban on other drugs.

75. A participant made a distinction between an essential drugs programme and limitation of drugs; an essential drugs programme is of obvious value, but exclusion of other drugs stifles competition, and competition lowers prices. Moreover, it was added, if in an essential drugs programme reliance is placed on a single antibiotic, say, or a single type of antibiotic, resistance to that antibiotic or type of antibiotic may be expected shortly to follow; any essential drugs programme must make allowance for such an eventuality. A reference was made to the EEC directive on the rationalizing of drug use in the European Community, under which a review carried out in Italy of the drugs on the market had resulted in the reduction of the number registered from 20,000 in 1973 to 6000 in 1985, although no essential drugs programme has been introduced. Similar reviews are under way in other EEC countries.

76. A participant described the situation in Norway (Part 4, pages 248-257), an affluent country that introduced a "need" clause in its legislation some 50 years ago and reduced the number of drugs on the market in that country to less than 2000 without detriment to the health of the country. The concept of need, the participant claimed, is not based in Norway on economic necessity but on the ground that it enables prescribers to have a thorough knowledge of the drugs that are available, pharmacists to have their shelves uncluttered with unneeded preparations, and governments to conserve foreign currency.

77. It was maintained by another participant that the need clause in Norway is largely bypassed by doctors, who apply in large numbers for permission to use unregistered drugs; but figures were cited for 1984 to show that there were only some 18,000 such applications as against 30-40 million prescriptions, and of the 18,000 two-thirds or so were for herbal or other preparations of no scientifically proved value, 3000-4000 for drugs in the process of registration such as cyclosporin, and 2000-3000 only for a wide variety of drugs registered in other countries, many of which were for patients whose treatment had started abroad.

78. The need clause gave rise to considerable discussion. It was pointed out that in Denmark, a neighbouring country, such a clause has been found unnecessary because asking the manufacturers questions about indications and the rationale for the drugs they wish to have registered frequently leads them to withdraw their applications. In Sweden, another participant said, the association of general practitioners has established a limited list of drugs for primary health care, a system that has the advantage of involving
prescribers at the community level and is preferable to one imposed from above. The view was also propounded that the therapeutic value of a new drug cannot be adequately judged without practical experience, whereas the concept of need mistakenly implies that it is possible to reach a definitive judgement on the drug before it is introduced on the market and that no future therapeutic benefit will occur. Moreover, according to this view, in relation to decisions that such and such drugs are needed, it has to be borne in mind that committees are far from infallible, and their decisions not infrequently wrong. To provide optimum treatment doctors therefore need to have a broad range of drugs at their disposal.

79. Many participants nevertheless felt strongly that governments, particularly in the developing countries, should institute limited lists of drugs; indeed, the need to do so was expressed constantly by these participants throughout the discussions. Within the national list of essential drugs sublists could be prepared for the various levels of the health system, starting at the primary health care level and rising through the various referral levels. Support was voiced for the views expressed by the WHO expert committees on the selection and use of essential drugs and for the WHO Action Programme on Essential Drugs and Vaccines. Participants suggested that governments should take steps to persuade health workers and the public of the value of essential drugs programmes and seek the cooperation of professional organizations and teaching institutions in carrying them out. WHO should promote such programmes more vigorously and help governments to implement them, and bilateral agencies should increase their support for them as part of the developing countries' strategies for health for all through primary health care. Because of its unique position, a participant maintained, WHO should urge countries not to look at the health of their inhabitants solely in terms of drug treatment; there are alternative ways of dealing with health problems, such as environmental sanitation and nutrition, and they too need to be utilized.

80. A participant thought that an important part of an essential drugs programme should be the provision of prescribing information and the instruction of prescribers on how to use essential drugs. Another held that such a programme should be made to apply to both the private and the public sector, since applying it only to the latter would inevitably doom it to failure. Yet another considered that a holistic approach is needed; it is not enough to institute an essential drugs programme, the programme must be accompanied by a strong drug control system and local manufacture of the essential drugs. It was also held that, given the demographic situation in the world today, a necessary concomitant of an essential drugs list is an essential contraceptives list. A participant expressed his approval of the presence of a placebo in the WHO model list of essential drugs, since it recognizes both the widespread need of people to have a medicine of some kind and the value of the placebo response.

81. A number of dissenting opinions were expressed. A participant disagreed with the whole concept of an essential drugs programme. In his country, he said, drugs were in the past severely restricted in number and

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the policy failed; now there is a free system and it works better. He added that most doctors prescribe a limited number of drugs anyhow and that educating them to keep prescribing within limits and providing them with balanced and unbiased information is preferable to restricting the number of drugs. Another participant thought that governments should aim at providing low-cost generic drugs for the majority of the population but should permit those who can afford them to buy innovative drugs, which are the essential drugs of tomorrow. Yet another participant feared that an essential drugs programme would amount to the promotion of drugs as the solution to health and social problems; it can form only a small part of the efforts to solve those problems, and its impact should be assessed before it is widely extended. A participant pointed out that two major United Nations conventions, the 1961 Single Convention on Narcotic Drugs and the 1971 Convention on Psychotropic Substances, include a number of drugs that appear in the WHO model list of essential drugs. He thought that WHO should add information on the joint activities of the United Nations and WHO in relation to those drugs to the background documentation.

82. The view was expressed that the pharmaceutical industry should mass-produce essential drugs and sell them to developing countries at a price those countries can afford. As incentives to the industry to do so, it was suggested, governments should consider measures favouring such action, for example exemption from import duties, relief on turnover taxes, and price discrimination in relation to the essential drugs. It was, however, pointed out that, whatever governments or pharmaceutical industries do, many governments in developing countries will lack the funds to finance the import of even a limited number of essential drugs, and it was again recommended that WHO and other international organizations should help them in their foreign exchange problems.

83. A participant described the role of UNICEF as a partner in the WHO Action Programme on Essential Drugs and Vaccines. As mentioned before, through UNIPAC, UNICEF's packing and assembly centre in Denmark, it supplies essential drugs and vaccines of good quality and modest cost to developing countries. In 1985 it supplied about US$ 35 million worth of such drugs and vaccines, nearly double the amount it had supplied two years earlier. The drugs and vaccines were purchased through an international public tendering system that has succeeded in lowering the price by nearly 50% in the past five years. UNICEF publishes the prices it pays for the drugs so that governments in developing countries can compare them with what they themselves pay, and on request suggests sources of supply for essential drugs. It ensures the quality of essential drugs by working closely with WHO, following the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce and arranging for independent quality analysis of batches of drugs purchased in support of the Action Programme. It has aligned its inventory to correspond with the model list of essential drugs and has agreed to stock for rapid delivery any essential drug for which there is a demand. It has increased the stock of essential drugs in its Copenhagen warehouse from a value of US$ 5 million to US$ 10 million. It supplies the drugs under a neutral label. In addition to its regular reimbursement procurement procedures, UNICEF is examining the possibility of export credit guarantees; it now accepts letters of credit;
and it hopes to set up a revolving fund,\textsuperscript{1} with a view to providing developing countries with a range of financial options.

\textbf{RESEARCH}

84. The establishment of an essential drugs programme, it was recognized, does not obviate the necessity for research into new drugs, particularly into the many tropical diseases for which drug treatment needs to be improved. One participant claimed that most of the research carried out by the pharmaceutical industry is on diseases in the developed countries, not in the developing countries where the need is greatest. Another maintained, however, that the pattern of disease is changing in the developing countries and coming to resemble that in the developed countries, in relation for example to cancer and cardiovascular diseases. It was also pointed out that in many developed countries a substantial amount of research is carried out in institutions and universities, but research discoveries need to be transformed into commercial products and the pharmaceutical industry has the major role to play in and a responsibility for such a transformation.

85. Only a fraction of the amount spent on research by the pharmaceutical industry, some participants contended, actually goes on research; by far the greatest amount goes on promotion, and much of what is spent on research is on frivolous matters like changing the colour of tablets or the mixture of ingredients, or even the name of the product. One participant stated that in general a quarter of the costs of research and development go to the creation of new active principles, half to developing those principles into a pharmaceutical product and preparing the data for registration, and the rest to marketing. Several participants urged the pharmaceutical industry to lift the veil of secrecy on its operations and costs, which give rise to perhaps distorted views about them.

86. Noting that WHO funds research through voluntary contributions in, among other things, tropical diseases and human reproduction, in which drugs play an important part, participants considered that more needs to be done in other priority health fields, though not necessarily through WHO. It was nevertheless recommended by some participants that WHO should seek to increase research on drugs needed for treatment, especially in developing countries, and incorporate drug assessment in health technology assessment, applying the same methodology. A participant suggested that research might be funded by selling drugs at a high price in developed countries while selling them cheaply in developing countries. Another suggestion was that research should not be limited to new drugs only but should cover all aspects of drug management and marketing such as prescribing, cultural attitudes, and clinical trials. Field research was advocated, especially in developing countries, to ascertain whether drugs are cost-effective, since the aspect of cost-effectiveness is poorly understood, even for essential drugs; and the research should be extended to traditional remedies and veterinary medicine. It was also thought that the introduction of essential drugs programmes would provide an admirable opportunity to conduct research.

\textsuperscript{1} See WHO document EB75/1985/REC/1, Annex 8.
on the limited number of drugs in use—clinical research perhaps, or research on the balance between the beneficial and adverse effects of the drugs.

87. A suggestion was made that the pharmaceutical industry might be encouraged to invest more in research if the patent life of new drugs was extended. That suggestion was opposed by a participant who considered that the intellectual property system under which patents are subsumed should not be regarded as sacrosanct but should be changed to meet a country's needs. Another participant found that view unacceptable; at meetings of the World Intellectual Property Organization representatives of developing countries as much as those of developed countries have recognized the importance of protecting creative work and the investments of people attempting to develop new technology.

88. A participant pointed out that progress in pharmaceutical research is rarely achieved by a major breakthrough; rather, it occurs through marginal but significant advances that cumulatively improve the quality of the treatment available to the patient. The clinical status of a new drug often takes years to determine, and restrictions at the moment of its launching may inhibit the development of knowledge about its therapeutic usefulness. Placing limits on new drugs entering the market introduces further uncertainty into the already uncertain research and development process, a process that in general only the pharmaceutical industry has been prepared to embark upon because of the expense and risks involved.

WHO CERTIFICATION SCHEME

89. There was general agreement that the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce is an efficient and low-cost mechanism for ensuring the quality of drugs that importing countries receive (Part 4, pages 287-298). It was felt, however, that it should be extended to include product information approved in the country of origin, as recommended by the Third International Conference of Drug Regulatory Authorities (1984). It was also considered that, as the Scheme covers finished products only, raw materials and unfinished products should be added. Again as recommended by the Third International Conference of Drug Regulatory Authorities, it should contain more systematic exchange of information on formal reviews of marketed products by national authorities and periodic status reports on categories of drugs reviewed by such authorities and those pending for assessment, negative information being as important as positive. More countries should be encouraged to take part in the Scheme, since important drug-exporting countries such as China, the German Democratic Republic, and the USSR are missing.

90. A participant, while agreeing that the Certification Scheme helps in ensuring the safety and efficacy of drugs, considered that it is less effective in relation to their quality. For that purpose some form of inspection is needed to make sure that good manufacturing practices are followed throughout the process of production and final quality control of finished batches. Another participant suggested that every certificate issued by an exporting country should contain the name of the country or
countries for which it is intended. This will make it easy for the exporting country to get in touch with the importing country if the drug is found to have undesirable side effects; and the importing country can make the information less one-sided by informing the exporting country of quality or other defects. It was observed that in Denmark only 1% of the approximately 5000 certificates issued annually by the Danish National Board of Health are of the WHO kind, the reason being that the importing countries specify the standards and do not call for a WHO certificate. WHO should try to persuade countries to ask for the WHO certificate. Another suggestion made was that national regulatory authorities of exporting and importing countries should correspond direct, without using the drug manufacturers as intermediaries. A participant described the new information exchange programme in the United States, which deals with drug approvals, withdrawals, etc. The Food and Drug Administration in that country is prepared to furnish information on an ad hoc basis to all requesting it.

91. All these recommendations would involve considerable changes in the Scheme, and it was recommended that WHO should convene a group of experts to study them. WHO should also consider arranging regional meetings of drug regulatory authorities to discuss ways of implementing the Scheme more effectively and study other aspects of drug policy.

QUALITY CONTROL

92. The Conference considered that developing countries should investigate the possibility of setting up a small national quality control laboratory where none exists at present, following the recommendations of the WHO Expert Committee on Specifications for Pharmaceutical Preparations. Such a laboratory, a participant said, should exercise quality control not only over drugs imported into the country but also over drugs manufactured locally, since in many countries quality control over local drugs is inadequate. Another participant noted that according to official sources, one drug in five of locally manufactured drugs in one developing country with a large production capacity is substandard, according to unofficial sources more. In that country there are only three quality control laboratories but 43000 drugs, and the problem of excluding drugs that do not meet quality standards is of major importance. It was observed by a participant that adverse reactions to drugs are often not caused by the active ingredients in the drugs but by defects in their quality; hence an additional need for effective quality control.

93. To meet the cost of setting up a quality control laboratory, it was suggested that a portion of WHO's programme budget allocation in the country concerned might be utilized, one participant advocating that WHO's financial support should be proportionate to the government's investment in quality control. It was recommended that developing countries should seek to increase their own technical cooperation, those with larger laboratories perhaps providing services and helping those with smaller or no laboratories regionally and subregionally; and that WHO and other international organizations should furnish guidance and help. In that respect, a

participant said that in the United States of America the Food and Drug Administration provides training in quality control for foreign government personnel in its own laboratories and, in association with a local university, has established a five-week course in quality control, the first of which begins in May 1986. The grant of fellowships for these courses is under discussion with WHO. Another participant said that comprehensive courses on quality control are given in Japan to drug regulatory personnel from Asian countries, fellowships being awarded for the purpose. Yet another participant said that since 1979 IFPMA has provided training in quality control to personnel from developing countries; so far 51 persons have been trained.

94. The Conference considered that governments should take the action necessary to prevent drug counterfeiting, which was characterized by several participants as a criminal act that all drug regulatory authorities must try to combat. One participant expressed the view that drug counterfeiting would stop if the prices of drugs were brought down, since only expensive drugs are counterfeited. It was recommended that WHO, with other international and nongovernmental organizations, should study the feasibility of setting up a clearing-house to collect data and inform governments about the nature and extent of counterfeiting.

EDUCATION AND TRAINING

95. The Conference agreed unanimously that education and training are required for all concerned with drug prescribing, regulation, and marketing, as well as for consumers. Health professionals need to be trained as educators so that they can communicate with patients and miss no opportunity of educating them in the proper use of drugs and awareness of the dangers, for example, of uninformed self-medication. They also should learn to judge the risks of drugs against their benefits and drug treatment of disease as against other forms of treatment. Health care professionals, it was stated, have traditionally been poorly educated for such purposes, one of the reasons being the inadequate development of clinical pharmacology, which spans the gap between basic pharmacology and therapeutics. Undergraduate education on drug treatment should be centred around the teaching of clinical pharmacology. Because of the shortage of clinical pharmacologists the same gap exists in postgraduate education and is partly filled—perhaps to too great an extent, a participant commented—by the pharmaceutical industry. In that respect a participant mentioned conservatism in universities and other teaching institutions and suggested that an important step for WHO would be to organize workshops for deans of medical and other relevant faculties so as to make them aware of their role in the teaching of clinical pharmacology. Another participant thought that teachers in such institutions should not be allowed to engage in private practice, so that their impartiality in relation to certain drugs is not endangered. It was suggested that education of health professionals on drug matters should be intensified at the undergraduate level, be an important subject of the qualifying examinations, and form a part of continuing education throughout their professional career. An essential step is to improve the teaching of clinical pharmacology, which, it was stated, has been neglected in the medical curriculum.
96. Another vital part of education is in management; participants returned time and again to the need, especially in developing countries, for personnel with managerial skills and economic knowledge to administer the country's drug supply and control system. Drug regulation, quality control, information, economics, the concept of essential drugs, and the assessment of health care technology, including drugs, were among other subjects in which it was felt that education and training were insufficient and needed expanding; again it was said that education in the art of communicating with people has been badly neglected. A participant spoke of the need for WHO and other organizations to sponsor courses on teaching skills for teachers of clinical medicine, pharmacology, nursing, and other subjects because all too often they lack such skills and communicate ineffectively with their students. It was also suggested that ministries of health should institute a programme of continuing education for prescribers and coordinate to that end the efforts of medical and pharmaceutical associations and the academic community. Participants called for research on new training approaches such as the preparation of learning materials to be included, for example, in the drug kits dispatched by UNIPAC. A reference was made to the United Kingdom diploma in pharmaceutical medicine and to Australian prescriber, a bulletin produced by an independent group of professors of medicine, pharmacologists, and others but funded by the Australian Government, which provides a kind of continuing education on drugs for medical practitioners, dentists, pharmacists, and undergraduates. Other countries might consider following that example.

97. It was recommended that WHO should provide fellowships for training in the subjects mentioned, convene meetings of experts to give guidance on the content and methods, hold seminars and workshops, and encourage bilateral and other training schemes. Mention was made of tripartite seminars in which representatives of government, the academic community, and the pharmaceutical industry take part; of regional approaches; of the designation of undergraduate and postgraduate centres; of the preparation of appropriate training curricula; of the creation and dissemination of teaching and learning materials; of the establishment of guidelines on a variety of subjects; of the institution of correspondence courses; and of the distribution of essential books. In all those matters, many participants stated, WHO has a major part to play in stimulating and coordinating education and training efforts.

98. One of the suggestions made was that, because education and training have an important institution-strengthening and research-capacity-strengthening component, WHO should launch an action programme on training in the rational use of drugs related to a programme on health technology assessment. Such an action programme should provide training in drug regulation, quality control, and post-marketing surveillance, encourage governments to train adequate numbers of clinical pharmacologists, particularly those concerned with primary health care, offer teaching by correspondence for essential drugs programmes, train people from developing countries as clinical pharmacologists, develop learning materials for doctors, pharmacists, and other health workers and the public as well as for the mass media and for distribution with drug kits, and sponsor the distribution of essential books. A participant
stressed the need for training programmes for pharmacists, who are of key importance in some countries in the rational use of drugs; nurses were also mentioned in this context.

99. The education of consumers was regarded as equally important. It should, it was stressed, seek to make consumers aware that health is their personal responsibility, that a single report on a drug may not be a true analysis of the situation, that drugs play only a limited part in the maintenance of health and the cure of disease, and that self-medication has its dangers. It should also acquaint consumers with their rights in relation to doctors and other health care providers and hospitals and instruct them on the questions they should ask as patients. The education of consumers, it was maintained, should lie in the hands not only of health professionals but also of schoolteachers, consumer associations, and parents. Consumers should also, it was suggested, be sensitized to information-assessment mechanisms, perhaps by exposing them to the preparation of drug information bulletins and involving them in the preparation of popular information on health matters in general and drugs in particular.

RESPONSIBILITIES

100. In his closing address (Part 1), the Director-General summed up the issues debated at the Conference, the proceedings and the potential implications for WHO's programme. He listed the responsibilities of the parties concerned that were identified during the Conference as follows.

101. Governments: to establish a national drug policy; to institute or reinforce essential drugs programmes and take steps to convince health personnel and the public of their usefulness; to ensure the objectivity and completeness of drug information in the country; to ensure relevant, good-quality information to the public on health matters, including drugs; to set up or strengthen drug regulatory authorities so as to ensure adequate registration of drugs of acceptable quality, safety, and efficacy; to safeguard the international nonproprietary names of drugs; to ensure improved training of health workers in health care, including drug therapy; to take steps to ensure that drugs cost as little as possible but are yet of acceptable quality and constantly available; to make more use of open competitive tenders for generic drugs so as to reduce costs in developing countries; to study methods of cost recovery; to decide who shall have the right to prescribe, distribute, and sell drugs; to establish lists of drugs permitted for sale over the counter; to establish ethical criteria for drug advertising and supervise compliance with them; to enact appropriate drug legislation and take action to enforce it; to adopt measures to improve prescribing practices; to improve distribution systems as required; and to study the technical and economic feasibility and extent of local drug production where it does not exist or exists only to a limited extent.

102. The pharmaceutical industry: to provide complete and unbiased information on pharmaceutical products to governments, prescribers, and consumers; to observe good manufacturing practices; to comply with established drug promotional criteria and avoid double standards in
different countries; to respond to the need of developing countries for low-cost drugs of acceptable quality; and to develop badly-needed new drugs in neglected fields, particularly to solve the health problems of developing countries.

103. Prescribers: to prescribe rationally in conformity with health, social, and economic criteria; to provide appropriate information on health care in general and drug therapy in particular to patients and the public at large (a responsibility that dispensing pharmacists also have); and to insist on being provided with truthful and complete information only.

104. Universities and other teaching institutions and professional nongovernmental organizations: to improve the training of the different categories of health workers in the rational use of drugs through appropriate curricula and modern educational technology; to introduce the concept of essential drugs in the training of health personnel; to provide continuing education for health workers; to ensure that symposia on drugs comply with acceptable educational norms; and to provide general education on proper health care and drug therapy to those not training as health workers.

105. The public, patients, and consumer associations: to seek to improve the relevance and quality of information to the public; to share responsibility with governments and nongovernmental organizations for the education of consumers on drug matters; to maintain vigilance and demand compliance with established criteria for drug advertising, drawing the attention of the health authorities to suspected infringements; and to support essential drugs programmes.

106. The mass media: to provide balanced information on health subjects, including drug therapy; to share in education of the public on the proper use of drugs; and to give favourable publicity to those complying with ethical criteria for drug advertising and unfavourable publicity to those not complying.

107. WHO: to prepare guidelines for national drug policies; to accelerate the promotion of national essential drugs programmes; to support countries in carrying out technical and economic feasibility studies on local drug production; to provide complete and unbiased information on drugs at the international level, as by issuing model data sheets and formularies on drugs in the WHO model list of essential drugs, extending the scope of the Drug information bulletin and publishing it more frequently, and producing monographs on selected drug issues; to make learning materials available so as to improve the training of health workers in the rational use of drugs and to help countries to use them; to reinforce national drug regulation, as by providing relevant information to countries, coordinating bilateral support for the strengthening of national drug regulatory mechanisms and facilitating the training required; to enlarge the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce; to issue guidelines on minimum requirements for drug regulation; to expand the work of the International Conference of Drug Regulatory Authorities (ICDRA); together with UNICEF and possibly the World Bank, to support
developing countries in procuring drugs internationally at the lowest possible cost; to define ethical criteria for drug promotion; to provide governments with information on drug legislation and help them on request to formulate such legislation; to stimulate technical and socioeconomic research on drugs and drug practices and publish the results; to fulfil the role of lead agency in the implementation of United Nations General Assembly resolution 37/137 with regard to the dissemination of information on drugs that have been banned, withdrawn, severely restricted, or not approved by governments on grounds of safety; and, with other appropriate bodies, to study ways of providing information to combat counterfeiting, which should be considered a criminal offence.

**WHO REVISED DRUG STRATEGY**

108. In closing, the Director-General presented a succinct outline of a revised drug strategy\(^1\) for WHO that he intended to elaborate further and place before the World Health Assembly.

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PART 3

OPENING ADDRESSES AND INTRODUCTORY STATEMENT
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Honourable ministers, Director-General of the World Health Organization, your excellencies, ambassadors, experts on drugs, ladies and gentlemen.

I welcome all visitors to Kenya, a country that in culture and national variation is rich and unique. Kenya has had her share of problems in drug procurement and distribution. I am happy to say that we have also made progress in solving this problem. The problems that we have faced in this field I am sure are not peculiar to us. I believe this may be one of the reasons why so many countries expressed the wish to have such a conference convened, and I am happy that Kenya is hosting this important meeting.

The choice of the subject and the interest that it has generated testifies to the concern that exists on the use of the drugs we have at our disposal. This concern is global and calls for worldwide cooperation for its solution. This cooperation on a bilateral or multilateral basis is necessary, as is that with the World Health Organization.

Kenya has an essential drugs programme which is fully operational in all government dispensaries and health centres. The details of this will be the subject of discussion during the Conference, hopefully to illustrate that the problem is not insurmountable. The essential drugs programme is also an example of how Kenya is using bilateral assistance and World Health Organization technical support.

Encouraged by the success of the essential drugs programme for the rural health facilities, we have together with the World Health Organization just finished a study on a possible comparable programme for governmental and nongovernmental hospitals. In all this what we are trying to do is to have a more cost-effective, efficient and rational use of drugs. Our performance in this field is a result of joint efforts, as I have already acknowledged. May I take this opportunity to request developed countries to assist developing countries in this important health component. To those who have helped us, I wish to thank them and to express our hope that they shall continue to give this valued assistance.

Medicines are important for health care systems. Better use of medicines therefore makes a lot of sense. Medicines can be expensive; their management therefore is good economics. In our effort for health for all by the turn of the century, through the strategy of primary health care the use of medicines should receive the necessary attention, as is not the case now. During the Conference, I hope the participants will have time to visit our health institutions to see the problems and the successes of this programme. I also hope that the participants will have time to visit different parts of the country after the Conference.
With these brief remarks, honourable ministers, Director-General, your excellencies, ambassadors, ladies and gentlemen, I have pleasure in declaring the Conference of Experts on the Rational Use of Drugs officially open.
ADDRESS BY DR H. MAHLER
DIRECTOR-GENERAL OF THE WORLD HEALTH ORGANIZATION
AT THE OPENING CEREMONY

Your Excellency Mr Nyakiamo, Minister of Health of Kenya, distinguished gathering, colleagues and friends.

I wish to thank you, and through you President Moi, for hosting on the soil of Kenya this important Conference of Experts. We had good reason to accept your kind offer because you have shown how diligent efforts can bring essential drugs to people, and in particular to people in rural communities, for well under one US dollar per person per year. I hope that if this meeting does nothing else it will at least show other countries that it is possible to provide people with the drugs they need most at a price they can afford without political and commercial upheaval.

To grasp the significance of the issues we will be debating at this Conference, it is necessary to consider them in the light of the goal that WHO's Member States set themselves some eight years ago—the attainment by all the people of the world by the year 2000 of a level of health that will permit them to lead a socially and economically productive life, popularly known as health for all by the year 2000. The key to attaining that goal is primary health care, and one of the key elements in primary health care is ensuring that everybody has access to essential drugs. But the goal of health for all too has to be seen in the broader perspective of socioeconomic development goals. Indeed, a minister of planning—an economist by profession—recently stated that for his country the strategy to attain health for all by the year 2000 was much more than a health matter, it was a new model for development.

Over the past three decades we have made mistake after mistake at the international level with regard to social and economic development. We naively believed that people's development can be brought about by proxy from the outside, by international action. We have since learned the hard way that it cannot. At best international efforts for development can support national ones; at worst they suppress them. So we must always keep in front of us the strengthening of national self-reliance. This applies to socioeconomic development in general, to health development as part of that, and to the establishment of rational drug systems as part of health development. This principle is in keeping with the Declaration of Alma-Ata—national self-reliance in health matters, not the least in drug matters.

This Conference is about people, particularly people in developing countries, and how to ensure that they have access to the drugs they need most at a cost they can afford. In some affluent countries, as well as in the large cities of some developing countries, the problem is how to manage the vast number of drugs on the market. In most countries, however, the most urgent problem is quite the contrary—how to make sure that people have access to the relatively few drugs that are vital to them for their day-to-day health care—usually 30 to 40 in number.
I sincerely hope we will emerge from this Conference enriched in our knowledge of ways of strengthening the capacities of countries, particularly developing countries, to set up and carry out rational drug policies and programmes along the lines endorsed by the World Health Assembly, WHO's supreme policy organ. By that I mean policies and programmes that will help them to ensure essential drugs for all by dealing effectively and efficiently with all the complex issues involved in modern drug use - from the conception of a drug to its ingestion by people.

That is precisely what the government and people of Kenya are succeeding in doing, and I should like to thank you once more, your Excellency, and through you all the people of Kenya, for acting as a shining example to many other countries in similar circumstances. I am sure this example will guide us in many of our deliberations. I sincerely hope that these deliberations will lead to concrete ways of making drug use throughout the world more rational. Many many people throughout the world are anxiously awaiting that of us.

Thank you.
INTRODUCTORY STATEMENT BY DR H. MAHLER
DIRECTOR-GENERAL OF THE WORLD HEALTH ORGANIZATION

Distinguished experts:

1. I shall repeat the word "experts" for it is in that capacity that you are here, and not as representatives of your government, your professional affiliation, your industry or the consumer organization to which you belong. That is part of the rules of the game of a WHO meeting of experts, irrespective of whether it is called a meeting or a conference.

2. I am relieved that we have been able to meet at all. Ever since May 1984, when the Health Assembly decided to hold this meeting, the climate surrounding it has been such that I have often wondered if it would not do more harm than good. First of all, some of the sponsors protested that the Secretariat was sabotaging the original intention by including too many issues on the agenda and inviting too many participants. And yet it was necessary to start the process of rationalizing drug use by outlining the main issues on a world-wide scale and placing them in their proper perspective; there had been far too much irrational oversimplification. Also, the clamour to participate was immediate, widespread and vociferous. Then came the openly-stated suspicions of some parts of the pharmaceutical industry on the one hand and of consumer groups on the other that WHO was sold to the other side and that the meeting would only be a cover-up for predetermined conclusions. These were accompanied by intimations of world-wide publicity campaigns. Following this came insinuations that the list of participants was a put-up affair aimed at ensuring the victory of the other side. The fear - justified I am sorry to say - that participants would be deluged with propaganda material made it necessary to keep the list of participants confidential until today. Fortunately, the social pathology surrounding this meeting now appears to be quiescent, and I hope it will remain that way.

3. Distinguished experts, this meeting is about people, particularly in developing countries, and how to ensure that when they need drug therapy the appropriate drug is prescribed for them, it is effective and of acceptable quality and safety, it is available at the right time at a price they can afford, it is dispensed correctly and it is taken in the right dose at the right intervals and for the right length of time.

4. Obviously, industry and consumers have a role in all of this, but they are not the only ones and this meeting is not, I repeat not, an international battleground for them to vent their differences. I expect you therefore, as WHO experts, to consider the problems of drugs in developing countries from the perspective of the situation in those countries and of the people in them, particularly the underprivileged people in rural areas and urban slums, and on no account to transfer to them the drug problems of the over-affluent industrialized countries or the urban elite in developing countries. I rely on participants from developing countries to make sure that we do keep the true situation in these countries first and foremost in our minds.
5. The papers you have before you attempt to describe succinctly the world drug situation, and particularly the situation in developing countries. They attempt to unravel the complex path of drugs from conception to ingestion and they do so in the context of the goal that has been adopted by all WHO's Member States, namely the attainment by all the people of the world by the year 2000 of a level of health that will permit them to lead a socially and economically productive life. One of the fundamental principles to attain that goal is a more equitable distribution of health resources both within and among countries, to be attained by the action of governments and of people and not by distant acts of poisoned charity. For if governments have responsibility for the health of their people, people have the right and the duty to participate in planning and implementing their health care. They can do so as individuals, as families, as communities, through their elected representatives, or as members of consumer groups or other associations.

6. So the papers show how governments and people can define national drug policies and set up programmes to give effect to them, starting by ensuring the 30 to 40 drugs that are vital for primary health care in the communities of the developing countries. They then go on to stress the importance not only of providing all concerned with objective information on drugs but also of governments, health care providers and people using that information correctly. That brings in the role of education and public information. Prescribers have to know if and when drugs are needed at all, and how to select an appropriate drug in each case, also taking into account the price. Pharmacists, nurses and other health care workers have to dispense the right drugs at the right times and guide people to use them correctly.

7. The papers also explain how drugs are developed, and the responsibility of industry and governments for the control of their safety, efficacy and quality as well as for their good manufacturing practices. If drug distribution is not a problem in industrialized countries, it is a major impediment to rational drug use in developing countries, particularly in rural areas. Another factor influencing the rationality or otherwise of drug use is drug promotion, and the papers describe the present situation and the responsibility of governments, the pharmaceutical industry, prescribers and consumers. The costs of drugs to society and the price to the individual are also considered, recent ways of controlling them are mentioned, and the need for further efforts in that direction stressed. The place of national drug legislation is considered too.

8. In spite of the wide range of issues covered, some have purposely been excluded, not because they are not important but because it was felt that the main ways of making drug use more rational could be clarified without them. These include the question of patents and specific issues such as narcotic and psychoactive drugs and traditional medicines.

9. You have also been provided with an outline of what WHO has already done to improve rationality in drug use. This includes the assignment of international nonproprietary names, the establishment of an international drug monitoring scheme, the International Pharmacopoeia and meetings of the international conferences of drug regulatory authorities. It also includes
the provision of updated information through drug information bulletins, the introduction of the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce and collaboration with the United Nations in connection with the General Assembly's resolution on the export of drugs banned from domestic consumption or sale on grounds of safety. In addition, it includes the adoption by the Twenty-first World Health Assembly as long ago as 1968 of ethical and scientific criteria for pharmaceutical advertising. Last, but certainly not least, WHO has developed the very concept of essential drugs. It issues model lists of such drugs from time to time and has a vigorous action programme to support countries in establishing and implementing drug policies that aim at ensuring the regular availability of essential drugs of good quality and at the lowest possible price. WHO has also joined forces with UNICEF to support the provision of essential drugs for primary health care in developing countries.

10. So countries already have at their disposal an effective array of measures for improving their drug situation. If they apply them properly, this could go a long way towards improving the rational use of drugs. But much more remains to be done. That is why we have presented for your consideration a number of suggestions for making the use of drugs more rational.

11. These suggestions relate to the responsibility of governments, prescribers, dispensers, and people in all walks of life and in various associations, for setting up national drug policies and introducing measures to carry them out. They present for your consideration possible ways of rendering drug information more objective, less biased and more accessible to prescribers and consumers. These include setting up national consensus groups to ensure that information disseminated by whomsoever conforms with the approved product monographs issued by the regulatory authority. Other suggestions relate to drug formularies and data sheets, better use of professional journals for the dissemination of complete and unbiased information on drugs, enhancing the information role of pharmacists and improving the relevance and quality of information provided to health personnel and the public. Universities are reminded of their role, in addition to that of governments and nongovernmental organizations, in improving the training of health workers in the rational use of drugs.

12. Suggestions are also made for improving drug marketing. These include the role of governments in the control of drug quality, safety and efficacy. Ways are suggested by which developing countries unable to establish comprehensive drug registration systems could at least create simple administrative procedures for identifying and listing drugs so as to be able to monitor and control their marketing. National and international measures are suggested to make sure that drugs cost as little as possible, consistent with acceptable quality and ensured availability, and the question of cost recovery in countries is touched upon. The responsibility of governments concerning the right to prescribe, distribute and sell drugs is raised. A number of suggestions are made in the field of drug promotion, including ethical norms for advertising, the relevant responsibilities of governments and industry, and the use of consensus groups to support social
control over the application of these norms. Proposals concerning national legislation on drug marketing and ways of enforcing it are also aired.

13. Suggestions are also made for rendering prescription practices more rational, including the related supportive roles of governments, nongovernmental organizations and industry. Moreover, suggestions are made for improving distribution systems, emphasis again being laid on the role of governments, particularly in developing countries. Ways of reinforcing the role of governments in setting up national essential drugs programmes are suggested and the pharmaceutical industry is asked to consider mass-producing essential drugs and marketing them at prices that people in the developing countries can afford, thereby creating a huge market for the future. The possibility is aired of voluntary funding of research to develop badly needed new drugs in neglected fields, such as tropical diseases. A number of suggestions are also scattered throughout for improving WHO's support to its Member States in all the fields I have mentioned.

14. I hope you will react to these suggestions with the same degree of seriousness and sincerity with which they have been formulated. I would go further and propose that these suggestions be the main focus of your deliberations. How can you deal with all of them in a few days? Well, first of all I should like to point out that you have had a month or so to reflect on them. I should like to suggest that you respond to them in clusters under the headings in which they have been presented, stating clearly and concisely your reactions to them. In this way, it should be possible to separate out quickly those suggestions that appear to meet with overwhelming approval or disapproval, leaving sufficient time to concentrate on those that require more detailed debate. Of course, you are free to make further suggestions, which I sincerely hope will be constructive, as we are accustomed to when they come from WHO experts.

15. In conducting your debate, I would urge you to leave behind any quarrels of the past and to participate constructively with open minds so that we leave here with better ideas of how to support countries, particularly developing ones, in using drugs more rationally. I earnestly beg of you to forget your affiliations and your preconceived notions as seen by some of you from your distant perspectives, and to focus on people, particularly in developing countries, on their problems as they perceive them and that they have so often dramatically expressed in public and in private. Distant demagogy will not bring drugs to the deprived. Irrational talk and facile oversimplification in board rooms, conference halls, the press and TV and radio studios will not lead to the rational production and sale of drugs by industry, their rational control by government, their rational distribution by the health infrastructure, their rational prescription by health personnel and their rational use by people. So please come forward with proposals for improving the situation that are both rational and feasible.

16. Some proposals are feasible, such as the assumption of greater responsibility by governments, the pursuit of socially responsible behaviour by industry, the display of maturity by prescribers, the intelligent
involvement of people as individuals, through their elected representatives, and as members of associations such as consumer groups, and the uncompromising revelation of objective information by WHO and staunch support by the Organization of its proper use by all concerned.

17. Other proposals are not feasible, such as the exercise by WHO of supranational executive powers to enforce courses of action on governments, on industry, on nongovernmental organizations or on people. WHO is not a supranational body, nor is it a ministry of health of a world government. It is an intergovernmental organization consisting of Member States cooperating among themselves and with others to promote the health of all peoples. The Strategy for Health for All by the Year 2000 is a social contract for health between governments, people and WHO; it is not a legally binding instrument. It works by Member States voluntarily carrying out domestically what they have agreed to collectively in WHO. Even regulations adopted by the Health Assembly under one of the articles of the Organization's Constitution only come into force for those Member States that accept them; others merely have to inform the Director-General within a given period that they reject them or have reservations about them.

18. WHO's role in this as in other fields is that of an objective pathfinder marking out for everyone the best ways of complying with the policy on drugs adopted by the World Health Assembly. It is up to you, distinguished experts, to advise the Organization on how best to fulfil that objective role in such a way that people everywhere will derive greatest benefit from it. The more you can agree upon at this meeting the greater will be our moral strength and our consequent ability to lead all our Member States towards national self-reliance in health matters and not the least in drug matters. I realize that some of you may have legitimately divergent views on a number of issues. In those cases, I submit that WHO can best fulfil its pathfinding role by bringing together reliable information so that there will be at least an objective basis for rational debate.

19. Of course, wonders cannot be expected from one meeting; this is only one event in a long-term process. But if this meeting helps to get the main directions right, it will be a historical landmark in the evolution of the action required to ensure that drugs are used more rationally throughout the world. I shall report on all of this to the Thirty-ninth World Health Assembly in May 1986, and in the meantime I wish all of you, all of us, a fruitful meeting. The world at large expects that of us.

Thank you.
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Drugs and health for all by the year 2000

1. One of the main aims in HEALTH FOR ALL BY THE YEAR 2000 is an equitable distribution of resources for health. Equity is certainly not a characteristic feature of the existing drug situation in the world. The most urgent need regarding drugs at this stage is to make it possible for the vast majority of the world's people who live in the developing countries to have access at a cost they can afford to those 30 to 40 drugs that are vital to them as part of their primary health care, and to ensure that these drugs are used rationally.

2. In the industrialized countries there are thousands and even tens of thousands of drugs on the market, many of them identical or highly similar but sold under different names, and many of them incorporating a variety of active ingredients. Moreover, the commercial exploitation of herbal and other remedies adds to the plethora of products on the market. In the developing countries, while the situation in the towns may resemble that in the industrialized world, the vast majority of people who live in the rural areas have little or no systematic access to allopathic drugs. They rely mainly on traditional medicines, and to obtain modern medicines they often have to travel far and pay prices that are far beyond their reach.

3. In the developed countries, there is no shortage of doctors. Doctors there face the problem of selecting the most appropriate preparation for each patient from the multitude of drugs available and the enormous amount of information available. When selecting drugs, they are thus liable to become influenced by drug promotion of various kinds, not all of which is based on complete and unbiased information. The role of pharmacists, too, has changed radically, and thanks to developed transport and communication systems, drugs now reach even those in the most remote areas. They make up few medicines nowadays, but rather sell ready-made drugs, both those for which prescriptions by a doctor are required and those which are available to the public without prescription. To fulfill that function properly, they too require access to complete and unbiased information.

4. In developing countries, particularly outside the main towns, the situation is vastly different. Doctors are few and far between and mostly concentrated in the cities. There they face the same problems as those of doctors in developed countries. In other areas people rely for health care mainly on other categories of health workers such as, in some instances, nurses and pharmacists, but more usually nonprofessional health workers with limited training or traditional practitioners. There are few, if any, pharmacies outside the towns, whether private or government-owned, and other arrangements have to be made to ensure the availability of drugs, in places such as hospital outpatient departments, drug corners in health centres, village drug cooperatives, and small village shops. The inadequacy of the health infrastructure and the weakness of distribution, transport and communication systems make it more difficult than ever for drugs to reach those who need them; and when they do reach them, people usually cannot afford to pay for them.
5. In both developing and developed countries, a comprehensive national drug policy forming an integral part of a well defined national health policy is the exception rather than the rule.

Criteria for rational drug use

6. The above describes in a nutshell the irrationality of the drug situation in the contemporary world. Sometimes the most appropriate therapy does not include drugs. When it does the rational use of drugs demands that the appropriate drug be prescribed, that it be available at the right time at a price people can afford, that it be dispensed correctly, and that it be taken in the right dose at the right intervals and for the right length of time. The appropriate drug must be effective, and of acceptable quality and safety.

National drug polices

7. The formulation and implementation by governments of a national drug policy are fundamental to ensure rational drug use. In 1982 the Thirty-fifth World Health Assembly endorsed the major components of such a policy. It is first necessary to identify therapeutic needs, to select essential drugs accordingly and to estimate the quantities needed for each of them. A drug supply system has to be devised or strengthened, including procurement, storage, inventory control, distribution, logistic support and related training of personnel. Proper use of drugs has to be promoted by such measures as providing different categories of prescribers with objective information and training them to use it properly, as well as informing and educating the public. The technical and economic feasibility of local formulation and production of drugs has to be considered. Quality control has to be ensured. Provision has to be made for monitoring adverse reactions. Appropriate legislation may have to be introduced and existing legislation brought up to date. Manpower requirements to conceive and implement the national drug policy have to be decided on and appropriate training provided. Measures have to be adopted to ensure the coordinated action of all sectors involved, such as health, education, planning, finance, industry, trade and communication. Monitoring and evaluation procedures have to be adopted. And finally, a financial masterplan has to be worked out for all such activities.

Information, education, and rational prescribing

8. To prescribe rationally, it is necessary not only to have speedy access to objective information on drug efficacy, safety and quality but also to use that information correctly. Prescribers, therefore, have to be capable first of judging if the information available to them is objective, then of selecting an appropriate drug in the right dosage form in the light of that information. They also have to be aware of the price of drugs since, if their patients or the public health service cannot afford them, they will not be bought. In addition, they have to be aware of adverse effects and how to deal with them, as well as of the danger of drug dependence. They have to know when not to resort to drugs and how to convince their patients on those occasions that it is in their best interest to abstain from drugs.
9. To facilitate rational prescribing, therefore, prescribers have to be trained accordingly. This is a major responsibility of schools of medicine, pharmacy, nursing and other categories of health personnel. Training is particularly important for nonprofessional community health workers in developing countries, who require guidance, supervision, and continued in-service training, particularly from the first referral level.

10. It is the duty of manufacturers and the regulatory authorities to generate and make available the drug information required for rational drug use. To do so manufacturers have to provide regulatory authorities with full information on their products; and regulatory authorities have to be sure that sufficient data are available to permit the products to be marketed and that objective information on each registered product is available to prescribers. This is particularly difficult within countries that have no or only rudimentary drug regulatory authorities. For them international cooperation and support are required, and WHO has a major responsibility to provide it.

Dispensing and consumption practices

11. Even when drugs are available and can be afforded, other factors in their rational use have to be considered. Pharmacists have to dispense the right drug and should be able to advise patients on how to use it correctly. They have to be properly trained for this and have easy access to complete and objective information - difficult enough in developed countries but a major obstacle in most developing countries. Since in most of the latter there are very few pharmacists outside the main towns, pragmatic solutions have to be adopted for dispensing drugs by others, with all the risks attached to the performance of this function by inadequately trained people. Patients have to understand the purpose and effects of the drugs they are taking, how to comply with the instructions for use and how to recognize and report adverse reactions. Non-observance of these requirements is a major source of error in drug use.

12. Pharmacists, nurses and other providers of health care have to dispense the right drugs at the right times and recognize and report adverse reactions. Throughout the world mistakes in dispensing to patients abound. To remedy this requires proper understanding of the use of drugs by those who dispense and administer them as well as strict managerial control.

Drug development

13. To ensure the availability of drugs, a country has to either manufacture them or import them. But they first have to be discovered, developed and approved.

14. To discover and develop drugs requires large-scale research and development. For each new drug as many as 10,000 compounds may have to be tested. Screening these requires laboratory studies including pharmacological and toxicological testing, as well as clinical trials, over a time scale of 8-10 years and at a reputed cost of up to US$ 100 million. Most of this research and development is undertaken by the pharmaceutical
industry. The research-based industries consequently tend to develop new drugs for an existing profitable market, paying less attention to such problems as tropical diseases for which the potential market is less attractive. Recent international efforts, however, have stimulated research into new vaccines and new drugs for tropical diseases. The need to develop drugs for which there is no commercial incentive is evident in government initiatives in some countries to promote the development of "orphan drugs".

15. Control over the safety, efficacy and quality of drugs is not only the responsibility of drug manufacturers but has also to be subjected to regulation by governments, a burdensome responsibility for even the most affluent administrative system. Countries that do not develop their own drugs (even if they manufacture some) and countries that import all their drugs also need to institute some form of regulatory control. Counterfeiting of drugs also has to be taken into account. A drug registration system is necessary as a basis for such control, but is still lacking or only rudimentary in many developing countries. Helping them to establish drug control systems is another area for international cooperation and support, particularly by WHO.

Drug manufacturing

16. Once drugs are approved they can be manufactured for sale. Good manufacturing practices should be observed. The technology of large-scale drug manufacturing from raw materials to finished product has become highly sophisticated. Modern drug manufacturing is mostly carried out by automated equipment, and robotized control of the process is beginning to be introduced. Moreover, new drug production processes involving sophisticated biotechnology are already gaining ground and will grow in importance. Under these circumstances the gap is growing between the capacity of the industrialized countries and that of developing countries to manufacture drugs of consistent high quality at an acceptable cost. Notwithstanding their legitimate desire for self-reliance in drug manufacturing, developing countries are having to take this situation into consideration.

Dosage forms, packaging and labelling

17. The same drug is often required in different dosage forms for different indications, different age-groups, and different degrees of severity of the conditions for which it is needed. There is a need for appropriate packaging for different requirements, including extremes of temperature and humidity. Drugs also have to be clearly labelled and accompanied by data sheets containing relevant information on the pharmacology of the drug, indications for its use, contraindications, warnings, precautions, adverse reactions etc.

Drug distribution

18. Once drugs are manufactured or imported and controlled for quality they have to be properly stored and distributed, either through the public health service or through private channels. Storage and distribution demand attention to proper conditions of temperature, for example the cold chain
for vaccines. In the public sector in many developing countries there is a need to improve the management and logistics of distribution including inventory control. Weakness in these, coupled with the weakness of the health infrastructure, hampers the availability of drugs, particularly for primary health care in rural communities. Drugs channelled through intermediate health institutions such as hospitals often do not reach their destination because these institutions too are short of drugs and need them. Often, too, drugs for the public sector infiltrate into the private sector. The improvement of distribution systems in developing countries is, therefore, a major imperative for a more rational use of drugs. Moreover, in some countries unscrupulous dealings occur between the initial procurement of drugs and their final sale to the public, adding considerably to the price to the consumer, and placing them beyond the means of many who need them. In the private sector in market economy countries, drugs are distributed through a network of middlemen before they reach retailers, obviously adding to their price.

Drug promotion

19. It is not easy for prescribers to select drugs properly and use them wisely when they face a bewildering amount and variety of information and consumers believe that there is "a wonder pill for every ill". To inform and influence prescribers and the public, manufacturers and distributors resort to various forms of promotion such as advertising, offering samples, using sales representatives, sponsoring symposia, and even providing financial and other incentives. Some of this conforms to acceptable ethical standards; some does not.

20. Drug promotion by the pharmaceutical industry has been the subject of much criticism because of its alleged aggressivity and bias, and there is wide agreement on the need for recognized norms, even if the nature of such norms and ways of enforcing them have met with less consensus. The multinational industry, through the International Federation of Pharmaceutical Manufacturers Associations, has issued its own voluntary code of marketing practices. Nevertheless, there has been a vigorous campaign for international action to curb the unethical promotion of drugs, particularly those being sold to developing countries. Whatever the nature of such action, it is abundantly clear that no international body has supranational powers permitting it to infringe on national sovereignty. Governments are responsible for the control of drugs and their promotion in their country, although that responsibility has to be shared by the pharmaceutical industry, prescribers, and consumers.

Costs and prices

21. The rise in drug costs and the consequent increase in their price to consumers are a source of worry in many industrialized countries and a very serious impediment to the purchase of drugs in most developing countries. Two interrelated aspects have to be considered - the cost to society as a whole and the price to the individual. A number of governments are attempting to control the cost to society by reducing the number of drugs available in the health service, requiring evidence that a proposed new
product fulfils a perceived medical need, limiting distribution costs, restricting manufacturers profit margin, and promoting the use of generic drugs wherever possible. The price of drugs is influenced by the cost of research and development for brand products, which research-based industries have to recoup through profits accruing during each drug's patent life. Profits are also required by these industries to enable them to pursue research on and the development of new drugs. Branded generic drugs, for which there are only limited research and development costs, are frequently sold at significantly lower prices than new drugs, and other products sold under a nonproprietary name, either by tender or directly, are frequently sold at even lower prices than branded generics.

22. The cost of drugs for developing countries gives rise to deep concern. In addition to lacking financial resources in general, these countries have severely limited amounts of convertible currency for drug procurement. Recent experience with international tenders for generic drugs in developing countries has been very encouraging; thanks to purchasing larger quantities required for a longer period of time and thus benefiting from the economies of scale, as well as to international market forces, good-quality drugs have been obtained at lower prices than ever before. But greater efforts are required to help developing countries overcome their convertible currency problems as they relate to drug imports.

National drug legislation

23. To control the distribution and marketing of drugs, national legislation is required in most countries relating to such matters as: the registration of drugs; the sale of brand and generic products; labelling and packaging; pricing; the right to prescribe, distribute, and sell drugs; promotion, including advertising and the use of sales representatives; post-marketing surveillance; and, last but not least, measures to ensure the enforcement of laws and regulations. For legislation to be effective it has to be appropriate to local circumstances, accessible, understood, and acceptable to all concerned - another formidable task requiring heavy investment in professional and public education. One particular bone of contention is regulation of the export of drugs that have not been approved for domestic use, with the rare but important exception of drugs that are required and requested by the importing country but not used in the exporting country, for example drugs for tropical diseases. If these are difficult issues to handle in developed countries, they are infinitely more so in developing countries. This is a further area for international cooperation and support, to which governments and WHO should pay particular attention.

WHO's initiatives

24. In response to the above situation, WHO has taken many initiatives, of which those in the paragraphs that follow are the most important.

25. The Organization is promoting and coordinating research, mainly through voluntary contributions, into the development of badly needed new drugs for tropical diseases and new vaccines.
26. To introduce rationality into the naming of drug substances, the
Organization assigns internationally recognized generic names, or
International Nonproprietary Names (INNs). It has established an
International Drug Monitoring Scheme on the adverse effects of drugs. It
provides specifications in the International Pharmacopoeia for assuring the
quality of drug substances. It promulgates standards for good
pharmaceutical manufacturing practices as embodied within the Certification
Scheme for the Quality of Pharmaceutical Products Moving in International
Commerce. It plans and co-sponsors the biennial International Conferences
of Drug Regulatory Authorities (ICDRA). Through a network of national
information officers it disseminates details of restrictive national
regulatory decisions taken in respect of marketed drugs, when necessary by
telex. It provides evaluated information on national regulatory decisions
through the WHO Drug Information Bulletin, and work is in hand to produce a
WHO model formulary based on the model list of essential drugs. WHO has
also developed a simplified system of drug quality control that could be
applied by countries with even the most limited resources.

27. As a result, several countries have now disestablished their
nomenclature commissions and automatically accept all recommended INNs;
and, where other national commissions still exist, each has come to accept a
common set of conventions for devising generic names, with the result that
nationally assigned names now rarely differ from INNs. The International
Conferences of Drug Regulatory Authorities are proving to be a useful
mechanism for intergovernmental exchange of information on drug regulation,
and there is a welcome increase in the number of developing countries
participating. As part of its responsibility for disseminating information,
WHO has developed a therapeutic classification of drugs and a comprehensive
dictionary of adverse drug reactions within the context of its International
Drug Monitoring Scheme. The International Pharmacopoeia is now being
radically revised with a view to bringing an effective measure of quality
control within the grasp of virtually every country. In establishing global
standards for good practices in the manufacture and quality control of
drugs, which are now recognized by 110 Member States, WHO has created a
basis for extending mutual recognition of inspection procedures to all
countries. This is the essence of the WHO Certification Scheme on the
Quality of Pharmaceutical Products Moving in International Commerce.

28. The WHO certification scheme deserves special attention. This scheme
provides a simple administrative mechanism whereby importing countries can

(1) ascertain whether a given product has been registered for
marketing in the exporting country and, when appropriate, request an
explanation of the reason why registration has not been accorded;

(2) obtain assurance that the manufacturing plant in which the product
is produced is subject to periodic inspection and conforms to
requirements for good practices in the manufacture and quality control
of drugs as recommended by WHO; and
(3) obtain details of the inspection and control procedures exercised by the authority in the exporting country and request relevant inquiries to be instituted by the exporting authority should a certified product be found to be of unacceptable quality.

29. Although not a WHO initiative, WHO collaborates with the Secretary-General of the United Nations to implement United Nations resolution GA 37/137 which aims at ensuring that products banned from domestic consumption and/or sale on grounds of safety are sold abroad only upon the request of the importing country or when the consumption of such products is officially permitted in the importing country, and that full information is provided to the importing country on products that are either severely restricted or not approved for domestic consumption and/or sale. This collaboration includes the provision of information on drugs that have been banned, withdrawn, severely restricted or not approved by governments.

30. In 1968 the Twenty-first World Health Assembly, in resolution WHA24.41, adopted ethical and scientific criteria for pharmaceutical advertising. These include the need for all advertising to be truthful and reliable, without incorrect statements, half-truths or unverifiable assertions; stress should be laid on facts, and statements should be supported by adequate scientific evidence. It is stipulated that promotional material should not be exaggerated or misleading and should maintain a fair balance between effectiveness on the one hand and adverse reactions and contraindications on the other. It should provide a full designation of the nature and content of active ingredient(s) per dose using generic or nonproprietary names; action and uses, dosage, form of administration and mode of application; side-effects and adverse reactions; precautions and contraindications; treatment in case of poisoning; and references to the scientific or professional literature. It is further stipulated that advertisements to the public should not be permitted for prescription drugs, for the treatment of conditions which can be treated only by a doctor, or in a form that could provoke fear or distress or that claims infallibility or suggests that the drug is recommended by members of the medical profession.

31. To answer the pressing question of which basic drugs are necessary for the health needs of a population, a WHO expert committee meeting in 1977 reached the conclusion that about 220 drugs and vaccines - "essential drugs" - are sufficient to deal with the vast majority of health problems. The committee established a WHO model list of essential drugs which is periodically updated. This model list does not imply that no other drugs are useful but simply that, in a given situation, these drugs are those most needed for the health care of the majority of the population and those, therefore, that should be available at all times in adequate amounts and in the proper dosage forms. The number of countries with lists of essential drugs or national formularies containing chiefly essential drugs now exceeds 80.

32. A WHO Action Programme on Essential Drugs was formally established in 1981 as an operational programme to support countries in the establishment of essential drug policies. Its aim is to help ensure the regular availability of essential drugs of good quality and at the lowest possible
price. In 1981 WHO also joined forces with UNICEF to support the provision of essential drugs for primary health care in developing countries. This includes supporting these countries to procure drugs at the lowest possible prices, through open international tenders and through the UNICEF Packing and Assembly Centre (UNIPAC).

33. In 1982 the Thirty-fifth World Health Assembly endorsed the principles of the WHO Action Programme on Essential Drugs and adopted a plan of action for the Programme. The plan of action includes the major components of a national drugs policy outlined in paragraph 7 above.

34. According to this plan of action WHO has two mutually supportive roles, coordination and technical cooperation. The Organization directly or indirectly coordinates international efforts in support of country programmes. It is also active in advocating the concept of essential drugs, which is gaining ever-increasing recognition. WHO cooperates with countries and a number of bilateral agencies in setting up essential drugs programmes in line with the above mentioned Health Assembly decisions.

35. WHO's Member States therefore have at their disposal an effective array of measures for improving their drug situation, that have been initiated by their Organization. If they apply them properly, they could have better access to objective information on drugs, improve their manufacturing practices and quality control measures, ensure that the drugs they import conform to the standards of the exporting country, introduce sound drug policies and country-wide programmes to give effect to them with a view to ensuring that all their people have regular access to the essential drugs they need, and reduce the costs of importing drugs and the price to the consumer. In short, they could take significant steps towards a rational use of drugs.
THE RATIONAL USE OF DRUGS: ISSUES SUGGESTED FOR CONSIDERATION^1

1. The world drug situation could be improved by properly applying the existing array of measures available (see pages 77-85). Nevertheless, a number of issues that follow are suggested for particular consideration in view of their potential capacity to increase rationality in the use of drugs.

National drug policies

2. Governments that have not already done so could formulate and implement a national drug policy, for example as outlined on page 78.

Drug information and education and training for rational drug use

3. The following are some possible ways of rendering drug information more objective, less biased and more accessible to prescribers and consumers.

4. Governments might consider setting up national consensus groups to monitor the objectivity and completeness of drug information disseminated by governments, industry, or consumer organizations. Such groups might be composed of members from governments, industry, the academic community, drug prescribers, professional nongovernmental organizations, and consumer organizations, and would conform with the information in approved product monographs issued by the regulatory authority. WHO should support Member States on request in setting up such mechanisms.

5. Governments that have not already done so may find it useful to prepare national drug formularies or at least national drug data sheets.

6. WHO should intensify its preparation and dissemination of drug data sheets for essential drugs for medical practitioners, pharmacists, nurses and nonprofessional health workers. Agreement on the information in such data sheets could be reached by, for example, using the Delphi method among panels of experts for different therapeutic categories. WHO should also actively support governments in preparing drug formularies or data sheets based on the model list of essential drugs.

7. Better use should be made of professional journals for the dissemination of complete and unbiased information on drugs. Editors should assume responsibility for ensuring that the information conforms with approved product monographs. Professional journals could also use information from national or WHO drug bulletins, the latter being translated into local languages; governments should be ready to assist journals in covering the costs involved.

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^1 This paper has been arrived at following consultation with the Peer Review Group. It is stressed that these issues are being suggested solely for the consideration of the Conference; no preconceived conclusions have been reached. This paper is therefore for the internal use of the Conference and no public statement should be made about it or its contents, nor should any suggestions contained in it be attributed to WHO, before the Conference.
8. In developed countries computerized drug information systems could be made easily accessible to prescribers and dispensers, the information content being controlled in the manner described in paragraph 4 above to ensure that it is complete and unbiased.

9. Pharmacists could assume a greater role in ensuring the provision of complete and unbiased information. Financial and other incentives could be given to them in some countries to encourage them to assume such a role.

10. Governments, nongovernmental organizations, and consumer groups should take measures to improve the quality of the information provided to the public. Thus they could supply information that conforms with approved product monographs in an attractive form. They could do this using modern communication techniques through the mass media, government-sponsored programmes, publications of consumer groups, and inclusion of the subject in general education in schools and universities.

11. Existing national and international measures should be reviewed for ensuring information on the long-term effects of drugs, particularly for chronic conditions, as well as the dissemination to health care providers and the public of information on adverse reactions and on withdrawals for whatever reason.

12. National drug regulatory authorities could consider what additional measures they need to take to make their decisions more widely known both domestically and internationally through WHO. For example, they might:

12.1 publish the reasons for regulatory decisions in extenso, including restrictive and negative reasons, making sure that any information that has to be kept confidential for any reason is reduced to the legal minimum;

12.2 formally designate a WHO liaison (or information) officer with a defined responsibility to ensure effective transfer and utilization of information in accordance with relevant World Health Assembly resolutions;

12.3 ensure that WHO is notified of the voluntary withdrawal of products by manufacturers when such action is taken for reasons of safety;

12.4 provide information to WHO, in compliance with United Nations General Assembly resolution 37/137, on drugs manufactured domestically that are available for export but have not been approved for use on the domestic market;

12.5 ensure that developing countries have ready access to independently validated information both through the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce and through the distribution of national compendia containing approved information on drugs to other regulatory authorities.
13. WHO could take the following additional measures to ensure the international availability of complete and unbiased information.

13.1 It might publish the Drug information bulletin more frequently and extend its scope by including more information on the determinants of national regulatory decisions, on teaching and learning materials, and on economic and financial aspects, and by incorporating a questions and answers section and book reviews.

13.2 It could give more active support to countries wishing to draw up national formularies by publishing monographs on selected therapeutic categories based on broad consultation with those interested, including governments, industry, the academic world, drug prescribers, and consumer organizations.

13.3 WHO could organize meetings of the parties concerned to seek agreement on important issues, in addition to presenting the different viewpoints as it now does in the Drug information bulletin.

14. National regulatory authorities with limited resources might consider to what extent existing international collaborative mechanisms provide a basis for drug assessment, thereby releasing national resources for the screening and adaptation of information that will determine the subsequent use of the drugs registered.

15. Since efficient international communication on drugs is dependent on a globally accepted system for designating international nonproprietary names (INNs), and is compromised unless all countries are legally entitled to refuse applications for trademarks that are similar to INNs, countries that have not already done so might consider instituting this safeguard and creating effective liaison between the national drug regulatory authority and the office responsible for the registration of trademarks.

16. Governments, universities, and nongovernmental organizations - both national and international - could reconsider their responsibility for improving the training of different categories of health workers in the rational use of drugs. In developing countries, further measures should be taken to ensure that non-professional primary health care workers are properly trained in the use of drugs. For example, each country might work out its own training programme; learning material already prepared in other countries could be a useful starting point; and support could be provided by first referral level personnel; WHO should actively support the above endeavours by making available appropriate learning material and helping countries to use it.

17. Improvements in training in the use of drugs might include making the information more assimilable and using modern educational technology. Emphasis might be placed on the main principles of drug action and drug use, the study of important representative drugs in each therapeutic category, methods of selecting from among similar preparations, taking account of social and economic factors, methods of evaluating published claims of efficacy and safety, and the concept of essential drugs.
Drug marketing

18. The following are some possible ways of improving drug marketing.

19. Governments that have not already done so should assume responsibility for ensuring that the drugs available in the country are of acceptable quality, safety, and efficacy, using for that purpose such means as: registration or licensing, the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce, and information provided by major national drug control authorities concerning the approval or non-approval of drugs.

20. Developing countries unable to establish comprehensive drug registration systems could at least create simple administrative procedures for the identification and listing of marketed drugs so as to be able to monitor and control their marketing. A basic multipurpose model system for smaller developing countries might be developed, complementary to the WHO Certification Scheme for the Quality of Pharmaceutical Products Moving in International Commerce and providing for the identification of priority needs, the rationalization of procurement, the assurance of quality, and the establishment of information standards with which all promotional activities must comply.

21. WHO should provide Member States on request with the information they need to decide on the regulatory option most suitable for them, depending for example on whether they have research-based pharmaceutical companies or not, rely entirely on imports, or produce certain drugs but rely mainly on imports. It should utilize its lead role in the International Conference of Drug Regulatory Authorities to ensure the maximum exchange of information on drug regulation and encourage Member States that do not already do so to participate in the meetings.

22. The feasibility should be studied of establishing international norms for labelling drugs, including a study of appropriate ways of combining clarity with comprehensiveness. WHO should assume responsibility for such a study.

23. Governments could consider the most appropriate measures to ensure that drugs cost as little as possible consistent with acceptable quality and ensured availability. This could be achieved for example through free market forces, government intervention, a Keynesian combination of free market forces and government intervention, the fixation of a reasonable margin of profit for the public and private domestic sectors with respect to "drug research and development countries" and "non drug research and development countries", fixation of a reasonable margin of profit from import through wholesale to retail, fixation of norms for the costs of distribution in the public and private domestic sector, bulk purchase and related packaging within individual countries or for a number of countries taking account of overhead costs, and the control of transfer pricing of raw materials and finished products.
24. To procure drugs internationally at the lowest possible cost for the public sector, governments could make more extensive use of open competitive tenders for generic drugs with accompanying quality control, as part of a national essential drugs programme. WHO and UNICEF should give active support.

25. Governments could consider measures to recover in whole or in part the costs of drugs in the public sector as part of their overall arrangements for financing health care. Consonant with the country's budgeting and financing practices and people's capacity to pay, this might include for example recovery of costs as part of health insurance schemes, drug insurance schemes, community drug cooperatives or taxation.

26. Governments that have not already done so should decide who should have the right to prescribe, distribute, and sell drugs. For example, in addition to the right of medical practitioners to prescribe, dentists could be authorized to prescribe specified drugs used in dentistry; in some countries pharmacists and nurses in the public sector could be authorized to prescribe specified drugs in the absence of a qualified medical practitioner, and non-professional primary health care workers to prescribe from a short list of drugs made available in the community. Governments could ensure that drug distribution is directed and supervised by a responsible person possessing the necessary managerial capacity. Some governments may find it necessary to authorize the sale of drugs not only by licensed pharmacists but also by other vendors in rural areas, for example village shops or community cooperatives, possibly under the guidance and supervision of the first referral level. National and international nongovernmental organizations could be more active in ensuring that their members abide by the regulations in force concerning the right to prescribe, distribute, and sell drugs.

27. Governments that have not already done so could establish lists of drugs authorized for sale over the counter without prescription and define who, if anyone, in addition to pharmacists should be permitted to sell them.

28. Any legal measures that governments take concerning the right to prescribe, distribute, and sell drugs should be based on a balance between the need on the one hand for people throughout the country to have access to drugs, and on the other for responsible prescribing, distribution, and selling.

29. WHO should provide Member States with information on experience in other countries in the above domains and cooperate with them on request in deciding on and introducing the necessary measures.

30. Governments could review the role of sales representatives with a view to deciding to what extent they have a rightful place in drug marketing. If they are considered acceptable, ethical standards could be defined for their conduct and they should be properly trained.

31. Up-to-date ethical norms for drug advertising could be established by governments, starting with those defined by the Twenty-first World Health
Assembly in resolution WHA21.41 (see page 149). National consensus groups of the kind mentioned in paragraph 4 above, could monitor adherence to these norms. The norms could for example include: the obligation to use for both prescription and OTC drugs only such information as has been approved by the national regulatory authority; the restriction of advertising of prescription drugs to professional journals; legislative sanction to facilitate compliance with the norms; and the use of the mass media for public education and to give publicity both to those complying with the norms and to those infringing them. Advertisements to the public should not be permitted for prescription drugs, for the treatment of conditions which can be treated only by a doctor, or in a form that could provoke fear or distress or that claims infallibility or suggests that the drug is recommended by members of the medical profession.

32. Ethical norms for promotion could also include those for the control of drug samples, permitting them, for example, only at the request of a prescriber and establishing limitations on the quantity supplied. Norms applied to symposia sponsored by industry should ensure that they are genuinely educational and not used for unethical drug promotion. Among possible requirements are prior approval by the postgraduate education committee or similar body, screening of the lecture material, obligatory attendance of competent staff from the pharmaceutical company concerned, participation of one or more independent medical specialists, separation of promotional material from the educational content, and limitation of sponsoring to the provision of light refreshments and printing of the programme.

33. The pharmaceutical industry, both national and multinational, should assume the major responsibility for complying with established drug promotional norms and avoiding double standards in different countries. However, governments could assume responsibility for supervising compliance; the health professions could insist on being provided only with information that has been properly screened; and the public could, as individuals, and through consumer groups and its elected representatives, demand compliance with the agreed norms and draw the attention of the health authorities to suspected infringements. The governments concerned could be more active in denouncing infringements of drug promotional ethics.

34. Governments that have not already done so might review their legislation on drug marketing practices. They might also consider how far such legislation can be enforced, particularly if supervision of a highly technical nature is required. Legislation has to be made known to those who need to know it, for example regulatory agencies, industry, importers, prescribers, professional organizations, patients and the general public. Governments might consider both formal ways of making the legislation known, as through official publications, and informal ways, as through consumer organizations and the mass media.

35. WHO should support governments that wish to adopt or update their legislation on drug marketing. This it could do through the dissemination of information on national legislation and the WHO Certification Scheme, monographs on specific issues, the preparation of guiding principles for
formulating legislation, and cooperation with countries on request in formulating legislation.

Prescription practices

36. The following are some possible ways of rendering prescription practices more rational.

37. With a view to improving prescribing practices, governments, nongovernmental organizations, and industry could collaborate to ensure that prescribers, particularly those outside hospitals, have trustworthy information on the therapeutic indications and the criteria for the selection of drugs from among a variety in the same therapeutic category. One means of ensuring this is the incorporation of relevant drug information in the continuing education of health care providers.

38. As better information alone does not necessarily ensure better prescribing practices, additional measures could be taken. Governments and professional organizations could be responsible for ensuring that health care providers meet acceptable prescribing standards.

39. The education of consumers could be undertaken through the mass media, including popular journals, to help people understand the need to follow the instructions for the use of drugs so that they take the right dose at the right intervals and for the right length of time. Governments, nongovernmental organizations, and consumer groups could share the responsibility for such measures.

40. In order to obtain a better understanding of drug use, governments might promote relevant behavioural and field research on prescribing practices in different settings in both developed and developing countries. WHO could collate and analyse the results of such research on an international basis with a view to improving the impact of drug information.

Distribution systems

41. The following are some possible ways of improving distribution systems:

42. To ensure acceptable drug distribution governments have to identify needs and estimate quantities required for all sections of the population. They may have to adopt political measures to ensure equity in the distribution of drugs, for example to overcome preferential distribution to the urban elite. They may also consider providing incentives to ensure equitable distribution.

43. The governments of developing countries could take measures to improve the physical conditions of importation, storage, inventory control and distribution, for example by diminishing spoilage through reducing the length of customs clearance and through proper storage in warehouses, by the control of distribution through authorized sources, by the control of
pilfering, by ensuring proper conditions of transport, and by ensuring proper storage conditions in pharmacies and particularly in other drug outlets.

44. Governments of developing countries could introduce additional measures to improve distribution, for example direct distribution from central warehouses to community health centres, short-circuiting intermediate hospitals; the proper use of middlemen, both public and private; and the setting up of adequate logistic and information systems, with an information feedback on the quantities required and the stocks remaining.

45. Governments, particularly those of developing countries, might note that limitation of the number of drugs through an essential drugs list, quite apart from its other advantages, would simplify the drug distribution situation.

National essential drugs programmes

46. The following are some possible ways of accelerating the development and implementation of national essential drugs programmes.

47. Governments might review their existing drug policies and programmes, institute effective registration procedures, and consider establishing or reinforcing essential drugs programmes along the lines adopted by the Thirty-fifth World Health Assembly.

48. Governments might take steps to convince health workers and the general public that the rational use of essential drugs is good medical practice. Nongovernmental organizations and associations of doctors, nurses and pharmacists might be encouraged to participate in essential drugs programmes. Teaching institutions might introduce the concept and principles of essential drugs in the training of health personnel. Consumer groups could add their influence.

49. WHO should accelerate the promotion of national essential drugs programmes, at the policy level through its governing bodies, in particular providing them with periodic reports on progress and effectiveness, and at the technical level through direct support to countries and guiding principles on such aspects of the programme as methods of selecting appropriate drugs and quantifying requirements.

50. Bilateral agencies could increase their support to the essential drugs programmes of developing countries as part of their strategies for health for all through primary health care.

51. To ensure the availability of good-quality low-priced drugs for the vast numbers of people in the public sector of developing countries ("medicines for the masses"), pharmaceutical manufacturers might agree to mass produce essential drugs and market them at prices that people in those countries can afford. This applies to national and multinational companies, and the research-based industry as well as generic manufacturers. Since industry cannot be expected to sell at a loss, governments might consider
fiscal measures favouring low prices for the consumer, for example exemption from import taxes, relief on company turnover taxes, and price discrimination in favour of essential drugs.

52. Governments might control expenditure on drugs by applying essential drugs policies appropriate to the country. They might better align budgeting and financial systems for procurement. Bilateral and multilateral agencies and development banks could investigate ways of alleviating foreign currency problems related to drug imports by developing countries. Some developed countries might be able to help in that respect as part of broader economic relationships with developing countries.

53. In addition to the funding of drug research from profits on patented drugs, other ways should be sought to generate funds for research to develop badly needed new or improved drugs in neglected fields. WHO has been a pioneer in this field by funding research through voluntary contributions for the development of new drugs, for example to control human reproduction and to treat tropical diseases. Some governments have introduced schemes to foster the development of "orphan drugs". Such funding, not necessarily through WHO, could be expanded to cover research in other priority health fields.

54. Developing countries wishing to attain the long-term goal of national self-reliance in drug production should consider carefully technical and economic feasibility and desirability, as advocated by the Thirty-fifth World Health Assembly. Developing countries accordingly might become more actively involved in technical and economic cooperation among themselves, taking into account the need to ensure that they produce drugs they really require rather than more easily manufactured products of less relevance. WHO could support them in establishing lists of drugs suitable for local manufacture and in calculating the quantities that could be sold in the light of present and future trends.

WHO Certification Scheme

55. The following improvements in the use of the WHO Certification Scheme could be considered.

56. The following recommendations of the Third International Conference of Drug Regulatory Authorities might be considered:

- the WHO Certification Scheme should be extended, by formal agreement if necessary, to include provision of product information approved in the country of origin;

- the Scheme should be complemented both by more systematic exchange of information on the results of formal reviews of marketed drugs undertaken by national regulatory authorities and by periodic status reports on the categories of drugs that have been reviewed by each national authority and on those that are pending for assessment.
57. To ensure quality control developing countries might consider:

- the utilization of a portion of their country programme budget allocations from WHO for this purpose;

- the merits and feasibility of establishing a small national quality control laboratory where it does not at present exist as recommended by the WHO Expert Committee on Specification for Pharmaceutical Preparations (WHO Technical Report Series, No. 704);

- the possibility of increased technical cooperation among developing countries, those with a larger national laboratory assuming service and training responsibilities on a regional or subregional level.

58. WHO should continue to collaborate closely with the Secretary-General of the United Nations in implementation of United Nations General Assembly resolution 37/137 on the dissemination of information to countries on drugs that have been banned, withdrawn, severely restricted or not approved by governments.

59. Governments should take necessary action to prevent drug counterfeiting. WHO should investigate with other international agencies and nongovernmental organizations the feasibility of creating a clearing-house to collect data and inform governments on the nature and extent of counterfeiting.
THE NEED FOR OBJECTIVE GUIDANCE ON PRESCRIBING PRACTICES

1. Whereas the cumulative rate of expansion of the scientific medical literature is prodigious and much of this is related to drug therapy, little of this output directly influences the prescribing practices of doctors. The original literature is largely inaccessible to the busy generalist and over the past two decades an appreciation has developed that greater efforts are needed to provide prescribers with readily assimilated, independent and objective information that will keep them adequately informed of changes in therapeutic practice throughout their professional careers.

2. The problem is evident in both developed and developing countries. It is a product of the current and unparalleled rate of therapeutic innovation, and it is exacerbated in market economy countries by the consequential promotional activities of competing pharmaceutical manufacturers. This, in turn, has resulted in varying measures of governmental and self-imposed control over the content and presentation of advertising material by pharmaceutical manufacturers. It has also stimulated governments and the medical profession to take a variety of initiatives in the supply of independent prescribing information.

3. An account of the available sources and channels of information on drugs is given perspective by a short account of the manner and sequence in which technical data are generated on a new product before and after its registration for marketing.

THE GENERATION OF DATA ON THE SAFETY AND EFFICACY OF DRUGS

National drug regulatory authorities as assessors of information

4. To an important extent the prescriber's need for information on drug products has been alleviated by the institution of national drug regulatory authorities, particularly in those industrialized countries where drug innovation is largely concentrated, since their influence has resulted in the elaboration of independent and authoritative standards of quality, safety and efficacy in marketed products. It is beyond the capacity and the competence of prescribers to assess at first hand the potential risks and benefits of the drugs that they use. Thus, the necessity of creating independent multidisciplinary bodies at national level to adjudge the acceptability of new products for general marketing, and to subject existing products to systematic review, would ultimately have become apparent without the emotive stimulus of the thalidomide tragedy.

5. Regulatory authorities in market economy countries are not, however, constituted to develop as primary sources of drug information. Although several authorities are becoming more active in this regard their terms of reference typically invest the licence holder - usually the drug manufacturer - with the prerogative and responsibility of informing and
advising prescribers on the use of the relevant product. The informational role of the regulatory authority is limited, in these circumstances, to ensuring that the product is advertised in a manner that is consonant with the terms of the product licence.

6. Whereas such control is readily instituted for new products, the control of those available before registration requirements were introduced demands a comprehensive national review of all products. In many cases it also demands the generation of new data to allow their assessment according to contemporary standards. This is a task that many national regulatory authorities have yet to complete, but it is not applicable, of course, to countries where drug requirements are centrally planned, and where manufacture, advertising and provision of prescribing information are, largely or totally, dependent upon the government's own commitment to support health programmes.

Exchange of information between regulatory authorities

7. Countries that have yet to introduce comprehensive provisions for drug regulation can draw from a diversity of national systems in determining their own requirements. Nonetheless, problems in establishing drug control in developing countries have, too often, resulted from the adoption of legislative provisions successful elsewhere, but of a complexity that precludes their effective implementation on the available resources.

8. As an alternative to adopting regulatory systems devised for countries with different economic, commercial and social circumstances, scope exists for developing countries to consider whether statutory recognition might be accorded to existing international systems for exchange of information. The full implementation of an essential drugs policy, for instance, as embodied in the various WHO reports on the Model List of Essential Drugs,1 is dependent upon the translation of an analogous list into national policy through an appropriate system of drug registration. Similarly, the regulatory capacity of a drug-importing country is enhanced if it takes advantage of the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce2 and the WHO sponsored network of formally designated national drug information officers to establish the status and labelling of imported products in their countries of origin.

9. More extensive exchange of technical information between regulatory authorities could result, not only in more effective use of available data, but also in a basic reorientation of drug regulation in countries that are primarily dependent upon importation of pharmaceutical products. A regulatory authority that is relieved of the necessity of undertaking an independent technical review of every product to establish its acceptability

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for marketing, and which may not have the financial or technical resources to undertake such assessments in depth, has greater opportunity to consider how each drug will be used within the domestic context and to ensure that appropriate information is available to prescribers at every level.

10. Whereas many national regulatory authorities still regard the technical data included in manufacturers' marketing applications as confidential, commercially-sensitive information, important initiatives resulting in freer exchange of this information have been taken over the past five years within the USA. The United States Food and Drug Administration now routinely issues summarized details of the biological information on which the approval of important new drugs is based. It also publishes lists of generic products deemed to be therapeutically equivalent to other marketed formulations of the same preparation on the basis of standardized criteria, including an appropriate demonstration of bioequivalence where this is considered necessary. Newly proposed US statutory provisions, if adopted, will further extend the opportunity for public disclosure of such data. It is important, if standards of preclinical and clinical drug development are to evolve and improve, that over-zealous protection of this information should be discouraged.

Information generated before drug registration

11. Drugs are currently authorized for use by regulatory authorities on the basis of their performance in biological models and in controlled, but limited clinical studies. The results of the preclinical experiments undertaken by the manufacturer establish the pharmacological profile of the compound in animal models (and of its antimicrobial or antiparasitic activity, where this is relevant); its immediate and delayed toxicity; its mutagenic and carcinogenic properties; its teratogenic potential; and its pharmacokinetic characteristics both in animals and man. The tests are conducted in animal species chosen, not with regard to their evolutionary proximity to man, but because of their adaptability to laboratory conditions and the large body of information that is available on their vital functions and on their responses to chemical exposure. They provide fair but fallible indicators of the potential effects and hazards of pharmacologically active substances in man.

12. Comparative toxicology remains a young and often empirical science. Its fundamental methodology is still evolving; demonstration and quantification of acute toxic effects based on statistically validated estimates of the lethal dose have recently been discarded; the necessary period of exposure used for demonstration of long-term toxicity remains in contention; the selection and interpretation of mutagenicity tests remain open to debate; and the relevance of traditional long-term, high-dosage

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1 Summary basis for approval. United States Food and Drug Administration.
carcinogenicity testing to clinical use remains in doubt. In what may well be a unique comparative toxicological study commissioned by a national regulatory authority, the Committee on Safety of Medicines in the United Kingdom in 1972 exposed the vagary of assessing the carcinogenicity of steroid contraceptive compounds in rodents. The fortuitous use of animals from more than one breeding colony demonstrated the existence of important strain-dependent variations in response.

13. This incident alone establishes an impressive case for further comparative analyses of toxicological data generated by pharmaceutical companies. Indeed, a data bank containing comprehensive animal toxicological data from pharmaceutical companies operating in the United Kingdom has been set up under the auspices of the industry to provide for this need and to enable a more rational approach to animal studies to be developed. Similar initiatives have been taken in other countries. These will operate most effectively to the advantage of public health — and, possibly, to the commercial interests involved — if both the data and the conclusions are made generally available.

14. The case for increased accessibility to pre-marketing safety and efficacy data applies, with the same validity, to the results of clinical studies. New drugs are typically registered for marketing on the basis of their performance in a small number of time-limited, controlled, comparative clinical trials. Even in the case of indisputably innovative products intended for prolonged use in man, therapeutic potential will rarely be assessed in more than a thousand patients, few of whom are likely to have received the product for more than a year.

15. Because these studies are limited in time they provide no more than inferential information on the long-term effects of drugs that palliate the signs and symptoms of chronic disease: the determination of long-term efficacy and risk demands experience of long-term usage. Similarly, studies limited in size, are not designed to detect — nor are they likely to generate information on — infrequent adverse reactions to treatment.

16. Moreover, sound design of a comparative trial based upon randomized allocation of the various treatment groups demands a measure of homogeneity among the patients admitted to the study. This implies that such studies are often undertaken only on a defined subsection of the ultimate target population for the drug. This being so, many new drugs enter into routine use before direct experience is gained of their performance in individuals liable to react anomalously, including the fetus, the very young, the elderly, the severely debilitated, and patients taking other drugs concomitantly for other conditions.

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2 A toxicology databank based on animal safety evaluation studies of pharmaceutical compounds. Human Toxicology, 1985, 4: 447-460.
17. Prescribers disposed to use a new drug would have an opportunity to gain a deeper insight into its properties if, in addition to the information carried on the labelling concerning indications, contraindications, precautions and warnings, they were informed of the clinical data on which the marketing approval is based and of any hypothetical risks identified by the results of toxicological testing.

Information generated after registration

18. The implications of these deficiencies in information at the stage of registration are readily apparent. That they exist is an inevitable consequence of new drug development as it is now perceived, and it is for society to judge at what point or in what circumstances risk of the unknown and unpredictable outstrips anticipated benefit. Certainly risk can never be totally excluded and the clinical investigation of a drug that is unlikely to offer clinical advantage over existing therapy raises ethical considerations for manufacturers and clinicians alike.

19. Unanticipated and unacceptable hazards are occasionally detected after a drug enters into routine use and there is increasing awareness that the performance of marketed drugs should be collated and analysed as effectively as is feasible. Only through systematic observation is it possible to obtain more precise insights into benefits, risks and relative performance of different drugs within the same therapeutic class. Relevant information is generated in a variety of ways. These include:

- prospective post-registration surveys required, on occasion, by national drug regulatory authorities as a condition of granting or renewing a product licence, normally to resolve specific concerns about potential adverse effects;

- prospective trials comparing different products, or different treatment regimens, under controlled conditions. Such studies may be conducted either in a hospital setting or in outpatient practice, often on a multicentre basis and, typically, with the financial support of an interested manufacturer;

- rare serendipitous observations by individual clinicians that result in the unanticipated discovery of a new therapeutic application for a marketed product;

- spontaneous reports of presumptive adverse reactions notified by practising clinicians to a national monitoring centre or to the manufacturer. At present some 26 countries pool the notifications they receive in a data base maintained by the WHO Collaborating Centre on International Drug Monitoring in Uppsala, Sweden with a view to generating early signals of unanticipated reactions. In
addition, at least two countries, France\(^1\) and the USA,\(^2\) have recently imposed a statutory responsibility on pharmaceutical manufacturers to disclose details of all presumed serious adverse reactions to products registered under their jurisdiction regardless of the country in which they are reported;

- epidemiologically-based studies, both prospective and retrospective, that attempt to provide a representative and statistically defined estimate of specific indicators of benefit and risk. These activities range from small retrospective case-control studies to large, prospective nationally-based or international surveys. Since the costs and organizational problems presented by the latter studies are formidable, they have hitherto been directed to issues of outstanding public health significance such as the value of treating mild hypertension and the long-term effects of systemically-administered steroid contraceptives. Although a statistically powerful methodology has been developed to address such problems, the vulnerability of even the most carefully designed studies to random and systematic error is now well appreciated and the possibility of confounding bias distorting apparent drug-induced effects raises complex problems in the analysis of results. There can be no doubt that the application of these methods to therapeutic investigation adds a new and vital dimension to drug assessment. The concomitant rapid development of computer technology creates a complementary potential for monitoring the health records of large samples of patients exposed to specific drugs by means of record linkage techniques that, in principle, have virtually limitless applications. The danger is that superficial and casual investigation will create problems of interpretation and that fact may become blurred by aberration and artefact.

PRESENTATION OF INFORMATION TO PRESCRIBERS AND THE PUBLIC

20. There is no stereotyped national pattern by which information from these various sources is presented to the end user of drugs. In many market economy countries the manufacturers, the government, representative professional bodies, technical journals, the media and, to a growing extent, consumerist organizations, have each assumed a role. In centrally-planned economies, in contrast, where industry is an arm of government, domestic drug advertising is designed to provide factual information rather than to promote sales. In these circumstances information flows primarily from governmental and professional sources.

21. A composite listing of the mechanisms by which information is regulated and conveyed around the world would include the following:

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The product licence

22. This is the instrument issued by the national licencing authority (a national drug regulatory authority, where such exists) to the licence holder authorizing the distribution and sale of a specific pharmaceutical product within the jurisdiction of the authority. It typically contains:

- a precise description of the product including the brand name (if any), the structural formulae of the active ingredients, their approved non-proprietary names, the source of starting materials, the route of synthesis, a comprehensive list of excipients, physical details of the dosage form, bioavailability data, quality control procedures and a requirement that no substantive change may be introduced into the method of manufacture without the approval of the licencing authority;

- details of packaging and labelling to make provision, in particular, for the approved non-proprietary name, the strength of the dosage form, a batch number and an expiry date;

- the category of the product to indicate any restrictions to be applied to distribution and sale, whether it is a prescription item, a pharmacy item or a general sale item, and whether additional restrictions to prevent abuse or to limit the drug to hospital or other specialized use are required;

- a document, or data sheet, with which all subsequent advertising and promotional material must comply.

23. With the exception of the data sheet and labelling material, the product licence in this context is a confidential document that contains commercially-sensitive information considered to be essential for precise registration and effective control of the product.

The data sheet

24. In a few countries it is considered mandatory that all doctors should receive objective, officially-approved information about the properties and use of each new prescription medicine before it is launched on the market. The data sheet, which also provides the basis of the package insert, serves this purpose and it must be posted individually to all registered medical practitioners within a specified period before marketing. It sets out the approved indications for the product, recommended dosage regimens, contraindications, precautions, warnings, details of packaging, pack size and optimal storage conditions.

Summary basis for approval

25. Although a data sheet defines the usage of the product in terms acceptable to the licencing authority, it provides no description of the preclinical or clinical data on which these conclusions were founded. To provide prescribers with an account of the nature and quality of these data
the US Food and Drug Administration now publishes summaries of the pharmacological, toxicological and clinical studies on which the marketing authorization was based. References to animal data are similarly included in product monographs that are updated from time to time by the Canadian Health Protection Branch, and in drug profiles produced by the Australian National Drug Information Service.

**Pharmacopoeial monographs**

26. Having regard to the potent biological activity of drugs and to the serious clinical situations in which they are often required, users need every reasonable assurance that their quality conforms to specification not only at the time of manufacture but throughout their shelf-life. Publicly accessible monographs defining these specifications are published both by national pharmacopoeial commissions and by WHO. The *International pharmacopoeia* produced by WHO is intended particularly to subserve the needs of developing countries. It is now complemented by a series of basic tests of identity of drugs included in the WHO Model List of Essential Drugs, simple tests of gross degradation and a compendium of stability data on these drugs under tropical climatic conditions. The objective is to provide peripheral health workers with some ability to test the quality of their stocks without recourse to laboratory facilities, and to be able to refer doubtful material for further analysis.

**Manufacturers' promotional activities**

27. The basic right to promote the products of private enterprise is conferred by statutory or even constitutional provisions in some countries. The advertising of pharmaceutical products is, nonetheless, extensively controlled in developed market economy countries both by regulation and by voluntary codes of practice, and some regulatory authorities routinely monitor advertising material. These restrictions place constraints on the format and presentation of advertising copy, the types of products that can be advertised direct to the public, and the use of the evanescent images of film and television. Particularly in countries where access to journals is limited, company representatives are widely deployed to promote products. Some of these representatives are highly trained, and they are in a position to offer constructive and practical advice. Their mission, however, is to promote the products of the company for which they work and it is not feasible to subject their activities to effective monitoring. At international level, the Twenty-first World Health Assembly, in 1968, adopted a series of ethical and scientific criteria for pharmaceutical advertising (set out in extenso on pages 142-151), and in 1982 the

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2 Ethical and scientific criteria for pharmaceutical advertising. World Health Assembly Resolution WHA21.41, May 1968.
International Federation of Pharmaceutical Manufacturers Associations produced its own Code of Marketing Practices.1

28. Notwithstanding the existence of these constraints, reservations are still expressed about the basic premise of treating drugs as normal commercial entities and soliciting their use through competitive advertising rather than objective evidence. New products, in particular, are intensively promoted when they are introduced to the market. At this time they have been subjected to limited clinical use. Their advantages and disadvantages with respect to alternative drugs are, at best, incompletely defined, and no secure judgement can be offered as to whether they will ultimately become established in routine practice. Moreover, with the exception of those authorities that are required to assess whether a proposed new product satisfies a medical need, national drug regulatory authorities are not empowered to undertake comparative assessments of products. In the latter case, no test is applied at the time of registration as to whether a new product is more or less efficacious than others already available.

29. It is important, however, to consider promotion in a broader and more neutral context. Doctors themselves have a valid promotional role, whether by publishing results of trials or other clinical studies sponsored by companies, by organizing symposia on new drugs or, not least, by the example of their own prescribing practices.

Lists of reimbursable products

30. Because of large price differentials that commonly exist between competing products and particularly the high cost of sophisticated dosage forms, such as slow-release preparations, several national administrations notify doctors and pharmacists that the charges for specific products are excluded from permitted reimbursements to patients participating in national social security systems.

Officially-sponsored prescribing advice

31. To further advise doctors on efficient and cost-effective drug use some national health authorities also provide tables or bar charts indicating the comparative costs of interchangeable products as well as authoritative prescribing advice issued on a regular or intermittent basis. The content and format of officially sponsored national formularies is also being changed in some countries to accord with the same general objective: entries are selective rather than comprehensive and they are prefaced and accompanied by didactic prescribing advice.

Drug compendia

32. In order to provide doctors with a comprehensive collection of data sheets in a convenient format, regularly updated drug compendia are

published in many countries. Some of these are published as private ventures and others are compiled by national associations of pharmaceutical manufacturers. In some cases, however, entries are included that have not been approved by national authorities. Whereas these are readily distinguishable in some publications, this is not invariably the case. In the case of some compendia sustained on advertising revenues — and issued gratis to doctors in many countries — there is no assurance that any of the entries conform to authorized texts, for the controls applied to information issued by manufacturers may not apply to information issued by independent publishers.

33. Other compendia, such as those produced by the American Hospital Formulary Service, the American Medical Association, the British Medical Association and the Pharmaceutical Society of Great Britain, are clearly independent, authoritative and encyclopaedic in their coverage. Such information, however, rapidly becomes dated and new editions of some of these works can only be produced at 3-5 yearly intervals. The development of computerized data bases offers the prospect that some of these compendia may soon be published more frequently. Meanwhile, on-line access to Martindale's Extra Pharmacopoeia, which is already available, offers an effective but costly means of obtaining updated information on selected topics.

Medical journals

34. Referred technical journals provide the ultimate, original source of much information on the properties and uses of drugs. Articles relevant to any one topic are so widely dispersed, however, that an extensive library with specialized search facilities is essential for adequate access to the literature. In any case, clinicians with onerous general clinical responsibilities rarely have the opportunity to undertake systematic literature surveys of the drugs that they use.

35. Several professional abstracting services now provide weekly or monthly updates on articles relating to a given specialized field that are published in major technical journals. Such information is available either in facsimile on microfiche or, in summarized form, in news-sheets. The preparation of this information, however, is a labour-intensive task; the output is directed to a relatively small, specialized readership and, in consequence, it is often prohibitively expensive for individual subscribers, even in highly affluent countries.

36. Faced with this situation, editors of many national and international medical journals now assume more responsibility for educating — as opposed to informing — their readers. Authoritative basic reviews of clinical and scientific topics, question and answer features, reports of the activities of professional governmental committees, and expanding correspondence columns challenge the traditional dominance of the original research paper, and leading articles have become concerned more with practical medicine and less with erudition.
Textbooks

37. Textbooks of repute, particularly those that are the product of a single author or editor, hold attraction for the undergraduate student because they are cohesive, comprehensive, yet concise. They possess these advantages because they offer a viewpoint rather than a dispassionate analysis of counter-arguments.

38. The viewpoint offered, however, has typically been that of the hospital-based consultant. The admittance of general practice as an entity in undergraduate curricula in recent years has yet significantly to influence this situation. Yet more striking is the lack of textbooks written from within the perspective of the developing world. Even standard texts of tropical medicine remain dominantly a product of specialized institutions in developed countries. In large measure, this situation reflects economic constraints. Textbooks are not commercially viable unless high volume sales can be guaranteed. This is not the case in smaller developing countries which are left no option but to resort to importation of books at prices that are now virtually prohibitive.

39. The domain of therapeutics presents an exceptional challenge to authors. Postgraduate textbooks, particularly if they are frequently updated, should offer a reliable distillate of existing knowledge on a given topic. It is becoming an overwhelming task, however, for a small editorial group, no matter how highly motivated, to keep abreast of current therapeutic information in an authoritative and comprehensive manner.

Review journals and drug bulletins

40. New types of publication have consequently emerged to provide both oversights and updates on important therapeutic topics. Journals have been created that present either detailed and comprehensive review material, or notes on recent therapeutic research presented in the mould of newspaper journalism. Independent, weekly or monthly bulletins published by academic groups, consumer groups and other bodies have exerted a notable influence on the assessment of marketed products and, in some cases, on the decisions of national drug regulatory authorities. Their authority is varied, being as strong as the consultative procedures and the editorial and advisory groups involved in their production.

41. A particularly encouraging feature of the past five years is the number of such bulletins that have appeared and sometimes become established in developing countries. The information, however, is often drawn largely from international sources and, as such, this is sometimes of questionable priority - or even relevance - to local needs.

The media

42. In some countries public television time has been accorded in off-peak hours to post-graduate education for doctors and, in recent years, the media have also become more attentive to the presentation of health issues to the general public. Under the influence of consumerist groups with the active
involvement of doctors, the mass media have created a greater awareness of
the importance of lifestyle to health, of the values and limitations of
self-medication, and of the strengths and shortcomings of the public health
services. Through these activities lobbying pressures have also been
exerted on drug manufacturers and governments to bring them to reappraise
their performance and attitudes in the promotion and control of drugs.
Undoubted successes have been achieved in obtaining or accelerating the
withdrawal of several marketed products and in stemming unacceptable
promotion of several drugs in countries lacking well-established regulatory
systems.

43. However, bias in media reporting, even when it is unintended, can
readily undermine public confidence in established practice. In the early
1970s, for example, reservations were expressed about the safety of
whooping-cough vaccine and particularly about its propensity occasionally to
induce encephalopathy and permanent brain damage. Subsequent controversy
cau sed pertussis immunization to be discontinued in some countries and
discouraged elsewhere; major epidemics of the disease followed resulting in
many deaths. The implementation of community health programmes commonly
presents governments, public health officials and pharmaceutical
manufacturers with onerous ethical responsibilities including the need to
make equitable provision for the rare and unfortunate victims of injuries
induced by drugs or vaccines. To dramatize remote yet tragic risk when this
is the inevitable price of community protection against the unacceptable
burden of serious communicable disease could mean that society, particularly
in developing countries, will forego potential benefits of new drugs and
vaccines and it may jeopardize established programmes of health care.

EVALUATION OF THE INFLUENCE OF DRUG INFORMATION

44. The significance of given factors on prescribing practices of doctors
is not readily assessed when a variety of messages compete for their
attention.

45. However, the considerable sums invested by pharmaceutical companies in
advertising their products are presumably known to be cost effective. Much
of this expenditure is directed to establishing and maintaining products in
key markets in which companies are interlocked in commercial competition.
This expenditure adds to the cost of health care without offering tangible
benefit and, unconstrained, it threatens to damage the performance and even
the stability of the industry itself.

46. Even in the light of authoritative objective evidence doctors are not
always readily induced to alter their established prescribing habits. For
example, short-term chemotherapy for pulmonary tuberculosis, which has been
shown to offer important economy as well as therapeutic and social advantage
in developing countries, has so far not gained wide acceptance in many
developed countries despite the persuasions of committed and authoritative exponents.1,2

47. Busy doctors, with onerous clinical responsibilities, particularly when they are working outside large institutions, tend to become isolated in their work. Without the opportunity of formal in-post training or even of informal discussion with colleagues, they need to remain highly self-critical if they are to adjust effectively to the steady evolution of therapeutic practice and the pressures of competitive advertising. The failure of doctors to seek out objective information on newly introduced drugs3 contrasts strikingly with the acknowledged success of local committees, particularly in hospitals, to institute and sustain efficient and cost-effective prescribing practices in both developed and developing countries. Collective discussion and decision-making among professional peers is evidently a potent stimulus to rational prescribing practices.

48. Rational prescribing devolves from sound education and not simply from access to objective information. In developing countries, the use of a limited number of essential drugs and their appropriate indications is a part of the basic information every young medical graduate and every health worker should possess. To achieve this, pervasive problems of communication have to be overcome in those countries with a multiplicity of cultures, local languages and dialects. Community health workers, no less than other prescribers within the health infrastructure, need the support of instruction and discussion to remain updated in their responsibilities. The staff of first-referral hospitals are well-placed to assume the role of educator, and arrangements could be made to outpost staff from time to time.

49. National drug regulatory authorities or associated national committees are also appropriately placed to provide independent and objective information on products registered under their aegis. They are competent to determine labelling requirements for medicines not only for doctors but for other cadres of personnel including community health workers and traditional birth attendants. They can also ensure that information on pharmaceuticals is placed in reasonable perspective with regard to the overall social, economic and educational development of the community. National authorities commonly have a large measure of assurance from regulatory decisions taken in other countries about the quality, safety and efficacy of products available in international commerce. More demanding than the decision to licence such products is the challenge of assuring, through appropriate control of labelling and distribution, that each product is used to best advantage within the national context. In the absence of a basic system of drug registration that addresses this need, a call for the rational use of drugs can never be securely founded.


THE ROLE OF WHO IN THE TRANSFER AND DISSEMINATION OF INFORMATION ON DRUG QUALITY, SAFETY AND EFFICACY

WHO (AND ITS CONSTITUTIONAL MANDATE)

1. Within the terms of its constitution WHO acts as the directing and co-ordinating authority on international health work. Among its functions it is required to assist governments, upon request, in strengthening health services, and to provide information, counsel and assistance in the field of health. Virtually from its inception in 1948, the governing bodies of the Organization identified drug regulation and control as a field in which these responsibilities could be applied to useful effect. Over the years, and particularly after the thalidomide tragedy in the early 1960s, many formal resolutions have been adopted by the World Health Assembly which call for the establishment of international norms, exchange of information, and multilateral collaboration to support the drug regulatory apparatus of national governments.

2. The key resolutions are set out in an Appendix (pages 137-141) and subsequent sections of this paper describe their implementation. However, in order to define the task of the Organization in a perspective that depicts contemporary concerns it is necessary briefly to review how current trends in drug control and drug development determine the structure of national markets.

THE STRUCTURE AND CONTROL OF NATIONAL DRUG MARKETS

The administrative control of pharmaceutical products

3. Contemporary approaches to the control of biological and pharmaceutical products have evolved in highly developed countries over more than fifty years. The course of the evolutionary path has been determined by the fact that the beneficial, therapeutic effects of marketed drugs are, in general, more readily demonstrable than their attendant hazards. Whereas it is incontestable that innovative development of new products has transformed the practice of medicine within the lifespan of a single generation of clinicians, it has become manifest that drugs are biologically active substances with an innate potential to exert adverse as well as beneficial effects at pharmacological dosage, and that therapeutic progress is inherently associated with risk. Evaluation of the costs, benefits, and hazards of drug treatment has consequently assumed a complexity that was formerly unappreciated.

4. As yet, the prediction, and even the detection, of some serious drug-related effects still presents a formidable technical challenge. Historically, drug control has tended to adjust empirically in response to unanticipated and dramatic incidents of drug-induced injury. The need for further adjustment will doubtless become apparent, but already the spectrum of controls applied to the research-based pharmaceutical industry is singularly comprehensive.
5. The greatest emphasis has been accorded to the need for exhaustive technical assessment of each new product prior to marketing. However, adequate assurance of quality, efficacy and safety is contingent on many other safeguards including the implementation of good manufacturing practices, efficient distribution and storage, informed use of products, and systematic collation and analysis of experience with marketed drugs. In highly developed countries controls are consequently exercised over manufacture and packaging, labelling and promotion, distribution, sale and use, and the reporting of post-marketing experience.

6. In turn, this requires not only a central agency to determine the conditions under which each product is accepted for registration, to oversee advertising and promotional practices, and to ensure adequate post-marketing surveillance, but also a highly educated cadre of doctors, nurses, and pharmacists qualified to prescribe and dispense the products with understanding and discretion, and a body of inspectors and chemical analysts to assure the quality of products throughout the distribution chain. The cost of the required administrative apparatus is burdensome even to the most affluent of countries and it is reflected in the prices of pharmaceutical products whether they are destined for domestic use or for export. Thus developing countries support an infrastructure of control, as well as a research base, in exporting countries that they are unable, for lack of resources, to institute themselves.

7. However, the need for drugs is no more forcefully apparent than in the developing world. To deny populations access to the benefits of medical technology for want of administrative capacity is inadmissible in concept. The problem has to be relieved by ensuring that national approaches to drug control and the provision of associated information to the profession and the public are optimally adapted to local circumstances. The extent to which success can be achieved is contingent upon the support offered by governments of exporting countries and by the manufacturers. If the technical competence of the pharmaceutical industry can be relied upon to advance exemplary promotional and marketing standards and to foster effective administration of drug control in developing countries, and not to exploit its weaknesses, progress will be greatly facilitated.

8. Meanwhile, governments in exporting countries are in a position to ameliorate the situation. They can ensure that their statutory provisions and regulations provide for adequate control of exported products without impeding the delivery or development of drugs legitimately needed elsewhere for which there is no domestic market. They can also assure the effective operation and further evolution of the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce, with a view to providing importing countries not only with an attestation of the quality of the product but also with authenticated information on its safe and effective use.

9. Finally, a complementary role exists for WHO in promoting contact and understanding between national drug regulatory authorities; in effecting the exchange of objective, unbiased technical information selected and presented in a manner that sustains countries in their quest for self-sufficiency; and in fostering and coordinating therapeutic research on an international basis, particularly within the developing world.

The technical assessment of pharmaceutical products

10. Whereas the WHO Model List of Essential Drugs contains less than 250 pharmaceutical substances, the number included in registered pharmaceutical products in some countries exceeds 3000. The total number of products available on these national markets is many times greater since most of these substances are offered in a variety of formulations - either singly or in combination - both as branded and as generic items. In many countries the number is further augmented by many herbal and other traditional remedies sold either as proprietary, labelled products or as extemporaneously dispensed concoctions. Traditional and unorthodox systems of medicine retain recognition and considerable patronage in many highly developed countries. In the rural areas of some developing countries it is the traditional healers that provide the most readily available resource for the development of primary health care services. Also at issue, however, is an extensive and highly remunerative illicit trade in fraudulent or spurious medicines which is not confined solely to countries with weak regulatory systems. Exploitation of the law by deliberate evasion has been attempted within the most sophisticated legal systems.

11. Comprehensive national licensing systems that require marketed drug products to meet independently determined standards of quality, efficacy, and safety have been instituted only within the past two decades and priority has consistently been accorded to the assessment of newly developed products. Few national regulatory authorities have, as yet, reviewed every product currently available on their domestic market, but many are committed to do so within the next few years. The recent demonstration that a substance as widely contained in herbal remedies as aristolochic acid possesses a potent carcinogenic potential has disposed of the complacent assumption that prolonged use is, of itself, sufficient to establish the safety of a medicinal product.

12. Even the assessment of newly-developed products is still evolving. After the thalidomide disaster expectations were raised that the safety of drugs in man might reliably be predicted from animal models. Subsequent experience has demonstrated the inadequacy of this hypothesis. Adverse drug-induced effects are protean in their manifestations and serious complications of therapy have occurred, such as the practolol syndrome, that cannot be reproduced, even retrospectively, in animal models.

13. Analogous difficulties arise in assessing the efficacy of drugs intended for long-term administration in chronic disease. The development of products used in such commonly occurring conditions as ischaemic heart disease, hypertension, hyperlipidaemias, diabetes and rheumatoid arthritis, remains commercially viable only while the prospect exists of introducing
them into routine use after a relatively short period of clinical assessment. Ultimate demonstration of their clinical value and of the possible risks of prolonged exposure can only devolve from observation of large populations of treated patients over many years.

14. The rational use of drugs evolves from a profound and secure understanding of their clinical performance. At present, much of this knowledge is superficial and incomplete. Whereas the deficiencies of the situation are manifest, perceptions of how to proceed have developed slowly. However, the emergence of epidemiologically-based approaches to the investigation of drug performance seems destined to create a shift of emphasis in drug assessment to a more balanced combination of pre-marketing evaluation and post-marketing surveillance.

15. The resources and organizational effort required to undertake such studies are daunting. Nonetheless, the development of computerized data bases of prescribing information on the one hand, and of patients' hospital records on the other, renders feasible the collection and analysis of more information on drug performance than has previously been possible. Governments, because of their general responsibility for their health services and pharmaceutical companies, because of their responsibility and liability for the safety of their products, have a direct interest in fostering such studies, and in exploring their logistic, financial and ethical implications.

16. Regardless of the approaches ultimately adopted, the efficiency with which the work is executed and the extent to which it influences the use of drugs globally will depend greatly on international coordination of efforts and timely exchange of information.

Economic factors as determinants of drug development and use

17. The concept of the rational use of drugs implies a need for socially oriented approaches to new drug development. The commercially-determined and competitive structure of the research-based pharmaceutical industry require research expenditure to be determined by the prospective return on investment as well as by medical need. The potential demand for a product tends to become an overriding factor in research planning, and the development of a drug intended to capture a share of an established market may hold more attraction than a bolder venture into therapeutic innovation. The problem is compounded by other perceived disincentives to innovative research: the lack of secure scientific leads for new forms of therapy; rising costs of drug development at a time of general economic recession; stringent price controls imposed within the public sector; and short effective periods of patent protection coupled with selective encouragement of generic manufacture and prescribing.

18. The consequential pattern of drug development, with its emphasis on treatment and prevention of the common diseases of affluent communities, draws criticism as being ill-adapted to global therapeutic needs. Thus the Sixth Cumulative List of International Nonproprietary Names for Pharmaceutical Substances published by WHO in 1982,\(^{(1)}\) shows that no fewer than 78 benzodiazepines and closely related compounds had been taken to an advanced stage of development. The inclusion in the list of 67 beta-adrenergic blocking agents, 53 non-steroidal anti-inflammatory agents of the ibufenac and ibuprofen groups, 57 penicillins and 42 cephalosporins offers revealing insight into the prevalence of repetitive research patterns. The thesis that molecular manipulation not infrequently offers dividends in terms of improved therapeutic performance is a valid but vulnerable argument. Large numbers of essentially interchangeable marketed products render effective therapeutic comparison impracticable. They create a situation in which therapeutic choice is determined by advertising pressure rather than objective evidence and, in the longer term, they threaten to frustrate evaluation of therapeutic performance.

19. Nevertheless, the recent introduction of drugs of uncontested value such as aciclovir, ciclosporin and clavulanic acid belies much pessimistic prognostication about the pace of therapeutic progress. Moreover, the ongoing clinical development of drugs such as ivermectin, mefloquine and praziquantel provides evidence of the commitment of some research-based companies to the advancement of tropical medicine. However, the gestation period for a new drug from the time of its first synthesis to its release for general clinical use commonly extends over a period of eight to twelve years. The full influence of prevailing economic pressures on the process may thus not become generally evident for several years. One disturbing trend is, nonetheless, already apparent: in recent years several leading manufacturers of vaccines have opted to withdraw from the field pleading reduced profitability and sharply increased liability for product-induced injury. At a time when the emergence of AIDS and legionnaire's disease provides a salutary reminder that infectious disease will never remain a static target; when vaccination holds encouraging prospect in the management of parasitic, as well as bacterial and viral infections; and when bioengineering techniques offer important new approaches to vaccine manufacture, this is an ominous portent.

20. Whether action is now required to redress these trends is an issue that is critical to the future of drug development. Some governments are either contemplating, or have already introduced, measures that offer a degree of protection or inducement to companies prepared to address societal responsibilities. Possible prolongation of the period of patent protection for new drugs is widely debated. National compensation funds or mutual insurance schemes funded from levies on companies and administered under the aegis of the state, have been set up in a few countries to settle claims arising from drug-induced injury. Several governments have also provided direct financial incentives to stimulate the development and production of drugs for rare diseases that would otherwise offer no commercial attraction.

21. At global level the call to increase the responsiveness of pharmaceutical research to contemporary needs brings the problems of the developing world into sharp relief. The prevalence of malaria has probably doubled over the past decade as both the parasites and the vectors have developed resistance against the available drugs and insecticides. No lasting amelioration of the situation can be expected until new approaches to its containment are available. Other conditions such as measles and diarrhoeal diseases, which rarely result in death in affluent countries, remain major causes of infant mortality in developing countries. Even so, national populations are increasing in these countries, as elsewhere, at a rate that is imposing an intolerable strain on economic resources already extended to breaking point.

22. It is against this background that WHO has initiated major research programmes in the fields of tropical and diarrhoeal disease and in human reproduction, in the expectation that much may be done on budgets that are modest by commercial standards to rationalize existing therapy and even to develop new therapeutic tools, both by coordinating and building upon resources that already exist within the academic world and industry and by judicious financial support of promising research.

23. Having established these programmes, WHO has become involved at first hand in the process of drug development. It now provides an important focus for technical collaboration between developed and developing countries in a complex multidisciplinary technical operation, offering a stimulus and a challenge to both academic departments and the pharmaceutical industry to address the health problems of the developing world through innovative research and reappraisal of current therapeutic practice.

24. Coincidently with the early development of these research programmes, the World Health Assembly endorsed, in 1975, a report of the Director-General pointing to the need for comprehensive centrally-directed drug policies within developing countries as a prerequisite to satisfying the basic health needs of under-served populations. Reference was made to experience gained in countries where schemes of basic or essential drugs had been implemented and WHO was called upon to advise Member States on the selection and procurement, at


reasonable cost, of essential drugs of established quality meeting their national health needs. It remains the responsibility of governments to determine the extent to which selective procurement policies are implemented and to adapt the WHO Model List of Essential Drugs to specific local needs and policies. Wide contrasts in national circumstances render it impossible to draw up a drug list of general applicability and acceptability.

25. Since the essential drugs concept was first elaborated it has gained wide recognition. It has provided a rational yet flexible basis for systematizing drug procurement and use at national level and for establishing drug needs at specific points, or for specific purposes, within the health care system. Indeed, it offers substantial advantage in terms of economy and efficiency in many settings. Even in affluent countries, where large numbers of drugs are readily available, the compilation of hospital formularies—often as a result of spontaneous institutional initiatives—has long found favour as a means of reducing prescribing costs and simplifying dispensing practices. Analogous initiatives by professional organizations have resulted in the publication of various quasi-official national formularies and other reference sources intended to promote efficient and cost-effective prescribing among doctors at large.

26. Whether it is primarily a function of government or of professional self-discipline to constrain prescribing costs is a political issue. Many national drug regulatory authorities are required, in their licensing function, to confine their attention to matters of quality, safety and efficacy. Others are empowered also to consider, as a condition of registration, whether a product meets a perceived medical need. Nonetheless, public expenditure on drugs is everywhere identified as an important and potentially negotiable element in the overall cost of public health services. Increasingly, governments reveal a determination to reduce drug costs, not only through direct price controls and selective registration but also through selective reimbursement of prescription costs, compulsory generic licensing, or promotion of generic prescribing and dispensing. The dilemma that emerges for all governments is to reduce public expenditure on drugs as far as is practicable without eroding the standards of the health services they provide and yet assuring a socially-productive investment in new drug development.

The exportation of pharmaceutical products

27. A majority of Member States import large quantities of both finished pharmaceutical products and bulk substances. Many do not, however, possess the technical and financial resources to undertake a comprehensive and independent assessment of the drugs on which they depend.

28. The major drug exporting countries have adopted divergent positions in their legislative responses to this situation. One approach, which derives from the doctrine of state responsibility and the concept of international minimum standards, is to disallow the export of pharmaceutical products that have not been approved for domestic sale. The other, based upon the principle of comity of nations, is to accept the right of each sovereign to decide what medicines it will import having regard to its own assessment of
its particular health needs, the diseases and health related characteristics of its population, the nature of its health care delivery systems, the availability of treatment and its own evaluation of benefits and risks.

29. Patterns of disease and the structure of medical care vary within wide limits from country to country. The balance of risk and benefit in using medicines varies correspondingly. The unacceptable burden of disease in many developing countries results from infections that either do not occur in developed countries or that are effectively contained where highly evolved medical services are available. In consequence, the administrations of many exporting countries consider that they are inadequately informed to make value judgements on the safety and efficacy of medicinal products that are to be used under circumstances, and for conditions, that are alien to their experience.

30. Developing countries, nonetheless, rely upon drug exporting countries to develop legislative and administrative mechanisms that will effectively block the shipment of unacceptable or substandard products. Such provisions should neither impede the movement of valuable medicines where they are most urgently needed, nor provide a disincentive to the development of new drugs for diseases endemic exclusively in developing countries.

31. Both these principles are embodied in a resolution of the UN General Assembly (GA37/137) adopted in 1982 on problems of international trade in all hazardous products, with particular reference to pharmaceuticals. It records that products either banned or withdrawn on grounds of human health and safety within the country of origin have subsequently remained available in export markets, and that newly-developed products intended - but not yet approved - for domestic use have been released prematurely for export.

32. The resolution also acknowledges that a product unauthorized in one country may subserve a legitimate need elsewhere. It therefore calls upon governments to prevent the exportation of any pharmaceutical product not authorized for domestic use, save at the specific request of the competent authority within the importing country or when evidence is available that its use is officially sanctioned within the importing country. In either case governments are requested to ensure that the supporting information and labelling are adequate to provide for the safe and effective use of the product. To assist importing countries to identify imports that present undue or exceptional hazards the General Assembly called for the publication and regular updating of a consolidated list of products that have been banned, severely restricted or not approved in the country of origin.

33. This listing complements the Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce, which was established by WHO in 1975. The scheme provides an administrative mechanism whereby regulatory authorities in developing countries may obtain, on request, details of the regulatory status of any imported product in the

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(1) Consolidated list of products whose consumption and/or sale have been banned, withdrawn, severely restricted or not approved by governments. UN, New York, 30 December 1983.
country of origin. It requires the competent authority of the country of manufacture to certify pharmaceutical products intended for export by supplying, at the request of the importing country, assurances that:

- the exporting country has approved the product for domestic sale, or if not, why not.
- the manufacturing premises are subject to regular inspection and conform with standards set by WHO in its principles of good manufacturing practice.

International exchange of information

34. The complexity of the international drug market and the urgency with which messages sometimes need to be conveyed leave no doubt about the need to develop efficient international channels of communication between national drug regulatory authorities.

35. The development of such channels also needs to take account of the existence of profound differences both in the structure of national drug markets, and in the circumstances in which drugs are used. A decision taken in one country may not be immediately applicable elsewhere.

36. Efforts to assure the safe and effective use of drugs extend resources even in the most affluent societies. Nonetheless, they have a place in every community, regardless of its resources and cultural background. In every case the need for rational usage demands that access to appropriate drugs be carefully planned and controlled. In the longer term it demands the development of therapies and dosage forms specifically for use in circumstances where skilled care is at a premium. Depot preparations such as injectable contraceptives, drugs intended for intermittent administration such as praziquantel and repletion doses of retinol and, most importantly, vaccines that confer prolonged immunity to endemic disease are effective not only by virtue of their therapeutic activity but also because the dosage regimens allow for efficient delivery.

37. For the most part, however, developing countries are constrained to use products that have been designed for use within totally different systems of medical care. In such circumstances the process of drug control should embrace not only consideration of evidence generated elsewhere - and most frequently in highly developed countries - on the performance of candidate drugs, but evidence of their relevance to health care within the national context. In some developing countries the concept of prescription control may apply only to hospitals and similar institutions. The rational use of drugs in other settings, and particularly in primary health care, then involves balancing the need for access to therapy against the possibility of misuse and abuse. The many local variables provide for many different national solutions.

38. International systems of exchange of information relieve regulatory authorities in developing countries of the need to undertake fully independent assessments of the drugs registered under their aegis. They are
thus allowed to focus their attention on the acceptability of products within the prevailing health care infrastructure. The extent to which WHO can facilitate the task of national authorities in their drug selection policies and in the generation of supporting information is developed further in subsequent sections of this paper.

39. No mechanism for international exchange of regulatory information can operate effectively, however, where there is no indigenous system of drug registration. Many developing countries have yet to create such a system. This may have been impracticable in the past, but advances in information science in recent years have yielded data storage and retrieval techniques that bring effective data management within the reach of virtually every country. International dissemination of technical information needs to be complemented by the development of information systems that can be readily adapted to the registration requirements of every national authority.

40. The purpose of central administration is to serve an effective peripheral infrastructure. This demands not only a flow of appropriate information to drug prescribers and the public but also the carefully planned, assured and controlled delivery of appropriate drugs at every level of the health-care system. In any situation, rational use of drugs is contingent on effective administration of health services and effective education of health care providers.

THE NORMATIVE FUNCTIONS OF WHO

Terms of reference

41. The primary responsibility for drug control, including the licensing of marketed products, the determination of the claims that may be made for them, and the conditions of distribution and sale, lies within the competence of national authorities. Although these decisions are primarily technical in nature, the foregoing sections show that they are also influenced by administrative, economic and political factors.

42. Nonetheless, trade in drugs is internationally structured and the same basic criteria regarding quality, safety and efficacy are recognized throughout the world. It follows that, if common standards and methods of technical assessment can be developed, much will be gained in mutual understanding between regulatory authorities and in the efficiency of the regulatory process. Drug assessment, however, remains an essentially empirical exercise: although internationally applicable technical guidelines for the evaluation of the safety and efficacy of drugs have been elaborated from time to time under the auspices of WHO, (1) matters of detail are determined by national preference and divergences of view are inevitable. National authorities, moreover, do not always agree in their precepts or in their interpretation of the evidence. These differences have profound consequences. They have impeded attempts at harmonization and unification of regulatory procedures even among closely associated trading partners.

43. Not all the early ambitions of the World Health Assembly to develop international standards in this technically complex field have proved practicable, but several of WHO's related informational activities remain normative in concept. Their objectives are diverse: they facilitate international communication in drug control, and in medicine generally, through the development of common systems of nomenclature; they establish globally recognized standards of quality for pharmaceutical products; and they create internationally accepted guidelines for therapeutic research in human subjects.

44. Thus, the Organization assigns internationally recognized generic names (or International Nonproprietary Names) to drug substances; it has developed, within the context of the International Drug Monitoring Scheme, standardized systems for the classification of drugs and their adverse effects; it provides specifications in the International Pharmacopoeia for assuring the quality of drug substances; it promulgates standards for good pharmaceutical manufacturing practices as embodied within the Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce; and, not least for the purposes of its own drug development programmes, it has produced, in collaboration with the Council for International Organizations of Medical Sciences, proposed international guidelines for biomedical research involving human subjects, and for the first administration of a new drug to man.

International nonproprietary names for drug substances

45. The need to identify each pharmaceutical substance by a unique globally-accepted generic name is self-evident. It is of critical importance in facilitating communication in medicine as well as in the labelling and advertising of medicinal products in international commerce.

46. Responsibility for the selection of International Nonproprietary Names (INNs) was first accorded to WHO in 1950 with the adoption of Resolution WHA3.11 by the Third World Health Assembly. With the subsequent publication of some 3000 names of newly developed drug substances, the task has gained considerably in complexity. The work is facilitated, however, by the confidence that governments have vested in the agreed procedures. Several countries have now disestablished their nomenclature commissions and automatically accept all recommended INNs. Whereas other national commissions remain extant, each has come to accept a common set of


(4) Safety Requirements for the First Use of New Drugs and Diagnostic Agents in Man. CIOMS, Geneva, 1983.
conventions for devising generic names, with the result that nationally assigned names now rarely differ from the INN.

47. The systematic development of the terminology is at risk, nonetheless, of becoming compromised. The procedure for selection requires that no conflict shall occur with licensed trademarks. Manufacturers are thus allowed opportunity to contest proposed names that are either identical to or similar to their own proprietary names. 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, particularly as a result of competitive promotion of products no longer protected by patents. Rather than market those products under the generic name, many companies apply for trademarks manifestly derived from INNs.

48. This practice undermines the principle that INNs are public property; it could well frustrate the rational selection of further INNs for related substances; and it may ultimately compromise the safety of patients by promoting confusion in drug nomenclature.

Classification of drugs and their adverse reactions

49. Emphasis was accorded, in the introductory section of this paper, to the importance of continued assessment of the performance of marketed drugs. Manufacturers are now commonly required to notify regulatory authorities of all presumed adverse reactions to licensed products that are subsequently brought to their notice, wherever they may have occurred.

50. These reports are of value for comparative purposes only if their terminology is adequately standardized. Over the past decade WHO has developed a therapeutic classification of drugs and a comprehensive dictionary of adverse drug reactions within the context of its International Drug Monitoring Scheme. These normative activities seem destined to acquire more formal significance and wider recognition with the introduction and further development of national statutory reporting obligations.

The International Pharmacopoeia

51. The Third World Health Assembly, in according to WHO the responsibility of producing the International pharmacopoeia (WHA3.10), envisaged that it would provide a set of global standards, or specifications, for assuring the quality of all pharmaceutical products moving in international commerce. The Assembly was not in a position to predict the unprecedented scale of new drug development over the ensuing thirty years. Nor could it anticipate that obligatory national drug registration systems, and the subsequent understandings on confidentiality developed between manufacturers and governments, would for a while create some uncertainty about the continued general publication of pharmacopoeial specifications.

52. In the event, the case for maintaining published compendia of pharmaceutical specifications has prevailed, though the task of compiling monographs for new drug substances has devolved, not upon WHO, but upon
national or regional pharmacopoeial commissions which operate within - or in close liaison with - the competent drug regulatory authorities.

53. These developments have led to a reappraisal of the International Pharmacopoeia. Opportunity has arisen, in particular, to consider the needs of developing countries, which are particularly vulnerable to substandard, spurious or degraded drugs, but which frequently lack any means to check at first hand the quality of imported or locally manufactured products.

54. As a result, the International pharmacopoeia is now being radically revised with a view to bringing an effective measure of quality control within the grasp of virtually every country. Priority has been accorded to developing monographs for substances contained within the WHO Model List of Essential Drugs; efforts are now directed to the compilation of monographs for final dosage forms; and, as far as is practicable, reliance is 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 virtually any country where no provisions for quality control as yet exist.(1)

55. The reorientation of the pharmacopoeia has recently inspired a number of complementary projects. Accelerated stability studies have been commissioned to identify essential drug substances liable to degrade readily under adverse conditions. Stability data are rarely published and singularly little precise information was previously available on the degradation characteristics of the longest established substances. The results obtained have created a data base that has been used to develop simplified tests for detecting gross degradation in these substances. The tests have been devised and verified in a collaborative study involving many national quality control laboratories and they will shortly be published,(2) together with a series of basic (or simplified) tests for confirming the identity of these substances.(3) These tests offer no substitute for the full chemical analysis required to assure the compliance of a product with a pharmacopoeial monograph. They hold advantage, however, in that they can be performed outside the laboratory to provide reassurance on the identity of products and to exclude gross degradation at any point in the distribution chain.

Good manufacturing practices

56. Proof that marketed pharmaceuticals are of adequate quality cannot be vested solely in the sampling and testing of finished products in independent laboratories. Evidence must also be available that every care has been taken throughout their manufacture to assure the requisite


standards. In major drug exporting countries periodic inspection of manufacturing premises and practices by an officially-appointed inspectorate is regarded as a vital component of quality assurance.

57. The scope of these inspections is comprehensive. They involve consideration of the qualifications and post-specifications of personnel; the adequacy of premises, sanitary standards and equipment; the standards of record-keeping and manufacturing operations; labelling and packaging procedures; arrangements for self-inspection and quality control; maintenance of batch distribution records and procedures for handling and notification of complaints.

58. A number of regulatory authorities reserve the right to inspect the premises of manufacturers of imported products. Some countries have entered into bilateral or multilateral agreements to recognize and accept each others' inspection provisions. WHO, in establishing global standards for Good Practices in the Manufacture and Quality Control of Drugs, which are now recognized by 110 Member States, has created a basis for extending mutual recognition of inspection procedures to all countries. This is the essence of the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce.

Harmonization of regulatory requirements

59. In the late 1960s, when many countries were first instituting statutory systems of drug regulation, WHO frequently provided a forum for the discussion and elaboration of norms employed in the technical assessment of drugs. Many basic recommendations on the pharmaceutical, toxicological and clinical aspects of drug evaluation were issued under the auspices of the Organization at that time. This tradition is now continued from within the WHO Regional Office for Europe which is issuing an extensive series of guidelines for the clinical evaluation of specific classes of drugs.

60. Overall, however, WHO 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. Until this knowledge is further advanced, the divergences now apparent in national policies and practices are unlikely to yield to attempts to forge an international consensus. WHO's harmonizing role has gradually become adapted to these changed circumstances and now takes several forms.

61. Within a purely scientific context it now promotes collaborative approaches to the validation of the methodological basis of drug control. The multicentre validation of analytical techniques described in the International Pharmacopoeia has recently been complemented in the toxicological field by a collaborative study on mutagenicity testing performed under the auspices of the International Programme on Chemical
Safety. (1) As practical experience of toxicological testing develops, and as more evidence becomes available to correlate the results obtained with the subsequent performance of drugs in man, the scope for internationally-based evaluations of toxicological practice will undoubtedly increase.

62. In one specific area, however, WHO has retained the initiative to develop and update guidelines relevant to drug assessment that are of unquestioned global relevance. They concern the need to safeguard the basic human rights, the safety and the welfare of human subjects involved in biomedical research. Clinical research is undertaken in many countries. If, in particular, the conquest of tropical disease is to be advanced, drug performance must be assessed in endemic areas, and even in countries that have not previously had cause to develop relevant regulations.

63. WHO is, itself, a sponsor of such research. It has, therefore, collaborated with the Council for International Organizations of Medical Sciences in broadly-based consultations that have resulted in the publication of two sets of guidelines: Proposed International Guidelines for Biomedical Research Involving Human Subjects, and Safety Requirements for the First Use of New Drugs and Diagnostic Agents to Man. These guidelines provide terms of reference for WHO in the implementation of its own research programmes; they provide models for analogous national regulatory mechanisms and they remain addressed to all individuals and institutions that assume responsibilities connected with the study of drugs in man.

64. Promotion of international collaboration and harmonization also underlies the concept of the biennial International Conferences of Drug Regulatory Authorities, which are planned by a regionally representative organizing committee convened under the auspices of WHO, and organized by the host country. The conferences were originally devised to offer drug regulators from all WHO Member States opportunity to exchange views and experience on the administrative and technical aspects of their responsibilities and to advance interagency communication. The first, which was jointly sponsored by WHO and the United States Food and Drug Administration, was held in Annapolis, Maryland, USA, in 1980 (2) and subsequent meetings have been convened, firstly in Rome (1982) (3) and most


65. A prime concern at all of these meetings has been to improve the flow of information between regulatory agencies and to promote the effective utilization of the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce. Each of these issues is discussed more extensively in subsequent sections. However, regulatory policy and administration also raise issues for discussion. At the next conference, which will be held in Tokyo in 1986, conceptual approaches to the registration of "orphan drugs", (or drugs developed for indications that provide little commercial incentive), and to traditional medicines, are prominently featured in the programme. Without mutual understanding of administrative systems, and without a collective will to approximate methods of work, international exchange of technical information between regulatory authorities will remain inadequate and unacceptably vulnerable to misinterpretation.

THE ADVISORY FUNCTIONS OF WHO

Technical reports and other publications

66. Many of WHO's technical reports bear upon the management and treatment of conditions of prime importance to community health standards. They reflect an internationally-based consensus of expert opinion and, as such, they influence the formulation of relevant national health policy in many countries. De facto, and as a direct consequence of its constitutional mandate, the Organization is cast in an advisory role on issues that impinge directly on drug marketing and the regulatory process.

67. Typically, these issues relate to the major health problems of the developing world. They are exemplified by the promotion of oral rehydration therapy in the treatment of infantile diarrhoea; the advocacy of combination chemotherapy in leprosy in the face of increasing dapsone resistance; and proposed constraints on the use of the newly-introduced antimalarial, mefloquine, to impede the emergence of resistant falciparum malaria.

68. However, its ability to inspire collaborative effort at international level places the Organization in a favoured position to contribute to the rationalization of drug use in other domains. In 1978, the publication of an internationally-based WHO-sponsored collaborative clinical study on the long-term use of clofibrate resulted in immediate, worldwide reappraisal of

the safety of hypolipidaemic agents. An ongoing multinational case-control study on the long-term effects of steroid contraceptives may well exert similar influence, and the ascendency of epidemiological approaches to drug assessment seems destined to provide opportunity for international collaborative research on a considerably broader basis.

Studies in drug utilization

69. The importance of applying quantitative methods and epidemiological techniques to the assessment of drug performance under routine conditions of use was anticipated fifteen years ago when a Drug Utilization Research Group, in which scientists from 14 countries are now participating, was founded under the aegis of the WHO Regional Office for Europe, following a Symposium on the Consumption of Drugs held in Oslo in 1969. The group was formed to examine striking documented differences in prescribing habits between physicians in neighbouring countries of Europe, and the extent to which drug use — which was acknowledged at that time to be increasing — was medically justified.

70. Ten years later, in a publication summarizing the activities of the members of the group from the time of its foundation, optimism was expressed that, although a series of problems had been identified that remained without adequate explanation, studies of drug usage and its correlates would eventually provide the basis for improving the cost-effectiveness of drug treatment with the least possible impairment of the quality of medical care.

The concept of essential drugs

71. In 1975 the Organization's mandate to provide advice on the socioeconomic aspects of drug use was considerably strengthened. In the light of a report submitted by the Director-General calling for rationalization and extension of primary health care services, particularly in rural communities, the World Health Assembly adopted a series of resolutions requesting WHO, inter alia, to cooperate with Member States in formulating drug policies and management programmes relevant to the health needs of populations, and to identify drugs and vaccines which, in the light of scientific knowledge, are indispensable for primary health care and control of diseases prevalent in the population at large.


72. Following wide consultation, an initial model list of essential drugs was issued in 1977 within the first report of the WHO Expert Committee on the Selection of Essential Drugs. This has subsequently been revised and updated in three further reports. The objective has been to retain under review a comprehensive yet limited array of drugs of proven value in the prophylaxis and treatment of commonly occurring conditions and to demonstrate that rationalization of procurement can hold advantage in terms of both economy and efficiency in any health care setting.

73. The criteria for selection are broad, since the parameters that would determine decisions within a national context— including disease prevalence; the nature of primary care and referral facilities; the training and experience of available personnel; financial resources; and genetic, demographic and environmental factors— are undefined. A list that is consonant with local needs and policies must be compiled, as appropriate, at national, or even institutional level. Nonetheless, the WHO list has exerted considerable influence in several respects:

- It has served as a stimulus to all countries to consider the available options for establishing cost-effective drug policies in the public sector.

- It has provided a systematized approach to drug selection that is applicable in a wide variety of situations.

- It has highlighted the outstanding yet discriminatory nature of therapeutic innovation. Whereas disorders of affluent society, including hypertension, arthritis and psychiatric disorders, have attracted the development of large numbers of compounds, several of the major endemic tropical diseases including filariasis, onchocerciasis and trypanosomiasis have engaged virtually no attention. The emergence of the essential drugs philosophy and of effective primary health care programmes within developing countries offers a renewed challenge and an incentive to pharmaceutical companies disposed to remain vigilant to global health issues.

74. The WHO Model List is comprehensive in its scope. Some of the listed drugs are intended exclusively for use in specialised hospital departments. Some can be prescribed safely only within a relatively sophisticated system of medical care, and many others can be used effectively only when continuity of treatment and availability of experienced supervision can be assured. Special attention is accorded, nonetheless, to drugs required in a primary health care setting that can be used safely and effectively by individuals with little formal medical knowledge.

75. The Committee, however, emphasises that the range of drugs supplied to community health workers must be determined at national level having regard, not least, to force of circumstance. In an ideal situation antibiotics, for instance, should be used only by individuals with advanced diagnostic skills with access to appropriate microbiological facilities. In practice, the lives of many children now dying from pneumonia in the developing world could be saved if injectable procaine penicillin were available at the time
of their initial presentation. The skills and resources that can be
developed at the most peripheral health care level to meet such
contingencies depend on the management offered from the first referral level
as well as the accessibility of these facilities. Achievement is also
heightened by the availability of accurate and objective information
understandable to each category of prescriber.

76. The generation of information that is attuned to local needs and
circumstances is, inherently, a national responsibility. WHO, however, has
given priority in several of its programmes to the development of resource
material included for local adaptation. Training material on case
management and on control strategies that has been generated within several
of the specialized technical units of the Organization is now being collated
and extended to provide the basis of a model formulary consonant with advice
already promulgated in various ways by the Organization.

77. This material is intended to supplement and eventually to replace model
information sheets prepared within the WHO Secretariat and commended to
governments within the reports of the Expert Committee on the Use of
Essential Drugs. It is anticipated that the more flexible format of a
formulary will avert two problems encountered in the preparation of drug
information sheets:

- the difficulty of ensuring that the WHO material is consonant with
  the officially approved product information already settled between
  manufacturers and national drug regulatory authorities
- the need to focus attention on practical aspects of case management
  in different clinical settings rather than on the innate properties
  of individual drugs.

78. It is vital that such information be available to complement
governmental efforts to develop and improve primary health care services.
It is also vital that advice on case management within the restrictive
perspective of primary health care be based, wherever possible, on practical
experience and rigorous assessment. Rational drug use is dependent, in
every setting, on controlled, comparative evaluation of therapeutic options.

INTERGOVERNMENTAL EXCHANGE OF INFORMATION

Mechanisms for collaboration

79. Resolution WHA37.33, in addressing the need for rational use of drugs,
assigns a key role to the Organization in developing activities at national,
regional and global levels that will improve the provision of unbiased and
complete information about drugs to the health profession and the public.
At the same time, the United Nations General Assembly, in a series of
resolutions relating to the export of hazardous products (37/137) and to
consumer protection (39/248), has recently emphasized the continued
importance of the intergovernmental systems of information long established
by WHO within the pharmaceutical field.
80. The broader charge now placed upon the Organization to provide technical information on drug use directly to the end-users must devolve from its existing intergovernmental remit if its message is to remain aligned with and responsive to nationally-determined policies and decisions. These functions, which are broadly-based, have been defined within a large number of resolutions adopted by the governing bodies of WHO over a period of more than two decades. In general terms they call upon the Director-General:

- to support national drug regulatory authorities by arranging for interchange of information on the registration of new products, and the withdrawal or restriction of existing products on grounds of safety

- to collaborate with these authorities in the collation, analysis and interpretation of reports of suspected adverse drug reactions.

81. National drug regulatory authorities operate within a rigid statutory framework constructed to control the domestic drug market. Much of their work is undertaken in camera since it demands access to privileged, commercially valuable information submitted by pharmaceutical manufacturers specifically and exclusively for regulatory purposes. Many of these authorities have no formal intergovernmental obligations and, where these do exist, they are directed to harmonization of administrative procedures and mutual acceptance of technical decisions among closely-associated trading partners.

82. The need to maintain confidentiality, however, is counter-balanced by an underlying commitment to safeguard health and, in particular, to ensure that sufficient information enters the public domain to permit the safe and effective use of registered drugs. Regulatory authorities, moreover, now find themselves publicly accountable in terms of their own performance. Drug regulation inevitably captures public attention and media coverage whenever drugs are withdrawn from use unexpectedly on grounds of safety.

83. In response to these factors and also, in some cases, to relaxation of governmental policy on classification of confidential data, several more highly evolved authorities have consciously expanded their informational role. This extends not only to the provision of officially-approved prescribing information but, in some cases, to summaries of the evidence on which licences are granted. Many authorities now regularly publish news sheets and bulletins on matters of current therapeutic concern; and some collaborate with national poison control centres, health councils and other nationally appointed bodies charged to develop public awareness of health-related issues.

84. These changes have not only promoted a flow of information into the public domain, they have fostered discussion and collaboration between regulatory authorities which has operated to the benefit of all countries. From WHO's standpoint these trends are reflected in:
- the recognition and support accorded to the biennial International Conferences of Drug Regulatory Authorities (ICDRA) planned and co-sponsored by WHO

- the large number of authorities that, at the request of the Director-General, have designated information officers formally responsible for assuring efficient lines of communication with the Organization

- the sustained impetus accorded to the WHO International Drug Monitoring Scheme by the collectivity of the participating countries

- increasing usage and discussion of the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce.

**Exchange of information on regulatory decisions**

85. In 1963, the World Health Assembly, in Resolution WHA16.36, requested Member States to communicate immediately to WHO any decision to prohibit or limit the availability of a drug already in use; any decision to refuse the approval of a new drug; and any approval for general use of a new drug accompanied by important restrictions, whenever these decisions are taken as a result of serious adverse reactions.

86. The Assembly has reaffirmed the importance it places on the efficient exchange of this information in several subsequent resolutions which additionally call for the inclusion of:

- decisions to withdraw or restrict the availability of a drug already in use on grounds of lack of effectiveness (WHA23.48)

- data on the scientific basis and the conditions of registration of individual drugs (WHA25.61).

87. Effective implementation of the open-ended collaborative effort that these resolutions require has proven to be dependent upon the creation of an organizational infrastructure. This is now provided through the network of designated information officers and the biennial ICDRA conferences. Nonetheless, logistic difficulties and considerations of confidentiality have frustrated the full implementation of the Assembly's aspirations.

88. Initially, governments were simply invited by the Organization to notify restrictive regulatory decisions of international relevance. These were then transmitted to all Member States in WHO Drug Circulars. For many years this scheme fell short of its potential, partly through default and partly because the removal of drugs from national markets by voluntary agreement with manufacturers rather than by enforcement of statutory controls were rarely reported, even when safety was at issue. Over a period of some 16 years extending up to 1979 a total of only 199 notifications was received by WHO, of which about one half was provided by the United States Food and Drug Administration.
89. The situation has since been greatly improved, both because national authorities have become more perceptive of the need to exchange information and because of intensified promotion of this need by WHO. In 1984 alone, WHO transmitted information on 622 regulatory decisions received from 37 countries. These are conveyed in monthly mailings to information officers in every Member State. The flexibility and informality of this channel of communication has, on several occasions, also proven its value as a means of canvassing opinion on a broad international basis on regulatory issues of immediate concern.

90. However, formal understandings on confidentiality between manufacturers and regulatory authorities still impose an important constraint on exchange of information. Very few regulatory authorities are prepared to disclose information on rejected marketing applications, even when approval is withheld on grounds of safety.

91. Similarly, with the notable exception of the material published by the US Food and Drug Administration, little information has become available internationally on the systematic reviews of efficacy that many authorities are committed to undertake on all currently marketed products. A recommendation adopted by consensus at the Third ICDRA, 1984 noted that:

"Effective international exchange of this information will directly assist regulatory authorities in their responsibility of removing products from national markets that do not conform with prevailing standards of efficacy and safety. It will also substantially reduce the technical and administrative burden on national administrations that derives from this responsibility, since it will reduce the need for independent and repetitive national assessments".

92. Immediately the proceedings of this Conference are published, information officers will be requested to communicate the following additional information to WHO for inclusion in the monthly mailing system:

- results of ongoing review procedures

- a summarized listing of categories of drugs already subjected to review together with a relevant bibliography

- a provisional timetable of projected review procedures.

93. Although information on newly registered drugs is more readily available, its presentation in an international communications system raises both logistic and policy issues. In particular, there is a strong case for selectivity since:

- the same product is frequently licensed in many countries under virtually identical conditions

- many newly registered products are not innovative, since they include new brands or new dosage forms of existing drugs
the information is already generally available to importing countries as an adjunct to the WHO Certification Scheme.

94. Nonetheless, the assessment of new products accounts for a high proportion of the total work load with many regulatory authorities, and many countries appreciate sight of a three-monthly updating of new products registered elsewhere. Some twenty highly developed countries regularly offer this information to WHO and a selective annotated listing is included in the quarterly WHO Drug Information Bulletin. The process of selection is directed exclusively to avoiding undue repetition and to eliminating non-innovative and combination products that do not accord with criteria of rationality proposed by the WHO Expert Committee on the Selection of Essential Drugs. It is emphasized that annotation does not in any way indicate approval of the product by WHO, and each entry is limited to a brief description of the pharmacological class of the active component together with the licenced indications, contraindications, warnings, precautions and serious known adverse effects.

95. Arrangements have also been made within the past two years to provide every competent national authority with comprehensive independent and authenticated information in the English language on marketed drugs. Through the good offices and generosity of several governments, of the International Federation of Pharmaceutical Manufacturers Associations, and of various national organizations within these countries, the following material is distributed on a complementary basis to all Member States:

Belgium:
- Répertoire commenté des médicaments. Centre Belge d'Information Pharmacothérapeutique
- Folia Pharmacotherapeutica. Centre Belge d'Information Pharmacothérapeutique

France:
- Dictionnaire Vidal. OVP Paris (information approved by the Ministry of Health is clearly designated)

United Kingdom:
- British National Formulary. British Medical Association/Pharmaceutical Society of Great Britain
- Data sheet compendium. Association of the British Pharmaceutical Industry (information in compliance with regulations of the UK Department of Health and Social Security)
United States of America:

Drug Evaluations. American Medical Association

Drug Information. American Hospital Formulary Service

Physicians Desk Reference. Medical Economics Co. (information in compliance with regulations of the US Food and Drug Administration)

Summary Bases for Approval. US Food and Drug Administration

96. Negotiations are now in hand to explore whether this service can be extended to material published in other widely used languages. Meanwhile a compendium of publications and documents prepared by national drug regulatory authorities, and by professional and consumerist organizations is issued at six-monthly intervals to information officers. In addition, relevant statutory instruments and regulations are either translated into the working languages of WHO in the quarterly Digest of Health Legislation or indexed by the WHO Collaborating Centre on Drug Information, Hungary.

Monitoring of adverse drug reactions

97. The governing bodies of WHO have identified a need not only for international exchange of information on regulatory decisions but also for central collation of the reports of suspected adverse reactions from which many restrictive decisions devolve. Accordingly, the Director-General was requested in Resolution WHA19.35 to establish an international system of monitoring reports of adverse reactions to drugs using information derived from national centres.

98. This was inspired by an expectation that infrequent and unanticipated drug-related hazards could be identified with greater efficiency by pooling case-reports submitted to individual national centres. Over 20 countries have contributed consistently to the scheme virtually from its inception in 1968, and the data bank, which is now housed in a WHO Collaborating Centre located within the Swedish Department of Drugs, currently contains some 400,000 case reports of suspected adverse reactions to drugs notified spontaneously by clinicians.

99. Spontaneous monitoring systems have an inherent flexibility in that all doctors notionally contribute and all patients are notionally included. They have provided a wealth of material for investigation and the signals they have generated have resulted in many labelling changes and in several withdrawals of marketed drugs. Nonetheless, the data need to be interpreted with caution: probably only a small proportion of drug-induced adverse reactions are reported to national centres and there is no assurance that these are reliably representative of the true hazards of treatment. In most instances spontaneous reports merely provide an alert to the possible existence of a hazard that requires independent investigation for its confirmation. It is for this reason that information in the data base is, as yet, confidential to the national centres participating in the scheme.
Nonetheless, summarized data of reactions within the Nordic Group of countries are now published without restriction and the question of access to the WHO data base will doubtless be reappraised in the light of experience with this initiative.

100. Whereas the long adherence of the participating countries to the WHO monitoring system attests to its importance, drug reactions are protean in their manifestations and no single system of surveillance is adaptable to every potential need. Spontaneous monitoring systems, in particular, are inappropriate to the detection and investigation of long-range effects of drugs, and especially of reactions that simulate naturally occurring disease. The emergence of epidemiologically-based approaches to drug monitoring has created possibilities for new approaches to post-marketing surveillance and the feasibility of developing a comprehensive array of surveillance mechanisms adequate for drug regulatory purposes is an issue that has preoccupied drug regulatory authorities and manufacturers for some years.

101. An ideal solution is possibly unattainable, but without a stimulus for international consultation and collaboration involving research-based pharmaceutical companies, university departments of epidemiology, toxicological centres and responsible government agencies, practicable possibilities of utilizing the diverse facilities that already exist to best advantage will remain unrealized. WHO, working together with the Council for International Organizations of Medical Sciences, is already engaged in promoting this dialogue and in exploring the extent to which various forms of surveillance might be feasible and cost-effective in generating information on drug-related hazards in developing as well as developed countries.

Evaluated information on regulatory decisions

102. In 1975 the World Health Assembly requested the Director-General to disseminate evaluated information on drugs to Member States. This brief has now been broadened and given a different focus with the adoption, in 1984, of Resolution WHA37.33 which requests the Director-General "to continue to develop activities at national, regional and global levels aiming at the improvement of use of drugs and of prescription practices and the provision of unbiased and complete information to the health profession and the public".

103. Since there is little prospect, having regard to prevailing economic circumstances, that a substantial increase in technical resources can be accorded either at national or international level to subserve this function, fulfilment of the need demands a reanalysis of priorities in drug control. At present, the norm in many countries is to place greater emphasis on the pre-marketing assessment of new products than on the information that will subsequently assure their responsible use.

104. Given that interagency communications are improving, that more effective use might be made of the WHO Certification Scheme, and that adoption of the essential drugs concept offers a basis for rationalizing
registration policies, many regulatory authorities, particularly in
developing countries, might now review the balance of their activities.
Whereas they might reasonably, for the most part, rely on pharmaceutical or
toxicological assessments undertaken by other national authorities or by
WHO, they are uniquely placed to determine the form and content of the
information required both by health professionals and by patients to assure
the effective use of the drug under prevailing national conditions.

105. WHO, with a view to supporting national authorities in their
informational responsibilities, has already embarked upon a threefold
strategy:

- production of a WHO model formulary based upon the model list of
  essential drugs
- preparation of discursive commentaries on regulatory policies and
decisions within the WHO Drug information bulletin
- renewed promotion of the WHO Certification Scheme, and consideration
  of its possible extension to provide for exchange of all nationally
  authenticated product information.

106. The Formulary and the Drug information bulletin are proposed as the
main vehicles for WHO's contribution to an integrated drug information
system because the Organization can use its constitutional mandate, its
technical competence and its working relationships with national drug
regulatory authorities, non-governmental organizations and individual
experts to best advantage within these contexts.

107. Work in developing the Formulary is already in hand. It is envisaged
as a handbook of treatment relevant to the first referral level of medical
care. It will also embody teaching material for primary health care workers
and the public that can readily be adapted to local educational standards
and cultural precepts. Although it will place greatest emphasis on drug
treatment, the information will be organized having regard to practical case
management. To the greatest possible extent the information will be drawn
from advice already issued within the technical reports of the
Organization. Completed drafts will be submitted in consultative form,
section by section, to designated national information officers, members of
relevant WHO expert advisory panels, interested pharmaceutical manufacturers
and non-governmental organizations.

108. Having regard to the wide circulation of the WHO Drug information
bulletin, the many requests that have been received from Member States for
permission to translate its contents, and the supportive references made
within the governing bodies of WHO, its preparation will retain high
priority. Efforts will be made to assure its timely production. Its
presentation will be changed to lend it greater appeal and it will be
forcefully promoted. Emphasis will be accorded, as in the past, to
discursive comparative commentaries on the regulatory status of essential
drugs and other important products in various countries, and the present
consultative procedures will be maintained to ensure that interested regulatory authorities and manufacturers receive sight of material in draft.

109. In order that these documents remain responsive to the needs of Member States the designated information officers will be asked to arrange that they be kept under review and to indicate how they are used and with what effect. This information will be submitted to the ICDRA which regularly receives a status report from WHO detailing progress in all aspects of the Organization's collaboration with national drug regulatory authorities. In turn, a short report of the proceedings of each Conference highlighting the adopted recommendations will subsequently be made available to the governing bodies of WHO.
APPENDIX

RESOLUTIONS OF THE WORLD HEALTH ASSEMBLY
RELATED TO THE TRANSFER AND DISSEMINATION
OF INFORMATION ON DRUG QUALITY, SAFETY AND
EFFICACY

(Extract from Handbook of resolutions and decisions of the
World Health Assembly and the Executive Board,
Vols I and II, 1948-1972, 1973-1984,
Looking with favour upon the offer of the Government of the United States of America to provide facilities for the processing of information on adverse drug reactions, under the auspices of the World Health Organization,

1. requests the Director-General to study further the requirements of an international programme for the collection, analysis, and dissemination to Member States of information on adverse drug reactions;

2. invites Member States to develop as soon as possible national monitoring systems for adverse drug reactions, with a view to taking part in an international system under the aegis of WHO;

3. requests the Director-General to examine the offer of the United States of America and of any other governments of data processing facilities as a part of an international monitoring system for adverse drug reactions, and to report on the matter to the Nineteenth World Health Assembly; and

4. thanks the Government of the United States of America for its offer.

May 1965 143,25

WHA19.35 The Nineteenth World Health Assembly,

Having examined the reports of the Director-General on the international monitoring of adverse reactions to drugs;

Recalling resolutions WHA15.41, WHA16.36, WHA17.39 and WHA18.42 of the Fifteenth, Sixteenth, Seventeenth and Eighteenth World Health Assemblies on the importance of systematic collection, evaluation and dissemination of information on adverse reactions to drugs;

Considering resolution EB37.R14 of the Executive Board on the international monitoring of adverse reactions to drugs;

Convinced of the urgent need to collect and disseminate at the international level information on adverse reactions to drugs; and

Taking into account that co-operation with national centres for monitoring adverse reactions to drugs and the utilization of the data-processing facilities available in the United States of America would facilitate the international monitoring envisaged,

1. requests the Director-General to initiate a pilot research project, along the lines indicated in his report, with the aim of establishing an international system of monitoring adverse reactions to drugs using information derived from national centres; and

2. accepts the generous offer of the Government of the United States of America of data-processing facilities for this purpose.

May 1966 151,16

WHA22.41 The Twenty-second World Health Assembly,

Emphasizing that, in addition to the pharmaceutical quality control of drugs, it is essential to evaluate their therapeutic safety and efficacy so as to prevent their unsuitable use involving, inter alia, excessive expenditures for the individual as well as the public;

Considering that the increasing variety of drugs renders their selection by the prescribing physician difficult; and

Recalling resolution WHA17.39 requesting inter alia the formulation by the World Health Organization of generally acceptable principles for the evaluation of the safety and efficacy of drugs,

requests 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.

July 1969 176,20

(b) invites Member States to arrange for a systematic collection of information on serious adverse drug reactions observed during the development of a drug and, in particular, after its release for general use;

4. requests the Director-General

(a) to transmit immediately to Member States the information received under paragraph 2;

(b) to study the value and feasibility, including the administrative and financial implications, of WHO collecting from and disseminating to Member States

(i) the non-proprietary and other names, chemical formulas and definitions of new drugs released or approved,

(ii) the information contained in (i) above;

(c) to continue the study of the possibility of formulating, and of seeking international acceptance of, basic principles and requirements applicable to the toxicological, pharmacological and clinical evaluation of drugs; and

(d) to pursue action in the matter and report to the Executive Board and to the Seventeenth World Health Assembly.

May 1963 127,18

WHA18.36 The Eighteenth World Health Assembly,

Recalling resolution WHA17.41 on the compliance of exported pharmaceutical preparations with the requirements applying to pharmaceutical preparations for domestic use;

Having examined the report of the Director-General on the quality control of pharmaceutical preparations, setting out an unsatisfactory situation in regard to the quality control of pharmaceutical preparations moving in international commerce;

Noting that large parts of the world population make use of pharmaceutical preparations without having in their countries adequate facilities for prior quality control; and

Recalling the provisions of Articles 2 and 21 of the Constitution,

1. invites governments to take the necessary measures to subject pharmaceutical preparations, imported or locally manufactured, to adequate quality control;

2. requests the Director-General:

(a) to continue to assist Member States to develop their own laboratory facilities or to secure access to such facilities elsewhere;

(b) to continue to study methods of securing, in the countries of origin, control of the quality of pharmaceutical preparations intended for export; and

(c) to pursue the establishment of internationally accepted principles and specifications for the control of the quality of pharmaceutical preparations; and further

3. requests the Director-General to report to the Executive Board and to the Nineteenth World Health Assembly on the possibilities of the Organization's playing an even more active role in the quality control of pharmaceutical preparations.

May 1965 143,22

WHA18.42 The Eighteenth World Health Assembly,

Considering resolutions WHA15.41, WHA16.36 and WHA17.39 of the Fifteenth, Sixteenth and Seventeenth World Health Assemblies on the importance of systematic collection, evaluation, and dissemination of information on adverse drug reactions;

Recalling the reports of the several groups of experts convened to consider and study the feasibility and desirability of instituting an adverse drug reaction monitoring programme on an international basis;

Convinced of the urgent need for the international collection and distribution of information on adverse drug reactions and
WHA22.50 The Twenty-second World Health Assembly,

Recalling resolution WHA21.37;

Having considered the report of the Director-General on the quality control of drugs;

Noting with satisfaction the formulation of the "Principles of Pharmaceutical Quality Control" and "Good Practices in the Manufacture and Quality Control of Drugs" as presented in the report of the Director-General;

Recognizing that general observance of such principles and practices is essential and, in particular, a prerequisite for a system of certification for drugs in international commerce;

Considering that general acceptance of such a certification system would be an important first step toward ensuring the desired level of quality control of drugs in international commerce,

1. **RECOMMENDS** that Member States adopt and apply
   (1) the requirements for "Good Practices in the Manufacture and Quality Control of Drugs" as formulated in the report of the Director-General,
   (2) the certification scheme on the quality of pharmaceutical products moving in international commerce as formulated in the report of the Director-General as amended;

2. **REQUESTS** the Director-General to report to the Twenty-third World Health Assembly
   (1) on those improvements in the requirements for good manufacturing practice and in the certification scheme which may appear to be necessary; and
   (2) on further progress with regard to the certification scheme and the implementation thereof.

_July 1969_ **176.24**

WHA23.48 The Twenty-third World Health Assembly,

Recalling resolutions WHA15.41, WHA16.36 and WHA17.39 of the Fifteenth, Sixteenth and Seventeenth World Health Assemblies on the importance of communicating to WHO any decision to refuse the approval of a new drug, or to withdraw or restrict the availability of a drug already in use if such decision is taken as a result of serious adverse reactions, and requesting the Director-General to transmit immediately to Member States the information received;

Acknowledging the value of information distributed through this intergovernmental information system so far;

Noting that it is not only the serious adverse reactions caused by drugs that must be taken into consideration as factors detrimental to the health of the individual, but also their inefficacy; and

Noting also that ineffective drugs are wasteful of individual and public economic resources,

1. **INVITES** all Member States to communicate to WHO any final decision made by national health authorities to withdraw or restrict the availability of a drug already in use if the decision is taken because of lack of substantial evidence of effectiveness in relation to its toxicity and the purpose for which it is used; and

2. **REQUESTS** the Director-General to disseminate these decisions in addition to decisions taken as a result of serious adverse reactions, as specified in resolution WHA16.36.

_May 1970_ **184.25**

WHA24.56 The Twenty-fourth World Health Assembly,

Recalling previous Assembly resolutions dealing with pharmacology and the control of drugs, and in particular resolutions WHA16.36, WHA17.39, WHA20.34, WHA21.37, WHA 22.50, WHA23.13, WHA23.42 and WHA23.48;

Convinced that matters relating to the discovery, production and distribution of drugs, to the control of drug quality, safety and efficacy and to the monitoring of adverse reactions, including dependence-producing properties, should be looked upon as a whole;

Realizing that the continuous development of medical science and of the pharmaceutical industry leads to the appearance of new and more effective drugs;

Being aware of the increasing need for the prescribing physician to know and fully understand the effects, side-reactions and possible interactions of drugs;

Considering the responsibility of the World Health Organization to assist in keeping the national health authorities and the medical profession abreast of such developments through expanded facilities for information on pharmacotherapy and for continuing education in clinical pharmacology; and

Further considering the necessity of devising the most efficient ways for the Organization to carry out this responsibility,

1. **COMMENDS** the increased emphasis in the programme of the Organization, and the work being done, on pharmacology and on the control of drugs;

2. **REQUESTS** the Director-General, keeping in mind the need for an overall approach to such matters, to study how best the Organization can cope with its obligations in this domain and expand its activities as required, and to report thereon to the Executive Board at its forty-ninth session and to the Twenty-fifth World Health Assembly;

3. **REQUESTS** the Director-General to consider the creation of a system of collection and dissemination of information on results of safety and effectiveness trials of new drugs and on their registration in countries having the necessary facilities, for possible use of these data by the health authorities of countries importing pharmaceutical products; and to report on the feasibility and financial implications of such a system to the forty-ninth session of the Executive Board and to the Twenty-fifth World Health Assembly; and

4. **FURTHER REQUESTS** the Director-General to publish a list of countries where the State authorities responsible for the quality control of drugs recognize and implement the requirements for "Good Practices in the Manufacture and Quality Control of Drugs" and the certification scheme on the quality of pharmaceutical products moving in international commerce as recommended by the Twenty-second World Health Assembly in its resolution WHA22.50.

_May 1971_ **193.31**
WHAAA5.61 The Twenty-fifth World Health Assembly,

Having examined the report of the Director-General on the quality, safety and efficacy of drugs;

Mindful of the importance of developing a comprehensive approach to ensuring drug quality, safety and efficacy, monitoring adverse reactions, and developing and disseminating accurate information about drugs;

Convinced of the need to assist national health authorities to meet their responsibilities in relation to drug quality, safety and efficacy,

1. REQUESTS with appreciation the activities that have been undertaken in accordance with resolution WHA24.55;

2. RECOMMENDS that governments, if they deem it necessary, take suitable measures for giving the public appropriate information about the use, hazards and limitations of drugs;

3. REQUESTS the Director-General to report to the fifty-first session of the Executive Board and the Twenty-sixth World Health Assembly:

(a) on the feasibility of an international information system providing data on the scientific basis and the conditions of registration of individual drugs;

(b) on practicable minimum requirements and on other efforts to develop a comprehensive approach to ensuring the quality, safety and efficacy of drugs, including the feasibility of implementing Article 21 (d) and (e) of the WHO Constitution;

(c) on the cost of any action foreseen;

4. URGES all countries participating in the monitoring scheme to ensure that reports of adverse reactions after validation are forwarded regularly and with the minimum delay to the Organization; and

5. REQUESTS the Director-General to undertake a study of the most feasible means of indicating by a uniform system of marking the limits of shelf life of pharmaceutical products under the conditions of their storage, as well as the date of manufacture and batch number, and the maintenance of records which facilitate tracing of distribution, and to report thereon to a future World Health Assembly.

May 1972 201,33

WHAA26.66 The Twenty-eighth World Health Assembly,

Having considered the report of the Director-General on prophylactic and therapeutic substances;

Recognizing the importance of further development of international standards and requirements for prophylactic and therapeutic substances;

Convinced of the necessity of developing drug policies linking drug research, production and distribution with the real health needs,

1. THANKS the Director-General for his comprehensive report;

2. URGES governments and professional bodies to ensure that the health personnel and the public are adequately educated and kept informed as to the proper use of prophylactic and therapeutic substances; and

3. REQUESTS the Director-General:

(1) to continue to develop activities related to the establishment and revision of international standards, requirements and guidelines for prophylactic and therapeutic substances in consultation, as appropriate, with relevant governmental and nongovernmental organizations in official relations with WHO;

(2) to develop means by which the Organization can be of greater direct assistance to Member States in:

(a) the implementation of national programmes in research, regulatory control, management and monitoring of drugs and, in so doing, also in the formulation of national drug policies;

(b) advising on the selection and procurement, at reasonable cost, of essential drugs of established quality corresponding to their national health needs;

(c) the education and training of scientific and technical manpower for research, production, evaluation, control and management of prophylactic and therapeutic substances;

(3) to study ways and means of optimizing inputs and outputs of the international system for drug monitoring so that it will be useful for both developed and developing countries;

(4) to disseminate to Member States evaluated information on drugs; and

(5) to report on the above matters to the Executive Board and a future World Health Assembly.

May 1973 209, 14

WHAA26.30 The Twenty-sixth World Health Assembly,

Recalling resolutions WHA24.56 and WHA25.61;

Having examined the report of the Director-General on the feasibility of an international information system on drugs,

1. THANKS the Director-General for his report;

2. CONSIDERS that the implementation of an international information system providing data on the scientific basis and the conditions of registration and withdrawal of individual drugs would be of considerable importance in the development of a more comprehensive approach to ensuring drug quality, safety and efficacy;

3. BELIEVES that the proposed feasibility study would provide the basis for assessing the potential value of such a system; and

4. REQUESTS the Director-General to develop the proposed feasibility study and to report to a future World Health Assembly on the findings of this study and on their financial implications.

May 1973 209, 14

WHAA26.31 The Twenty-sixth World Health Assembly,

Recalling resolutions WHA16.36 and WHA23.48; and

Reiterating that all drugs made available to consumers should comply with adequate standards of quality, safety and efficacy, and that the World Health Organization has a major role to play in the collection and dissemination of information on drugs,

1. INVITES Member countries to continue to communicate to the World Health Organization any decisions by the national control authority resulting in the withdrawal from the market of any pharmaceutical product, and to indicate in the communication the name of the product, its composition, its dosage form, the name of the manufacturer and the findings of the studies which resulted in the withdrawal; and

2. REQUESTS the Director-General to continue to disseminate information concerning such decisions without delay and to make this information activity part of the proposed feasibility study on the international information system on drugs.1

May 1973 209, 15

1. See resolution WHA26.30

1. This paper outlines the various factors involved in the marketing of drugs and focuses on those most pertinent to the developing countries in their efforts to establish and maintain health care at a cost they can afford. Drug marketing is often mistakenly considered as synonymous with drug advertising. In fact it has many components, beginning with the registration of a drug and ending in its safe delivery to the end user, with many steps on the way. This paper considers the various steps.

Registration of drugs

2. Modern drugs have potent influences on the body. Their very potency, laudable in itself, is however a source of danger since it carries the risk of adverse effects either on the organ or system for which the drug is intended or on other organs or systems for which it is not intended. Control over the safety, efficacy, and quality of drugs must therefore not only be the responsibility of the manufacturer but also be the subject of regulation by the government. This principle of drug approval is fully accepted by all responsible pharmaceutical companies. Prescribers, consumers and their elected representatives, and industry all have a role to play in determining the nature of such regulation and ensuring compliance with it.

3. The assessment of efficacy, safety and quality requires sequential studies - first in the laboratory, including pharmacological and toxicological testing, then possibly in volunteers, then clinically in controlled clinical trials. Even when these have been completed, large-scale field trials accompanied by epidemiological analysis are now often required before it can be concluded with any degree of certainty that a drug is indeed effective and safe. However, at a certain stage a decision has to be taken whether to permit the use of the drug in clinical practice. This is only one episode, however, in the assessment of the drug; post-marketing surveillance, including the monitoring of adverse reactions, has to be maintained, in the course of which the drug may occasionally have to be reconsidered in the light of experience.

4. In addition to the basic problems of legislation on drugs, starting with the need to have them registered before they can be marketed, there are quite fundamental differences between countries in relation to the nature of studies required before drugs can be approved. For example, the law currently does not require studies on healthy human volunteers in France; and in the United States of America extremely rigid protocols exist for the design of clinical studies.

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1 The Director-General acknowledges with appreciation the contribution to the preparation of this document of Dr A. Worlock, Corporate Finance Adviser, Health Care, Bache Securities (UK) Inc., London, England.
5. Even though each drug regulatory authority evaluates the data submitted under the same general criteria of safety, quality, and efficacy, the complexity of the criteria often leads to different results arising in different countries due to different interpretations of the data. What is important, however, is that in the developed countries approval of new drugs does take place and procedures are being used, even if these are not necessarily identical in all countries and give rise on occasion to somewhat different indications for drug use. Fundamental differences in medical practice, attitudes, and traditions may also result in different standards. Moreover, since certain conditions such as tropical diseases do not occur in certain countries, drugs to treat them are not registered there but may be exported from them to countries that do need them, thus giving the erroneous impression of double standards. A real issue of double standards would arise if a drug tested and not approved for use in one country were to be allowed to be exported from that country to other countries, or a drug withdrawn from use in one country because of its adverse effects continued to be exported to others, or information provided for the domestic market in an exporting country were withheld when the drug is sold elsewhere, or claims not permitted in the country of origin were made in other countries.

6. To the uninitiated the process of drug approval may seem complex and often confused, although through patient and prolonged efforts between regulatory authorities, the pharmaceutical industry, and WHO a movement is beginning toward similarity rather than difference. This is particularly the case for the many well-established drugs for which there is general agreement about their indication, use, adverse reactions, manufacturing standards, formulation, etc. This being so, developing countries should perhaps in the first instance consider accepting the marketing approval of countries with well-developed regulatory mechanisms, particularly where these involve a comprehensive product data sheet or detailed labelling and package insert requirements. Moreover, they have at their disposal the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce, which currently is the only umbrella scheme that attempts to provide the relevant technical data in a form easily assimilated by any regulatory authority (see pages 287-295). It could be complemented by additional information such as the product data sheet from the country of origin, particularly if this is designed to incorporate the indications, dosage, use, precautions, adverse effects, drug interactions, etc. The international pharmaceutical industry has stated that it will support WHO along these lines and participate in this information transfer.

Brand and generic products

7. Newly discovered products in market economy countries are usually sold by their proprietary or brand name. However, after the expiry of the patent, other companies may manufacture an identical product either under the international (or a national) nonproprietary name, a generic name, or another brand name (so-called "branded generics"). The sale of drugs by their brand name on the one hand or generic name on the other usually affects their price, as is explained below.
Labelling and packaging

8. The labelling of pharmaceutical products depends on the registration requirements of a country and the end user, who may be professionally qualified or a member of the public. The method of end use must be clearly indicated, e.g. prescription, pharmacy only, or general sale. Simple clear instructions are required regarding the indications, dosage, contraindications, precautions, side-effects, interaction with other drugs, action to be taken for overdosage, storage conditions, expiry date, etc. They should be specifically addressed, as appropriate, to the prescriber or the consumer, and may require simple illustrations for example, of the method of administration. Incomplete information, or inadequate emphasis on certain information, for example side-effects or interaction with other drugs, can lead to improper use of the drug; hence the importance of complete and unbiased information in package inserts. Packaging components must match the environmental storage and transport conditions that the formulation will be subjected to, and the unit pack size must be appropriate to the final user. Moreover, the name and other essential information must be clearly printed on the package to avoid mistakes in dispensing or consuming.

Pricing

9. Many factors affect drug prices. Since the pharmaceutical industry is divided broadly into two sectors, the first carrying out research and developing new drugs, the second not carrying out research but supplying already existing drugs, the marketing of a drug from either of these two sectors will obviously affect its price. The calculation of the real price of a drug also has to be considered, in relation for example to its cost/benefit and proper utilization or otherwise. Moreover, pricing normally takes into account the market size and potential and the competition from other drugs in the same therapeutic class.

10. To discover and develop drugs requires large-scale research and development. For each new drug as many as 10 000 compounds may have to be tested. Screening these requires laboratory studies and clinical trials as outlined in paragraph 3 above. All this may require a time-scale of 8-10 years at a reputed cost of up to US$ 100 million. Demands for increased safety require more toxicity testing, so that an increasing proportion of projects fail. Higher standards are being demanded for quality. All these factors raise the cost of developing new drugs considerably. In market economy countries, industrial property developed at such a risk needs protection for a limited time, and this is secured through patents. Research-based industry in these countries must recoup its investment and make a profit during the patent life of the drug.

11. It should be noted that research and development, product registration, etc., are normally regarded by pharmaceutical manufacturers as part of their fixed costs as they find it extremely difficult to allocate them to specific products. The remaining costs go to production, distribution, and
promotion, and additional costs are now accruing in the field of post-marketing surveillance. A breakdown of costs for each of these items is not generally available. A report by the Office of Health Economics, London, mentions a study carried out in seven countries in 1982 which revealed the following expenditures on research and development as a percentage of output: Switzerland 15.2%, Federal Republic of Germany 13.1%, United Kingdom 12.1%, France 10.8%, Italy 8.4%, United States of America 7.4%, Japan 7.1%. However, the authors of the report state that the figures have to be treated with caution in view of the difficulties in compiling national data that are both accurate and comparable. Costs in Switzerland have been subdivided into two parts, manufacturing and distribution, the former accounting for 55.7% of the total, the latter for 44.3%. Manufacturing costs were broken down as follows: production 40%; research, development, and licensing 15%; information to physicians 11%; sales 9%; publicity 4%; administration 11%; profits 10%. Distribution costs were broken down as follows: wholesalers 13.5%; pharmacists—auxiliary staff 36.5%; storage 9%; other operational costs 11.5%; capital expenditure and amortization 8%; basic income of pharmacists 13.5%; profits and business risk 8%. It is difficult to discern from the above exactly what items to include under promotional expenditure. One estimate of average promotional expenditure as a percentage of sales is as follows: United States of America 22%, Federal Republic of Germany 22%, Italy 22%, Sweden 18%, France, 17% United Kingdom 15%, and India 10%.

12. There are great differences in the price of the same drug in different countries, sometimes by as much as tenfold. While it may be possible to explain them in part by such circumstances as retail margins or direct or indirect subsidies, many of the reasons are less apparent. The above-mentioned report of the Office of Health Economics in London quotes a study carried out in 1982 that showed the following index of pharmaceutical prices in six countries: Japan 100, Switzerland and the Federal Republic of Germany 83, United Kingdom 58, Italy 38, France 33. The authors of the report observe that one of the most serious consequences of the effects of price control as shown in the above figures has been the encouragement of so-called parallel imports, that is, the practice whereby traders buy in cheap markets and then sell in competition with the original manufacturer in higher-priced markets. Another factor affecting prices may be transfer pricing, that is, the charges made within a company as a product moves from one location to another at different stages of its manufacture. Such pricing may be at the origin of high costs in countries in which there are daughter companies of a parent company in another country, the latter "selling" its products or raw material to the former at inflated prices.

2 La santé publique en Suisse—prestations, coûts, prix. Bâle, Pharma information, 1984. (Available only in French and German.)
13. Branded generics, which are products sold under distinctive brand names and promoted in the same way as the leading brand, can be sold at a lower price because of the minimal research and development input, that is, lower development costs. They have marketing support, technical information, and selling costs, but are usually sold at significantly lower prices than new drugs. Other products marketed under the generic name have minimal promotion and are usually sold by tender or direct sale. Such products are frequently sold at even lower prices than branded generics.

14. Distribution costs can affect the end user price remarkably. In market economy countries the manufacturer normally sells to a wholesaler, who distributes to pharmacies, naturally adding to the cost; or alternatively drugs may be purchased directly by a group, which may be a regional or national unit, and the distribution costs may not be passed on directly to the end user. This occurs, for example, with many supply contracts. On the other hand, even with supply contracts to a central body at a negotiated price, the ultimate price to the end user may be considerably higher, particularly when relatively small amounts of a drug are required urgently on a non-routine basis, as well as for a variety of other less ethical reasons.

15. The distribution system must have a feedback to each source of supply and establish lead times for order and supply. It must provide for the delivery of drugs in good condition to the patient and for proper storage conditions on the way. Such a logistic system is essential to ensure the rational use of drugs but it costs money, and if the cost has to be covered by consumers the price they have to pay will be proportionately higher than the purchase price at the source. In many government health systems the distribution cost is not transferred directly to the consumer but included in the overall cost of the health service.

16. Direct and indirect control over pricing can be exercised in many ways, for example by cutting promotional and distribution costs. Some countries have a reimbursement list and commercial success can only be achieved when a product is included. Other countries establish a price by calculating from the bottom up, i.e., beginning with the raw materials and adding the various incremental factors such as production cost, overheads, research and development, promotion, etc.

17. Whereas in countries with centrally planned economies domestic prices are determined by governments, having regard to projected needs and costs, in market economy countries market forces affect prices depending on whether the supply arrangements are for a single purchase, a commitment for purchase over a period, a small volume, or a large volume in which economies of scale come into force. Other factors influencing prices are whether drugs are produced locally, need to be trans-shipped, are made under contract to the specifications of the buyer, or are supplied under special conditions. International procurement is affected in addition by such factors as whether the drugs are purchased free on board (f.o.b.) or cost, insurance, freight (c.i.f.). One way of keeping prices down is by open tenders - national and international. Recent experience with international tenders for generic drugs in developing countries has been very encouraging; good quality drugs
have been obtained at lower prices than ever before, thanks to purchasing larger quantities required for a longer period of time and thus benefiting from the economies of scale, as well as to international market forces. Moreover, research-based companies have provided generic products, sometimes through subsidiary companies, and have done well in the competition. They include their company name on the label in addition to the generic name. These factors may well have to be taken into account by developing countries when they contemplate introducing large-scale local drug production, notwithstanding their legitimate desire for self-reliance in drug production.

Rights to prescribe, distribute, and sell

18. In many countries rights to prescribe, distribute, and sell are governed by regulation and licence. Where there is a dearth of professional health personnel licensing requirements may have to differ from those of more developed countries.

19. In most countries only registered medical practitioners are entitled to prescribe allopathic drugs of the type known as prescription drugs. Registered dental practitioners may prescribe drugs specific to dentistry. However, in many countries the public health service, particularly in rural areas, is sorely lacking in doctors and it is necessary to permit other categories of health worker - including nurses, pharmacists, and in many cases nonprofessional primary health care workers - to prescribe certain drugs, following suitable training. In some countries, particularly in the large towns, the public has almost unlimited access to all forms of drugs, including prescription drugs, which they can purchase without a prescription. In many of these countries, however, the rural population, which makes up the vast majority of the population, has little or no access to a regular supply of drugs.

20. The right to distribute drugs wholesale from manufacturer to retailer also varies in different countries. Distribution entails not only physical distribution but also proper storage and handling and often involves good stock control advice to users, such as attention to shelf life, since the medical products are often held in general stores. For these reasons the wholesale distribution of drugs requires both pharmaceutical and managerial skills, whether in private or government distribution systems.

21. The right to sell prescription drugs to the end user is usually governed by licence, e.g. permitting a pharmacist to dispense them. However, in many countries such drugs are sold without prescription or as over-the-counter (OTC) commodities in non-pharmacy outlets, often as a single treatment purchased on a daily basis, sometimes even as a single dose. OTC drugs are products sold in pharmacies and, to a limited extent, other outlets without prescription. They are normally less potent than prescription drugs and include mild analgesics, laxatives, cough and cold preparations, topical preparations, and the like. They are often sold as branded generic formulations as a means of conveying an assurance regarding their quality, safety, and efficacy. In many countries, particularly
developing ones, the OTC market is an outlet for the uncontrolled supply of prescription drugs. OTC drugs are usually supported by substantial promotion directed at the general public. In some countries many such drugs are sold in food stores, masquerading as food supplements and thus avoiding the normal control exercised over drugs. Counterfeiting is an additional compounding factor.

22. In many developing countries patients have not the money to purchase the total treatment and frequently buy one dose at a time. Moreover, while some purchase drugs on the advice of health personnel, many purchase without such advice and without the minimum knowledge required to make a rational decision. In most industrialized countries, too, the right to sell most drugs to the end user is limited to qualified pharmacists, but in many developing countries this restriction is often not possible outside the main towns, and village stores, community cooperatives and the like may have to be granted permission to sell.

Promotion

23. The promotion of drugs takes many forms, such as providing information to prescribers in attractive ways, often accompanied by generous samples; advertising in professional journals as well as in the lay press, and in some countries through radio and television for OTC drugs; providing incentives to prescribers and pharmacists in proportion to the volume of drugs they prescribe and dispense; using sales representatives to sell to prescribers in much the same way as is done with other consumer goods; and sponsoring or subsidizing scientific symposia at which related drugs are promoted in diverse ways. Some of this promotion conforms to acceptable ethical standards; some does not. The proportion of drug costs devoted to promotion varies widely by product; in all cases the costs naturally fall ultimately on the consumer.

24. Advertising is one of the means of disseminating information on drugs. It usually presents information in an attractive manner and can thus be useful, on condition that it is objective and accurate. However, if this condition is not fulfilled it can be dangerously misleading because it is likely to take precedence over objective and accurate information presented in a less attractive form. This emphasizes the need for scrupulous integrity in all forms of drug advertising. It goes without saying that such integrity has to be universal, with no double standards for developed countries on the one hand and developing countries on the other.

25. Advertising of prescription drugs is restricted to health professionals through such means as medical journals, product literature, slide/tape and video presentations, exhibitions, and meetings either read about or attended by doctors and pharmacists. In some countries advertising of OTC drugs aimed at the public is permitted through the media but not by direct mailing. Governments and the pharmaceutical industry have a responsibility, particularly in developing countries, to use the media for the education and information of health workers and the public.
26. Drug advertising has been the subject of much criticism because of its alleged aggressivity and biased content. As far back as 1968, the Twenty-first World Health Assembly asserted in resolution WHA21.41 that drug advertising must adhere to certain fundamental principles and that, if not objective, it is detrimental to the health of the public. It adopted the following ethical and scientific criteria for pharmaceutical advertising:

"All advertising on a drug should be truthful and reliable. It must not contain incorrect statements, half-truths or unverifiable assertions about the contents, effects (therapeutic as well as toxic) or indications of the drug or pharmaceutical speciality concerned.

Advertising to the Medical and Related Professions

In describing the properties of a drug and its use, stress should be laid on rendering facts and data, whereas general statements should be avoided. Statements should be supported by adequate and acceptable scientific evidence. Ambiguity must be avoided. Promotional material should not be exaggerated or misleading.

A full description, based on current scientific knowledge, should include information on the producer and sponsor of the product advertised; full designation (using generic or nonproprietary names) of the nature and content of active ingredient(s) per dose; action and uses; dosage, form of administration, and mode of application; side-effects and adverse reactions; precautions and contra-indications; treatment in case of poisoning; and references to the scientific or professional literature.

A fair balance should be maintained in presenting information on effectiveness on the one hand and adverse reactions and contra-indications on the other.

Advertising to the Public

Advertisements to the public should not be permitted for prescription drugs, for the treatment of certain diseases and conditions which can be treated only by a doctor and of which certain countries have established lists, or in a form which brings about fear or distress, or which declares specific remedies to be infallible, or suggests that they are recommended by members of the medical profession."

May 1968.

27. Sales representatives are frequently a much criticized part of the selling operations of pharmaceutical companies. Evidence shows that use of sales representatives is a highly effective way of promoting drugs since doctors often regard them as a useful source of information. If they are to be employed, however, they should be properly qualified to carry out their job. In some developed countries they need to pass an examination, the responsibility for training and ethical standards resting with the company; they are also accountable for their actions and strict rules are laid down.
Thus, they are expected to give objective information about their products in an ethical way and to be willing to discuss published data from independent sources and know the maximum and minimum limits of the products. In many countries there is need for improvement in the standards; evidence shows that several companies are trying hard and that improvements have taken place over the past 10 years, but more needs to be done. One of the problems is the custom in some countries of doctors demanding discounts and incentives before seeing representatives. This leads to competition and to abuse of medical practice.

28. Particularly when promoting new drugs, samples are used to encourage doctors to try them out. Too many samples can - and do - lead to abuse either by being used for current treatment and charged for or by becoming an exchange commodity and used as a discount. If they are to be permitted they have to be carefully controlled, for example, being supplied in limited amounts only at the request of a prescriber and their use being monitored and results recorded.

29. Symposia can be useful for exchanging information and improving medical and therapeutic education. Those sponsored by the pharmaceutical industry are best used in collaboration with organized postgraduate education with guidelines like, for example, the following:

1. Meetings sponsored by a pharmaceutical company may be allowed subject to the approval of a clinical tutor or postgraduate education committee.

2. Arrangements must be made by the same person or committee and competent staff from the pharmaceutical company invited to attend.

3. Lecture material and films should be vetted.

4. A suitably qualified independent doctor experienced in the topic must be available at such meetings.

5. Promotional material from the pharmaceutical company is allowed but must be separate from the educational content of the meeting.

6. Sponsoring should be limited to the provision of light refreshments and the printing of programmes, due acknowledgement being made.

If such guidelines are complied with, the sponsoring of symposia may be regarded as ethical and useful.

30. In many developed countries there are regulatory constraints on promotional methods, but in many developing countries governments are not yet in a position to assume that responsibility. This places even greater responsibility on the pharmaceutical industry to apply in these countries the same norms that they apply in developed countries. Examples have often been quoted of alleged flagrant breaches of promotional ethics by pharmaceutical companies. Industry has responded by initiating remedial
action. Thus the International Federation of Pharmaceutical Manufacturers Associations (IFPMA) issued a voluntary Code of Pharmaceutical Marketing Practices in 1982. It includes a clause to the effect that claims for drugs should not be stronger than the scientific evidence or responsible medical opinion warrants and that every effort should be made to avoid ambiguity. The IFPMA periodically publishes reports on action taken to ensure compliance with the Code, including action taken in response to complaints about infringements, and has expressed its willingness to report to the World Health Assembly on progress made in applying the Code. Nevertheless, the IFPMA Code has been criticized as weak and ineffective.

31. In partial reply to such criticism, multinational companies have stated that even if policy decisions are taken centrally, the decisions may not be carried out by all subsidiaries. Moreover, they add, it is often erroneously assumed that the corporate headquarters of a multinational company know all the time what is happening in every market. Experience has shown that drawing attention to misdemeanours will help to elicit positive action from responsible management; consumer groups have been active in that respect, the governments concerned less so.
This document provides a brief review of national health legislation relating to the marketing of drugs (pharmaceuticals). A large number of countries now have legislative provisions on drugs covering a wide and varied spectrum. In preparing this review, the laws and regulations of some 80 countries were analysed. Any comprehensive review based on such a large volume of legal instruments is likely to run into several hundred pages. With a view to producing a document which enables the legal status of drug marketing to be surveyed rapidly, this review contains a synthesis of general approaches that are common to many countries. The review, therefore, does not specifically mention some or all of the 80 countries that have laws and regulations representative of the general approaches described. However, where there are significant additions to or departures from the general approach the review makes specific reference to them. The examples have been selected at random when the addition or departure occurs in more than one country. Reference in the document to any one country in relation to a particular approach does not, therefore, necessarily mean that such approach is confined only to that country.

The review is based largely on legislative texts that have appeared in the International Digest of Health Legislation (IDHL) published by WHO since 1948. A few texts to be published shortly have also been included. Most of the references in the document are to laws and regulations currently in force. Any reference to a law or regulation no longer in operation is only for the reason that such law or regulation reflected a legislative development still worthy of note. In addition to national laws and regulations, reference has been made to a few codes of conduct that contain relevant provisions. However, for the purpose of this review, no survey was made of codes of conduct and the references in the document to codes are based on published material. The review also contains references to various comparative surveys that have been published from time to time, which provide more detailed information on some of the aspects covered. They are, however, based on a survey of the laws and regulations in fewer countries than in this document. Since WHO is compiling an annotated bibliography of literature on drug marketing, this document does not contain any references to books, articles, conference proceedings, or other materials dealing with the legal status of pharmaceuticals in any individual country.

1 The Director-General acknowledges with appreciation the contribution to the preparation of this paper of Dr D. C. Jayasuriya, Attorney-at-law.

2 In many of the countries covered in this review there is separate legislation dealing with narcotic drugs and psychotropic substances and largely based on the principles set out in the international drug control treaties. This review does not cover such legislation, nor does it deal with the special legislation on poisons and vaccines and allied products.
BACKGROUND

1. While this review is primarily concerned with national legal controls over the marketing of drugs, account needs to be taken of controls prior to the availability of drugs for marketing.

2. Legal controls tend to differentiate between various categories of drugs, the controls ranging from very tight to relatively loose. The categorization of drugs and the nature of the controls applicable to the different categories of drugs vary from country to country. A 1960 WHO survey of existing legislation on the classification of pharmaceutical preparations pointed out that there is a total lack of uniformity. Some legal texts have a single list of substances, others up to five lists. In addition, some texts deal specifically with special categories of drugs, such as those liable to cause addiction. Even within this broad classification there are subclassifications reflecting, for instance, the different schedules in the international drug control treaties. In a review of this nature, covering a large number of legal and health care systems, it is not possible to make generalizations regarding the different levels of controls applicable to various categories and subcategories of drugs. All that can be attempted is an enumeration of certain common categories of drugs as a background to a discussion on specific aspects. It is important to note that, since there is no uniformity in terminology, the use of the identical concept in two or more legal texts does not necessarily mean that identical controls are applicable.

3. The basic categorization of drugs into prescription drugs and non-prescription or over-the-counter (OTC) drugs is important for the reason that controls and requirements relating to advertising and labelling often tend to be based on such categorization. Prescription drugs are generally subject to stringent controls. For registration purposes laws generally tend to use general terms such as "pharmaceutical speciality" or "medicinal product" to cover a wide and varied range of drugs. Exclusions from such a classification are limited to a few categories such as drugs prepared in hospitals and pharmacies. For registration purposes general terms such as "new drugs" are also used, often in relation to the availability of a drug in relation to a specific period of time. For instance, in the new Chinese Pharmaceuticals Control Law, "new pharmaceutical" means a pharmaceutical that has not yet been produced in China. Antibiotics, oral contraceptives, combination drugs, drugs that induce anaesthesia, drugs for prophylactic use, biological preparations, sera and vaccines, blood and blood products, etc. are sometimes specifically included within, or excluded from, the general definition of drugs. Homoeopathic, ayurvedic, and herbal drugs are generally subject to different controls, even though a single law may cover all these substances.

4. A drug, to be available for marketing, must be either manufactured in or imported into the country, and controls at the stage of manufacture or importation need to be taken into account in determining the nature and magnitude of the marketing controls to be subsequently applied.
5. Safety, quality, and efficacy have been the general considerations governing traditional controls over manufacture. Licensing systems are of different kinds. Some countries grant licences for the manufacture of drugs generally, others for a named drug or specific categories of drugs. Registration of the drug to be manufactured is often a condition to the issue of the licence. Some laws provide for the issue of licences even for supplementary activities such as filling, packing, and labelling. In addition to licensing, compliance with good manufacturing practices, regular inspection of manufacturing premises, quality verification of manufactured products, compliance with pharmacopeial standards, etc. are features of the controls over manufacture generally applied through appropriate legal instruments. In this context note may be taken of the role of WHO in the formulation of good manufacturing practices and in the compilation of the International Pharmacopoeia, both designed to promote the safety, quality, and efficacy of manufactured products. Many countries have accorded legal or administrative recognition to requirements of good manufacturing practices and the standards in the International Pharmacopoeia. Through bilateral and other arrangements importing countries accept inspection of manufacture by exporting countries as equivalent to their own.

6. The vast majority of countries in the world, particularly the developing countries, obtain their drug requirements through imports. Controls over imports have taken different forms, ranging from liberal import policies as part of general trade policy permitting the import of any drug (with the exception perhaps of those which are banned or are spurious, counterfeit, misbranded, adulterated, substandard, etc.) to those which restrict imports to specific categories of drugs (such as essential drugs, registered drugs, licensed drugs, or drugs listed in a pharmacopoeia or national formulary).

7. The system of issuing import licences enables the regulatory authority responsible for drugs to determine what drugs should be permitted to be imported, by whom, and subject to what conditions. Naturally, therefore, countries have recourse to a licensing system to regulate the inflow of drugs. Considerations of safety, quality, and efficacy are among the main factors taken into account in determining what drugs should be permitted to be imported. Additional considerations are registration of the drug as a pre-condition, restrictions on the quantity to be imported (for a single consignment or over a period of time), medical need, price, etc. The requirement that the drug to be imported has been manufactured by an establishment or plant adhering to good manufacturing practices and the place and process of manufacture have been subject to regular inspection is an additional safeguard. The submission of documentation relating to quality, safety, efficacy, registration, and pricing and provision for quality verification at the time of import is a general condition of import licences.

8. National laws provide for a variety of situations in which imports or import licences can be cancelled or suspended, the commonest being those relating to unsatisfactory quality, safety, or efficacy of the drug. Drugs not of the accepted quality, safety, or efficacy and spurious, counterfeit,
or adulterated drugs cannot be imported and, if imported, are liable to confiscation. Some countries have provided additional grounds for prohibiting, suspending, or cancelling imports. In Bahrain, for instance, imports can be suspended if the price exceeds the limits accepted in neighbouring Arab countries. Australia prohibits the importation of drugs that do not comply with stipulated labelling and packaging requirements.

9. The WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce is designed to facilitate the efforts of importing countries to obtain assurance regarding the quality, safety, and efficacy of imported drugs. This Scheme, in which more than 100 Member States now participate, provides an administrative mechanism:

(1) to provide assurance that the product has been authorized to be placed on the market in the exporting country (if not, the reason why such authorization has not been granted, as, for example, that the drug is meant mainly for tropical diseases);

(2) to provide assurance that the manufacturing plant conforms to requirements for good practices in the manufacture and quality control of drugs as recommended by WHO and that the plant is subject to inspection at suitable intervals;

(3) to exchange information on inspection and controls exercised by the authorities in the exporting country (including dealing with inquiries about serious quality defects in the importing or exporting country).

10. Countries without adequate technical resources to conduct clinical trials and quality verification stand to benefit from this scheme. By appropriate legal or administrative measures the principles underlying the scheme can be made applicable to import licences and other import arrangements and the monitoring of adverse reactions to drugs. Many importing countries, for instance, before issuing a licence require documentation relating to registration in the country of manufacture or origin.

Strategies for the rationalization of drug manufacture/importation

11. The concept of essential drugs was developed by WHO in response to the need for the optimal utilization of limited financial resources to purchase and distribute those basic drugs necessary to the health needs of the population. Based on considerations of quality, safety, efficacy, and reasonable price, lists of essential drugs have been compiled in a large number of countries. These lists are followed in purchasing drugs and distributing them to various outlets in the health care structure.

12. Recognition has been accorded to lists of essential drugs both administratively and legally. In China a national list of essential drugs was issued in 1981, containing 278 commonly used drugs intended to meet the general medical care needs of the population. Manufacturing
establishments are required to accord priority to the production of essential drugs, medical units to ensure that such drugs are used rationally and there is no wastage or abuse. While the Chinese approach exemplifies the administrative measures possible, in countries like Niger legislative measures have been taken to accord recognition to essential drug lists; in 1980 an order\(^{(14)}\) was made listing some 80 medicaments that district medical services and dispensaries are entitled to order. By another order\(^{(15)}\) the number of drugs for hospitals was restricted to 210. Prior sanction is necessary to obtain drugs other than those listed in the orders. Effect has also been given to the concept of essential drugs by listing drugs in a national formulary and restricting the use of drugs to those listed. In Peru the Ministry of Health, the Peruvian Social Insurance Scheme, public welfare agencies, the National Institute for the Care and Promotion of Minors and the Family, local authorities, public agencies, etc. are required by a decree\(^{(16)}\) to prescribe or use only the basic medicaments listed in the Official Formulary of Basic Medicaments in the Health Sector. Similarly, in Guatemala, by an order\(^{(17)}\) enacted in 1979, the National Therapeutic Formulary has been declared to be the definitive text listing drugs to be used in national hospitals, health centres, and health posts. In Bolivia there is a prohibition on the importation of products similar to those produced by the national pharmaceutical industry.\(^{(18)}\)

13. A recent publication of the Pan American Health Organization\(^{(19)}\) deals with the development and implementation of drug formularies. It defined a formulary as "a compilation of pharmaceutical products approved for use in a given health care system".\(^{(20)}\) Formularies are of different kinds, depending on their intent, nature and scope. Some are mainly for local use, for instance within a hospital or group of hospitals. As far back as 1959 Sri Lanka, for example, had a hospital formulary and all state-sponsored medical institutions were obliged to use the drugs listed in it and no others.\(^{(21)}\) This was achieved through administrative procedures and the formulary had no legal base. Whether a law is needed to accord sanction to a limited formulary depends on the organic structure of the health-care institutions that would be bound by it; autonomous institutions may not feel obliged to give effect to administrative schemes. Moreover, procurement procedures may have to be changed and in some countries this may necessitate a legal instrument that will have an overriding effect. As against local or limited formularies, a few countries have adopted national formularies. In Bolivia, for instance, legislation\(^{(22)}\) has described the National Therapeutic Formulary as "the authoritative instrument which alone is binding on centralized and decentralized public agencies of the State with regard to the following matters: (a) the application of therapeutic criteria prescribed in accordance with the advances in and principles of pharmacology; and (b) the rational use of drugs in health administration, including planning, acquisition, preservation, distribution and supervision".\(^{(23)}\) The National Therapeutic Formulary is required to contain the information essential to ensure a proper regard for the principal requirements concerning medicaments, including concentration and therapeutic guidelines such as indications, contraindications, precautions and adverse effects. It must also include the basic list of medicaments, comprising the details required for administrative purposes such as the
generic or permitted description, the level of use, the form of presentation, and the unit of measurement.

14. Countries that have adopted formularies have established mechanisms to review and update their contents and ensure the administrative, fiscal, and other measures needed to facilitate the availability of the basic medicaments. In Costa Rica the Technical Committee on the Formulary is required to undertake cost-benefit and drug utilization studies. The National Medicaments Council in Bolivia has to collaborate in drawing up standards for industrial production and technological development.

15. The manufacture and importation of drugs can be rationalized by a mix of strategies instead of a single strategy, as exemplified by the Bangladesh drug law reforms of 1982. The drugs available on the market were curtailed by five measures. Firstly, no medicine of any kind could be manufactured for sale or be imported, distributed, or sold unless it was registered with the licensing authority. The authority had to act on the recommendations of the Drug Control Committee. Secondly, certain medicines listed in three schedules were subject to special restrictions that were to become operative within a stipulated time-limit. Medicines specified in the first schedule had to be destroyed, medicines in the second to be registered after changes in their formulation as directed by the licensing authority. Non-registration meant that it was not possible either to manufacture or to sell these medicines. Drugs listed in the third schedule were prohibited from being manufactured or imported, thus resulting in a complete withdrawal of such drugs from the market. A fourth schedule was introduced subsequently by way of an amendment to the principal legislation. Unless the medicines listed in this schedule were registered it was not possible to manufacture, distribute, or sell them. Thirdly, the legislation did not permit a drug to be locally manufactured under licence granted by a foreign company that had no manufacturing plant in Bangladesh, if such drug or its substitute was already being produced in Bangladesh. Fourthly, the prior approval of the licensing authority was required for the importation of pharmaceutical raw material. Fifthly, the Government was empowered to review any licensing agreement between a Bangladeshi concern and a foreign concern for the manufacture of any drug in Bangladesh and to give directions for modifying the agreement. In the event of non-compliance with any direction, the manufacturing licence was liable to be cancelled.

16. The rationalization of drug manufacture in relation to the concept of essential drugs has taken the form of requiring manufacturing establishments to manufacture such drugs. Reference has been made to the Chinese requirement. In Ecuador a decree was enacted in 1977 requiring companies manufacturing medicaments to produce at least two medicaments for the basic social medicaments programme of the Ministry of Public Health in accordance with the list of medicaments issued by the Ministry.

Export

17. Restrictions on exports are designed primarily to give importing countries assurance regarding the quality, safety and efficacy of drugs they import. On the basis of available information it would appear that most
countries do not have specific legal provisions regulating the export of
drugs that have not been approved for domestic use.

18. Controls over exports at the national level take different forms. The
Canadian approach has been to exclude the application of the drug
legislation(28) to drugs meant exclusively for export, provided: (a) the
package is distinctly overprinted with the word "Export"; and (b) a
certificate has been issued that the package and its contents do not
contravene any known requirement of the law of the country to which it is to
be consigned. In the United States of America, under federal
legislation(29) no new drug can be exported until it has been approved or
licensed by the Food and Drug Administration for use in the United States.
However, antibiotic drugs can be exported to other countries even though
such drugs are not approved for domestic use, provided that they meet the
specifications of the foreign purchaser and do not conflict with the laws of
the country of import. Under French legislation(30) every drug prepared
in advance with a view to export and presented in a ready-for-use form is
subject to prior licensing by the Minister of Health. A licence is granted
only on the condition that the manufacturer provides justificatory evidence
as to quality and inspection as required for drugs marketed in France. In
Guatemala there is a requirement that only drugs duly registered and
licensed by the General Directorate of Health Services can be
exported.(31) In Bahrain the law(32) prohibits any export unless the
sanction of the Minister has been obtained.

19. In the Medicines Act(33) of the United Kingdom there are several
restrictions relating to the export of drugs, but the imposition of these
restrictions has been postponed until an Order is made to impose them. No
such Order has yet been made though the Act has been in operation since
1968. However, the Act does provide for certificates to be issued in
respect of drugs to be exported as envisaged by the WHO Certification Scheme
on the Quality of Pharmaceutical Products Moving in International Commerce,
in which the United Kingdom participates. On the application of an exporter
of medicinal products of any description the licensing authority can issue
to him a certificate containing any such statement relating to medicinal
products of that description as the licensing authority may consider
appropriate having regard (a) to any requirements (whether having the force
of law or not) which have effect in the country to which the products are to
be exported, and (b) to the provisions of the Medicines Act and to any
licence granted or other thing done by virtue of this Act. In addition to
the United Kingdom there are countries such as Austria which participate in
the Scheme and issue certificates even though national laws(34) exempt
drugs meant for export from registration.

20. The export of drugs not authorized to be marketed in the country of
manufacture either because they do not meet domestic regulatory standards or
for other reasons has generated a fair amount of discussion in recent
times. The laws of exporting countries generally do not specifically
address that issue. Some drugs are manufactured primarily for diseases
endemic in other parts of the world and there may never be an occasion for
their use in the country of manufacture. According to the drug and
antibiotic regulations(35) of the United States Food and Drug
Administration that became operative with effect from 23 May 1985, an antibiotic drug product or drug substance subject to certification under the Federal Food, Drug, and Cosmetic Act but not certified or released may be exported provided that (a) it meets the specifications of the foreign purchaser, (b) it is not in conflict with the laws of the country to which it is intended for export, (c) the outside of the shipping package carries the label that it is intended for export and is not sold or offered for sale in the United States.

21. In considering the statutory framework relating to exports, it is important to note that some importing countries have legal provisions that have a bearing on this matter. Under a 1959 decree of El Salvador, pharmaceutical specialities are not allowed to be imported into the country unless their use in the country of origin has been authorized. In Chad, under a decree of 1966, a licence can be issued in respect of specialities manufactured and packed abroad only if they are effectively and legally marketed in the country of origin.

22. As well as national controls, various arrangements at the international level are designed to offer some measure of assurance regarding the quality, safety, and efficacy of drugs subject to international commerce. The WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce requires Member States participating in the Scheme that export drugs to take certain measures designed to ensure the quality of the drugs. WHO issues a monthly communication regarding regulatory decisions on drugs and a bulletin entitled Drug information bulletin dealing with policy and other issues of interest to regulatory authorities. WHO also disseminates information on the toxic effects of drugs as part of its monitoring programme on adverse reactions to drugs, in which 27 national collaborating centres participate.

23. The United Nations has been given a mandate to prepare lists of products, including pharmaceuticals, that are banned, withdrawn, restricted, or not approved by various governments.

24. Finally, international and regional forums such as the biennial conferences of national drug registration authorities and various geopolitical groups on pharmaceuticals provide opportunities for the exchange of information and data and for the establishment of informal communication networks.

LEGAL DIMENSIONS OF MARKETING REGULATIONS

Registration of drugs

25. More and more countries now provide for the registration of drugs. A registration system, when fully operational, facilitates the regulation of what is marketed. Non-registration normally means that the drug cannot be marketed except perhaps with prior approval for limited purposes.
26. Registration systems and licensing systems often cause confusion. Some countries do not have a system for registering drugs but have a licensing system enabling drugs to be marketed. In countries with both registration and licensing systems, licences are normally granted for marketing registered products only. What is important in this context is the existence of a system that provides for pre-screening of drugs intended to be marketed. The pre-screening has to be on the basis of scientific and other criteria and procedures such as clinical trials designed to assure the quality, safety and efficacy of the drugs.

27. Different countries have different authorities and agencies entrusted with the responsibility of reviewing applications for registration and for registering drugs that have received favourable consideration. In Pakistan registration is effected by the Registration Board, headed by the Director-General of Health. Registration is a responsibility of the Federal Government. Once a drug has been registered by the Board it must notify all the provincial governments. The Pakistan legislation requires provincial governments to take all such steps as may be necessary to ensure compliance with the conditions subject to which a drug is registered and to prevent the manufacture or sale of a drug that has not been registered or the registration of which has been suspended or cancelled.

28. Registration requirements generally apply to all drugs. The information most countries require can be classified into two broad categories: administrative data and pharmaceutical, pharmacological, toxicological, therapeutic, and clinical data. Within the first category is information relating to matters such as the name of the product and details of the manufacturer, the status of the product in the country of origin and other countries, and the content of labelling and advertising material. The second category comprises detailed information of a technical nature supported by scientific facts and figures.

29. Countries differ in their criteria for registration. In the application of criteria the three common denominators are quality, safety, and efficacy. Countries apply other criteria as well. The following table provides a representative sample of such criteria, with one or two national examples selected at random.
<table>
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<td>Norway, (43) Gambia (44)</td>
</tr>
<tr>
<td>Medical justification</td>
<td>Norway (45) Mali (46)</td>
</tr>
<tr>
<td>Availability of speciality with identical or similar formula</td>
<td>Indonesia (47)</td>
</tr>
<tr>
<td>Production techniques</td>
<td>United States of America (48)</td>
</tr>
<tr>
<td>False or misleading labelling</td>
<td>Czechoslovakia (49)</td>
</tr>
<tr>
<td>Combination product</td>
<td>Sweden (50)</td>
</tr>
<tr>
<td>Harmlessness</td>
<td>Mexico (51)</td>
</tr>
<tr>
<td>Of real benefit to the country</td>
<td>Bolivia (52)</td>
</tr>
<tr>
<td>Whether imported product can be manufactured locally</td>
<td>Rep. of South Korea (53)</td>
</tr>
<tr>
<td>More than five products with the same active ingredients already on the market</td>
<td>Switzerland (54)</td>
</tr>
<tr>
<td>Brand name or trade name misleading</td>
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</table>

30. Registration of the drug in the country of export is generally regarded as being sufficient to warrant registration. Documentation is usually required on the preregistration clinical and related investigations and on other matters relevant to the quality, safety, and efficacy of the drug. Some countries have a different procedure. In Kenya the Pharmacy and Poisons Board is required to consider the results of investigations and clinical trials under local conditions before it registers a new drug. (55) However, in certain circumstances the Board can register such a drug and require the investigations and clinical trials to be conducted after registration. It may be noted that the WHO Certification Scheme provides for information regarding the status of the product in the country.
of export to be furnished, if requested by the importing country. Clinical trials and the evaluation of scientific and other data require qualified manpower, time, and financial resources. For that reason several countries attach considerable weight to the registration decisions of other countries.

31. One approach that has been followed in Bermuda is to permit the import of a drug provided the country of origin is a designated country and it is lawful to use that drug in that country. This approach is based on the premise that the designated countries have good regulatory systems, including supervision of manufacturing practices. The requirement that at the time of exportation it was lawful to use the drug in the country of export can give rise to problems, especially in respect of drugs meant for diseases endemic in the country of import but not in the country of export, e.g., drugs for tropical diseases manufactured in non-tropical countries.

32. In operating a registration system certain guidelines need to be formulated to enable applications to be systematically as well as speedily processed. Many countries have devised administrative procedures for this purpose, a few legislative provisions. In Spain the registration system is structured on a threefold classification basis. The drugs in respect of which applications for registration are considered are divided into three groups. In group 1 are drugs where no speciality having similar therapeutic indications has been registered, or the mode of action or chemical composition of the speciality is completely different from that of specialities already licensed and the speciality represents a far-reaching therapeutic innovation. In group 2 are drugs that by reason of the composition, dosage form, or combination of or new therapeutic indications for known active principles represent a substantial therapeutic advance on similar existing specialities. Group 3 consists of drugs that do not fall within group 1 or group 2. Priority is given to drugs in group 1. For drugs in this group and in group 2 there is no annual quota or limit on the number of applications to be approved. Drugs in group 3 are subject to a quota. However, applications proposing a price significantly lower than that of similar specialities already on the market are accorded priority.

33. The period for which a drug is registered varies from country to country. Some countries have a mandatory period within which the registered product should be marketed. Renewal of the registration can also be conditional on the product being marketed. Fees levied for the first registration as well as for renewals can be the same for all drugs or vary with the category of the drugs. In Kenya, for instance, the fee for drugs manufactured locally is one-fifth of that applicable to drugs manufactured abroad. Sometimes such fees are utilized to cover the whole or part of the expenses of the regulatory agency.

34. In registering a drug various conditions can be imposed, if the legislative instrument in terms of which registration is effected provides for the imposition of such conditions. For instance, there can be a mandatory requirement to report side-effects, withdrawal of the product in other countries, etc. Changes in the package insert and text of the advertisement can be subject to prior screening. Changes in trade marks can
be accepted subject to the registration being amended or an altogether new application being made.

35. Several countries have specified different grounds on which the registration of a drug or the licence for marketing can be withdrawn. In Kenya (59) a certificate can be suspended or revoked if the premises on which, or on part of which, drugs are manufactured, assembled, or stored by or on behalf of the holder of the certificate of registration are unsuitable for the manufacturing, assembling, or storage of drugs, or if new information has been discovered by the Pharmacy and Poisons Board showing that the drug is unsafe or dangerous. Other grounds are procurement of the registration by fraud or misrepresentation, violation of the conditions subject to which the drug was registered, public interest, contraventions of the provisions of the legislation, and misleading or exaggerated advertising.

36. In Saudi Arabia (60) registration of a new drug can be cancelled if it is not imported within one year following registration or if it is unobtainable from the agent for a six-month period. It can also be cancelled if the technical committees of the Ministry of Health or WHO have reported that it is toxic, or if it has been prohibited in the country of origin. In Sweden (61) one of the grounds for the cancellation of the registration of a drug is that it has been the subject of publicity containing erroneous, greatly exaggerated, or fallacious information as to its action or its properties.

37. One of the reasons often advanced against registration is delay in processing applications. In Mali the National Commission on Marketing Licences is under a legal duty (62) to finalize its view on an application within four months. The time-limit is suspended if the manufacturer is requested by the Commission to supply additional information or carry out additional tests. If the Commission is inclined to reject an application, the applicant must be notified so that within a period of one month he may make further representations. Such representations, if any, must be considered by the Commission when it transmits its views to the Minister responsible for Public Health. The Minister is required to substantiate any decision to reject an application.

Marketing outlets and the sale of drugs

38. Countries differ widely in the requirements relating to who can prescribe and dispense drugs and under what conditions. In some countries these matters are governed not by laws and regulations on pharmaceuticals but by those relating to professionals such as medical practitioners and pharmacists. Since this review is primarily concerned with the marketing of drugs, no attempt is made to review in detail the different categories of prescribers.

39. In relation to the right to prescribe and dispense, national laws fall into two broad categories, the first permitting prescribers to dispense drugs as well, the second prohibiting prescribers from dispensing drugs, pharmacists being the sole persons authorized to dispense prescriptions issued by prescribers. However, even within those two broad categories
there are various conditions, requirements, and limitations. For instance, countries that permit medical practitioners to dispense drugs may have a requirement that such practitioners should employ a qualified pharmacist for the purpose. In addition to requirements and conditions there are limitations, as in Rwanda, where private practitioners are authorized to keep and supply drugs only if there is no pharmacy open to the public within a radius of 10 km.

40. Besides specifying who can exercise the right to dispense, national laws and regulations deal with a variety of aspects such as the establishment and location of outlets, storage requirements, and conditions of sale. Apart from the requirement that to establish a pharmacy a licence must be obtained, some countries have requirements regarding the premises, the qualifications and experience of the persons to be employed at pharmacies, etc. In addition to pharmacies some countries have authorized the establishment of other outlets such as medicament stores and drug stores. In Bahrain legislation has empowered the Minister to suspend the further issue of licences for medicament stores as soon as there are a sufficient number of pharmacies in the country.

41. To ensure that priority is accorded to the establishment of pharmacies, some countries, especially in the developing world, have assigned this responsibility to a specific institutional mechanism. In Algeria the legislation in terms of which the central pharmacy was established requires it to establish pharmaceutical agencies in all communes to give patients access to basic pharmaceutical products. The Ethiopian Pharmaceuticals and Medical Supplies Corporation is required by legislation to organize and operate pharmacies and medicament stores. In Bahrain legislation has empowered the Minister of Health to decide on the number of pharmaceutical centres that may operate in each town or village. In Benin the National Pharmaceutical Office is required to establish a supply point (depot) in each provincial capital to facilitate the procurement of drugs by certain institutions and sales outlets such as private pharmacies.

42. Besides a statutory responsibility to promote the establishment of pharmacies, legislation in some countries provides for regulation of the location of pharmacies and distribution outlets so as to ensure a fair geographical distribution. In Senegal a decree in 1981 set out the criteria for the establishment and distribution of pharmaceutical dispensaries. While each regional or departmental administrative centre and each commune must have a pharmaceutical dispensary irrespective of the population it serves, no dispensary can be established in the Cape Verde region (the region surrounding Dakar) unless the minimum number of inhabitants to be served is 15 000. The minimum population target in respect of other regions is 30 000 inhabitants. These criteria come up for revision every five years.

43. Some countries have requirements additional to the general requirement that drugs must be stored in places or premises that are physically and hygienically suitable for the purpose. In Bahrain pharmaceutical centres must be air-conditioned. Such requirements, of course, depend on the country's infrastructure and resources.
44. Marketing outlets are of different kinds. Some engage in wholesale as well as retail trade. Others cater only for individual consumers and medical practitioners who may need certain quantities of drugs in connection with their practice. Licensing systems and record systems generally differ depending on the nature of the trade carried out. Within the retail trade too there is a distinction depending on whether the drugs can be dispensed with or without a prescription. Depending on whether drugs are subject to a prescription system or not, different marketing and record systems operate. In many countries the marketing of OTC drugs is relatively free from controls. Depending on the nature of the health infrastructure and the health manpower situation, many countries, especially in the developing world, permit a large variety of personnel to prescribe as well as dispense OTC drugs. Such drugs are often subject to special advertising and labelling requirements.

45. The sale of drugs is regulated basically in two broad ways, by total prohibition and by the operation of various conditions. The sale of a drug can be totally prohibited by listing the drug in the main legislative text or in the regulations, as in the case of thalidomide in Canada(71) and Sri Lanka, (72) or by not issuing a licence for its manufacture or importation where a licence is a condition precedent to its manufacture or import. Enforcement is facilitated by listing in the legislative text or in the regulations the drugs that cannot be sold, the availability of such drugs in the market then being prima facie proof of a contravention of the law. Provision is often made to enable the list to be updated whenever the sale of a drug has to be prohibited. Information on the adverse reactions of drugs disseminated by WHO and various organizations and countries may require that such lists should be reconsidered from time to time. Licensing authorities need such information to make timely and well-informed decisions on whether the manufacture, import, or sale of a particular drug should be permitted or not.

46. The sale of certain drugs and certain categories of drugs (e.g. antibiotics and psychotropic substances) is regulated by law by way of the requirement of a prescription. Prescription requirements vary from country to country. In Norway(73) there is a requirement that a register should be maintained in pharmacies for prescriptions given by telephone. The register must be preserved for a period of three years from the date of the last entry. In Mauritius(74) no person can dispense a prescription unless he recognizes the signature of the prescriber and is satisfied that it is genuine. In Trinidad and Tobago(75) prescriptions in respect of certain scheduled drugs cannot be dispensed unless the signature of the prescriber is known to the dispenser or, if not known, he has first certified it. Several countries such as Uganda(76) and Trinidad and Tobago(77) require prescriptions to be preserved for a two-year period.

47. Some countries have built into their legislation safeguards additional to the requirement of a prescription. In Uganda(78) the Code of Ethics for the Practice of Pharmacy stipulates that drugs should not be supplied to any person when there is reason to believe that they are destined for illicit channels or will be misused. In Zimbabwe(79) certain restricted drugs (psychotropic substances) can be supplied only from the pharmacies of
the hospitals listed in the regulations, and the prescription issued by any medical practitioner for a restricted drug must be countersigned by the medical superintendent or his deputy at such hospital. In Malta, no medical practitioner can issue a prescription for any preparation consisting of certain substances such as amphetamines or methaqualone unless he has had the prior written authorization of the Superintendent of Public Health. Furthermore, the Superintendent has to be notified when such a prescription is dispensed.

48. The mode of sale has been regulated in some countries. In Uganda there is a prohibition on the supply of drugs by means of an automatic vending machine. Exemptions have been made in respect of the use of automatic or vending machines in hospitals, for instance in the State of Nebraska in the United States of America. Such exemptions are designed to facilitate access to certain categories of drugs when pharmacies are not open. However, such machines can generally be operated only by special cards or coded devices. In the Netherlands sales through self-service systems are prohibited. Belgium has prohibited the offer of gifts or benefits when pharmaceutical preparations are supplied. The solicitation or acceptance of such gifts is also prohibited.

49. National laws contain a variety of requirements regarding the maintenance of registers and other records regarding the sale of drugs. Laws generally contain a requirement that such registers and records must be made available for inspection if drug inspectors or other law enforcement personnel need them.

Advertising of drugs

50. The laws and regulations applicable to the advertising of drugs and the dissemination of information through the medium of advertising are generally different from those applicable to labels, package inserts, and warnings. This section considers the regulation of advertising only, though there are instances where identical provisions apply in respect of both advertising and labelling, package inserts, etc.

51. In many countries legislation on drugs contains provisions governing advertising. However, some countries, such as India and Malaysia, have enacted separate laws dealing specifically with the advertising of drugs. There are also countries such as Portugal where a general law on advertising also covers drugs.

52. Advertising restrictions fall into three broad categories: those applicable to specific drugs or categories of drugs; those of a general nature; and those in respect of certain audiences or target groups. Each of these categories needs to be dealt with separately, though there is a certain overlap.

53. With regard to the restrictions applicable to specific drugs or categories of drugs, many countries do not permit drugs available only on prescription to be advertised. According to a 1980 survey of about 50 countries, nearly 40 had a restriction of this nature. A few
countries permit such advertisements with prior approval. Some countries permit such advertisements if they are intended only for medical practitioners or appear only in medical journals. In Israel, registered new drug products cannot be marketed until the manufacturer has advertised the approved indications in a medical journal. Norway does not permit advertisements of unregistered specialities or of medicaments prepared in a pharmacy and not included in an approved formulary.

54. Restrictions of a general nature are generally those applicable to drugs in general and to drugs for specific diseases. In Pakistan no drug can be advertised in a manner that encourages self-medication or use to the extent that it endangers health. In Belgium the Higher Council of Public Health can specify the diseases or ailments in respect of which no drugs can be advertised.

55. With regard to restrictions in respect of target groups, in some countries prescription drugs cannot be advertised to the general public and medical practitioners alike, but in others advertisements meant for the latter are permitted. In the United Kingdom there is a requirement that before an advertisement is sent to a medical practitioner he should have, within the preceding 15 months, been sent a data sheet containing prescribed particulars. Among the required particulars are the name of the product, the presentation (description of appearance and pharmaceutical form), the uses, the dosage and administration, contraindications and warnings, pharmaceutical precautions (storage, etc.), the legal category, and package quantities.

56. The mode of advertising has been restricted in some countries. In Denmark drugs cannot be advertised in films, on radio or television, outdoors by means of signboards, posters, illuminated signs and the like, in vehicles used for transport, or in premises accessible to the public (other than the premises of pharmacies). The regulatory provisions in Singapore prohibit door-to-door advertising. In Thailand, there is a prohibition on advertising by song, by showing the suffering of a patient, by offering premiums or awarding lottery prizes, or in an impolite manner.

57. Several countries have established institutional mechanisms for screening advertisements. In Malaysia the Medicine Advertisement Board is headed by the Director-General of the Ministry of Health. In France the Commission for the Control of Advertising has over 20 members, including pharmacists from the industry and representatives of consumer organizations. In some countries there are statutory functionaries or institutional mechanisms with whom or which advertisements have to be registered prior to publication.

58. In some countries laws and regulations on advertising have special provisions. Three examples may be cited here to illustrate the range of matters that lend themselves to regulation. In Pakistan no person is entitled to spend more than 5% of his turnover on advertisements, sampling, or other promotional activities. In Guatemala advertising agencies are required to ensure that the drugs they have been requested to advertise
have been duly registered with the Directorate General of Health Services. In New Zealand, for the purpose of protecting the health of the public, the Director-General of Health can publish a statement relating to any matter contained or implied in an advertisement. Any statement so published is protected by qualified privilege—a legal defence in the event of an action based on such a statement.

Labelling, packaging, package inserts, and warnings

59. Requirements relating to labels and printed packaging materials vary from country to country. Different countries require different items of information to appear on either or both of them. The following list indicates the range of items from which different countries have specified those required to be set out in printed packaging materials or labels:

- Name of product (trade mark; approved name; generic name; international nonproprietary name)
- Dosage form (strength)
- Content of active ingredients (quantity/proportion of each)
- Inactive ingredients
- Indications and contraindications
- Directions for use
- Recommended dosage
- Whether for free sale or only on prescription
- Route of administration (or for external use)
- Warnings and cautions
- Storage precautions
- Type of packaging
- Contents of package (weight, volume, units)
- Name of manufacturer (or of local representative)
- Name of importer (and/or person responsible for marketing)
- Date of manufacture
- Expiry date (shelf-life)
- Price
60. Some countries require additional information. In Nepal the manufacturer must indicate on the label whether the drug is produced for the allopathic, homoeopathic, ayurvedic, or Unani system. The New Zealand Medicines Regulations of 1984 require labels of drugs available for sale without a medical prescription to contain certain items of information in a special panel on the label, the "CONSUMER INFORMATION PANEL". The information must include a statement of the purpose for which the drug is recommended. This panel has to be conspicuously placed in relation to other information included on the label and be clearly differentiated from all other promotional material or illustrations.

61. National requirements relating to labelling cover even such aspects as language, colour, and symbols. Some countries require that the labelling of imported drugs should be in the national or official language. Requirements for colours and symbols apply to a wide range of matters. In the United Kingdom labels of drugs for sale only in pharmacies are required to have a capital letter "P" in a rectangle containing no other matter. The container and package of prescription drugs must be labelled "POM" in capital letters within a rectangle. In Bahrain labels of different colours must be used depending on whether the medicament is for internal or external use. In Colombia the labels, containers, and packaging of drugs liable to cause dependence must have a purple stripe. In the Netherlands preparations intended for oral administration must carry a white label. For other methods of administration the upper part of the labels must have a pale blue strip bearing the words: "Do not swallow" or else a strip of coloured paper with the method of administration printed thereon.

62. Some countries have a system of screening labels. Screening takes place at various stages, when registration is under consideration or later, as in Poland, where the granting of a marketing licence is conditional on approval of the text of the labelling and of the printed information regarding the drug. Some laws provide for the inspection of labels when a drug is imported. In Guyana a drug with a label that does not conform to local labelling requirements is permitted to be imported for the limited purpose of relabelling, and if not properly relabelled within the stipulated time-limit must be exported. If the consignment is not so exported it is liable to be confiscated.

63. The variations in national approaches to labelling can be best illustrated by one or two national case studies selected at random. In Ecuador labels must be submitted for approval within three months of registration of the product. The label must indicate the name of the product, the pharmaceutical form, the net contents of the package, the qualitative and quantitative formulae, the active principles, the routes of administration, the batch number, the contraindications, the warnings, paediatric use (if appropriate), the storage temperature (if appropriate), whether a prescription is required, the name and address of the manufacturer, and the registration number.
manufacturer, the name of the pharmacist responsible for the preparation (if appropriate), the date of preparation and expiry date, and the registration number. If the packaging size is small only the name of the product, the name of the manufacturer, the batch number, the concentration of the active principle, the expiry date, and warnings, if any, need appear on the label. The Directorate General of Health may require warnings such as: "To be sold only on medical prescription", "May be habit-forming", etc., to appear on the label. In addition to other warnings, if any, the label of every OTC medicament must state that if the symptoms persist the physician should be consulted. The labels of medicaments intended for promotional purposes must state that they are samples not intended for sale. No drawings or figures suggestive of the therapeutic value of the product or inciting the public to use it are allowed to be printed on any label, packaging, or package insert. Names that suggest improper use or the presence of active principles that are in fact not present or that exaggerate the therapeutic properties of the product are not permitted. Official names using formulae that are not exactly those officially prescribed are also not permitted.

64. The Ecuadorian approach can be compared with that of Sri Lanka. Under the Cosmetics, Devices and Drugs Act there is no provision for prior screening of labels. The control mechanisms are based on negative stipulations, contraventions of which have penal consequences. The term "label" has been defined in the Act as any tag, brand, mark, pictorial or other descriptive matter, written, printed, stencilled, marked, embossed, impressed on, or attached to a container of a drug. In terms of the Act there is a prohibition on any person labelling any drug in a manner that is false, misleading, deceptive, or likely to create an erroneous impression regarding its character, value, potency, quality, composition, merit, or safety. For purposes of penal liability this prohibition is deemed to apply to a drug that is not labelled as required by regulations made under the Act. Where a standard has been prescribed for any drug, no person is entitled to label any drug that does not conform to such standard in such a manner that it is likely to be mistaken for the drug for which a standard has been prescribed. Where a standard has not been prescribed for any drug but a standard for that drug is contained in the International Pharmacopoeia, the British Pharmacopoeia, the Pharmacopoeia of the United States of America, the British Pharmaceutical Codex, the British Veterinary Codex, the Japanese Pharmacopoeia, or the European Pharmacopoeia, no person is entitled to label any drug that does not conform to the standard contained in those publications in such a manner that it is likely to be mistaken for the drug for which the standard is contained in those publications. If a standard has not been prescribed for any drug or a standard for that drug is not contained in any of the pharmacopoeias listed above, no person is entitled to sell, offer for sale, or distribute such a drug: (a) unless it is in conformity with the standard set out in the label accompanying the drug, or (b) in such a manner that the drug is likely to be mistaken for a drug for which a standard has been prescribed or for which a standard is contained in any of the above pharmacopoeias.

65. The legal provisions on packaging in most countries deal with labelling requirements. Argentine legislation requires laboratories to produce medicaments not only in packages intended for direct sale to the public but
also in economic packages, the contents and packaging of which make possible the sale by pharmacies of the number of individual units (tablets, coated tablets, capsules, pills, etc.) prescribed by the physician by means of simple subdivision of the contents.

66. In certain countries package inserts are compulsory. In respect of specified categories of drugs it is sometimes mandatory that the package inserts should be addressed to both prescribers and patients. Some countries require separate leaflets. Inserts in OTC drugs are normally required to be addressed only to patients. Package inserts generally cover most of the items listed above. Where some of the information has appeared on the label the inserts may contain more elaborate or detailed information, especially in relation to contraindications and warnings. Some countries require advance clearance of package inserts as part of the registration procedure or independently. In Italy there is a requirement for a translation of the package inserts or instructions used in the country where the drug was first manufactured. Failure to comply with this requirement entails the withdrawal of registration.

67. In relation to requirements for product monographs, package inserts, and other information to health professionals, a 1968 WHO survey on pharmaceutical advertising noted that

"... it is quite rare to find, in the legislation, any precise or detailed specification of the requirements applicable to medical advertising, the greater part of the legislation, as in the case of the countries dealt with in this survey, being concerned with advertising to the public." (113)

68. A monograph has been defined in some countries, such as Chile, as the technical and scientific description of a product. The monograph must be submitted when application is made for the registration of the product. It is a form of record to which reference can be made for information on the formula and the properties of the product, etc. Some countries require scientific and technical information to be furnished to medical practitioners. The 1984 Crown Order of Belgium, dealing with information and advertising concerning medicaments, requires that all medicaments be provided with two information notices, one scientific for persons entitled to prescribe or supply medicaments, the other for the public, containing such information as is considered necessary for it. It may be noted that in Belgium only persons entitled to practise as physicians, pharmacists, or veterinarians are eligible to be licensed as persons responsible for pharmaceutical information. In Denmark the National Board of Health may require manufacturers and importers to circulate alterations and additions to the information contained in their advertisements addressed to physicians, pharmacists, etc. The form and content of such alterations and additions can be prescribed by the Board. A 1982 Council of Europe resolution on information concerning medicines to persons qualified to prescribe or supply them states that the information should include particulars on the legal provisions governing the prescribing and supply of the medicine. Under the heading of inducements, there is a prohibition on giving persons qualified to prescribe or supply...
medicines rewards, pecuniary advantages, or other inducements, with the exception of objects of negligible intrinsic value. However, this does not affect normal trade discounts. A 1984 Council of Europe resolution on packaging leaflets requires a distinction to be made between the information supplied with medicines available only on a medical prescription and that supplied with medicines that can be sold without a prescription. The distinction is reflected in the nature and scope of the information to be furnished.

69. Under some national laws there is a requirement that various cautionary phrases should appear on labels and in advertisements and package inserts. In some countries the requirements apply to most drugs. "Keep out of the reach of children", for instance, is a warning that most countries require in respect of many drugs. In addition, special warnings are required for certain drugs. There are drugs that affect specific categories of patients such as pregnant women and patients with cardiac conditions. There are also drugs that affect psychomotor skills such as driving or working with machines. In respect of such drugs many countries require that the patient be warned in advance. In Brazil labels of all new drugs in use for less than five years must carry a warning that in the case of unforeseen suspected adverse reactions the prescribing physician must be notified.

Drug sales representatives and samples of drugs

70. The primary task of a drug sales representative, known also in some countries as medical representative, pharmaceutical consultant, or medical detailman, is to promote the sales of pharmaceutical products manufactured or imported by the company that employs him. No global statistics are available as yet of the ratio of drug sales representatives to the number of doctors or to the range of products available for marketing. The scope for the introduction of new products into the market, the availability of opportunities for advertising and other promotional activities, etc. are factors that determine the number of drug sales representatives employed by a particular company or group of companies.

71. Drug sales representatives often give samples of drugs they are promoting to doctors as well as to the health administrators who decide which drugs are to be ordered for a hospital or other institution.

72. National legal controls and voluntary codes in relation to drug sales representatives and the distribution of samples may relate to one or the other or to both. Only a few countries around the world have regulatory measures relating to drug sales representatives and the distribution of samples of drugs. These measures can be best considered in relation to national examples under the headings of qualifications for employment as drug sales representatives, permissible activities and circumstances under which samples can be distributed, and mandatory duties of drug sales representatives.
(a) **Qualifications**

73. A 1976 law of the Federal Republic of Germany\(^{(122)}\) on medicaments includes provisions on pharmaceutical advisers. In terms of this law pharmaceutical dealers can appoint only such persons as have the requisite specialized knowledge. Persons who are deemed to have such specialized knowledge are: pharmacists or persons holding a certificate certifying that they have passed an examination after completing university studies in pharmacy, chemistry, biology, medicine, or veterinary medicine; pharmacy assistants and persons who have completed a course of training as technical assistants in pharmacy, chemistry, biology, medicine, or veterinary science; and persons whose training or further training has been recognized as sufficient by statutory ordinance. An ordinance enacted in 1978\(^{(123)}\) provided that the competent authority should organize or arrange for the organization of courses of further training leading to the examination of pharmaceutical consultants. The examination is designed to determine whether candidates have the necessary knowledge, skills, and experience to provide members of the health professions with comprehensive and critical technical information concerning medicaments, and to record and make available to their employer reports from the members of the health professions regarding side effects, contraindications, and other hazards associated with medicaments. The course of training for pharmaceutical consultants lasts for 1000 hours and is spread over a period of 12 months.

(b) **Permissible activities**

74. On the general premise that what is not expressly prohibited by law is permissible, drug sales representatives engage in promotional and educational activities, including giving samples. A few countries\(^{(124)}\) such as Czechoslovakia, Hungary, and Yugoslavia have expressly prohibited the distribution of samples. Some countries such as Argentina\(^{(125)}\) do not permit samples of certain categories of drugs, e.g. psychotropic drugs, to be distributed. In Mexico it is an offence to keep samples in pharmacies.\(^{(126)}\) In Morocco samples can be given only on request.\(^{(127)}\)

Under the French Public Health Code\(^{(128)}\) samples cannot be given within premises that are accessible to the public during medical and pharmaceutical congresses.

75. Samples of drugs are primarily intended to enable medical practitioners to become familiar with them. National laws, therefore, generally require that labels of packets containing samples should indicate that they are not intended for sale. There are restrictions in some countries on the size of sample packages, the quantity of the drug, and the frequency of the distribution of samples (e.g. a specified number of years\(^{(129)}\) from the first date of marketing of the drug and thereafter only on request). Since samples are intended to familiarize medical practitioners with the particular drug which is promoted, sample packages must comply with the usual labelling requirements (including those relating to package inserts).

76. In Singapore regulations\(^{(130)}\) have been made under the Medicines Act, 1975,\(^{(131)}\) to regulate drug sales promotion. For the purpose of the regulations, sales promotion means any sales campaign (including
door-to-door sales), exhibition, competition, or other activity for the purpose of introducing, publicizing, or promoting the sale or use of any medical product. In terms of the regulations no one can carry out sales promotion without first obtaining a permit from the licensing authority. Licences are valid for a three-year period and may be granted subject to various terms and conditions. In conducting any sales promotion, gifts or prizes cannot be offered.

(c) Mandatory duties of drug sales representatives

77. In the Federal Republic of Germany(132) pharmaceutical advisers are required to keep a record of the recipients of samples and the nature, amount, and date of their supply. Such records must be presented to the competent authority on request.

78. The Pharmaceuticals and Poisons Act,(133) 1978, of the United Republic of Tanzania provides that the competent Minister, after consultation with the Pharmacy Board, should make regulations regarding the activities of medical representatives. Regulations(134) made under the Act require that if any pharmaceuticals or pharmaceutical products supplied contain certain specified poisons, the medical representative must, within 24 hours of having so supplied them, enter in a book details such as the name and quantity of the poison supplied and the person to whom it was supplied.

79. The activities of drug sales representatives have not been viewed solely as a matter of promotional interest to drug companies. In the Federal Republic of Germany legislation(135) requires them to record and forward in writing to their employers reports from members of the health professions concerning side effects and contraindications or other risks due to medicaments.

(d) Regulation through codes of conduct

80. Besides legislative interventions of the various types enumerated above, the pharmaceutical industry in certain countries has formulated its own rules relating to drug sales representatives. In Sweden the rules(136) have been widely publicized and have come to be recognized officially as the applicable norms. According to these rules medical representatives must have received a basic medical education in accordance with the standards laid down by the Association of the Swedish Pharmaceutical Industry and the Association of Representatives of Foreign Pharmaceutical Industries and should have been specially trained for this work by the pharmaceutical companies employing them. Examinations are conducted by a five-member training council consisting of three physicians and two representatives of the pharmaceutical industry. Field training for six months under the supervision of the employing firm is obligatory. As well as rules relating to qualifications for medical representatives, there are rules dealing with ethical conduct. Drug information conveyed by the medical representative must be based on factual data that can be assumed to be of value to the doctors concerned. Visits of a reminder character are not allowed. The representative must ascertain from the doctor his
experience with the drug and his opinion regarding its use and transmit this information to the pharmaceutical company.

**Brand names, generic names, and generic drugs**

81. The question of generic versus brand names has loomed large in recent discussions in relation to a variety of issues such as the cost of medicines to the consumer, the transfer of technology, the capacity of national infrastructures to verify the quality of drugs, and incentives to drug innovation. Some of those issues need to be considered in the context of patent and trademark legislation. However, this review is concerned primarily with the extent to which national drug laws treat generic names and generic drugs rather than with the broad framework of intellectual property laws and industrial policies.

82. A generic name usually contains an informative stem reflecting the pharmacological class to which the drug belongs. Generic drugs are products that are marketed under their nonproprietary or approved names rather than their proprietary or brand names. A generic name, unlike a brand or trade name, being nonproprietary in character, cannot be the subject of legal protection in favour of individual persons or corporate bodies. Generic drugs or drugs marketed under their generic names are usually cheaper.

83. Legislative measures to promote generic nomenclature are of relatively recent origin. The most widely cited example is the Drugs (Generic Names) Act, 1972, of Pakistan, which banned any drug prescribed, dispensed, sold, or distributed under any brand, patent, or proprietary name. The scientific or official names — the generic names — of the drugs were set out in the National Formulary. The Act, however, had a relatively short life-span, mainly because of the infiltration of drugs of doubtful quality into the market.

84. Legislative trends in relation to brand names and generic names cover requirements relating to the use of names for registration and in advertisements and labels, and generic substitution by pharmacists when prescriptions are dispensed. In relation to the former, a few national examples will suffice to illustrate the range of national approaches. Pakistan generally requires single-ingredient drugs to be registered by their generic names, compound drugs by their proprietary names. Norway requires the generic names to be included in drug advertisements for the general public. Greek legislation requires the generic names of the active principles of all pharmaceutical specialities to appear on the inner and outer packaging.

85. With regard to generic substitution, the substitution of a product, especially a cheaper one with the same active ingredients, for the product prescribed by the medical practitioner has received legislative sanction in only a few countries. In the developing world, Barbados has a law that authorizes the pharmacist, unless the prescriber has otherwise specifically directed, to select and dispense an interchangeable product that is cheaper than what has been prescribed; no liability attaches to the
pharmacist or to the person prescribing the drug by reason only of the fact that the pharmacist has dispensed such a product. The pharmacist has to exercise his discretion as to whether a cheaper substitute should be dispensed or not. In the developed world, generic substitution has been the subject of legislation in a number of states in the United States of America. Since generic substitution or drug product selection, as the process is sometimes called, is regulated not by federal legislation but by state legislation, the United States provides a range of approaches containing different modalities, conditions, and requirements. Two examples suffice to demonstrate the legislative strategies available. In the State of Maryland, the law authorizes the pharmacist to dispense a different cheaper drug product of the same dosage and strength as the brand-name drug product prescribed. The different product must be one that is generically equivalent. The pharmacist is required to pass on any savings in cost to the consumer. In the State of Massachusetts every prescription must contain two different lines for the practitioner's signature. A signature on one line means that interchange is permitted, on the other that the product should be dispensed as directed. A prescription becomes invalid if the practitioner has not affixed his signature on one of the two designated lines. If the practitioner has indicated his preference for interchanging, the pharmacist is required to dispense a less expensive reasonably available interchangeable drug product as listed in the most current formulary or supplement thereof. The fact of interchange has to be reflected on the label. In the event of noncompliance by a pharmacist the drug purchaser is entitled to lodge a complaint with the secretary of the executive office of consumer affairs, who will refer the complaint to the board of registration in pharmacy for appropriate action.

**Pricing of drugs**

86. In most countries prices of drugs are regulated when there is a system to regulate the prices of other products as well. Price fixation and the monitoring of price changes of drugs therefore need to be viewed in the context of national trade and consumer policies. Decisions as to whether there should be price control and, if so, the products to be controlled and the nature of the controls are often based on such policies. The mechanics of controlling the prices of drugs are sometimes to be found in statutes dealing with price control in general and not with pharmaceuticals in particular.

87. Different countries have different authorities or officials vested with functions relating to price control or the monitoring of the prices, or both. In Denmark there is a Monopolies Control Authority with jurisdiction over drugs as well as other products. On the other hand, in Nepal the jurisdiction of the Department of Drugs Administration is confined to drugs.

88. Drug prices are relevant as a criterion in the registration of drugs, in the fixation of the sale price, in the regulation of price increases after registration, and in labelling and advertising requirements.
89. In some countries the price of the drug is one of the criteria on which registration can be refused. According to a 1980 survey of registration requirements in approximately 50 countries, it was a criterion in Argentina, Egypt, Finland, Hungary, India, Mexico, Morocco, Pakistan, Spain, and Tunisia. In Austria, Greece, the Islamic Republic of Iran, Peru, Portugal, Switzerland, and Turkey, if the price is excessive registration is not granted. In some of those countries as well as in a few others the price of the drug in the country of export must be furnished when an application is made for its registration.

90. The price is sometimes determined in relation to both retail and wholesale sales, and different minimum and maximum price scales are sometimes applied. Price fixation involves the consideration of various factors and items of information, as is exemplified by Norwegian legislation, in terms of which no pharmaceutical speciality can be placed on the market in Norway unless its price has been approved. Such approval is conditional on the price not being exaggerated in relation to the actual value of the product, account being taken of the price of equivalent preparations manufactured by other establishments and information supplied on production costs, etc.

91. Some countries permit price changes to be effected after registration only with prior approval. In Austria prior approval is necessary, while in other countries such as Bolivia the authorities must be notified of changes in price.

92. The requirement that the price of the product must be stated on the label and in advertisements, etc. is often to be found in legislation dealing with prices or consumer protection. In countries such as Lebanon and the German Democratic Republic the relevant pharmaceutical laws contain a requirement that the selling price must be indicated on the label.

93. During the past two decades there has been a great deal of discussion regarding the factors that have resulted in the high price of drugs that perhaps could otherwise be supplied at lower prices. In this context, there is a ceiling on promotional expenditure in Pakistan. The law does not permit any person to spend more than 5% of his turnover on drug advertisements, sampling, or other promotional activities.

94. Price fixation has often taken place only with regard to drugs. Recent Bangladeshi legislation, however, has empowered the Government to determine the maximum price at which any pharmaceutical raw material may be imported or sold.

Sponsorship of medical symposia

95. The sponsorship of medical symposia, congresses, seminars, and similar activities by pharmaceutical companies or associations representative of the interests of such companies has been the subject of regulation in a few countries. They have adopted different approaches. An Italian ministerial decree requires scientific congresses and conferences on drugs to
comply with strictly technical criteria; the topics discussed at such congresses and conferences must be free from promotional or advertising interest, and pharmaceutical companies and other institutions responsible for organizing such meetings must submit in advance to the Ministry of Health details concerning the congresses and conferences. A recent Greek law\(^{(157)}\) has made the organization and financing of congresses, seminars, and other means of disseminating information by pharmaceutical manufacturers or commercial undertakings or by advertising agencies or other service companies subject to the prior approval of the National Organization for Medicaments. Approval may be granted subject to certain conditions. In Spain cash contributions for purely scientific activities such as conferences, lectures, talks, film shows, and publications are subject to certain conditions.\(^{(158)}\) Under the French Public Health Code\(^{(159)}\) the supply of samples is prohibited within premises that are accessible to the public during medical and pharmaceutical congresses.

Financial interests

96. The 1983 Pharmacy Act\(^{(160)}\) of Mauritius has a provision dealing with what is described as "illegal arrangements". In terms of the Act no manufacturer, licensee of a wholesale pharmacy, or pharmacist can enter into any arrangement with an authorized person (a medical practitioner, dentist, or veterinary surgeon) under which such person is to receive any gain or benefit in return for the custom he brings to the manufacturer, licensee of the wholesale pharmacy, or pharmacist. Furthermore, no authorized person can have any share, participation, or other financial interest in the manufacture or sale, whether wholesale or retail, of pharmaceutical products.

Enforcement of laws and regulations on marketing

97. The responsibility for enforcing pharmaceutical legislation is generally entrusted to specifically designated personnel such as inspectors, who are authorized to inspect manufacturing, processing, and packaging establishments and wholesale and retail outlets. The inspection of books and records and the taking of samples are some of the important functions they perform. Interference with the exercise of the powers of an inspector or obstructing him in the course of duties are generally the subject of penal sanctions.

98. Facilities for the analysis of drugs provide one of the best forms of ensuring the quality and safety of the drugs available in the market. Analysts have to be specifically designated and their functions and powers clearly set out. Legal provision permitting their reports and certificates to be accepted as \textit{prima facie} evidence of the matters stated therein is generally sufficient to dispense analysts from being summoned to court to give oral testimony on matters of routine. Their oral testimony is, however, required in the event of any of their findings being challenged or if further clarification is needed on the methods followed for the analysis of drugs or the rationale underlying their findings or conclusions.
99. The establishment of the administrative infrastructure for enforcement has taken different forms. In Uganda, legislation provides for the establishment of a Drugs Bureau under the Office of the Inspector of Drugs. The Bureau maintains a register of all registered drugs as well as a list of all toxic substances, their composition, toxicity, and antidotes. Information regarding drugs is transmitted to medical practitioners. In Pakistan, legislation requires provincial governments to set up provincial quality control boards and provincial drug-testing laboratories.

100. Besides general provisions relating to inspection and the analysis of samples, some countries have specific legal provisions. In the Australian state of Victoria, there is a statutory requirement that every municipal council must submit for analysis during each year not less than three samples of drugs for each thousand persons of the population of the municipality.

101. Laboratories have many roles, ranging from the establishment of standards to the examination of samples. They have been established both by administrative and by legal measures. When laboratories are the subject-matter of legislation it is usual to assign specific statutory duties to be performed by them and to specify in the statute the powers they can exercise. The Medicaments Laboratory of Finland has been legally empowered to obtain samples, without charge, from manufacturers, importers, suppliers, vendors, and other persons dealing in drugs.

102. To facilitate monitoring the movement of drugs, countries require various kinds of recording systems to be maintained. In Chile there is a requirement that each batch or series of a pharmaceutical product must have a code or key permitting its identification at any stage in its production, storage, distribution, or marketing. The key must be registered with the Public Health Institute and appear on the labels and boxes or wrappings of each unit of the finished pharmaceutical product. In the Philippines, complete records must be maintained of the distribution of each batch of drugs in a manner that will facilitate its recall if the need arises. Records must be maintained for a two-year period. The name and address of the consignee, the date and quantity sold, and the lot or control number identifying the batch sold must be included in the records.

POST-MARKETING SURVEILLANCE

103. The view that drugs, by their very nature, need to be constantly monitored even after they have entered the market has now gained wide currency; more and more countries now accord priority to the establishment of appropriate procedures for post-marketing surveillance. For the effective operation of a post-marketing surveillance system there are two basic requirements, namely, procedures to obtain information on defective drugs and procedures to take appropriate action in respect of such defective drugs.
104. National approaches towards obtaining information on defective drugs are two. One is by legislation to require manufacturers, physicians, and other personnel (e.g. drug sales representatives) to notify the competent health authorities regarding defective drugs. The other is to obtain such information voluntarily.

105. A variety of different measures can be taken when a defective drug has been identified in the market. Among them are: recall of the drug from the market; prohibition of further sales; suspension or cancellation of the registration and marketing licence; destruction of defective stocks; warnings to pharmacists, physicians, and consumers; further investigation; legal action against those responsible for contravening laws and regulations; and inspection of production and quality control facilities.

106. The national approaches can be illustrated by way of a few examples. In Yugoslavia, health organizations using approved medicaments must notify the competent federal administrative agency of any adverse side-effects occurring in clinical practice that are not indicated on the label or in the package insert. The agency is required to take appropriate action on receipt of information of adverse side-effects detected in the country or elsewhere. Under the compulsory notification system in Austria, physicians, pharmacists, and persons engaged in trade are obliged to transmit to the Federal Ministry of Health and Environmental Protection information in relation to the safety of medicaments, including their abuse potential. In Italy, pharmaceutical companies that manufacture or market drugs are required to submit periodic reports concerning toxic or other side-effects associated with their drugs that have come to their knowledge. In New Zealand, a fine of $1000 can be imposed on an importer or manufacturer who, having reason to believe that any substantial untoward effects have arisen from the use of the medicine, whether in New Zealand or elsewhere, fails to notify the Director-General of Health of the nature of those effects and the circumstances in which they have arisen. Under the legislation the licence of a licensee who is convicted of an offence can be cancelled. In Guyana, there is a requirement that, when a manufacturer receives any report of any unexpected side-effect, injury, toxicity, or sensitivity reaction associated with clinical use, studies, investigations, and tests respecting a drug manufactured in Guyana, he should immediately inform the Government Analyst. In the case of new drugs (used in Guyana after 1 January 1977) the duty to inform is not only incumbent on the manufacturer but also on any person who receives such a report. In Nepal legislation provides for the recall of drugs that are not safe, effective, or of the requisite standard. Furthermore, in the event of death or injury caused to any person by such drugs the manufacturer is liable to pay compensation to the successor of the deceased person or to the person who has suffered injury. In most countries the civil or criminal law or both provide various forms of remedies to an aggrieved patient.

107. Several countries have established separate institutional mechanisms for drug monitoring. Two of the more recent examples may be noted here to illustrate such mechanisms. In 1982 France established a National
Commission on Drug Monitoring, (173) whose functions are: (a) to compile and evaluate information on the unexpected or toxic effects of medicaments subsequent to the issue of the marketing authorization; (b) to advise the Minister of Health on the measures to be taken in order to stop incidents and accidents found to be associated with the use of a medicament or the simultaneous use of several medicaments; and (c) to propose to the Minister such investigations and studies as it considers of value in conducting drug monitoring. The legislation also provided for the establishment of regional centres to collect information from hospitals, physicians, pharmacists, etc. and to transmit them to the Commission.

108. In 1983 Greece established a National Organization for Medicaments with provision for the establishment of an adverse reactions committee. (174) The committee has the responsibility of collecting, processing, evaluating, and registering all data and information concerning indications, contraindications, adverse reactions, precautions in use, and the interaction of pharmaceutical substances or combinations of them.
REFERENCES

1. IDHL, 11: 4-56 (1960).


3. For a review of national good manufacturing practices in relation to aspects such as organization and personnel, buildings and facilities, equipment, control of components, drug product containers, and closures, production and process controls, packaging and labelling control, holding and distribution, laboratory controls, records and reports, returned and salvaged drug products, quality audits and contract manufacture, see Anisfed, M. H. & Anisfed, E. R., ed. International G.M.P.'s. Illinois, Interpharm Press, 1979. See also Good manufacturing practices in the pharmaceutical industry, Zurich, IPPMA, 1972 and Legal and practical requirements for the registration of drugs (medicinal products) for human use, Zurich, IPPMA, 1980.

4. World Health Assembly resolution WHA28.65.

5. It is of significance that as at present 110 out of the 164 WHO Member States have agreed to participate in the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce (resolution WHA28.65). Exporting countries issuing certificates have to certify that (a) the manufacturing plant in which the product is produced is subject to inspection at suitable intervals, and (b) the manufacturer conforms to requirements for good practices in the manufacture and quality control, as recommended by WHO. See also the Convention for the Mutual Recognition of Inspections in respect of the Manufacture of Pharmaceutical Products (also commonly referred to as the Pharmaceutical Inspection Convention).

6. While private individuals and corporate bodies wishing to import drugs are usually required to obtain an import licence covering the drugs to be imported, in some countries the right to import drugs is vested in an agency or authority to the exclusion of other importers unless specially authorized by such agency or authority. Examples of such import monopolies are the Algerian Central Pharmacy (Ordinance No. 69-14 of 25 March 1969 establishing rights of importation for pharmaceutical products (IDHL, 21: 667 (1970); Ordinance No. 76-79 of 23 October 1976 promulgating the Public Health Code (IDHL, 29: 261 (1978); and Decree No. 82-161 of 24 April 1982 amending Decree No. 77-6 of 23 January 1977 approving the statutes of the socialist undertaking known as the Algerian Central Pharmacy (IDHL, 35: 108 (1984)); and the Norwegian Medical Supplies Centre in Norway (Crown Decision of 19 February 1965 embodying provisions as to the powers granted solely to the Norwegian Medical Supplies Centre and its right to engage in trade in pharmaceutical products and poisons (IDHL, 17: 138) (1966).
7. See page 8, Registration of Drugs. Countries differ in their registration requirements. Generally, it is a requirement that the drug should be registered in both the importing country and the exporting country. Importing countries that do not have a registration system, however, normally consider it adequate that the drug is registered in the country of export or, as in some cases, at least in a designated country or countries.


10. World Health Assembly resolution WHA28.65.


12. It is of interest to note here that one of the statutory functions of the recently established Medicines Board of the Gambia is to advise the competent Minister on the use of essential medicinal products at different levels by specified categories of personnel in the public health care system (Medicines Act, 1984).


19. Development and implementation of drug formularies. Washington, DC, Pan American Health Organization, 1984. This publication deals with the mechanics of adopting formularies and updating them, and offers some useful suggestions on evaluating their impact and identifying potential pitfalls. It concludes with the observation that the formulary, as the cornerstone of the pharmaceutical logistics system, must be supported and reinforced by realistic purchase estimates, prudent procurement policies, adequate quality control, efficient inventory control, warehousing, distribution, and drug utilization review, and patient education.

20. Ibid., p. 3.


23. Ibid., section 6.


28. Food and Drugs Act.

29. Federal Food, Drug, and Cosmetic Act, as above.


32. Decree-Law No. 26 of 1975 regulating the profession of pharmacy and pharmaceutical centres. IDHL, 30, 509 (1979).


38. United Nations General Assembly resolution No. 37/137.

39. See Legal and practical requirements for the registration of drugs (medicinal products) for human use, Zurich, IFPMA, 1980.


41. Pharmacy and Poisons (Registration of Drugs) Rules, 1981.


49. Ibid, p. 75.


54. Ibid, p. 80.

59. Ibid.
63. Ministerial Order No. 001/1.2.12/81, 1 September 1981.
71. Food and Drugs Act.
74. Pharmacy Act, 1983.
75. The Food and Drugs Regulations, 1965 (IDHL, 21: 200 (1970)), as amended by the Food and Drugs (Amendment) Regulations, 1974 (IDHL, 26: 883 (1975)).

79. Drugs and Allied Substances Control (General Amendment) Regulations, No. 7 of 1981.


88. Legal and practical requirements for the registration of drugs (medicinal products) for human use, Zurich, IFPMA, 1980, pp. 302-319.

89. WHO Information Circular PHA/DIA/84.6, 29 June 1984.


98. Decree No. 76-807 of 24 August 1976 to amend the Public Health Code with regard to the regulation of pharmaceutical advertising and advertising for products, objects, apparatus, and methods presented as being beneficial to health, as well as the labelling of pharmaceutical specialities. IDHL, 27: 744 (1977).


107. Decree No. 75 of 1 March 1963 enacting provisions under the conditions referred to in items (a), (b), (c) and (d) of section 26 of the law on the supply of pharmaceutical products (Practice of Pharmacy Decree). IDHL, 15, 420 (1964).


112. Decree No. 9763 of 2 December 1964 embodying regulations for the implementation of Law No. 16,463. IDHL, 16: 621 (1965).

113. See Legal and practical requirements for the registration of drugs (medicinal products) for human use. Zurich, IFPMA, 1980, pp. 266-301.


119. Resolution AP(82) 1 on regulations governing information concerning medicines and the advertising of them to persons qualified to prescribe or supply them. Adopted by the Committee of Ministers on 2 June 1982 at the 348th meeting of the Ministers' Deputies. IDHL, 36: 96 (1985).

120. Resolution AP(84) 2 on the inclusion of packaging leaflets in pharmaceutical specialities and the nature of the information shown on such leaflets. Adopted by the Committee of Ministers on 21 June 1984 at the 374th meeting of the Ministers' Deputies. IDHL, 36: 99 (1985).


123. Ordinance of 2 May 1978 on further professional training leading to the examination for pharmaceutical consultants (IDHL, 30: 551 (1979)) and Ordinance of 5 May 1978 on the recognition of technical knowledge for the position of pharmaceutical adviser (IDHL, 30: 552 (1979)).

124. See Legal and practical requirements for the registration of drugs (medicinal products) for human use. Zurich, IFPMA, 1980, pp. 303, 305, and 309.

125. Resolution No. 494 of 6 March 1980 prohibiting the production, supply, and circulation of "free samples", "samples for professional practitioners", "samples having no commercial values", or similar samples, however designated, of certain pharmaceutical specialities. IDHL, 32: 483 (1981).

126. Regulations of 16 December 1974 on advertising for foodstuffs, beverages, and medicaments (IDHL, 27: 163 (1976)). It is of interest to note that in Iceland samples cannot be given to pharmacists or to nurses and midwives. However, samples of drugs (other than "addictive drugs") can be given to doctors (Pharmaceuticals Act, 1978).

128. Decree No. 76–807 of 24 August 1976 to amend the Public Health Code with regard to the regulation of pharmaceutical advertising and advertising for products, objects, apparatus, and methods presented as being beneficial to health, as well as the labelling of pharmaceutical specialities. IDHL, 27: 744 (1976).

129. A period of three years, for instance, in Austria and Turkey.


136. Rules 17 and 18 of the General Rules of Conduct as to the Content and Form of Drug Information.

137. The Sixth World Health Assembly recognized that the wide acceptance of nonproprietary names for drugs serves "the best interests of world health, assists the growth of international commerce in drug products and constitutes an additional basis for improved international relations" (World Health Assembly resolution WHA6.15).


141. Decree–Law No. 96 of 2 August 1973 on general trade in pharmaceutical, dietetic, and cosmetic products (IDHL, 29: 369 (1978)) as amended by Law No. 1316 of 10 January 1983 on the establishment, organization, and functions of the National Organization for Medicaments (NOM), the National Pharmaceutical Industry (NPI), and the National Drug Distribution Company (NDDC), and amending pharmaceutical legislation and prescribing other provisions.


149. Ibid.


159. Decree No. 76–807 of 24 August 1976 to amend the Public Health Code with regard to the regulation of pharmaceutical advertising and advertising for products, objects, apparatus, and methods presented as being beneficial to health, as well as the labelling of pharmaceutical specialities. *IDHL*, 27: 744 (1976).


166. Administrative Order No. 60a. 1968 of 5 March 1968.


1. Not less than 75% of the world's consumption of drugs takes place in the developed countries, where three-quarters of mankind live. In the developed countries, too, each inhabitant spends more than US$ 50 on drugs every year, whereas in the developing countries the average is US$ 6 (1). This profound imbalance between North and South is one of the expressions of the world's maldevelopment: while millions of human beings suffer from lack of medicaments, other millions, mostly in another hemisphere, use too many.

2. This paper considers some of these problems and some of the solutions.

Drug distribution

3. The object of distribution systems is to make the drugs required to meet the health needs of the population always available everywhere in the country at all levels of the health services. Developed countries have little by little created such systems in accordance with their needs; the drugs authorized by the regulatory authorities are distributed through commercial intermediaries and pharmacies.

4. In some developed countries the geographical distribution of pharmacies is regulated by law on the basis of such criteria as the density of the population served, the distance between pharmacies, or transport facilities (2). To enable patients living in sparsely populated areas to have access to drugs, the authorities provide extra remuneration for pharmacists who have a very low turnover; this occurs, for example, in Denmark, Italy, Norway, and the United Kingdom (3).

5. The situation is totally different in developing countries. On the basis of a number of actual incidents in countries, the following chain of events might occur. Reports of shortages of essential drugs (obtained in bulk through a non-profitmaking agency) lead to the discovery that the freight van in which half the year's supply is shipped is still in the customs warehouse because of a dispute with the Ministry of Finance over clearance and demurrage charges. Once cleared, a crate of drums of bulk tetracycline powder falls off a central stores truck during a rainstorm. Some drums are recovered, soaked through, and others are later found in bazaars, the contents being sold as antidiarrhoeal powder in glassine envelopes to individuals. Meanwhile someone measures the interior temperature of the vans transporting the drugs to remote health centres, a three-day journey in a tropical area, and finds it to be 82°C. No one asks which drugs are spoilt or rendered toxic. Pilferage at the docks and along the way decimates the stocks, drugs being a valuable commodity. The

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1 The Director-General acknowledges with appreciation the contribution to the preparation of this paper of S.J. Fabricant, M.S., Consultant in Health Management, Norbert Hirschhorn, M.D., John Snow International, Boston, Mass., USA, and Mrs P. Brudon-Jakobowicz, Scientist, World Health Organization, Action Programme on Essential Drugs.
remaining drugs are then allocated to health centres by dividing what is available by the number of centres. A survey soon shows that centres in populous areas have run out of their annual allotment of drugs within three months, while the drugs accumulate in the centres in remote underpopulated areas. Patients then stop coming to the centres where there are no drugs and the whole rural health network is dislocated (4).

6. Yet another picture is of the main teaching hospital in a drought-stricken country receiving as many drugs as the entire rural health network, although it serves only 5% of the population. Government-supplied oral rehydration salts have not been delivered to village dispensaries for several months, as the Ministry of Health lorries have little fuel and fewer spare parts. However, a well-known soft drink, a commercial brand of sulfamethoxazole-trimethoprim, a useful antimicrobial, and some ineffective antidiarrhoeal drugs are found even in population clusters of 10,000, delivered by private truckers (5).

7. These sketches of real situations show that distribution systems in developing countries rarely meet the needs of the population for drugs and especially for essential drugs. Why is this so, whether the distribution systems are entirely controlled by the government, as in Mali (6) or Guinea (7) or a public and a private sector co-exist, as in Cameroon (8) or Kenya?

8. A number of reasons explain the notorious ineffectiveness of the public sector. One is the low budgetary allocation to the Ministry of Health for the purchase of drugs; in a number of developing countries the allocation for health is a mere 1-2% of the GNP and even if a considerable proportion was spent on drugs it would be insufficient. Although, too, many countries have accepted the concept of essential drugs and established lists of such drugs, a part of their health resources still goes to the purchase of pharmaceutical products that do not meet the priority needs of the population.

9. Another reason for the ineffectiveness of the public sector is that a number of developing countries must, in the absence of a drug manufacturing industry of their own, import all the drugs they use. The currency they need for that purpose is scarce, and drugs must compete for it with other commodities that sometimes have a more strategic value for the governments.

10. Most health systems are still oriented towards curative services, and the few drugs available in the developing countries go to supply the hospitals rather than other branches of the health services (10). This inequitable distribution is accentuated when each health echelon distributes drugs to the echelon below; health centres and, especially, dispensaries, the last to be served, get little or nothing.

11. The ineffectiveness of supply and distribution systems is an additional factor contributing to the scarcity of essential drugs. The reasons for its ineffectiveness are complex and in part purely technical, arising from the lack of resources, the shortage of personnel, and a certain bureaucratic
mentality that places administrative precepts before initiative and a sense of responsibility. As a result:

- it takes years for orders to be delivered, mostly because of the complexity of the administrative labyrinth;
- information systems do not work, so that, for example, the quantities of drugs needed cannot be calculated;
- storage conditions are bad and drugs are not protected from sun, rain, or theft;
- transport is not properly organized, and in the absence of means of transport alternative solutions are not considered.

12. Ineffectiveness is found throughout the echelons of the health services, the drug situation not being followed up or the records properly kept. A large number of drugs are utilized by health personnel for their private purposes (nearly 30% in some cases) (11), and storage conditions are often defective. This state of affairs has disastrous consequences for peripheral health services, which have lost all credibility in many countries; the rural dispensaries, lacking drugs, are no longer frequented by the population but the government continues to pay the staff, which without the attraction of drugs has not even the possibility open to it of carrying out health education (12).

13. The private sector, on the other hand, is on the whole expanding; in Cameroon it distributed 75% of drugs in 1978 as against 60% in 1976 and its sales had quintupled in two years (13). This sector, which consists of pharmacies and pharmaceutical outlets, may purchase drugs from a government importing agency which has a monopoly of importation, as in Algeria, or order direct from foreign suppliers or local wholesalers, as in Cameroon. In the first case the range of drugs distributed by the pharmacies and pharmaceutical outlets is theoretically under the control of the government; but in practice in some of the countries concerned such control is little exercised to ensure that drugs meet health needs adequately.

14. The private sector, which is actuated by the profit motive, is much more efficacious than the public sector, but suffers from major disadvantages in the developing countries:

- because of the weakness of control measures, drugs of doubtful efficacy, sometimes dangerous and often inessential (tonics, multivitamin products, etc.) are strongly promoted and therefore in demand and use up scarce currency (14);
- drugs sold by pharmacies are in general expensive branded drugs and so not accessible to most of the population (15);
- most pharmacists do not wish to establish themselves in the rural areas where purchasing power is low, thus perpetuating the inequitable distribution of drugs.
15. Because of the inadequacies of the two sectors and their inability to meet the needs of the population, some governments have created a paragovernmental sector, with the objective, as in Togo, of developing a health-oriented not exclusively commercial form of distribution that would provide the rural areas with proper supplies of drugs. These paragovernmental bodies (Togopharma, the Office national de pharmacie du Bénin, etc.) were entrusted with the purchase and distribution, through pharmaceutical outlets, of a limited range of essential drugs to be sold cheaply to the public. Often the initial objective has not been attained, the bodies concerned having increased the range of their products and distributed a number of relatively inessential drugs (16). The main reason is that all these drugs sell easily and make money for the government.

On the proper use of drugs: prescription practices and compliance problems

16. "Modern drugs are such potent weapons that the responsibility for their safe production and use can no longer be left entirely to the manufacturer and prescriber" (17). "Physicians should note that very often patients do not speak the truth when they assert that they have taken their medicines" (18).

17. Whereas the problems of the distribution of drugs are entirely different in the developed and developing countries, the problems of taking drugs on prescription or in self-medication are relatively similar in both. They may be illustrated as follows:

- A woman in her forties goes to her doctor. "Doctor, I'm tired and don't want anything. At night when the children are in bed and the house is in order I can't read or prepare my course for tomorrow or even get to sleep". The doctor prescribes vitamins, a tranquillizer, and a mild hypnotic.

- A veiled woman stands in a crowded clinic, her uncle by her side. "What's your problem?" asks the doctor without looking up. The complaints are commonplace: generalized pain in the back and chest, palpitations, dizziness, and "a jerking soul". The doctor diagnoses beriberi and rheumatism and prescribes vitamin E, vitamin B injections, and analgesics (19).

- Mexican village men flock to a pharmacist's helper's house. He has a new supply of intravenous saline, "artificial life", which they greatly desire. Each man feels stronger after the infusion (20).

- A paediatrician examines a child with diarrhoea and prescribes an antibiotic combination, a constipative, and rehydration fluid. "But doctor", the mother wails, "he has had diarrhoea so many days." The doctor adds an antimotility drug and vitamins. This is the third physician consulted and the child now has a total of 12 drugs, some identical chemically but in boxes of different colours and labelled in a foreign script. Seven different antimicrobials may be found in the dozen preparations. The child is given intermittent doses of
some of the drugs in the succeeding days because the mother tries, with help from neighbours, to give the most appropriate drug for this "hot" disease. As the stool changes in colour and consistency she applies different therapies (21).

- A child is ill with fever and a cough. The parents, too poor to consult a doctor, try a variety of home remedies and changes in diet and consult a spiritual healer to get amulets. Finally they administer tablets from a red box left over from an earlier illness that may have been similar (22).

- A university hospital internist in a developed country takes a detailed case history from a 45-year-old sales executive who complains of tiredness and mild pain in the chest and arms. The physical examination and laboratory tests indicate nothing special, but the patient is obviously tense and his systolic blood pressure approaches the upper range of the normal. The internist prescribes a cardiotonic, an antihypertensive, a diuretic, and a tranquillizer, which the patient takes for a few days and then forgets in a cupboard (23).

18. These illustrations show that medical personnel and other prescribers are far from utilizing drugs rationally. The reasons for such a situation are many and complex.

19. All countries are affected by the steady increase in drug consumption. In the United Kingdom the number of prescriptions in the National Health Service rose by 22% between 1974 and 1977, much faster than the increase in the population. In the United States the number of prescriptions per head rose from 2.4 annually in 1950 to 7.2 in 1977 (25). In France drug consumption is rising on average by 13% per annum (26). Should the conclusion be drawn that people are therefore in better health? There is much evidence to cast doubt on such a conclusion; the reasons for increased drug consumption are rather to be sought in prescription practices and the attraction that drugs exert.

20. Much has been written on prescription practices. The main problems are excessive prescribing - a drug is prescribed when it is not necessary or when there is no medical indication for its use; inadequate prescribing - no drugs or not enough drugs are prescribed; and incorrect prescribing - the drug is not in keeping with the diagnosis or is ineffective (27).

Excessive prescribing

21. A study carried out in seven European countries showed that there are marked differences in the utilization of antidiabetic drugs, specially oral preparations. There are no data available to suggest that the incidence of diabetes differs as markedly as does drug utilization between the countries (28). Another comparative study has shown that patients hospitalized in the United States receive twice as many drugs as patients hospitalized in Scotland (29). There is a similar great variation in Nordic
countries in prescribing antihypertensives, a variation that cannot be explained either by differences in morbidity or in the training of or information received by those prescribing (30). Whereas the number of drugs per prescription is around two in Switzerland (31), in the hospitals of South Brazil it is 8.6 (32), three as a minimum in Tunisia (33) and in Kenya (34), and five in most health centres in Cameroon (35). In France in 1983 one prescription in four was for antibiotics, in 57% of cases for respiratory infections of viral origin that do not respond to antibiotics (36).

22. The volume of sales of certain drugs far exceeds the incidence of the disease they are supposed to treat. Skegg has shown in a population of 40 000 that 33% of women between the ages of 45 and 59 years were receiving tranquillizers, as against 9.7% for men of all ages (37). As an advertisement of the pharmaceutical industry suggested, this is a method of producing "a less demanding and complaining patient" (38). All these studies concur in the conclusion that for a considerable proportion of the population in the developed countries taking drugs has become a habit that is often encouraged by the medical profession and the pharmaceutical industry. The public demand for drugs accords very little with real needs, and the resulting polypharmacy is not without economic consequences - waste of public and private money; social consequences - medicalization of society; and health consequences. In the comparative study mentioned above 26% of the American patients who were taking more drugs had side effects, as against 15% of Scottish patients. According to Steel et al. (39), side effects occur on the average in 18-30% of hospitalized patients; 80% of these effects could be avoided and are due to the prescriber's lack of therapeutic knowledge (40). Iatrogenic diseases caused by drugs, most of which have been prescribed by doctors, are responsible for 20% of admissions to American hospital services (41).

Prescribing in inadequate quantities

23. In developed countries it is difficult to give exact examples of prescribing in inadequate quantities, but it seems to exist for certain classes of drug (42). In developing countries drugs are not always available or are available in such small quantities that the prescriber gives too little to each patient, thus often favouring the development of drug resistance. Many common but serious conditions no longer respond except to second-line drugs, which are generally more expensive (43).

Incorrect prescribing

24. Incorrect prescribing is also a major cause of the development of drug resistance. It is probably the commonest form of irrational prescribing and has at least two aspects: either the drug prescribed is ineffective or doubtfully effective for the condition concerned or, although it is pharmacologically active, it is administered in unsuitable circumstances.
25. In the United States, according to Kunin et al. (44), more than 60% of hospitalized patients are wrongly given antibiotics. Antibiotic abuse has generated a considerable amount of literature, but antibiotics are not the only class of drugs that are incorrectly prescribed. Also in the United States the prescribed treatment is not in accordance with the diagnosis in 20-40% of cases (45,46). In France an analysis of some 500 prescriptions showed that 36% contained anomalies; in 31 the same active principle was present in several drugs, 23 contained antagonistic substances (for example stimulants and sedatives), and 41 (8.3%) were of potential danger to the patient (47). The same problem exists in Spain, since in 1980 the second drug on the market in the class of antimicrobials was a combination of penicillin G, streptomycin, dihydrostreptomycin, albuminoids, etc. and was alleged to provide "non-specific immunotherapy". The fifth drug in the same class was a combination of tetracycline, sulfadiazine, dexamethasone, trifluromazine, pentetrazol, sodium benzoate, and balsam of tolu (48). In India a recent study carried out at Hyderabad showed that 16% of doctors had prescribed at the same time several vitamin preparations that contained the same ingredients and that more than 30% of prescriptions contained an antibiotic (49). Many other examples could be cited that would merely strengthen the conclusion that, in the developed as in the developing countries, prescribing is far from meeting the scientific criteria established by the therapeutic sciences.

26. A second problem brought out in the illustrations is that of the use of drugs by patients, whether prescription drugs or drugs taken in self-medication. A correct diagnosis and appropriate treatment are of little value if the patient does not follow the treatment prescribed. Non-compliance is nowadays considered to be a major problem in the health services of both developed and developing countries; it has been the subject of more than a thousand publications, mostly Anglo-Saxon, and a recent review of the literature suggests that the compliance rate is approximately 50% and decreases with time (50). Another analysis shows that between 30% and 75% of patients do not take all the drugs prescribed, do not take them in the prescribed dosage, or use them wrongly; and 40% of the mistakes may be harmful (51). The low compliance rate with effective remedies results in the failure of curative or preventive treatment and may have negative effects on the patient and society, such as the development of resistant strains, or economic costs.

27. Self-medication is a phenomenon that exists in every society and is tending to increase in the industrialized countries, as is shown by the increase in the number of books devoted to the subject. A WHO study in Canada showed that 50% of the population observed had taken medicaments in the 48 hours before the investigation, half of which had not been prescribed by doctors (52). Self-medication, while desirable in certain cases, may at times have negative effects on the consumer, inasmuch as the mode of action of the medicaments is rarely well understood, the length of treatment is difficult to judge (53), and very often the manufacturer's labelling does not provide sufficient data for appropriate treatment. The rationality of self-medication may also be queried in the light of the finding of the United States National Academy of Sciences that only 42% of 400 OTC preparations studied were effective or probably effective (54).
28. How have drugs within no more than three decades managed to become so widespread and in such great demand and yet be so badly used? How can the differences in patterns of prescriptions in similar countries be explained? Why do so many prescriptions not correspond to any satisfactory therapeutic norm? Why, in spite of the attraction of drugs, do patients follow their course of treatment so badly? Why, in spite of the many efforts to improve the use of drugs, is the situation so far from being satisfactory?

29. In fact, when a doctor prescribes a drug for a patient, many factors other than the biochemical properties of the drug come into play, a process Mazzullo has called "the non pharmacological basis of therapeutics" (55). The doctor is primarily influenced by the education in therapeutics he has received, an education that explains in part the existence of therapeutic schools or habits that create certain regional or national differences. The education he receives should give him the necessary basis for his profession. According to some studies, however, "the lack of knowledge and sophistication in the proper therapeutic use of drugs is perhaps the greatest deficiency of the average American physician today" (56), and there is no reason to think that the situation is any better in the rest of the world. Very often the doctor is simply not in a position to choose the best drug for his patient. In many countries continuing education is lacking (57) and this reduces the positive effect training in prescribing could have. Many studies suggest that training has indeed a positive effect on the quality of prescribing (58).

30. The promotional efforts of the pharmaceutical industry play a considerable part. Multinational firms produce a large number of drugs, many of which add little to the therapeutic armamentarium. An analysis of volume 25 of the scientifically objective Medical letter (Medical Letter Inc., New Rochelle, United States of America) shows that ten new products were reviewed that were biochemically similar to existing products. Two were considered an improvement; six provided no additional benefit and were more expensive; and two were thought less effective. In the United States 94 generic antibacterials are available; Medical letter recommends 31 as first-line, and then only 13 that need no elaborate diagnostic tests for proper use (59). All these drugs are promoted by aggressive and well-contrived methods. Promotion, as is shown by an analysis of 14 quantitative studies between 1940 and 1964, seems to be the factor that has most influence on medical prescribing (60); and Hemminki reached the same conclusions, stressing the role of sales representatives (61). A study carried out in 1978 in Switzerland showed a very significant correlation between the turnover of a drug or therapeutic group and the number of pages of publicity given to it in medical journals; thus the number of pages of publicity for the "nervous system" group represented 15.5% of the total analysed and the turnover for the group was 18.2%, the corresponding figures for one of the drugs of the group being 40.9% and 43% (62).

31. The availability of the preparations placed on the market by the pharmaceutical industry also influences prescribing. This could be illustrated by the following hypothetical conversation between doctor and
patient: "Well, Mr Smith, I have listened to your story and examined you, and it seems to me that you are a case of diazepam. You had better have some anxiety." (63). Most of the doctors questioned do not realize to what extent this commercial promotion influences their prescribing. In a study of propoxyphene, considered by scientific opinion to be less effective and more dangerous than aspirin, the doctors who considered it very effective did not think that they were influenced by unscientific sources of information (64).

32. The pharmaceutical industry is not solely responsible for irrational prescribing practices. The demands of society and patients also push the doctor into prescribing for, we must not deceive ourselves, the responsibility for overconsumption of medical care and drugs falls not only on those who sell the drugs but also on those who buy them. Prescribing has a powerful symbolic effect, confirming the roles played by the doctor and the patient and maintaining their relationship. For many doctors "it is prescribing which makes a clinical situation legitimately medical" (65). In prescribing the doctor assures himself that he is treating the patient, gives him visible proof that he has done well in coming to consult him, and increases his dependence so that he will come again. For the patient, prescribing symbolizes the doctor's interest in him and confirms his own role as a patient (66). The result is a tacit complicity between the prescriber and the patient, a complicity that may also include the pharmaceutical industry since it places the desired drugs at their disposal. Although the demands of the patients undoubtedly exercise a powerful influence in concert with that of the pharmaceutical industry, they are possibly less powerful than doctors would like to have it believed. A study by Stimson shows that in 80% of cases the doctor thinks that the patient has come to consult him so as to get a drug, whereas only 50% of the patients interviewed really wanted one (67).

33. Other factors that play a part are the influences of colleagues, government regulations, the characteristics of doctors, etc., but their role is minor and difficult to delineate exactly. On the other hand, the genuine placebo effect of drugs has to be taken into account. Medical literature has abundantly documented the placebo effect, both positive and negative, of drugs on hypertension. In its extreme, however, the practice of administering placebos may replace more fundamental support to people in coping with their problems. In some societies the ability of people to cope with misfortunes through family and community rituals has been replaced by treatment with drugs; thus grief is treated with tranquilizers (68, 69).

34. Another factor favouring irrational drug consumption is the emphasis some people place on prevention and the strengthening of the body against outside forces. In traditional contexts prevention is achieved through diet, cleanliness, purges, and rituals. Many people assume that it can now be bought, manufactured tonics, vitamins, calcium, and saline intravenous infusions having a special status (70, 71).

35. In developing countries, even more than in developed countries, communication between the patient and the health staff is a problem. Very often the health staff subscribe to norms that are different from those of
the patients, and by their training belong to a subculture close to that of health staff in other countries than to that of the population in which they work. Communication is established with difficulty, and the easiest method of meeting the needs and expectations of patients in such circumstances is to prescribe drugs.

36. But it should not be forgotten that what people ultimately seek is a cure for illness. Even the poorest family will spend money and time and mortgage its assets to cure a sick child; and polypharmacy is a way of assuring it that it has done everything possible. Doctors and other prescribers are only too happy to encourage this feeling; thus their prestige and their income are linked to long prescriptions and the system becomes self-reinforcing. The family may not, in the heat of the moment, realize that it can no longer afford to buy enough food for the sick child or its siblings.

* * *

37. Like prescribing, compliance is a complex phenomenon. Much research has gone into attempts to define the most important factors influencing compliance; but the results vary and are difficult to systematize. The illness, the treatment, the form in which the drug is administered, and the number of doses or of preparations to be taken daily all have a positive or negative influence on compliance. But the most important factor seems to be the doctor; a study has shown that compliance improves when the doctor demonstrates that he is competent and takes the situation and the needs of his patient into account (72). Many investigators have similarly found higher compliance levels when the prescriber provides ample information and follows up the patient attentively (73).

38. These results, however, have not been confirmed by a recent study based on 185 compliance studies: "An interesting finding at sharp variance with conventional wisdom is that there appears to be no relationship between patients' knowledge of their disease or its therapy and their compliance with the associated treatment regimen. Although some studies have concluded that patient knowledge does lead to better compliance, a statistical comparison reveals that studies concluding no relationship are of greater methodological soundness. Accordingly it appears that the gap between clinical prescription and the patient's subsequent compliance behaviour is at best marginally narrowed by knowledge possessed or, indeed, imparted to the patient. That this is so is further supported by a lack of association between patients' intelligence or educational achievements and compliance" (74). This conclusion is strengthened by recent research on compliance. In opposition to the studies cited, which start from the hypothesis that the doctor prescribes and the patient must comply, these studies see the patient as an active agent in treatment. Non-compliance then becomes a voluntary act of the patient, who evaluates the behaviour of his doctor and the drugs prescribed in the light of his knowledge of and beliefs about the illness and the drugs (75), which are not always rational and influenced by education.
39. People all over the world have definite ideas about health, about how to strengthen health, how to prevent illness, how to cope with sickness. These ideas are part of the larger fabric of beliefs, assumptions, and practices concerning the body and people's relationships with each other and to natural and spiritual forces. The preparations used to provide care or cure are at several levels: they may be popular, provided by the individual himself or by relatives or neighbours, or "folk", provided by traditional healers using sacred or secular methods, or professional, provided by persons with formal training and qualifications. The more complex a society, the greater the range of choice an individual has for health care. This range of choice is termed "medical pluralism" and it exists in traditional rural communities as well as in westernized urban societies (76).

40. Modern pharmaceutical preparations are now part of the armamentarium of medical practitioners and healers at every level and are universally perceived to have - and often do have - powerful effects. They are consequently beginning to create a common medical system. They arose from a specific rational scientific model which assumes that virtually all illness is attributable to measurable biochemical mishap, either from without, as by infection, or from within, as from genetic susceptibility or immunological deficiency, and that a chemical preparation can be found to prevent, overcome, or improve the biochemical situation. Modern science lends weight to this view: cancer and the illnesses of age are increasingly being related to immunological and genetic failures; some mental illnesses to imbalances of small peptide molecules; and infections to imbalances between external assaulting organisms and multiple internal defence mechanisms. Drugs are being developed specifically to combat each biochemical failure or shore up normal biochemistry. Since the beginning of the twentieth century, when Ehrlich discovered a specific drug for the treatment of syphilis, medical scientists have aimed at discovering "a pill for every ill". This search for specificity is illustrated at present by the prospects being held out for gene replacement therapy. People throughout the world in all forms of society have great expectations for such "magic bullets". But while allopathic drugs are being absorbed into all systems of health care, they may not always be used in accordance with the scientific model.

41. With increased access to drugs, which is one of the stated goals of primary health care, the misuse of drugs may increase. A vital question that has not received an answer is whether the proliferation of drugs is on balance helpful or harmful, or even justified in terms of opportunity costs for poor families or poor countries. The question is almost irrelevant for the vast majority of people living in the developing countries, particularly in the rural areas; for them access to the 20 or 30 drugs essential to their health needs can make the difference between life and death, or at least between a life plagued by disease and a life that is socially and economically productive.

A more effective distribution of drugs

42. Given the economic situation of most developing countries, it is not very likely that the financial resources at the disposal of health
ministries will increase much in the coming years. It is therefore essential that they be used to good effect. A first step, one that many governments have already taken, is to adopt a national list of essential drugs; not only can developing countries not afford the luxury of ineffective drugs (77), but among effective drugs they must also choose in the light of the priority needs of the population (78). Governments that have not created a system of purchase by tender could, as a second step benefit by making use of the experience of other countries or could request WHO to help them organize their purchases more economically.

43. In the public sector the management of drug distribution agencies could technically be fairly easily improved by increased staff training, the creation of information networks to determine what drugs are essential (on the basis of a simplified collection of morbidity data), the introduction of more efficient stock control procedures, etc. The use of a restricted list of drugs is already an important step forward, for with such a list the number of drugs to order, stock, and distribute is reduced, management is greatly simplified, and costs fall as a result.

44. Such measures, which are relatively easy to introduce, will improve the performance of the system, but they will not really be effective unless they are accompanied by measures to motivate the personnel and make them responsible. Research is required to study ways of motivating the various categories of personnel in government service.

45. The problem of distributing drugs from the centre to the periphery is more difficult to solve, for indeed vehicles and fuel are often lacking in the public sector. Governments may have to find alternative solutions for distributing drugs to the health services; in some cases private transport can be used, since it often goes to the most remote areas. Research should be carried out on other systems of distributing drugs to the rural areas, systems that could achieve a more equitable distribution between urban hospitals and rural centres such as that developed by WHO and already in operation in Kenya, in which appropriate quantities of essential drugs are sent directly to dispensaries and rural health centres in sealed containers (79).

46. The free distribution of drugs in health services has been denounced by many authors as one of the principal causes of wastage and drug shortages. It would be desirable to study the possibility of replacing such a costly free public distribution by one selling essential drugs at low prices. Studies in this area should take into account the successes and failures of existing systems (cooperative pharmacies, revolving funds in the health services, etc.) and propose feasible solutions.

47. A number of solutions for the improvement of the performance of existing systems will be without effect unless the roles of the different sectors in the supply and distribution of drugs at the national level are redefined with precision. Additional research is required on the impact of the expanding private sector on the services of the public sector, which comprise not only the supply of drugs.
48. Because of the difficulties of supplying the rural areas in many countries and the effectiveness of the private sector, a solution might be considered integrating that sector in a system of distribution of drugs in the villages; pharmacies might be authorized to procure and sell certain essential drugs at a low price. But for such a measure to be successful it would be necessary to take steps to encourage pharmacists to install themselves in the rural areas, as for example by subsidizing the price of essential drugs.

The rational use of drugs

49. How can the behaviour of prescribers and patients in relation to drugs be transformed? How can the use of drugs be rationalized? Most of the attempts in this area have tended to control drug prescribing by regulation or by persuasion (80). In general regulatory measures are taken more against those who make profits - the pharmaceutical industry, distributors, and pharmacists - and are accompanied by structural changes, whereas in the case of prescribers and patients the control system rests essentially on voluntary changes. Regulatory measures include drug control, prescriber control and patient control.

Drug control

50. The control authorities that ought to be established in all countries have to ensure inter alia that all old and new drugs on the market fulfil a certain number of basic conditions in relation to safety and efficacy.

Prescriber control

51. In certain states of the United States the maximum amounts of drugs that can be dispensed on prescriptions paid for by Medicaid are fixed in advance (81). In France, Social Security exercises qualitative control over prescribing, the best example of such control being the "medical profile", which represents each doctor's prescribing costs and makes it possible to discover who departs from the agreed norms and to take the necessary steps (82). The steps range from drawing the doctor's attention to the situation to excluding him from the Social Security agreement.

52. Another and probably more effective form of control is to limit prescribing to the drugs included in a formulary or list. In a recent study of the effect of several methods of control over prescribing antibiotics and tranquillizers in an American hospital, the most effective method of reducing prescribing was to withdraw them from the formulary, the next being the requirement that the prescription should be countersigned by the head of the service. In the first case the administrative difficulties in obtaining the drugs discouraged the prescribers; in the second the prescribers gave more thought to prescribing because they had to account for their action to a superior (83).
53. These restrictions, although very effective, are little appreciated by doctors, who see in them an infringement of their freedom to prescribe; but they are being more and more imposed in developed and developing countries. One method of persuading the medical profession to accept formularies is to create local and national therapeutic committees animated by prescribers. Formularies, however, are not a guarantee that the medical profession will use drugs rationally, but they limit the use of dangerous, ineffective, or very specific drugs.

Patient control

54. The main forms of control over drug consumption exercised by government are (1) the obligation to provide a prescription for certain drugs - an obligation that exists everywhere to a greater or lesser extent and is more or less respected; and (2) price fixation. In France, Social Security reimburses only 40% of the cost of drugs treating minor upsets (84). A Commission de la Transparence has been entrusted with the task of studying and proposing prices and reimbursement rates to the Ministry of Social Affairs.

Methods of persuasion

55. Although legislation is an important weapon in combating drug misuse, it needs to be accompanied by more persuasive methods to make the medical profession and consumers aware that drugs are not ordinary commodities and must be used in accordance with certain scientific criteria. One of the causes most often identified of the misuses noted in prescriptions is the prescribers' lack of knowledge of therapeutics and pharmacology. Better training in those subjects during their studies and then during their active career is therefore essential. Clinical pharmacology needs to be taught more extensively. The basic training must aim at developing in the student a critical attitude that will enable him to judge rationally the flood of information to which he is subjected. For postgraduate training, methods have been developed (85) that help prescribers to criticize themselves and to discuss their prescriptions with their colleagues. Such methods could be used more widely and adapted to the different countries.

56. It is also necessary in each country for reference works and periodic information bulletins prepared by official agencies to be provided for prescribers. Objective drug information services should be encouraged and, if the country cannot itself furnish them, WHO should do so. In Great Britain, for example, several journals (Drug and therapeutics bulletin, Prescribers' journal) that are completely independent of the pharmaceutical industry and the British national formulary are distributed free to doctors (86).
57. In some countries advisers are available on request to help doctors (87). They are doctors (Netherlands), clinical pharmacologists, or pharmacists (United States). Such a measure is difficult to take in most developing countries, but advisers of that kind could have a part to play in the organization of seminars or programmes of continuing education.

58. Another measure, home visits to doctors by clinician pharmacists, has been shown to be very effective in the United States. Prescribers who had received such visits accompanied by "anti-advertisements" cut down their prescriptions of target drugs by 14% (88). This new form of medical visitor may provide a way of improving prescribing and reducing costs in a number of countries.

59. Other measures can be envisaged and are widely discussed in the literature. One that might be mentioned is the value of drug utilization studies at local or national level (89,90).

60. As far as patients are concerned, education is the essential method of breaking the vicious circle of medicalization. This has to begin at school and has to stress that treatment without drugs is sometimes preferable to treatment with drugs and that a visit to a doctor need not always end with a prescription. In the United States public and private organizations, including the American Medical Association, have set up a National Council on Patient Information and Education (NCPIE), which has embarked on a widespread public education campaign recommending that patients ask doctors about the drugs they prescribe and trying to develop people's critical judgement in this hitherto relatively "reserved" area (91). Several initiatives in Sweden are aimed at improving the information of the public. The Association of the Swedish Pharmaceutical Industry publishes regularly a manual for patients containing a description of all the drugs on sale in Sweden (92); the information, provided in a language easily understood by the public in general, is approved by the Swedish National Board of Health and Welfare. At the national level a group of experts nominated by the Government also prepares general manuals on self-medication, and each county council group does the same, the manuals being distributed free in the pharmacies.

61. Non-compliance, which represents another aspect of the misuse of drugs by patients, may also be remedied by education enabling consumers to better understand the role of drugs. Compliance would be improved too by such simple measures as simplification of prescriptions, improved presentation of drugs, written and spoken information given by the prescriber and the dispenser, and directions in simple language prepared in collaboration with consumers.

62. All these measures to influence the behaviour of prescribers and consumers, whether by the control of promotion, education, information, or other, have an impact on drug use, but their effect has very often been exaggerated and none has been irrefutably shown to be both necessary and cost-effective. In fact "the concept of the rational man or woman, be that
doctor or patient, has limited, albeit, important applicability" (93); more searching studies are needed on the cultural, anthropological, and social factors influencing the prescribing and use of drugs. Studies, for example, on the behaviour of individuals in relation to drugs, on popular knowledge of the properties and use of medicines, or on the beliefs of doctors would enable better strategies to be developed to influence behaviour. Research comparing the situation in different countries should also enable drug use to be better understood, forecast, and improved.
REFERENCES


3. Ibid, p. 54-55.


5. Ibid.


92. LINFO, Läkemedelsinformation AB. Patient-Fass. Sweden, different years.

Sources, types and availability of information

1. The main sources of information relating to the rational use of drugs are the Ministry of Health and Population Control, the Directorate-General of Health Services, the Directorate of Drug Administration, the Bangladesh Medical Association, the Bangladesh Dentist Association, and the Chemist and Druggist Association. The Ministry of Health and Population Control is concerned with all types of information that may be required, the Directorate-General of Health Services with the procurement and distribution of the drugs required for Government hospitals and thana health complexes.

2. The Bangladesh Chemist and Druggist Samity, the association for retail drug shops, can give information about drugs prescribed by the doctors and the supply position of all types of drugs manufactured in the country or imported from abroad.

3. The drugs used include essential drugs and other newer drugs specially for the bigger medical college hospitals of the country. The Directorate of Drug Administration, under the Drug Act, 1940, the Drug Rules, 1945, and the Drug (Control) Ordinance, 1982, is responsible for the control of the manufacture, sale, and distribution of all type of drugs in the country through a licensing system covering both manufacturers and pharmacies. There are at present some 15,500 licensed retail drug stores in the country. New licences are issued on the recommendation of district drug licensing committees. A drug licence is granted only if the premises proposed for the drug shop are suitable and the sale and stock of medicines can be supervised by a registered pharmacist. There is a system of registration for each product either manufactured in or imported into the country. Two government drug testing laboratories in the country test drugs for safety and efficacy.

4. The standard of private hospitals and clinics is upheld by the Directorate-General of Health Services. These private hospitals and clinics play an important role in the medical care of the people, particularly those living in metropolitan areas. The Bangladesh Medical Association plays a vital role in maintaining the professional standard of doctors. This body sometimes transfers professional information among doctors through its services and symposia. There is another important body called the Bangladesh Medical and Dental Council, responsible for the registration of doctors and dentists. There are eight medical college hospitals which provide medical education side by side with medical care. Apart from these medical colleges, the Institute of Post Graduate Medicine and Research is the highest centre for medical education. There is a diabetic hospital exclusively for the treatment of diabetic patients. The International Centre for Cholera and Diarrhoeal Disease is located in Bangladesh.

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1 The Director-General acknowledges with appreciation the contribution of this case study by the Government of Bangladesh.
Drug control and distribution

5. A company has been set up by the Government to produce essential drugs for the hospitals and health complexes of the country. Another company is under construction for the same purpose. There are 150 essential drugs produced in Bangladesh. The selection of essential drugs is based on the WHO list of essential drugs. The Government encourages all the manufacturers to produce essential drugs. As compared with that for specialized drugs, the process of registration for essential drugs is simplified.

Drug marketing

6. Drug marketing in Bangladesh falls into a number of categories. The pharmaceutical industry distributes its own products, which are either manufactured locally or imported from abroad. Some local companies work as agents on behalf of foreign pharmaceutical firms. Drugs are distributed by the Central Medical Stores to the government hospitals and thana health complexes. This is exclusively a government distribution. Drugs are also distributed by the Social Marketing Department, particularly contraceptives for the family planning programme of the country. Various charitable or missionary hospitals procure drugs either locally or from abroad. Finally, international agencies provide drugs as a gift to be distributed among the people of the country according to need.

Review of national health legislation relating to drug control and distribution

7. The concept of health has undergone tremendous change over the last few decades. Health is no longer regarded as merely the absence of disease but is now considered to be an essential component of physical, mental, and social wellbeing.

8. Bangladesh is committed to ensuring minimum medical care for every citizen with a view to achieving the national objective of Health for all by the year 2000. With the development of medical science and technology as well as of the concept of health, the National Health Service has to assume a progressively expanding role in terms of its content and its links with other sectors.

9. In any country the importance of health legislation as an instrument for providing legal coverage to health activities, including drug control and distribution, can hardly be overemphasized. Appropriate and effective legislation providing adequate coverage for all health activities is necessary for the protection of the people from disease and health hazards, for the promotion of health, and for drug control and distribution. Most of the health laws inherited by Bangladesh, enacted long ago, were inadequate to cope with the demands of the present day.
10. Whereas the major problems of drug regulatory control in developed countries are related to the introduction of new drug entities, their testing in animal and man in clinical trials, the monitoring of adverse reactions, etc., Bangladesh, like most other developing countries, was struggling primarily to ensure for its population the availability of essential drugs in good quality at a reasonable price. The Drug Act, 1940, as amended from time to time, the basic drug law in the country, was enacted to regulate the manufacture, import, export, sale, and distribution of drugs. Control over the import and export of drugs was made the responsibility of the then Central Government, control over manufacture and sale the responsibility of the provincial governments. The same practice continued in Pakistan. By the time Bangladesh emerged as a sovereign republic the situation had changed with the rapid developments in the pharmaceutical and medical sciences; the administrative and legal procedures laid down in the Drug Act, 1940, had become virtually ineffective. After years of litigation in the country, manufacturers of spurious drugs, including injectable ones, often got away scot-free or with a nominal fine. A drug licensed earlier could not be withdrawn unless it could be proved to be harmful or substandard. It was the view of the experts that the Act of 1940 had lost its effective force with the passage of time and was no longer suitable for an independent drug policy in a sovereign country. The people of Bangladesh were denied the benefits of effective drug control and protective measures in law. The result was that alcoholic, harmful, and substandard products achieved registration and were widely sold through successful advertising methods. This caused immense harm to people in general and the poverty-stricken population in particular. On the other hand, a lot of money accumulated in the hands of manufacturers and traders out of the profits from those products; a phial of gripe water used to cost the manufacturer not more than one taka whereas it used to be sold at 10 to 15. It was estimated that, out of the total expenditure by the people on drugs, nearly one-third was spent on unnecessary and useless ones. Moreover, drug policy did not protect the national interest. There were 177 licensed pharmaceutical manufacturers, but drug production was dominated by eight multinational companies that manufactured about 75% of the products.

11. Homoeopathic, unani, and ayurvedic drugs were exempted from control under the Drug Act. As a consequence, unethical, harmful, and useless products multiplied. There was no control over the price of pharmaceutical raw materials or packing materials, which constituted more than 60% of the trade price. These materials were imported from different sources by different manufacturers at widely varying prices. In conformity with the recommendation of WHO, essential drugs were required to be made readily available at reasonable cost with a view to achieving the national objective of Health for all by the year 2000. The worldwide strategy designed by WHO to achieve that objective is considered to be a rationalization of the manufacture, marketing, and sale of pharmaceutical drugs. A WHO document states: "While drugs alone are not sufficient to provide adequate health care, they do play an important role in protecting, maintaining and restoring the health of the people".
12. In view of the situation, the present Government, soon after assuming power, convened an expert committee to advise on a new drug policy. The expert committee's report began: "Recognizing the right of every citizen to enjoy the highest possible level of health care, there is an urgent need to mobilise and make economic and effective use of all available resources for improving the state of health of the people. Drugs, being most essential tools for health care, cannot be treated just as any other commercial product. At present not more than 20% of the population have access to even the most essential drugs for their health care and yet the market is flooded with hundreds of useless or non-essential products".


14. The Committee recommended that the Drugs Act 1940 should be revised or replaced by new drug legislation incorporating the following provisions:

- a system of registration for all medicinal products including ayurvedic, unani, and homoeopathic medicines
- enforcement of good manufacturing practices
- full control of labelling and advertising
- control of the prices of finished drugs and pharmaceutical raw materials
- prescription control of toxic and habit-forming drugs
- summary trial for offences in special drug courts
- heavy penalties including confiscation of equipment and property for the manufacture and/or sale of spurious and substandard drugs
- departmental adjudication for fines up to Taka 10 000.00
- heavy penalties for possessing or selling drugs stolen from government stores, hospitals, and dispensaries
- regulation of technology transfer and licensing agreements with foreign concerns
- restriction of ownership of retail pharmacies to professional pharmacists
- control of the manufacture and sale of unani, ayurvedic, and homoeopathic drugs
- revision of the patent laws in respect of pharmaceutical substances.
Guidelines for evaluation of drugs

15. The expert committee also drew up guidelines for the evaluation of all registered/licensed drugs and recommended that registration should be granted only on the basis of the guidelines. They are as follows:

16. In general, combination drugs should be accepted only where no alternative single drug is available for the purpose or where the single drug is not cost-effective. Exceptions should be made for oral rehydration salts, certain antimalarials, co-trimoxazole, iron with folic acid for use in pregnancy, combined oral contraceptives (containing up to 35 mcg estrogen), and formulations specified by the licensing authority for multivitamin (B complex) tablets and paediatric drops, hydrocortisone with antibiotic skin preparations, and a haemorrhoid preparation.

17. The combination of an antibiotic with another antibiotic or with corticosteroids or other active substances should be prohibited. Antibiotics harmful to children (e.g. tetracyclines) should not be allowed to be manufactured in liquid form.

18. The combination of analgesics in any form is unacceptable as there is no, or only trivial, therapeutic advantage and such combinations increase toxicity, especially in the case of kidney damage and overdoses. The combination of analgesics with iron, vitamins, or alcohol is irrational and unacceptable.

19. The use of codeine in any combination form is not acceptable, as it carries no advantage and may be subject to abuse.

20. Vitamins should be prepared as single-ingredient products with the exception of the vitamin B complex. Vitamins of the B complex, with the exception of B12, may be combined into one product. B12 should always be produced as a single-ingredient injectable product for use by specialists only. Other members of the B complex may be produced as single-ingredient products (e.g. B1). Vitamins should not be allowed to be combined with non-vitamins, e.g. minerals or glycerophosphates. Vitamins should be in tablet, capsule, and injectable form only. The reason why no liquid forms should be permitted is the wastage of financial resources and the tremendous misuse that has occurred. An exception should be made for paediatric liquid single and multivitamin preparations (without vitamin B12, vitamin D, vitamin E and vitamin K and/or minerals) in bottles up to 15 ml with droppers.

21. No multiple-ingredient cough mixtures, throat lozenges, gripe water, antacids, etc. should be accepted (either locally manufactured or imported), as they offer no therapeutic advantages to outweigh their cost.

22. The sale of tonics, enzyme mixtures/preparations, and so-called restorative products flourishes on consumer ignorance. Most are habit-forming and, with the exception of pancreatin and lactase, are of no therapeutic value. Henceforth local manufacture or importation of such products should be discontinued. However, pancreatin and lactase should be allowed to be manufactured and/or imported as single-ingredient products.
23. Some medicines are being manufactured with only trivial differences in composition from other products but with a similar action. Such duplication confuses both patients and doctors and should not be acceptable in future.

24. Products whose therapeutic value is doubtful, trivial, or absent and products that are judged harmful or subject to misuse should be banned.

25. Prescription medicines and galenical preparations not included in the latest edition of the British Pharmacopoeia, the British Pharmaceutical Codex, or the United States Pharmacopoeia should be prohibited, unless there is enough evidence of need and of efficacy.

26. Certain drugs, having a favourable risk-benefit ratio, in spite of known serious side-effects and the possibility of misuse, should be permitted for restricted use by specialists.

27. Where a drug or a close substitute is produced in the country importation should not be allowed, as a measure of protection for local industry. This condition may be relaxed in some individual cases where local production is insufficient.

28. A basic pharmaceutical raw material that is locally manufactured should also be given protection. The role of multinational enterprises in providing medicines for this country is acknowledged with appreciation. In view of the manufacturing and technical know-how they possess for producing important and innovative drugs for the country, the task of producing antacids and vitamins should be entrusted to national companies, leaving the multinationals free to concentrate their efforts and resources on preparations not so easily produced by smaller national companies. Multinationals should, however, be allowed to produce injectable vitamins as single-ingredient products.

29. No foreign proprietary medicines should be allowed to be manufactured under licence in any factory in Bangladesh if the same or similar products are available/manufactured in Bangladesh, as this leads to unnecessary high prices and payment of royalties. In the light of this policy, all existing licensing agreements should be reviewed.

30. No multinational enterprise without its own factory in Bangladesh should be allowed to market its products by manufacturing them in another factory in Bangladesh on a toll basis.

The Drugs (Control) Ordinance, 1982

31. The Drugs (Control) Ordinance, 1982, was promulgated on 12 June 1982, but the Drug Act, 1940, was not repealed. This means that the Ordinance is in addition to the provisions of the Drug Act, 1940, and the Drug Rules, 1946. The provisions of the Ordinance may be summarized as follows. Out of a total of about 4000 brands of registered allopathic drugs, the registration or licence of 1666 brands of locally manufactured or imported drugs was cancelled. Under the Ordinance 299 brands are listed in a
schedule as harmful. These were destroyed by 12 September 1982. Under schedule II of the Ordinance 127 brands were to be reformulated by 12 June 1983.

32. The import, manufacture, and sale of 1240 brands listed in schedule III were prohibited after 12 December 1983. In a subsequent ordinance 71 brands and ointments listed in this schedule were allowed to be manufactured or sold after the expiry of the above scheduled time limit if they were registered again. The ordinance prohibits the manufacture of drugs under licence granted by a foreign company having no manufacturing plant in Bangladesh, if such drug or its substitute is produced in Bangladesh. However, manufacture of such products under existing licensing agreements continues till the expiry or termination of the period or validity of such agreements.

33. The manufacture or sale of any drug without the personal supervision of a registered pharmacist is prohibited. Under the ordinance a drug control committee has been constituted. Approval, suspension, or cancellation of registrations of drugs is now subject to the recommendations of this committee. The ordinance requires the manufacturer to adopt good practices for manufacture and the quality control of drugs as recommended by WHO. This makes the manufacturer responsible for producing drugs of standard quality. Any violation of that provision on the part of a manufacturer may lead to suspension or cancellation of his manufacturing licence.

34. The ordinance provides for control of advertisements in respect of drugs, with punishments for violations. Provision is made to penalize the manufacture or sale of unregistered, adulterated, spurious, or substandard drugs and the import of any drug or pharmaceutical material without the prior approval of the licensing authority. Penalties have been provided in the ordinance for selling or importing any medicine or pharmaceutical raw materials at prices higher than the maximum prices fixed by the Government. There is provision too for the punishment of thefts of drugs that are the property of the Government and of illegal advertisements and claims relating to medicine. The punishment for the theft of drugs from government stores or hospitals is rigorous imprisonment for a term that may extend to 10 years or a fine up to Tk. 2 lacs, or both. Provision has been made to set up separate drug courts, which will specifically try offences against the drug ordinance.

35. The ordinance provides for setting up a National Drug Advisory Council to advise the Government and to coordinate the various ministries. The Council has been set up, with the Minister for Health and Population Control as chairman. Provision has been made to fix the maximum prices of drugs and pharmaceutical raw material to be imported or sold.

36. No medicine of any kind can be manufactured or imported without registration with the licensing authority.

37. Under the ordinance unani, ayurvedic, homoeopathic, and biochemical medicines have been declared as drugs and therefore are now under the control of both the Drug Act, 1940, and the Drugs (Control) Ordinance,
1982. The existing unani, ayurvedic, and homoeopathic medicines were listed under three schedules as follows:

Schedule I: Permissible drugs
Schedule II: Drugs requiring changes of name

38. The Government adopted the following policy and guidelines in respect of unani, ayurvedic, and homoeopathic medicines: (1) general guidelines for the control of unani, ayurvedic, and homoeopathic medicines; (2) guidelines for the quality control of such drugs; (3) lists of essential, specialized and restricted drugs in the unani, ayurvedic, and homoeopathic systems of medicine; and (4) guidelines for evaluation of the recipes of such drugs. It also laid down that in dosage form no drugs should contain more than 5% alcohol, any metallic element, or any other ingredient proved to be poisonous or harmful. Measures should be taken so that no fungi grew in the product.

39. Within three months of its promulgation the Drugs (Control) Ordinance, 1982, was amended to allow time for certain items banned under the ordinance. It was further amended in July 1984, to remove certain difficulties in initiating legal proceedings against offenders and to provide for appeal from the aggrieved by an order or decision of the licensing authority in respect of registrations of medicines and their cancellation or suspension. The appeal is heard by the appellate authority, already constituted with the Minister for Health and Population Control as chairman and eminent physicians of the country as members. The 1984 amendment also prohibited the prescription of unregistered medicines.

The WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce

40. Bangladesh has not yet agreed to participate in the scheme because pharmaceutical raw materials, which are of vital importance, have not been included in it. Moreover, Bangladesh prefers to pursue an independent drug policy, including the quality control of imports and exports. The quality and safety of imported as well as local pharmaceutical products is a most active concern of the Government.

41. For quality control the Government has made provision for the periodic inspection of manufacturing and trading premises, random sampling at various levels of the distribution network, and analyses in the drug control laboratories. Drug testing is required for pre-registration evaluation as well as for post-registration surveillance. Properly equipped drug control laboratories are a prerequisite of a good quality control system. The facilities in the existing laboratories are inadequate. The Government has approved a plan for setting up a national drug control laboratory and several regional ones. These laboratories will require modernization with foreign help.
The drug supply system

1. The organization and supervision of the Hungarian drug supply system are the responsibility of the Ministry of Health. The legal basis is furnished by Government acts, especially the Health Act of 1972 and its executive order 16/1972 of the Council of Ministers, decrees and regulations issued by the Ministry of Health, and the authority given to the National Institute of Pharmacy (NIP) in respect of all regulatory measures.

2. Drug manufacture is confined to licensed state-owned manufacturing companies, 75% of the drugs used in Hungary being supplied by those manufacturers. The export and import of pharmaceutical products are carried out exclusively by Medimpex, a joint trading enterprise of the state-owned manufacturing companies. It imports medicaments for domestic consumption.

3. There is just one drug wholesaler in Hungary, the state-owned drug distribution enterprise, GYOGYERT, which is under the direct supervision of the Ministry of Health. GYOGYERT is the key organization in the Hungarian drug supply system; all pharmaceutical products, manufactured in the country or imported, are distributed by it to the pharmaceutical centres and hospitals.

4. The management of community pharmacies is the task of the pharmaceutical centres of the county councils. There are 20 county councils and consequently 20 pharmaceutical centres in Hungary. These centres provide the administrative apparatus for the management and maintenance of the community pharmacies in the county as well as storage depots and analytical and galenical laboratories. Drug substances and medicaments produced by GYOGYERT are distributed by the centres. Pharmacies have the exclusive right to compound, dispense, and sell medicaments over the counter. Hospitals, all of them state-owned, receive their drug supply directly from GYOGYERT.

Prescribing and drug availability

5. Drug prescribing is exclusively reserved to physicians (the limited rights of dentists are regulated separately by ministerial order). The right to prescribe some specified medicaments is restricted to specialists (for example psychiatrists). Some other specified medicaments can be prescribed by any physician on the basis of a diagnosis established by a specialist. A limited number of medicaments can be prescribed and used for inpatients only.

6. The question of prescription drugs is decided by the Ministry of Health. The overwhelming majority of medicaments are prescription drugs. Except for narcotic drugs (including codeine), psychotropic substances and

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1 The Director-General acknowledges with appreciation the contribution of this case study by the Government of Hungary.
some other sedatives, drugs for parkinsonism, stimulants, antibiotics, glycocorticoids, and some others, prescriptions can be validated by the prescribing physician for three refills during a period of 90 days.

7. The number of medicaments exempted by the Ministry of Health from prescription is about 100. Their ingredients are considered to be relatively safe and they are used mainly for symptomatic treatment. The guiding principle in selection is that the population should have access to drugs for the treatment of any symptom that does not necessitate the immediate intervention of a physician. Examples of such drugs are minor analgesics, antipyretics, sedatives, antacids, antitussives, laxatives, antidiarrhoeal preparations, disinfectants, and antihaemorrhoidal preparations. The dispensing of these non-prescription drugs is restricted to pharmacists, who must limit the quantity dispensed to a maximum of two weeks' supply.

8. Pharmacies can sell only medicaments, surgical dressings, specified herbal products, medicated food, some specified medical devices and health care products, veterinary medicines, and pre-mixes.

**Pricing**

9. The population in Hungary is entitled to medical care free of charge and to preferential treatment in relation to medicaments. In conformity with this principle there are no consumer prices in Hungary. At the moment of marketing a consumer fee, that is, the amount actually to be paid by the patient, is established by the Ministry of Health. For the establishment of the consumer fee the Ministry is guided by the principle that the population's contribution should cover 15%-20% of the real cost, this principle being applied in general to all drugs. The actual price of individual medicaments is based on health and social need considerations. Some medicaments (e.g., for diabetes, tuberculosis, epilepsy) are free of charge and so, like hospital treatment itself, are drugs used in hospitals. The actual consumer fee varies between 3 and 10 Forint (at present 50 Ft = 1 US$).

10. The difference between the manufacturer's price and the consumer fee is covered by the Government.

**Drug regulation**

11. In Hungary the National Institute of Pharmacy is the national drug regulatory agency. Its main responsibilities are as follows:

- selection of materia medica

- authorization of clinical trials in man with substances not previously used as medicines in Hungary
- drug registration
- supervision of drug production and manufacture
- drug regulation, including removal of unsuitable pharmaceutical products from the market
- study of drug utilization and updating of drug therapy
- supervision of drug information and monitoring of adverse drug reactions
- fulfilment of responsibilities within the context of international obligations for cooperation.

Criteria and mechanisms for drug registration

12. Hungary has a selective drug registration system, i.e., pharmaceutical preparations containing the same active ingredients in the same drug dosage form under different brand or generic names are in principle not registered.

13. In Hungary the NIP is authorized by the Ministry of Health to decide, on the basis of the results of pharmacological, toxicological, and clinical tests and following consultations with experts, whether or not the marketing of a new drug meets a health need. The aim is to provide the medical profession and the public with new pharmaceutical preparations of proved therapeutic value and at the same time to avoid the circulation not only of medicaments of doubtful therapeutic value but also of different but practically equivalent medicaments and unnecessary drug combinations. Through the existing selection system the number of registered preparations has been kept under reasonable limits. Other criteria for drug registration are standardized constant quality, relative safety, and efficacy.

14. The process of registration starts with the submission of preclinical data by the manufacturer to the NIP. All the requirements for such data are prescribed by the Institute. The data are scrutinized by the specialized staff of the Institute and evaluated with the aid of outside experts and expert committees. The outcome of a positive scrutiny and evaluation is a decision authorizing clinical pharmacological research in man. Unauthorized human experiments and the supplying to doctors of unauthorized new drug samples are prohibited.

15. Clinical pharmacological tests on man are carried out by specialized units of the Clinical Pharmacological Network, located in clinics and large hospitals. The results are evaluated by the NIP and outside expert committees. In the light of the results a decision is made whether or not to authorize clinical trials.

16. Controlled clinical trials are authorized by the NIP. The first investigators are designated by the Institute, an extension of clinical trials granted after evaluation of the first results by an expert
committee. Extension must be requested by the manufacturer. Clinical trials of new non-registered drugs cannot be carried out without the authorization of the NIP.

17. Evaluation of the clinical results by expert committees and formal approval of the therapeutic suitability of the new drug by the NIP are a prerequisite to registration. The manufacturer must submit his application for registration to the NIP. The format for the presentation of chemical, analytical, dosage, and biological data, the proposed control methods, the description of stability tests, etc. is prescribed in detail by the NIP. All the data are carefully evaluated and checked experimentally in the NIP's laboratories. At the time of registration the official quality specification of the drug preparation is established by the NIP.

Labelling, packaging, information for prescribers, advertising

18. Advertising pharmaceuticals to the general public is strictly prohibited in Hungary. The sources of information on drug use are different for patients and for practitioners. Information for patients is contained in labels and package inserts. Registration of a pharmaceutical preparation also includes prescription of the text of the label by the NIP and approval of the text of the package insert.

19. Information for practitioners is contained in leaflets, brochures of the manufacturer, and advertisements in medical and pharmaceutical periodicals intended for health professionals exclusively. The pharmaceutical industry must send information to every physician and pharmacy on each new drug at the time it is marketed. Authorization by the NIP is required for the texts of the leaflets and brochures mentioned and for the advertisements published in medical or pharmaceutical periodicals.

20. There is no sales representative system in Hungary. The manufacturers are authorized to maintain person-to-person contact solely with clinicians conducting clinical trials with their products.

21. The NIP's own drug information services comprise publications and management of the network of pharmacists specialized in drug information.

22. A small book, Guide for drug prescribing, containing all the necessary information on the Hungarian materia medica (composition, indications, contraindications, doses, side-effects, interactions, etc.) is published every two or three years. A periodical is also published and distributed free of charge; it contains information on new drugs, new indications, etc.

23. About 50 pharmacists working in pharmacies are trained by the NIP in drug information. They work in different parts of the country as information centres for physicians and pharmacists. They are independent of the pharmaceutical industry, consequently the lectures and information they give are objective and completely free of commercial bias.
Training and education

24. Pharmacists are trained in the pharmaceutical faculties of two medical universities, one in Budapest, the other in Szeged. Organization of the postgraduate education of pharmacists is the task of the department of pharmacy of the postgraduate medical school, which is based on the NIP. Postgraduate training covers 12 special branches of pharmacy.

25. Pharmacy technicians are trained in special secondary schools. Their postgraduate education is also organized by a special school.
NEW DRUG SUPPLIES MANAGEMENT SYSTEM
FOR RURAL HEALTH FACILITIES IN KENYA

INTRODUCTION

1. The Ministry of Health in Kenya has committed itself to a programme for improving the health services of the rural population of the country, which comprises the majority of Kenyans. At the heart of the programme is a network of rural health facilities - health training centres, health centres, and dispensaries. Currently, 227 health centres and 682 dispensaries are in operation, providing comprehensive health services. The administration and supervision are provided by district health teams.

2. Recognizing the adverse effects of the shortage of drugs, the Ministry of Health in 1979 carried out an in-depth analysis of the problem. The rural health facilities, often in very remote areas, came at the end of a long chain starting with the Central Medical Stores in Nairobi and passing through the district hospitals. Less than optimal planning at the Central Medical Stores, shortage of foreign exchange, and an unsuitable procurement policy often had the result that the drugs most needed by the rural health facilities were not available. Losses through pilferage or damage in transit made the situation worse. Patients would often be forced to walk many kilometres to the nearest government or mission hospital just to find drugs, thus bypassing the rural health facilities. This obviously gave rise to considerable socioeconomic problems.

3. The Ministry of Health has been fully aware of the problems created by the shortage of drugs, particularly in the rural health centres and dispensaries. It has already initiated action to alleviate the problems.

The problems

4. The major problems specifically identified were as follows:

(a) Shortage of drugs, owing to poor planning and procurement policies at the level of the Central Medical Stores, made worse by poor transportation and distribution. Many drugs destined for rural health facilities were diverted to district hospitals or lost through pilferage. Whatever drugs finally arrived at the rural health facilities were either grossly inadequate in amount or of the wrong type.

(b) Shortage of essential equipment, which was often either missing or in poor working order.

(c) Quality. The drugs supplied to rural health facilities were often of poor quality or time-expired.

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1 The Director-General acknowledges with appreciation the contribution of this case study by the Government of Kenya.
(d) **Inadequate diagnosis and prescribing.** Health workers were often unable to make an accurate clinical diagnosis or prescribe the right drug in the correct dosage. Much over-prescribing and polypharmacy, often at the insistence of the patient, only made the general drug shortage worse.

(e) **Attitude of patients.** Some patients had become accustomed to misusing the free health service, coming for trivial ailments and demanding different kinds of drugs, which would afterwards be thrown away or distributed or sold to friends and relatives. The health workers found it difficult to resist such pressures.

**THE NEW MANAGEMENT SYSTEM**

5. In response to these problems, the Ministry of Health in 1980 introduced a new system to ensure that rural health facilities would be supplied with the drugs they needed and health workers trained how to use them.

**Objectives**

6. The main objectives of the new management system are:

1. to ensure that rural health facilities are regularly supplied with adequate quantities of essential drugs according to the needs of patients and within budgetary limits

2. to ensure that essential drugs arrive at rural health facilities without loss or breakage and in good condition

3. to ensure that essential drugs are used by health workers as cost-effectively as possible, through training in better clinical diagnosis and patient management

4. to guarantee the quality of all drugs supplied, i.e., to ensure that they conform to international standards of purity and safety, are of fresh manufacture, and are suitably labelled and packaged

5. to inform and educate the public on the proper attitude towards drugs and the health services.

**Principal components**

7. **Essential drugs list.** On the basis of the WHO list of essential drugs, adapted to Kenya's morbidity patterns, a list was drawn up of 40 essential drugs for health centres and 30 for dispensaries. These have been found adequate for the rural health centres and dispensaries. It was also laid down that generic names only should be used in labelling and duplication, combinations, and sophisticated forms should be avoided.
8. **Essential equipment.** A list of medical equipment essential for rural health facilities was established by the Ministry. The equipment was distributed at the start of the new system together with the essential drugs.

9. **Drug supplies.** A fundamental principle of the new system is that rural health facilities should be supplied with enough, but not more than enough, of the essential drugs needed for their patient population, the needs being based on the disease pattern.

10. **Standard treatment schedules.** Correct dosages for different age groups, the duration of treatment, the precautions to be taken, etc. were established for all the drugs selected. The objective is to achieve a rational and effective management of basic health problems.

11. **Training.** An essential part of the new management system is the training of health workers to diagnose the common conditions better and to make more accurate prescription and referral decisions. Emphasis is placed on training in the examination of patients and diagnostic procedures making use of aids such as the WHO flow charts. Thorough information on the essential drugs is given - the indications, precautions, and side-effects, as well as proper storage and management.

**DRUG LEGISLATION AND QUALITY CONTROL**

12. The drug legislation came into force in 1964, but has undergone several revisions since, with additions and deletions. The legislation covers all the trade in pharmaceuticals as well as the conduct of the profession of pharmacy. It includes legal specifications for the manufacture, importation and exportation, and distribution and storage of pharmaceuticals, as well as requirements concerning advertisement, labelling, and packaging. The Pharmacy and Poisons Board is the authority responsible for the enforcement of the regulations. It performs the functions of a central administrative agency.

**The Pharmacy and Poisons Act (Cap. 244)**

13. The Pharmacy and Poisons Act is mainly concerned with the distribution of poisons as defined in the Act, but only very briefly and somewhat inadequately addresses the issues of manufacture, packaging, labelling, advertising, etc. The Act, however, specifies that the manufacture of poisons shall only be made from licensed or registered and approved premises; and that only those products whose manufacture has been approved by the Pharmacy and Poisons Board shall be manufactured. Most manufacturing enterprises have adopted the "Orange Guide" as their official guidelines to good manufacturing practices (GMP).

**The Dangerous Drug Act (Cap. 245)**

14. The Dangerous Drug Act is very comprehensive and detailed as concerns the handling, trade, and production of narcotic drugs.
15. The Food, Drugs and Chemical Substances Act, in the absence of a drugs act per se, contains supplementary legislation controlling the manufacture, labelling, and transport of drugs. It is, however, inadequate as it touches only the basic hygiene aspects of pharmaceutical manufacture.

Importation of drugs

16. Importation of drugs is granted only on authorization by the competent authority (the Pharmacy and Poisons Board) of the Ministry of Health, and only to licensed, authorized, and registered wholesalers (pharmaceutical distributors). Individuals and retail pharmacies may import drugs only by special dispensation, as for instance when an individual or pharmacy is the domiciled agent of an overseas principal.

17. Special provisions govern the importation of narcotic and psychotropic substances. They conform strictly to the guidelines established under the Geneva Convention I and II and the International Convention on Psychotropic Substances, to which Kenya is a signatory. The control authority maintains a record of all import authorizations issued in any one year. It also regularly forwards returns for both narcotic and psychotropic substances to the United Nations Narcotics Control Board.

18. The above acts also control the exportation of drugs from Kenya. Only authorized and licensed wholesalers and manufacturers may export drugs, authorization being provided by the appropriate export permit from the Ministry of Health. Records are maintained for all export authorizations granted in any year.

PROCUREMENT OF DRUGS

19. There are both statutory and administrative specifications regarding the labelling and packaging of drugs. The basic drugs purchased on tender by the Ministry of Health are obliged to have the statutory markings "KG.KMD" on the container or label. In addition, all the products must be appropriately labelled with the generic (and other) names, dosage, strength, presentation (formulation), quantity contained, manufacturing date, including the formula (composition), expiry date, batch, number, name, and address of the manufacturer and any special usage and storage precautions.

20. In the procurement of essential drugs for the new management system, strict specifications have been drawn up for drug type, dosage form, packaging, labelling, quality, and delivery. Before contracts are awarded, potential suppliers are visited and screened by joint Ministry of Health/UNICEF/WHO technical teams. As far as possible, local manufacturers have been favourably considered, as long as they fulfilled the necessary requirements for good manufacturing practices and quality. It is one of the management system's principles to give support to reputable local manufacturers and to build up the nation's independence and self-sufficiency for at least the basic essential drugs. As a check, samples are taken
randomly from stocks in the Central Medical Stores as well as in the rural health facilities and sent to UNICEF in Geneva for analysis. The results are usually obtained within three to four weeks.

**DRUG REGISTRATION**

21. The first edition of a Kenya Pharmaceutical Index listing all the drugs in the market was published late in 1984. Since the enforcement of product (drug) registration in April 1982 the proliferation of drugs in the market has been effectively curbed. To date there are between 5000 to 6000 drugs in circulation. Of these it is expected that only about 2000 items will have been registered by the end of 1985. Government institutions have a list of basic essential drugs comprising some 200 items from which they are obliged to draw their drug requirements. This list of essential drugs has been largely derived from the WHO model list of essential drugs. There are 40 drug items for health centres and 30 for dispensaries.

22. Each dosage form and strength requires separate registration. A technical evaluation committee is charged with scrutinizing and recommending for registration all the applications received. Product registration must be renewed every five years for products externally manufactured and three years for products locally manufactured. The specifications on product quality control in respect of registration are aligned to the requirements of the WHO guidelines on good manufacturing practices.

23. Owing to lack of physical, financial, and human resources, some of the regulatory control programmes are deficient, the lack of resources preventing the full application of a comprehensive system of drug quality assurance. The WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce consequently finds wide application. Kenya recently became a signatory to this certification scheme.

24. The authority to monitor and control the quality of drugs in our pharmaceutical supply system is vested in the Drugs Inspectorate Control Section of the Pharmacy Department of the Ministry of Health. The administrative and regulatory procedures for the control of pharmaceuticals, such as notification, authorization, or registration, are carried out by the Pharmacy and Poisons Board. Inspection, sampling, and analysis of pharmaceutical products on the market, supplemented by information from other sources (manufacturers, distributors, other regulatory agencies and advisers, investigations of reported defects) provide the basis for action to minimize the health hazards due to poor-quality products. These functions are performed by the Drugs Inspectorate Control Section.

25. Verification by inspection includes assessment of manufacturing and distributing firms as well as of retail and dispensing outlets such as pharmacies and hospitals. Drug quality surveillance should be supported by inspection and laboratory services, but in Kenya a government central analytical quality control laboratory is lacking.
The right to distribute

26. The regulations require that distributors should be authorized sellers of poisons or licensed wholesale dealers, with the business under the control of a registered pharmacist. A licence for this purpose is issued by the Pharmacy and Poisons Board. The distribution must be carried out from approved and registered premises.

The right to prescribe

27. National legal duties are imposed on such key persons as the pharmacist and the prescriber, who are involved in the final steps of the distribution of pharmaceutical products. These persons have statutory responsibilities concerning product quality. The pharmacist and prescriber also have the responsibilities placed on them by their professional standards and professional codes in relation to defective products.

28. There are no regulations or legislation obliging the prescriber to prefer a brand product to a generic equivalent or vice versa. Brands and generic products are given the same preference in regard to registration, quality control, trade, and use. In the public sector, however, more encouragement has recently been given to generic prescribing as a result of the essential drugs list mentioned above, in which the drugs are identified by generic or international nonproprietary names.

29. The right to prescribe drugs is vested by the appropriate legal and professional authorities in duly qualified and registered practitioners (medical practitioners, dentists, veterinary surgeons) or people approved or otherwise authorized by the Director of Medical Services.

Drug promotional activities

30. The importation, manufacture, distribution, and sale of drugs and other pharmaceutical preparations are controlled by the acts mentioned above. Under those acts the Pharmacy and Poisons Board licenses the various activities and persons or establishments concerned with pharmaceuticals and vets all advertising of drugs. It does not allow advertisement in the media of drugs for certain diseases and medical conditions listed in the schedule to the Pharmacy and Poisons Act or of certain psychotropic and narcotic drugs.

31. There are no standard regulations or format that must be satisfied before drug promotional activities may be allowed.

Pricing

32. The pricing of pharmaceutical products is not controlled in the same way as that of general commodity items. Normally the price of any drug is negotiated at a figure acceptable both to the supplier and to the Price Controller in the Ministry of Finance. Neither the Pharmacy and Poisons Board nor the competent authority in the Ministry of Health has any
influence in the pricing of pharmaceuticals. Once it has been determined, however, the price remains the same for all parts of the country.

Symposia

33. It is open to any establishment wishing to promote a new product or disseminate new or additional information on its own product to hold symposia. The only requirement is that the target groups for such symposia must be clearly defined. Such target groups are usually practising medical professionals or medical students. In this case the provisions concerning advertisement must be strictly followed. This does not preclude the provision of information to prescribers and other users in the form of texts and other information aids. Such technical information is disseminated by medical (sales) representatives, who are themselves required to be licensed as such for the purpose of possessing medical samples. The question of giving samples has been debated widely in the meetings of the Pharmacy and Poisons Board. Normally sales representatives are drawn from people who have been trained in the biomedical professions, such as pharmacists, pharmaceutical technologists, or nurses.

34. Thus the control the Ministry of Health exerts on the promotional activities and distribution of drugs by pharmaceutical manufacturers is as follows:

- the products manufactured are registered and licensed by the Ministry of Health
- the manufacture and distribution are carried out in and from registered and approved premises
- the manufacturer is under the supervision of approved persons who are technically qualified
- the distribution is effected under the supervision of a registered pharmacist
- the dissemination of technical information and the supply of medical samples are carried out by licensed medical representatives
- any advertisement complies strictly with the provisions of the Act.

Distribution

35. A major problem under the old system was losses on the way from the Central Medical Stores to rural health facilities, due to breakages, pilferage, careless handling, exposure to the weather, etc. Whatever drugs arrived at district hospitals, were usually retained by them for their own use.

36. Under the new management system drugs are packed at the site of manufacture in strong sealed kits so designed as to withstand rough handling, transport hazards, and the most inclement weather. The drug kits
are sent to the district hospitals, where they are stored in clean dry conditions before onward transportation under the supervision of district health teams to the rural health facilities. At no time may the kits be unsealed or opened before they reach the rural health facilities.

37. Excess stocks are collected once every three months by district supervisors, returned to the district hospitals, and redistributed to other health facilities that may have a greater need for them.

38. Drug kits are sent to the district every three months and to the rural health facilities every month, depending on the patient workload.

Control

39. Control of the essential drug supplies is carried out by the Ministry's Management Unit of Drug Supplies, working in close coordination with district and provincial health teams. A simple but effective bin card system is in use in the health facilities to give all parties a better check on supplies and use. This can easily be correlated with patient workloads and diagnoses/treatments, which have to be recorded accurately by health workers.

Organization and administration

40. At the start of the new management system a new unit was established in the Ministry of Health in Nairobi, whose task was to coordinate the implementation and running of the new system. This Management Unit of Drug Supplies to Rural Health Facilities (MDS), working as a staff unit in the Rural Health Project in the Ministry, has the following main functions:

- to review and update at regular intervals the lists of essential drugs, standard treatment schedules, and guidelines for clinical diagnosis
- to evaluate the adequacy of clinical diagnosis and management of patients in rural health facilities
- in liaison with the Central Medical Stores, to manage the procurement, storage, quality control, and distribution of essential drugs in accordance with the budget allocated
- to promote the training of district and provincial health teams and rural health facility staff in clinical diagnosis and patient management
- in consultation with district health teams, to determine drug requirements for rural health facilities.

The cost

41. It is important to note that the new management system in Kenya does not necessarily mean a vast growth in expenditure on drugs. The system is
based on the concept of rationing, that is, on a drug supply tailored to the patient workload and to morbidity, on the training of health workers to diagnose more effectively and treat more efficiently, and on the procuring of essential drugs as generics at world market prices; and it is expected that the rural health facilities will be able to provide a vastly improved service within budgetary constraints.

42. However, more important than cost is the benefit in terms of human wellbeing that the new management system will bring. Apart from the purely therapeutic benefits, an adequate supply of drugs increases the utilization of health services as a whole, fosters staff motivation and morale, and significantly improves the health care delivery system.

43. Although considerable savings are already apparent in drug procurement under the new system, as well as savings due to better packaging, distribution, and use, it is not to be expected that the new system will cost less than was spent on rural health facility needs previously. However, at that time the rural health facilities were seriously undersupplied. It is certain that the new management system will enable all Kenya's rural health facilities to be supplied with essential drugs adequately at much less cost than under the old system. Moreover, applying the same principles to the hospital service will no doubt have similar if not greater effects. The Ministry of Health is about to embark on this initiative.

Results

44. The new management system has been in operation for three years and covers all districts. The public is now using the rural health services much more than before, thus relieving the district hospitals of a heavy burden. Health workers are much more motivated in their work, having the drugs necessary to cope with the main diseases and conditions seen in rural health facilities. Transport, storage, and distribution have been simplified. Losses due to breakages, pilferage, and wastage have been eliminated.

45. Apart from health workers and patient satisfaction with and enthusiasm for the new system, another more objective benefit from the new system is already evident. Outpatient attendances at district hospitals are down by 30-40%. Patients are now returning to their rural health facilities, leaving district hospitals breathing space to attend to more serious or referral cases. Important socioeconomic and family benefits will ensue from this return to the local health facilities.
THE RATIONAL USE OF DRUGS

MEXICO: A CASE STUDY

1. The following account of the experience and activity of Mexico up to June 1985 in the field of drugs attempts to describe the control and distribution of drugs.

BACKGROUND

2. As a developing country in Latin America, Mexico has a pharmaceutical industry which must be placed in group 5 of those defined by Gerefi, Morrison, Fefer & Antezana in various documents published by the Pan American Health Organization. In a few particular respects, however, its situation differs from that described for the years 1977-1980 in those documents.

3. The present population of Mexico is already almost 80 million, 65% in urban areas and the remainder scattered throughout the country in communities of less than 2500 people. The annual population increase, which was 3.23%, has fallen to 2.6% in the decade 1975-1985. Notwithstanding this fall and optimistic assumptions concerning family planning, Mexico will have a population of 110 million by the year 2010. The morbidity and mortality rates are beginning to show the familiar dual trend of the more advanced developing countries; while mortality rates for respiratory and gastrointestinal infections and malnutrition continue to be high, chronic degenerative diseases and accidents are now among the 10 leading causes of death in the relevant age groups.

4. Although Mexico is at present in the fifteenth place in the world economy, the financial and economic crisis of the last three years has revealed structural weaknesses in the pharmaceutical industry in the country: a serious dependence on foreign imports of basic intermediates; control by the multinational industry extending from parent companies down to national subsidiaries; difficulty in obtaining appropriate technology for the Mexican industry; lack of coordination in research and development in the pharmaceutical field; all compounded by an unreasonably large and chaotic market for pharmaceuticals in the private sector.

5. In December 1982 and the first quarter of 1983 the country suffered severe shortages of drugs and intermediates, partly because of the chronic scarcity of foreign exchange. At that point the President, the Treasury and the Ministry of Health launched an emergency plan for the import or production of vital drugs during the crisis. Although the shortages no

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1 The Director-General acknowledges with appreciation the contribution of this case study by the Government of Mexico.

2 For example, PAHO/AMRO document CD29-DT-4, 1983.
longer exist, the Federal Government has subsequently undertaken a series of measures in the health, economic, financial, and structural fields as part of a national development programme to strengthen, stimulate, and regulate the pharmaceutical industry on a rational basis.

6. Fortunately a number of earlier developments helped the country to overcome the emergency by serving as an infrastructure on the basis of which new systems and mechanisms could be created. Briefly, they were as follows:

- From 1958 to 1960, when the Mexican Social Security Institute was rapidly developing into an organization able to provide health care of a high quality for its beneficiaries and the National Medical Centre was founded, Dr Bernardo Sepúlveda, whose death this year is deeply regretted, and a group of expert advisers in pharmacology and other related fields drew up the first list of essential drugs and the first National Drug Formulary. These two policy instruments were compulsory only for the Mexican Social Security Institute since at that time there was no real health sector in the sense in which we now understand it and as it operates today.

- In 1977 the National Formulary (Cuadro Basico) for Drugs in the Public Sector, containing 444 generic drugs and 636 presentations or dosage forms, was drawn up, with the aim of introducing it in all health care establishments. The same year saw the establishment of the Interministerial Commission on the Pharmaceutical Industry, which was composed of representatives of the Ministries of Trade, Finance, Health, National Heritage and Industrial Development, and Agriculture, and of the Mexican Social Security Institute (IMSS) and the State Workers' Institute of Social Security and Services (ISSSTE). This Commission proposed a set of minimum standards to be met for the facilities and equipment of the pharmaceutical industry, registration or authorization being accorded to the industries that complied with them.

- Since 1980 consolidated tendering for the procurement of drugs by the health sector has also become official practice, although this system is still being strengthened and perfected.

7. The above developments not only paved the way for the emergency to be surmounted but also led to the decision to establish and strengthen systems and mechanisms for the present and future development of the Mexican pharmaceutical industry.

STRUCTURE OF THE MEXICAN NATIONAL HEALTH PROGRAMME

8. The health sector in Mexico is headed by the Ministry of Health and also comprises the IMSS, the ISSSTE, the National System for Integrated Family Development, and the Medical Services of the Federal District.
The IMSS provides health care and other labour-related benefits and is made up of three major groups: (i) the Federal Government, (ii) employers, and (iii) industrial workers and other employees in commerce and services. All members and their families receive social benefits, which include the preventive, curative, and rehabilitative health care they require. The IMSS, which has been operational since 1944, covers the health care needs of about 30 million Mexicans and provides the drugs needed for the preventive care or treatment of the insured population at no additional cost over and above the general contributions paid by workers, employers, and the Federal Government to finance the Institute's total budget.

The ISSSTE comprises the Federal Government and the employees who work in the various departments and ministries that make up the Federal Government. Its activities are similar to those of the IMSS and it provides white-collar workers with health care and the drugs this involves. The ISSSTE provides services to about seven million people.

The Ministry of Health, financed solely by the Federal Government, is responsible for the provision of health services for the general population, i.e., those who have no social security cover. To this end hospital services are being decentralized to the States and the Federal District, so that they will be able to run hospital establishments and provide health care for deprived urban and rural populations. The Ministry of Health also has authority over the national health institutes, which are high-level teaching and research institutions. It provides health services for about 10 million Mexicans through its decentralized establishments and the national health institutes.

The other establishments that form part of the health sector cover a population of about 2-3 million.

About 50 million Mexicans thus have some kind of access to institutions that provide health care services and procure drugs for them. These 50 million Mexicans represent 65% of the total population of the Mexican republic. This is the majority of the population and therefore the main target of the Government's health programme.

The national health programme also includes activities in the field of environmental sanitation that must be carried out on an intersectoral basis throughout the country and activities to promote primary health care in accordance with the Alma-Ata Declaration.

NATIONAL FORMULARY FOR DRUGS IN THE HEALTH SECTOR

When the health sector was formally constituted by virtue of a resolution published in the Official Gazette of the United Mexican States on 9 June 1983 the President of the Republic, taking as a basis the experience of the IMSS and the official health system with the National Drug Formulary
as described above, established the National Formulary for Drugs and Other Inputs for the Health Sector. This new Formulary is considerably wider in scope, covering not only drugs but also laboratory reagents and medical instruments and equipment, dressings and other medical supplies, and relevant scientific information.

12. Under the provisions of the same resolution the Interinstitutional Commission on the National Formulary was set up as a working group of the Council for Public Health, a collegiate body under the authority of the President of the Republic and chaired by the Minister of Health. The resolution entrusted the Commission with the task of keeping the National Formulary under permanent review and making adjustments as necessary.

13. The Commission immediately established its own rules and proceeded in accordance with its mandate to set up special committees composed of representatives from the institutions of the health sector to deal with each section of the National Formulary. It also established relations with the various existing committees and internal commissions in each of those institutions.

14. A procedure was thus set up that would ensure the involvement of the component institutions of the sector in successive stages of the work, as well as providing for participation by experts in the various fields concerned, who were required to reach consensus on the final form of the various sections of the National Formulary.

**Formulation of the list of essential drugs**

15. Once the procedure described above had been established, the next step was to select the products that should be included in the list of essential drugs for the health sector. This was done on the basis of the following criteria:

1. selection of drugs with the greatest efficacy and the lowest risk
2. elimination of drugs superseded by others of better quality, and inclusion of new products of proven therapeutic value
3. deletion of duplicate drugs with the same pharmacological action
4. exclusion of unjustified combinations of drugs.

16. The above criteria are in line with the norms established by WHO and a number of other international agencies and follow the precedent established by the previous National Formulary for the public sector in that generic drugs and, whenever possible, single-component drugs are used, in accordance with modern pharmacological practice. The most authoritative recent publications on the subject were also consulted and the views of specialists heard before conclusions were reached on a number of points under discussion.
17. A variety of opinions were expressed and, although there were certain differences, which are only to be expected in matters of this complexity, consensus was achieved. This resulted in a list of essential drugs consisting of 329 generic drugs in 485 presentations or dosage forms. The list included 20 new generic drugs with 34 codes, while 148 generic drugs from the older National Formulary were excluded without in any way detracting from the therapeutic efficacy of the new list, since the drugs excluded were duplications and associations of drugs for which there was thought to be no justification and which were therefore considered unnecessary.

Preparation of the National Formulary for Drugs in the health sector

18. After careful selection of the products to be included in the list of essential drugs, the next step was to draw up the National Formulary for Drugs. This process took into account the established condition that the National Formulary should be an instrument to give clear, precise, and concise guidance to doctors in one of their most important activities, namely the prescribing of drugs. Consequently the Formulary was divided into 24 groups, in which drugs were mostly classified in alphabetical order according to their use in different specialties such as anaesthesiology, cardioangiology, and dermatology, or according to their use for specific diseases such as immuno-allergic, infectious, or parasitic conditions. In some cases classification is based on the main indication, such as analgesia or family planning; or on the composition of the drug, e.g. electrolyte solutions or plasma substitutes; or lastly, on the nature of biological agents, such as vaccines, antitoxins, and immunoglobulins.

19. Again following the established pattern, each of these groups was in turn divided into subgroups according to the specific therapeutic action of the drugs, so as to ensure to the greatest extent possible a systematic presentation of their pharmacological effects. The number of subgroups in each group obviously varies in accordance with the particular composition of the different groups.

The National Formulary as a guide to therapy

20. The new National Formulary has various important features that provide guidance for treatment. One is the informative text that precedes the subgroups and summarizes the therapeutic indications, undesirable effects, and contraindications. This material has been updated and arranged in a uniform manner to serve as a useful introduction to each chapter for rapid reference.

21. Another feature is the summary tables, in which a description is given of each individual drug. Generally speaking the format used in the earlier version of the National Formulary has been followed, so that it contains a series of columns for the initials of the family doctor, general practitioner, or specialist or the hospital, as required for prescription at different levels. It also includes the generic name of the drug, its code,
its dosage form and packaging, the dose and route of administration, and the
indications for adults or children. Some changes have been made to these
columns in order to make them consistent with the modifications to the
National Formulary.

22. The next two columns are of particular interest and contain first of
all the indications, carefully revised, followed by the contraindications
and undesirable effects. In the light of our better understanding of the
risks and hazards of the indiscriminate use of drugs, the contents of this
latter column are especially relevant. In the drafting process the
contraindications have been reviewed and updated and the list of undesirable
effects considerably extended; these effects are enumerated but no attempt
is made to rank them according to frequency of occurrence, and the list is
not exhaustive. Two further items, entitled "Cautions" and "Pharmacological
Interactions", have been added. The "Cautions" point to the particular care
with which the drugs should be used in certain specific circumstances, while
the "Pharmacological Interactions" indicate, to the extent that this is
known, the reciprocal effects of drugs within the body, which sometimes
enhance their activity and sometimes do the opposite, with all the
concomitant dangers and drawbacks.

23. In general, the old rule that the wrong dose of the right drug is just
as likely to result in failure as the administration of the wrong drug
should be accepted. The usual doses for the vast majority of cases have
therefore been indicated. However, in extreme situations and in other
special circumstances doctors must use their judgement and take account of
their colleagues' opinion to determine the appropriate use of drugs for the
particular needs of individual cases.

Exclusive packaging for the health sector

24. The institutions that make up the health sector have decided to adopt
an exclusive form of packaging for all drugs included in the National
Formulary. This is another distinctive feature of the Formulary and a sign
of cohesion among the institutions of the sector. In addition to the
practical advantages for the identification of drugs and their use by
patients, the intention is to stress the quality of the products selected
for the National Formulary. The institutions of the health sector have
published a Manual of standards for health sector packaging, which contains
all the relevant specifications so as to facilitate their uniform
application by suppliers.

25. Advances in pharmaceutical science, scientific innovations leading to
the development of therapeutically significant new drugs, and scope for
improvement of the list of essential drugs as contained in the National
Formulary result in the need for its continuous review and updating. Hence,
following the WHO recommendation that models should be used but adapted to
the particular needs and requirements of individual countries, the Council
for Public Health in 1985 published a supplement updating the National
Formulary for Drugs and incorporating the amendments and suggestions made by
the country's scientific community, doctors, pharmacists, and chemists, the
analytical quality control system of the health sector, and the pharmaceutical industry. Some 95% of the modifications concern points of detail relating to international nonproprietary names, specific salts and their active ingredients and, in some cases, dosages and dosage forms. Two further generic drugs have also been included and two excluded on the ground of their long-term toxicity.

26. The National Formulary for Drugs is now in use in 90% of the sector's institutions.

LEGISLATION ON DRUGS AND ON THE PHARMACOCHEMICAL AND PHARMACEUTICAL INDUSTRY

27. All the measures described are aimed at obtaining the best, most effective, safest, and least expensive drugs so as to benefit both the final consumer and the intermediary, i.e., the physician. It has therefore become very important to update and adapt the legislation to make it into an adequate and reasonable framework for activities.

28. The right to health protection has been embodied in the Constitution.


30. This legislation takes into account the history of the industrial infrastructure up to 1982, the critical drug shortage that occurred during the first quarter of 1983, and procedures and mechanisms for enabling Mexico, following a thorough analysis, to produce and regulate its own drugs rationally without neglecting the complex and expensive research and development work on genuine therapeutic innovations, including the biotechnical pharmacological revolution. Advances resulting from this work will be incorporated into the National Formulary for Drugs whenever justified, bearing in mind the need to encourage the national industry financed mainly with Mexican capital, but without discriminating against international industry insofar as it complies with general industrial, commercial, and health promotion policies.

31. The General Health Law that came into force on 10 July 1984 contains legislative provisions governing both the setting-up of pharmaceutical enterprises and their products, i.e., drugs as finished products made available to the public.

32. In order to make the legislation on the Comprehensive Programme and on the Pharmaceuticals Decree clear and comprehensible, rules for implementing the legislative measures were published, following negotiations and hearings, in October 1984. The Government encountered opposition, as provided for under the country's democratic system: 38 pharmaceutical companies established within the country, all of them branches of multinational concerns, challenged the three legislative measures enacted.
It should be pointed out that 38 other multinational companies and 308 national companies financed mainly with Mexican capital did not take any legal steps to challenge the measures. The four main points in the legislation that led to the objections were as follows:

(1) An inaccurate interpretation of the Programme and Decree as totally protectionist measures favouring the Mexican industry, which is to make greater efforts to bring about vertical integration in the national production of starting materials and active intermediates for the preparation of essential drugs in accordance with the health requirements of the Mexican people. This measure does not exclude or discriminate against multinational companies in regard to the manufacture of new pharmaceutical products.

(2) The use of generic names without the registered trademarks on all products on sale to the health sector in accordance with the National Formulary, and addition of the generic name to the registered trademark of products in the private sector that contain the same generic substances, formulae, and dosage forms as those in the National Formulary. In such cases the rules stipulate that the dosage forms of private sector drugs, like those in the National Formulary, must be adjusted to contain the same number of units as stated in the National Formulary and include on their labels the code number for the drug given in the National Formulary.

(3) Following the inclusion of a drug of therapeutic importance in the National Formulary, the rules provide for a period of three years' grace before the generic name must be added to the label and the dosage form adjusted.

(4) The elimination of drugs from the register - the provision that approved therapeutic novelties must be genuinely important advances, the refusal to register a large number of duplicate formulae (there are 68 trade names for the generic drug ampicillin, 112 registered trademarks for vitamin preparations and similar products, etc.), and the ban on irrational combinations of drugs that lead to large numbers of toxic reactions and to dosages that are not appropriate for individual therapeutic needs.

33. All these objections, which led to the challenge by 38 multinational companies, were the subject of negotiations with the Departments of Trade and Industrial Promotion and the Department of Health. The objections were given a full hearing and, after some minor concessions, they were approved in the Resolution establishing Rules for Implementing the Decree on Promotion and Regulation of the Pharmaceutical Industry, which was published on 2 April 1985 and annulled the previous resolution. The Comprehensive Development Programme and the Decree on the Promotion and Regulation of the Pharmaceutical Industry remained unchanged.

34. The present Resolution on Rules for Implementing the Pharmaceuticals Decree, which makes new national procedures for vertical in-depth integration compulsory, is consistent with the implementation of Mexican and
international joint investments and has led to 30 new tenders for the manufacture of pharmaceutical preparations and active intermediate substances included among the 70 listed as priorities, so that 40% of these substances are now being manufactured in the country as compared with 20% in 1982.

35. The practical implementation of the rule that the registered trademark must be accompanied by the generic or international nonproprietary name produced some opposition from the international pharmaceutical industry, which argued that the generic substances are not bioequivalent with the national products. Studies of the bioavailability and dissolution of some of these products have already been made, and show that some drugs from the international market present serious problems of absorption, pharmacokinetics, and pharmacodynamics as compared with similar products manufactured within the country (IMSS, 1984). Strictly speaking, this has created greater requirements in regard to the pharmacokinetics of the drugs, regardless of whether they are manufactured by multinational or by national companies, and the origin is not taken into account when conducting the analytical tests. Fortunately the quality control system of the health sector exercises strict control in this respect, only giving approval to optimum batches.

36. The Resolution also lays down the terms of reference and purposes of the semi-State drug companies Vitrium and Proquivemex, the only two semi-State pharmaceutical companies run by the Mexican Government, in respect of fundamental aspects that are also covered by the 1984 Decree on the Promotion and Regulation of the Pharmaceutical Industry. Vitrium manufactures starting materials and priority intermediates of drugs and active principles which private industry does not produce: vaccines, biologicals, oligopoly drugs, "orphan" drugs, and drugs for the health sector that are chronically in short supply. Proquivemex is responsible for the manufacture of some finished products on the list of essential drugs given in the National Formulary.

PRESENT STATUS OF THE PHARMACOCHEMICAL AND PHARMACEUTICAL INDUSTRY

37. Sales of drugs in Mexico currently amount to approximately US$ 1200 million. In 1982 the health sector accounted for 25% and the private sector for the remaining 75%. In 1985 sales to the health sector have increased to about 40% of the total.

38. Consolidated tendering for procurement of drugs and other supplies for the health sector underwent some changes in 1984. For the first time the total sales of Mexican companies to the public sector exceeded those of the multinationals, 53% as against 47% (44% and 56% in 1982), and a Mexican company now occupies first place in terms of sales to the health sector.

39. In 1982 there were 76 pharmaceutical companies in Mexico financed mainly by foreign capital, and their sales in that year accounted for 72% of the total market. The remaining 28% was distributed among the 242 companies financed mainly by Mexican capital. There are at present 380 registered
pharmacochemical and pharmaceutical companies, and the total share of sales of those financed mainly with Mexican capital, although still lower than that of the multinational companies, has increased to 38%. In 1981 only 11 Mexican companies were among the 50 pharmaceutical companies with the highest production and sales; in 1985 there were 16 Mexican companies in this group.

40. The pharmaceutical industry established in Mexico is not self-sufficient in active principles and intermediate materials for drugs. In 1982 approximately 80% of active principles and intermediates had to be imported, entailing an annual outflow of some US$ 250 million. This was the largest item of expenditure on imports in the sector total of US$ 300 million. Since income from exports was only US$ 100 million, there was a deficit of US$ 200 million. At present 40% of starting materials and basic intermediates are produced within the country and the aim is to attain 65% by 1988. In 1984, the trade deficit was US$ 106 million.

41. In contrast to the sector manufacturing finished drugs, the 60 pharmacochemical companies financed mainly by Mexican capital accounted for 65% of total sales in 1984, as against 46% in 1977, and have thus overtaken the multinational pharmacochemical companies.

42. As is evident throughout this document, the national policy of the pharmaceutical industry has been formulated and guided by the firm political, health, and industrial policy of the country's highest authorities, who despite the difficulties that have been encountered remain determined to achieve the objectives of the programme.

RESULTS AND CONCLUSIONS

43. The policy for the registration of new drugs can be seen to have undergone a substantial change: from July 1983 to June 1984 350 products were registered, 90% of them duplicating already existing formulae, but during the corresponding period in 1984-1985 only 57 products were registered, of which 8 were important novelties and the remainder were generic drugs identical with those in the National Formulary and single-component drugs.

44. Similarly, and in compliance with the Rules for Implementing the Decree, 1200 products intended for the private market had the number of units in their dosage forms adjusted by June 1985, and already display the generic name or international nonproprietary name together with the trademark. These 1200 private sector products represent 245 generic drugs contained in the National Formulary, i.e., progress has been made on about 75% of the process initiated in February 1985. The 1200 adjusted drugs are manufactured by 122 pharmaceutical companies, including 16 multinationals that have expressed reservations but have already complied with this provision under the new Resolution on Rules after lengthy talks and negotiations with the Departments of Health, Trade, and Industrial Promotion. It should be pointed out that these multinational companies explicitly consider that the step they have taken of their own accord will
facilitate settlement of the legal process instituted against the Federal Government so that the reservations can be withdrawn.

45. The new regulations concerning the General Health Law will enable the national health authorities to carry out the process of purging the registers by eliminating ineffective and obsolete products and, above all, by reformulating the numerous multi-component drugs or associations of drugs (50% of the total) that have been a feature of the irrational proliferation of trademarks in the private market.

46. The section of the National Formulary dealing with drugs has already been introduced in 90% of the health sector, and the section dealing with curative and prosthetic equipment in 100%. This has made it possible to strengthen bulk purchasing within the health sector by building up a grading system for suppliers, cutting costs, putting an end to discretionary expenditure and purchases, rationalizing the procurement of supplies and equipment, facilitating distribution and transport and, a very important point, genuinely promoting the industries manufacturing supplies and equipment, for the National Formulary is an instrument for and a guideline to the priority activities of the health sector.

47. These last three points give greater relevance to the measures taken to ensure the rational use of drugs in both prescribing and retailing and supply to the public. Even self-medication is becoming less chaotic. The measures also enable the trade authorities to fix equal prices for equal products, thus rationalizing the process and ensuring greater savings for the final consumer.

48. A programme of basic drugs derived from the list of essential drugs has been initiated. These drugs may be retailed freely at preferential prices on account of their high level of consumption.

49. Mechanisms for research and technological development in Mexico have since 1984 been effectively integrated and coordinated under the sponsorship of the State departments involved, higher education establishments, and groups of research workers in pharmacology and pharmacy, under the guidance of the Health Department and the National Council for Science and Technology. Industry has joined in this work, and 30 projects concerning new active pharmaceutical substances are already in progress. The research and development function within the companies has likewise been strengthened through a commitment to invest at least 4% of their sales of starting materials in this activity.

50. In September 1984 a standing committee for updating the Pharmacopoeia of the United Mexican States was officially set up. It has completed about 40% of its work.

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51. An endeavour has been made to summarize what Mexico has been doing to ensure the rational use of drugs. Although much still remains to be done, it is believed that the steps initiated and now in progress will provide a more rational basis for the control and distribution of drugs.
DRUG CONTROL AND DISTRIBUTION IN NORWAY

Introduction

1. The basic aim of a drug policy is to ensure that effective and safe drugs of good quality are available to cover the health needs of the country. A national drug policy should be considered as an integral part of any comprehensive health care policy. The formulation of national drug policies varies even between similar countries because of conflicting interests and different political, economic, and social pressures. It is influenced by such factors as:

- the health situation of the country
- the medical care system
- the education and training of health personnel
- the social security and health insurance schemes
- drug research and development possibilities
- the domestic production of drugs
- the determination of the demand for drugs
- the system of drug distribution
- the possibilities for evaluation and control of drugs
- international policies on medicinal products.

2. The implementation of a national drug policy requires a national drug control system. Drug control in all its aspects is a basic element in a rational drug policy, and a well functioning drug regulatory agency is a major instrument in implementing control.

3. Some drug control functions are listed in Fig. 1.

Selection of drugs

4. Since 1928 quality, safety, efficacy, and cost requirements have formed the basis for drug evaluation and registration in Norway. Some 10 years later the concept of need was included. The present criteria for selection of drugs are summarized below:

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1 The Director-General acknowledges with appreciation the contribution of this case study by the Government of Norway.
- selection should be based on scientific documentation
- the efficacy/toxicity ratio must be weighed against the severity of the disease
- new drugs should represent better therapeutic alternatives than those already on the market
- drug combinations should be avoided unless the combination shows a clear advantage over that of each ingredient
- there should be a clear-cut medical need for any new product
- the number of drugs should be limited
- approval should be given for a limited period (5 years)
- the drug may be restricted to the use of hospitals or specialists.

Additional criteria are price, local therapy traditions, etc.

The need clause

5. The assessment of needs forms the basis of most evaluations of programmes, products, or personnel. If there is no need to be met, there is usually no reason for determining the merit of a drug. This is obvious enough in a product or programme evaluation, but less true in other areas, e.g., aesthetic evaluation.

6. The term "need" may be defined in different ways and may differ from time to time and from one community to another. What is considered a dietary need in Norway would be regarded as somewhat of a luxury in many other parts of the world. The definition of need is a matter of considerable controversy, and even if we use a loose definition we shall almost certainly have to distinguish between needs and wants because we must rank for urgency.

7. According to the Norwegian regulations a pharmaceutical speciality must be medically justified and be considered to be needed. As the term "need" has not been defined more precisely, the registration board has had to establish its own practice. By using the need clause, the number of similar preparations and synonyms has been limited. By allowing some synonyms, price competition as well as the supply of drugs have been ascertained. Medical need has been used to avoid the registration of too many combinations.

8. A study of decisions taken by the Specialities Board during the years 1981-1983 shows that approximately 40% of applications are rejected. Need considerations are involved in more than 60% of the rejections. One striking effect of the assessment of need is the limited number of drugs on the market: about 1100 different drugs (1950 including different dosage
forms and strengths of drugs) are registered in Norway compared with 10 times that number in some other European countries. The number of drugs is probably also influenced by the small size of the Norwegian drug market.

**Fixed combinations**

9. When rationally formulated, combination drugs may provide greater convenience, cost less and sometimes confer greater therapeutic efficacy. However, when formulated solely for commercial purposes without regard to therapeutic principles, combination products are at best fraudulent and at worse dangerous.

10. The Norwegian policy has been based on some essential requirements:

   - each component should make a contribution to the claimed effect
   - a component may be added to enhance the effectiveness or safety of the active ingredient to minimize the potential abuse of the ingredient
   - the components should have approximately the same half-life and duration of action.

In addition, a patient population of reasonable size should benefit from the combination. The limitation of the number of fixed combinations has been made possible by using the need clause.

11. Reasons advanced for the limitation of the number of drugs are simplicity, safety, and economics. The physician has the possibility of working with an armamentarium he can keep in mind. In the distribution chain both the wholesalers and the pharmacies can keep a limited number of drugs in stock. No unneeded preparations clutter the shelves. The total drug bill is kept down to a reasonable level.

12. By including the need clause in the Norwegian legislation some 40 years ago, a social dimension was introduced into drug policy at a very early stage. Drugs were not only assessed from a scientific or technical point of view but also in the light of health priorities and the delivery of health care to the population as a whole.

13. The WHO approach on essential drugs corresponds very well with this way of thinking. The report on the selection of essential drugs is of importance not only to developing countries but also to developed countries. The Norwegian registration policy has for several decades demonstrated that it is possible to limit significantly the number of drugs on the market without detrimental effects on patients.
Advertising

14. In Norway all advertising, price lists, catalogues, etc. must be approved before use. This provision applies to advertising both to the public and to physicians. Advertising must be moderate and objective, not give a misleading or exaggerated impression of the product's medical value, and not be so formulated as to encourage unnecessary or non-medical use of the product. Any advertising of non-registered specialties or of drugs included in the Pharmacopoeia or approved formularies is prohibited.

15. Advertising of drugs to the public is permitted only for non-prescription drugs and on certain conditions. Drugs may not be advertised on radio or television or in cinemas, public premises, or streets or roads.

16. Advertisements to physicians, dentists, and veterinarians must contain only generally approved indications. Quotations, curves, etc. from medical literature should be adequately reproduced with a complete indication of the source. The advertising must state the composition of the product, the contraindications, and the most important side effects. If a generic name exists, it must be clearly indicated. There are also strict rules on the distribution of samples.

17. The pharmaceutical industry spends a substantial amount of its budget on marketing. During recent years it has put more stress on the use of manufacturers' representatives in its promotional efforts. It commonly arranges symposia and smaller product-oriented meetings in hospitals and pharmacies. Another trend is the extensive use of new technical equipment such as video cassettes.

Information

18. To counteract the promotional activities of the pharmaceutical industry, various initiatives have been taken to produce prescriber-oriented information from sources independent of the producers such as:

- drug information bulletins
- drug sheets for new drugs
- comprehensive therapy-oriented booklets for all major therapeutic classes and problems
- therapy-oriented drug formularies giving comparative criteria for selection by the prescriber
- national and local (clinical pharmacology and hospital pharmacy units) drug information centres
- drug information to the public (pamphlets, books).
19. In Norway a distinct academic institute, the Institute of Pharmacotherapy, was established at the University of Oslo as early as 1964. In addition to its academic staff the Institute has a network of some 10 therapy groups. Literature on relevant drugs and their use can be obtained through the Institute, and 4-6 pages of digested information are published as therapy letters in most issues of the *Journal of the Norwegian Medical Association*.

**Pricing**

20. Norwegian price control covers all categories of pharmaceutical preparations, both prescription and non-prescription drugs. Price control seems rather comprehensive compared with the situation in other European countries. According to the Norwegian legislation the price of a pharmaceutical speciality shall not be "in disproportion to its value". The cost of a drug should be set against its direct or indirect benefits compared with alternatives. Data on these matters are scarcely available in optimal form, most countries appearing to adopt an arbitrary approach. In Norway price consideration is an integral part of the registration procedure. Negotiations are conducted with the manufacturer to agree upon an acceptable price. Prices of new products are compared with the prices of similar products on the market and with the prices charged in other European countries, particularly in the country of manufacture.

21. It is less difficult to judge whether a price increase is reasonable. In many countries the authorities have concentrated on this kind of control. In recent years the Norwegian public health authorities and the pharmaceutical industry have developed models for price adjustments. In these formulas inflation, changes in exchange rates, etc. are taken into account.

22. Measures need to be taken to obtain a greater insight into the cost of developing, producing, and marketing drugs. A greater degree of openness on these issues could lead to more equitable policies.

**Distribution system**

23. In establishing a pharmaceutical service one of the basic requirements must be that patients have a safe and reasonable access to medicines, appliances, and other goods for medical use. This implies a sufficient number of pharmacies, an even geographical distribution, opening hours according to the patients' needs, an adequate stock of medicines, and enough qualified personnel. In most European countries the geographical distribution of pharmacies is controlled.

24. All the Scandinavian countries have a rather high population/pharmacy ratio. However, it is always dangerous to use averages. On the face of it, in countries with a low population/pharmacy ratio the public has more convenient access to a pharmacy. This may not necessarily be true. Where there is no control over the establishment of new pharmacies it may well be
the case that the population per pharmacy in the highly populated areas is substantially lower than the figures indicate and that the pharmacies in less densely populated areas serve a much larger number of people spread over a wide geographical area. Within the 19 provinces of Norway the population per pharmacy varies from 20,000 in certain rural areas to 10,000 in the Oslo area.

25. The Directorate of Health decides whether pharmacies shall be established or closed. They are established when it is desirable or necessary from the point of view of the public. The Board of Health or the local authorities are responsible for raising the question of establishing a new pharmacy when there is a need for it. The decision to open a pharmacy is based on such considerations as population per pharmacy, distance between pharmacies, and transport facilities. There are more than a few pharmacies in Norway that do not have enough business to make them profitable. Nevertheless, they must be maintained for the doctors and people of small isolated communities who would otherwise be put to no end of delay and trouble to get medicines. Here private enterprise would fail if social control was not exercised. To keep these pharmacies going the Government has set up a tax system that evens out the inequalities of income stemming from either better or less favourable locations.

26. The system of tax and subsidies is of fundamental importance for the operation of Norwegian pharmacies. The Parliament imposes the tax each year. The tax is progressive and is calculated on the basis of the annual turnover of the individual pharmacy. The greater part of the tax is used to subsidize pharmacists whose profit patterns are not satisfactory. The subsidies are not granted automatically, but only after consideration of the accounts, especially with respect to wholesale costs, the cost of wages, and depreciation. If the costs are within acceptable limits, all pharmacists may rely on making a reasonable livelihood.

27. The wholesale distribution of pharmaceutical products in Norway is carried on by a state monopoly, Norsk Medicinal Depot (NMD). The main premises of the NMD are in Oslo; branch depots have been established in three other regions of the country. Although pharmacies may vary widely in size and many are situated at a great distance from the nearest branch depot, the prices charged are the same, irrespective of the quantity ordered or the delivery distance. All orders are processed with the aid of computers, and the computing unit provides drug statistics for administrative, scientific, and other purposes.

28. Part of the net income of the NMD is used for supporting the Institute of Pharmacotherapy, which provides the medical profession with information on drugs. It is also used to support clinical pharmacological research. The NMD also pays transport costs from the pharmacies to the patients.

29. Towards the end of 1984 there were 263 pharmacies in Norway, with a few branch pharmacies linked to larger pharmacies. The sale of medicines is generally restricted to pharmacies only, but to meet the needs of the public in some areas, mainly areas where the population is insufficient to support a pharmacy, sales from other nominated outlets are permitted. These 1300
outlets are subject to control by a pharmacy, and only prescription medicines are distributed from them. All the Scandinavian countries operate this system of distribution. The policy of restricting to pharmacies the right to sell medicines reflects recognition of the important protective role played by pharmacists in health care. The public accepts this pattern of medicine distribution.

30. In addition to dispensing prescriptions, the pharmacist sells medical products, dressings and surgical appliances, and other health and hygienic preparations. More than 90% of sales consist of pharmaceuticals; the other products account for less than 10%. The items that may be sold in a pharmacy are restricted; such things as photographic goods, optical goods, or hearing aids are not available from Norwegian pharmacies.

31. The Norwegian pharmaceutical service is characterized by its exclusively professional nature and the very strict government control over both professional and economic matters.

**Drug utilization**

32. When the NMD was established a unique opportunity arose for obtaining data on the overall sales of pharmaceutical specialities and raw materials. Since the start of the NMD's operations an integrated on-line computerized system for drug purchasing, sales, invoicing, and stocktaking has been gradually developed. The NMD has also paid attention to the medical advantages of having convenient drug sales and utilization statistics.

33. A drug classification system has been developed. This system - the ATC Classification System - is based on the same main principles as the International Marketing System anatomical classification system, extended to include chemical groups and substances.

34. As part of an international collaborative effort the NMD has also contributed to developing a convenient methodology for establishing comparable drug statistics within and among countries. For this purpose a "defined daily dose" is used as a unit of comparison. A complete list of daily doses for all drugs given for systemic use in Norway has been available since 1975. Such daily doses have now been defined for most of the drugs registered in the Nordic countries. With the data for drug sales in terms of defined daily doses per unit time and population, it is possible to estimate roughly the number of patients being treated with a drug or group of drugs within the country or region. Another advantage of using this unit of measurement rather than a monetary unit is that the unit is independent of price and currency variations with time and among countries.

35. Drug utilization data may be used for the following purposes:

- to describe patterns of drug use
- to look at the development of therapeutic profiles with time
- to make rough estimates of the number of patients exposed to various drugs
- to measure the effects of educational, information, and regulatory efforts, price policies, etc.
- to define areas for further investigations of the efficacy and safety of drug therapy
- to indicate overuse, underuse, misuse, and abuse of drugs
- to estimate drug needs in terms of morbidity patterns, thus aiding in the planning of drug selection, supply, and distribution.

Drug utilization data should be part of the material that drug policy discussions are based on.

36. A detailed monitoring system for drugs covered by the Single Convention on Narcotic Drugs makes it possible to follow the prescribing pattern down to each single drug, doctor, and patient. This system has proved useful in the control of such drugs. The number of prescriptions for narcotic drugs issued in outpatient facilities decreased substantially in the period 1970-1980.

* * *

Comments and conclusions

37. How can we promote the rational use of drugs? The problem is complex and heterogeneous. From a global perspective the level of sophistication in the developed countries may appear irrelevant to the needs of the less developed countries, where the major problem may still be a desperate lack of proper facilities, including professional manpower at most levels, money, and even the most important drugs. To what extent can we assist and give advice to others on the basis of our own experiences? To what extent are our criteria for the evaluation of drugs generally valid?

38. The Norwegian criteria for registration of drugs have been much discussed, especially the medical need requirement. By including the need clause in the Norwegian legislation some 40 years ago, a social dimension was introduced into drug policies at a very early stage. Drugs are assessed not only from a scientific or technical point of view but also in the light of the health care of the population as a whole.

39. The WHO approach on essential drugs corresponds very well with the Norwegian approach to drug registration. The report on the selection of essential drugs is of importance not only to developing countries but also to developed countries. The Norwegian registration policy demonstrates that it is possible to limit the number of drugs on the market significantly without detriment to the patients.
40. In examining the solutions in various countries, one must give consideration to the historical development of health care, geographical conditions, and other factors which may have considerable influence. While Norway has one of the largest territories of European countries, it is one of the most sparsely populated, with only four million people. The southern part of Norway reaches as far south as the northern tip of Scotland. The northernmost tip is found at 71°12N, that is about 1000 km further north than Anchorage, Alaska. About one-third of the territory, with one-twelfth of the population, lies north of the Arctic Circle. Providing a good pharmaceutical service to the whole population under such conditions may require special arrangements, e.g. as regards the remuneration of pharmacists. The system of tax and subsidies is of fundamental importance for the operation of Norwegian pharmacies, enabling all pharmacists to gain a reasonable livelihood. One obvious advantage is that the Norwegian pharmacist can devote most of his time to professional matters, and conflict with commercial interests is to a great extent avoided. The Norwegian pharmaceutical service is self-financing; any increase in services must be paid for by price increases or by cost reductions in other parts of the system.

41. The Norwegian pharmaceutical service is characterized by its exclusively professional nature and the very strict government control of both professional and economic matters.

42. The establishment of the Norsk Medicinal Depot - a state monopoly for the import and wholesale distribution of drugs - has been an important tool not only for the distribution of drugs but also for the support of drug information and research and the improvement of drug utilization.

43. In small countries only limited resources are available and extensive programmes for the continuous evaluation of all kinds of drug therapy problems are beyond reach. This situation calls for international cooperation. Within the Nordic area the control authorities have for many years maintained close cooperation on the evaluation, standardization, and post-marketing control of drugs, including statistics on medicines. In recent years this cooperation has been further developed to include the harmonizing of requirements for clinical trials, application forms, labelling, etc.

44. Drug problems are international by nature. Norway contributes to several activities within the drug field such as the WHO drug action programme, including the development of drug policies, essential drugs programmes, and the training of health personnel. It supports the international control of dependence-producing drugs and, at the regional level, supports and participates in drug utilization studies, studies of drug regulation, etc. Through bilateral assistance to and cooperation with other countries such as Botswana, it has gained experience and developed new approaches to drug problems that could serve as useful models for future work.
FIG. 1. *Drug control functions to be executed by official bodies*

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DRUG MARKETING PRACTICES

Regulatory control of medicines

1. The United Kingdom has a comprehensive system of controlling human medicines which has developed over the years.

2. High standards generally existed in the pharmaceutical industry, although until 1964 there was no necessity for a manufacturer to seek approval from an independent body before commencing clinical trials or putting a new drug on the market in the United Kingdom. These matters did not come under control until the Committee on Safety of Drugs was established in January 1964 in consultation with the medical and pharmaceutical professions and with the pharmaceutical industry following the thalidomide disaster.

3. Although the terms of reference of the Committee were to review the available evidence for new drugs and to advise on their toxicity, the Committee had no legal powers and operated strictly on a voluntary basis. A very important consideration to the successful operation of this system was that the major pharmaceutical manufacturers, members of the Proprietary Association of Great Britain (PAGB) and of the Association of the British Pharmaceutical Industry (ABPI) agreed to seek the Committee's approval before commencing clinical trials with a new drug and also before placing it on the market. The voluntary system worked well but it was realized that this was only an interim measure until comprehensive legislation could be established to provide legal controls over the supply and sale of medicines.

4. The Medicines Act (1968) is a comprehensive piece of legislation. It was implemented in September 1971 and exercises control over the manufacturer, importation, sale and supply, labelling and advertising of medicines. A Medicines Commission has been established to give general advice on the various aspects of the enforcement of the Act. It also functions as an appeal body for the activities of a number of expert advisory committees. In this context, the best known of these expert committees is the Committee on Safety of Medicines (CSM) which replaced the Committee of Safety of Drugs (CSD) in 1971.

5. The Biological Standards Act (1975) established the National Biological Standards Board. This Board, appointed by United Kingdom Health Ministers and funded by the Health Department, is responsible for standards and control of biological substances, i.e. substances whose purity and potency cannot be adequately tested by chemical means such as hormones, blood products and vaccines. The Board operates through the executive arm, the National Institute for Biological Standards and Control.

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1 The Director-General acknowledges with appreciation the contribution of this case study by the Government of the United Kingdom of Great Britain and Northern Ireland.
6. Before a clinical trial on patients can be conducted on a new drug or a new drug marketed in the United Kingdom, the supplier must hold a valid Clinical Trial Certificate (CTC) or Product Licence (PL). Studies in normal healthy volunteers are not subject to the Medicines Act and notification to the Licensing Authority is not required. In practice many clinical trials are carried out under the exemption scheme introduced in 1981 (see paras 14-17).

7. Licences are issued by the Licensing Authority which acts for the Health Ministers. In practice the licensing of human medicines is handled by the Medicines Division of the Department of Health and Social Security (DHSS), staffed by a total of 19 doctors, 81 pharmacists, 158 administrators and four lawyers.

8. The Act defines a medicinal product as a substance or article intended for use mainly or wholly for a medicinal purpose for administration to human beings or animals.

9. In determining whether licences should be issued, and the conditions under which they should be issued, the Licensing Authority obtains advice on the quality, safety and efficacy of medicines from various advisory committees and the National Institute for Biological Standards and Control as appropriate. These advisory committees consist of independent experts such as hospital clinicians, general practitioners, pharmacists and clinical pharmacologists, not the staff of the DHSS, and are appointed by Ministers on the advice of the Medicines Commission. The relevant advisory committees are:

(i) Committee on Safety of Medicines (CSM). This committee advises the licensing authority on questions of the safety, quality and efficacy of new medicines for human use. It is also responsible for collecting and investigating reports on adverse reactions to medicines already on the market. A number of sub-committees have been established to assist the main committee in its work.

(ii) Committee on the Review of Medicines (CRM). This committee advises the licensing authority on the review of the safety, quality and efficacy of products already on the market.

(iii) Committee on Dental and Surgical Materials (CDSM). This committee as its name implies, provides advice on a range of products which fall outside the expertise of the CSM.

10. The British Pharmacopoeia Commission (BPC) is responsible for preparing future editions of the British Pharmacopoeia and for selecting non-proprietary names for medicinal substances.

Clinical Trial Certificates

11. A clinical trial in the terms of the Act is an investigation, or series of investigations, consisting of the administration of one or more medicinal products, where there is evidence that they may be beneficial, to a patient
by one or more doctors or dentists for the purpose of ascertaining what effects, beneficial or harmful, the products have.

12. The Licensing Authority does not lay down rigid requirements concerning the data which must be provided before authorization can be given for the clinical trial of a new drug. It issues guidelines for applicants. Essentially the application will consist of a detailed clinical trial protocol together with the supporting experimental animal data. The latter will include: the chemistry, pharmacy and pharmacological activity; pharmacokinetic studies in animals which provide information on the likely absorption, distribution and excretion in man; preliminary metabolic studies in man may also have been performed. Other data received at this stage will include acute and chronic toxicity studies and information on possible effects on reproduction. Taken together these data give information on the therapeutic potential of the new drug and on its likely margin of safety. Details of animal and clinical studies performed abroad are relevant and will be considered.

13. These data are assessed by the professional pharmaceutical and medical staff of Medicines Division of the Department of Health and Social Security (DHSS) and are then referred to the relevant Sub-Committees of the Committee on Safety of Medicines. Most applications are referred to the Sub-Committee on Chemistry, Pharmacy and Standards and to the Sub-Committee on Safety, Efficacy and Adverse Reactions. A separate Sub-Committee considers Clinical Trial Certificate applications for biological substances. If the data are considered to be satisfactory, the Committee on Safety of Medicines will advise that a Clinical Trial Certificate can be issued by the Licensing Authority for the supply of the drug for the specified trials and clinical indications detailed in the application. It is important to note that the holder of the certificate has an obligation to inform the Licensing Authority of any serious or unexpected adverse effects which occur during the course of the trial. Rights of appeal against a decision to refuse a Clinical Trial Certificate are the same as detailed in the section on product licences.

Clinical Trial Exemption Scheme (CTX)

14. The Clinical Trial Exemption Scheme (CTX) came into operation on 11 March 1981 to provide the statutory basis for a new scheme under which pharmaceutical companies may secure exemption from the need to hold a Clinical Trial Certificate and proceed to rapid clinical trial for chemicals of interest as prospective medicinal products. This has been a major advance in permitting studies of promising compounds at an early stage so that manufacturers can decide whether to continue with further expensive studies or to discontinue work on the compound. The scheme also effectively encourages clinical trials to be performed in the United Kingdom rather than elsewhere. Since its inception the scheme has been well received by industry and has been an undoubted success.

15. The basis of the CTX scheme is that together with a detailed clinical trial protocol, summaries of chemical, pharmaceutical, pharmacological,
pharmacokinetic, toxicological and human volunteer studies may be submitted instead of the additional details normally required for a CTC or PL application.

16. This exemption scheme is based on the requirement that: (a) a doctor must certify the accuracy of the data; (b) the supplier undertakes to inform the Licensing Authority of any refusal to permit the trial by an ethical committee; and (c) the supplier also undertakes to inform the Licensing Authority of any data or reports concerning the safety of the product.

17. The Licensing Authority has 35 days in which to consider and object to the application if it wishes; an additional 28 days may be invoked if necessary. If the Licensing Authority refuses the exemption then the applicant has no right to make representations but will need to apply for a Clinical Trial Certificate in the usual way.

Product Licences

18. A Product Licence authorizes the holder to sell and supply the named product. A Product Licence also applies where the licence holder has made arrangements for a supply which is manufactured elsewhere. The Product Licence thus covers all the main activities associated with the marketing of a pharmaceutical preparation.

19. Applications for Product Licences are made to the Licensing Authority. They must be accompanied by the relevant supporting data relating to pharmaceutical quality, safety and efficacy for the proposed indications. Detailed guidelines on quality, pre-clinical testing and clinical trial requirements are issued by the DHSS. The Licensing Authority must satisfy itself regarding the quality, safety and efficacy of the product before issuing a licence. The "need" for the product, its price and its efficacy compared to existing products are not considered. Applications are assessed by the professional staff of Medicines Division and referred to the appropriate advisory committee, usually the Committee on Safety of Medicines. If the Licensing Authority wishes to refuse an application the applicant has the right to make representations, in writing or orally, to the Committee; the applicant also has the right to make further representations to the Medicines Commission if the Licensing Authority still intends to refuse the application after considering the representations made before the Committee. In all cases the various advisory bodies only provide advice - the Licensing Authority is the only body with power to grant or withhold licences, although the advice of the advisory committee is nearly always accepted.

Adverse reactions voluntary reporting system

20. A most important aspect of the United Kingdom regulatory system is the scheme provided by the voluntary reporting of adverse reactions to marketed drugs.
21. Since most serious adverse reactions are rare events they are unlikely to be detected in early clinical trials. The problem is essentially one of numbers since relatively small numbers of patients are exposed to a new drug before it is released on to the market. Marketing may, therefore, be the first adequate safety trial.

22. The main functions of the adverse reaction reporting system are (i) to provide an alerting signal of a risk due to a particular drug, (ii) to provide confirmation of an alert detected by some other method and (iii) to provide data to assist in the evaluation of comparative risks of related drugs.

23. The input to the system is essentially derived from the spontaneous voluntary reporting of adverse reactions by practising physicians on the prepaid postage reporting forms which are distributed widely to the profession and to the pharmaceutical industry. Other important sources of information are the Government's Office of Population Censuses and Surveys (death certificates, congenital abnormalities, cancer registers and mortality statistics), professional publications and the WHO adverse reaction monitoring system in Uppsala, Sweden.

24. Approximately 12,000 reports are received per annum and some 145,000 have been enter into the Adverse Reactions Register since it was initiated in 1964. It must be emphasized that all reports are treated in the strictest confidence and the identity of the patient or reporting doctor is not revealed without the written permission of the latter. The information is stored by computer after evaluation by the medical staff of the DHSS. Problems signalled by this system may lead to immediate action or initiation of special studies involving follow-up by a team of 200 part-time medical officers who can interview doctors in any part of the United Kingdom. After consultation with the pharmaceutical company and presentation of the problem to the Committee on Safety of Medicines through the Sub-Committee on Safety, Efficacy and Adverse Reactions (SEAR), action may be taken voluntarily by the manufacturer, or the Committee may decide to issue a letter in the medical journals or to send an individual letter to every doctor (and possibly dentist and pharmacist) in the United Kingdom, or to publish a statement in the Adverse Reaction series (which first appeared in 1964) or in Current Problems (which first appeared in 1976). This may be accompanied by the publication of a scientific paper in the case of a detailed study. Occasionally, this action will result in a variation to the Product Licence for the drug concerned or, rarely, to withdrawal.

25. Since the reporting of adverse reactions by the practising doctor is voluntary, the most serious limitation of the system is under-reporting, since only a proportion of those adverse reactions which actually occur are reported. An indication of drug usage is often valuable in assessing the importance of a problem, and prescribing statistics from a sample of prescriptions in general practice are often helpful.
Harmonization within the European Community


27. A move towards harmonization within the European Community was taken when Council Directive 75/319 was adopted in 1975. It provides for the setting up of a Committee for Proprietary Medicinal Products (CPMP) in Brussels, and a procedure for obtaining marketing authorizations throughout the community. The CPMP is made up of one official from each of the member states. It discusses problems of common interest, particularly on exchange of information on adverse drug reactions, and it plays a central role in the community procedure for obtaining marketing authorizations. This procedure is invoked when a company obtains a marketing authorization in one member state and wishes to obtain similar authorizations in five or more other member states. The application is forwarded by the first member state to the EEC Commission and to the other states in question. The various states concerned have 120 days in which to grant marketing authorizations or raise objections.

28. In November 1985 Council Directive 83/570 comes into force. This Directive amends the earlier ones with respect to the format and data requirements for applications for marketing authorizations throughout the community. It also changes the community CPMP procedure.

Brand and generic names

29. The British Pharmacopoeia Commission is authorized by the Medicines Act 1968 to assign generic names to drug substances and to other materials used in the formulation of medicines. The names are known as British Approved Names (BAN).

30. This work is carried out in very close collaboration with other national nomenclature agencies, such as the United States Adopted Names Council. The endeavours of such national agencies are co-ordinated by the World Health Organization which publishes most of the names as International Nonproprietary Names (INN). The Member States of WHO are then encouraged to accord official recognition of INN in their domestic drug legislation.

31. In contrast to generic names which relate to ingredients, brand names relate entirely to the finished product, and serve to identify the manufacturer. In the absence of a brand name or of a visually distinctive assembly, identifying the source of a product can be a serious problem. Brand names are usually, but not necessarily, based on a registered trade mark which confers upon the manufacturer certain protective rights akin to patents rights.
The labelling of medicinal products

32. The labelling of medicinal products in the United Kingdom is strictly controlled by the Medicines Act and subordinate legislation. These controls exist to ensure correct description and identity of medicinal products, to prevent false or misleading information, to give proper instructions and warnings and generally promote safety. Existing regulations are comprehensive and cover all categories of medicines. As well as statutory warnings (e.g. keep out of reach of children) for over-the-counter medicines, some specific label warnings are required through individual product licences. All labelling must be in English, though other languages are not prohibited and must be clear and indelible.

33. Various campaigns exist for medicines to be labelled with warnings relating to driving, pregnancy, overuse of steroids, etc. The Department of Health and Social Security policy is that medicines bought over-the-counter need full warnings but that it is for the doctor to decide what is to be labelled on medicines obtained via a prescription. The British National Formulary (the prescribers' handbook) contains authoritative advice to prescribers about the labelling of the products. Because of their size, labels can only contain a limited amount of information and it is important therefore that this is of relevance to the patient concerned. One statutory addition to labelling currently under consideration is a declaration of certain additives to which some patients are allergic (e.g. tartrazine).

Packaging

34. At the present time United Kingdom legislation requires solid-dose aspirin and paracetamol preparations, intended for use in over-the-counter retail sale, to be packed in child-resistant containers.

35. United Kingdom legislation is supplemented by a voluntary agreement between the medical and pharmaceutical professions which states that all solid dose oral preparations should be dispensed in child-resistant containers. Ordinary containers are also provided at the patient's specific request. This voluntary scheme has been in operation since March 1981 and according to independent research carried out by the Pharmaceutical Society of Great Britain has been implemented by virtually all pharmacists. There is no doubt that child-resistant packaging has been very effective in reducing the number of cases of accidental poisoning.

36. Child-resistant containers are currently manufactured to a minimum British standard. The United Kingdom is actively participating in negotiations with other countries aimed at achieving an international standard for child-resistant packaging. The United Kingdom has no regulations in force at present relating to tamper resistance so far as medicines are concerned. Most manufacturers of over-the-counter products subscribing to the Proprietary Association of Great Britain are moving towards tamper resistance which is described as "security packaging".
37. There is a well-defined system of drug distribution in the United Kingdom which is controlled by a licensing system covering manufacture, wholesale and retail supply. For every medicinal product there has to be a Product Licence and the product may only be manufactured (or imported) and distributed for sale in accordance with that licence. In addition, manufacturers are required to hold a Manufacturer's Licence and those who deal in medicines wholesale must hold a Wholesale Dealer's Licence.

38. An important factor in the control of the manufacture of human medicines in the United Kingdom is the activities of the Medicines Inspectorate of DHSS. Inspection of premises is carried out before the granting of a Manufacture's Licence and at regular intervals thereafter. Withdrawal of licences and, rarely, prosecutions can result if standards are not maintained. In this respect DHSS gives detailed guidance regarding good manufacturing practice (GMP).

39. The distribution of medicines from manufacturers to retailers is mainly a private enterprise function, the wholesaler covering his costs and earning his profit through the margin allowed to him in the retail price. Wholesalers must hold a Wholesale Dealer's Licence which amongst other things, seeks to ensure adequate record keeping in case a batch of medicines has to be recalled.

Retail supply

40. There are three ways in which medicinal products may be distributed at retail level in the United Kingdom: (a) "prescription only medicines" (POM) supplied only by or under the supervision of a pharmacist and in accordance with a doctor's or dentist's prescription; (b) "pharmacy medicines" (P) may be sold over the counter only at pharmacies by or under the supervision of a pharmacist; and (c) "general sale list medicines" (GSL) may be sold at any shop such as a village store. Mention should also be made of hospital pharmacies, which supply prescription medicines to hospital patients and to patients attending hospital clinics.

41. "Pharmacy medicines" are the usual form of sale. The decision whether a medicine should be restricted to prescription only or should be allowed on general sale is taken by Ministers and published in statutory orders. Ministers are guided in this by independent expert advisory bodies - in particular, the Medicines Commission, which advises on broad issues of policy, and the Committee on Safety of Medicines, which advises about the safety of particular drug substances or products.

42. As a broad guide, medicines are included in the Prescription Only Medicines List where, in the Ministers' opinion, treatment with them needs to be supervised by a doctor because of (a) a known or potential toxicity hazard to the user, or (b) a likelihood of producing drug dependence, or (c) some danger to the health of the community at large. There is a small amount of movement of drugs from prescription only to non-prescription status as drugs which are initially included in the list only because they
were new, become older and doubts about their safety are resolved. The Medicines Act classifies medicines as P unless restricted to POM or relaxed to GSL. Every new chemical entity is classified as POM but reverts to P status after an initial period, usually at renewal of Product Licence, unless specifically retained as a POM medicine.

43. Although "pharmacy medicine" status is the norm, the Medicines Act empowers Ministers to specify in a General Sale List those medicines which in their opinion could with reasonable safety be sold freely at non-pharmacy premises. The medicines which have been listed in this way are, broadly, those considered suitable for self-medication, where the hazard to health, the risk of misuse and the need to take special precautions in handling are all thought to be small and to be outweighed by the convenience to the public of wider sale: e.g. the well-tried home remedies such as cough mixtures, laxatives, antiseptic creams, indigestion tables and (in small packs) analgesics. There is a large number of such products which can legitimately be sold from non-pharmacy outlets, and it is constantly being added to as new products suitable for self-medication come into the market, and, after very careful and thorough scrutiny, are assessed as reasonably safe for general sale.

44. Medicines on the General Sale List may be sold by self-service methods in any lockable shop or other premises occupied by the seller, but the medicine must have been pre-packed elsewhere and must be sold unopened. General Sale list medicines may also be sold by means of automatic machines, provided the machine is located on premises which can be closed at certain times so as to exclude the public.

Prescribing

45. In the United Kingdom, prescriptions are required for all medicines supplied under the National Health Service and for all prescription only medicines. For such medicines prescriptions may only be written by a doctor or dentist if registered in the United Kingdom.

46. The United Kingdom National Health Service (NHS) is financed primarily out of taxation and is available to all residents. Most people are registered with a general medical practitioner, in contract with the NHS and paid mainly on a capitation basis, who provides primary care and is the normal route of referral to hospital and specialist services, whether in the NHS or private sectors. A small minority of the population obtain some or all of their medical treatment privately, mainly through insurance schemes.

47. As part of primary care, the general practitioner is free to prescribe virtually any medicine which he considers desirable for his patient, with the exception of medicines in certain therapeutic categories referred to below.

48. In some mainly rural areas the doctor may also dispense the medicines he has prescribed but more usually the patient takes the prescription to a community pharmacist, also in contract with the NHS, who dispenses the medicines and claims reimbursement at predetermined rates. Unless exempt,
the patient pays at the time of dispensing a prescription charge of £2 for each item on the prescription. In practice, however, more than 70% of prescriptions are exempt from the charge on grounds mainly of young or old age, pregnancy, low income or for those suffering from specified diseases. Under the National Health Service, medicines for patients in hospital are provided free of charge.

49. From April 1985, within certain therapeutic categories, general medical practitioners have been restricted in the medicines they may prescribe under the NHS to those included in a selected list. The medicines concerned are generally those which can be purchased directly by the patient without a prescription, i.e. cough and cold remedies, tonics, vitamin preparations, antacids, laxatives, and minor analgesics, but also include some prescription items such as benzodiazepine sedatives and tranquillizers. The principle underlying this economy measure is that in the therapeutic categories concerned, the only medicines prescribable at NHS expense should be those which meet real clinical need at the lowest cost. The list will remain under review by an expert advisory committee, the Advisory Committee on NHS Drugs. For medicines no longer available under the NHS but for which a prescription is necessary it is open to the doctor to prescribe these and to the patient to pay for them privately.

50. The prescribing practices of general practitioners are monitored. Because after dispensing the prescriptions are sent to one central point for authorization of reimbursement, it is possible to analyse each practitioner's prescribing habits and costs. A summary is sent to each practitioner together with a note of the area and national averages. If a practitioner's costs are significantly higher than the average, this may be discussed with him by a doctor from the Regional Medical Service of DHSS.

Control of prices

51. Prices of medicines supplied under the National Health Service (NHS) are controlled mainly through the Pharmaceutical Price Regulation Scheme, a non-statutory agreement between the industry and the Department of Health and Social Security (DHSS). Under this scheme companies supplying medicines for the NHS are in effect reimbursed the costs incurred and are allowed to earn an agreed level of profit expressed as a return on the capital employed. The scheme operates on the basis that since the health departments are effectively monopolist buyers of all prescribed medicines sold in the United Kingdom, the prices of individual products are not for practical purposes significant if the overall costs and profits of the company producing these medicines are reasonable; a high profit on one product will be offset by a low profit on another.

52. In practice, a company is allowed itself to set the initial price of a new product but subsequently has to seek approval before increasing the price of this and other existing products. Approval is given only if DHSS is satisfied that the increase sought would not enable the company to exceed its profit target and that the costs as declared are reasonable. In considering the latter, DHSS recognizes the importance of research and development and makes an appropriate allowance for this in the costs.
Each company is required to submit an annual financial return which enables DHSS to check in retrospect whether the level of costs and profits was reasonable and, if the profit target was exceeded, to negotiate an adjustment. Among the allowable costs is that for distribution from the manufacturers to the community pharmacists through the wholesalers.

While companies supplying generic medicines are formally within the Price Regulations Scheme, in practice the prices of generics are determined by competition in the market place. Medicines used in hospitals may be bought through wholesalers but for large-user items tenders are usually invited. The price then depends on the terms negotiated. Many hospitals have special committees composed of doctors and pharmacists to formulate lists of drugs which may be prescribed and consequently which medicines will be purchased.

**Controlled drugs**

Special arrangements apply to the prescribing of drugs of dependence in the United Kingdom under the provisions of the Misuse of Drugs Act 1971.

Drugs controlled include cocaine, dipipanone, diamorphine (heroin), methadone, morphine, opium, pethidine, phencyclidine, lysergide (LSD), amphetamines, barbiturates, cannabis, codeine, pholcodine and certain drugs related to the amphetamines such as chlorphentermine and diethylpropiion.

For all controlled drugs, prescriptions must be signed and dated by the prescriber and the following particulars included in the prescriber's own handwriting: name and address of patient, form and strength of preparation as appropriate, total quantity in both words and figures, and dose.

Only medical practitioners who hold a special licence issued by the Home Secretary may prescribe diamorphine, dipipanone or cocaine for addicts; other practitioners must refer the addict to a treatment centre. This stipulation only applies to addicts and does not preclude the prescription of diamorphine or cocaine for the relief of pain due to organic disease or injury.

**Drug Promotional Practices**

**Provision of Information to Prescribers**

Information to prescribers can be broadly divided into that sponsored by the pharmaceutical company marketing the drug and that sponsored by the government. While the activities of the pharmaceutical company are commercially oriented and directed at the promotion of their product, government-sponsored publications aim to adopt a critical approach and to present data on new drugs in comparison with existing remedies. Regulations and codes of practice exist to ensure that promotional material from pharmaceutical companies is presented in a fair and objective way.
60. Medical journals represent an important source of pharmacological and therapeutic information for prescribers, particularly on new drugs. Journals such as Lancet and the British Medical Journal are highly regarded, concerning the quality and independence of the clinical data reported. Journals such as Pulse and Doctor, which are circulated exclusively to doctors, provide an independent source of information, news and comment on medicines. Although these journals are not funded by the pharmaceutical industry they are entirely dependent on advertisements of various types (not solely pharmaceuticals) for their revenue.

61. Pharmaceutical companies provide a wide variety of material on their products. Non-promotional material includes data sheets and specialized information packages for researchers, prescribers and patients. Promotional activities include journal advertisements, printed communications such as letters, booklets and brochures, audiovisual communication, symposia and activities of medical representatives. Under the PPRS (see para. 51) only a limited amount of expenditure on sales promotion may be reflected in the prices of NHS medicines; from April 1985 the limit has in broad terms, been 9% of turnover.

62. Data sheets provide an important source of information to prescribers. A data sheet is a concise document containing basic information about the composition, uses, dosage, side-effects, contraindications and warnings relating to a medicinal product. Detailed regulations under the Medicines Act specify the form and content of data sheets. The data sheets for new products are inspected by Medicines Division of DHSS as are the data sheets of older products as they are reviewed. If a product is promoted to doctors a data sheet must be sent or delivered within the previous 15 months, to any doctor likely to see the advertisement. Any information in an advertisement must be consistent with the particulars on the data sheet. In practice most data sheets are included in an annual compendium compiled by the Association of the British Pharmaceutical Industry (ABPI) which is sent to all doctors. The current edition (1985-86) contains 1037 pages. Mention must also be made of the Monthly Index of Medical Specialties (MIMS), a commercially-produced publication which provides compact information on proprietary medicinal products and is distributed free to all general practitioners.

63. Advertising controls are provided by a mixture of statutory measures and by means of various voluntary codes of practice. The main regulatory powers are contained in the Medicines Act (1968) under which it is an offence to issue false or misleading representations. Advertising claims have to be consistent with the Product Licence. Detailed regulations apply to the information which must be contained in normal advertisements and abbreviated advertisements.

64. Where advertising to the professions is concerned, the Association of the British Pharmaceutical Industry operates a code of voluntary marketing agreed with DHSS which has been in existence for 23 years, to which their members subscribe and to which most pharmaceutical companies who are not ABPI members also elect to adhere. The code emphasizes the importance of providing the medical profession with accurate, fair and objective
information. The code is enforced by a Code of Practice Committee chaired by an independent chairman who is a QC. The ABPI Code of Practice Committee submits detailed reports of infringements to the Pharmaceutical Journal and the British Medical Journal for publication. To complement these arrangements the DHSS monitors advertisements generally and investigates all complaints. This joint control between government and industry has proved to be highly successful.

65. The Department of Health and Social Security (DHSS) in the United Kingdom produces very little information on medicines directly, but has a strong interest in encouraging effective and economical prescribing by doctors and exerts its influence by sponsoring certain independent publications. Two publications are paid for by the DHSS, but are produced independently: Prescribers Journal and the British National Formulary (BNF). The former produces short authoritative independent review papers on therapeutic subjects and is produced every two months. The BNF is a long-standing joint publication by the British Medical Association (BMA) and the Pharmaceutical Society of Great Britain (PSGB) which was radically revised in 1981 and is now a unique, compact source of information intended for those concerned with prescribing, dispensing and the general administration of medicines. It includes most medicines, especially commercial products, available in the United Kingdom but has retained a small formulary section for providing extemporaneous preparations. Revisions are produced every six months and the BNF is distributed free to all medical students and practising doctors.

66. More recently the DHSS has sponsored the free circulation of Drug and Therapeutics Bulletin and Adverse Drug Reaction Bulletin to doctors and final year medical students. The former is published fortnightly by the Consumers Association and the latter every two months by Adverse Drug Reactions Research Unit, Shotley Bridge General Hospital. Drug and Therapeutics Bulletin provides up to date assessment of products or therapeutic practices.

67. The DHSS also distributes copies of the BNF and other literature to other governments on request. On this basis, copies of Martindale's Extra Pharmacopoeia were distributed in 1984.

Employment of medical representatives

68. The employment of medical representatives or detail men is permitted in the United Kingdom and forms an essential part of the promotional activity by the pharmaceutical company in respect of their medical products.

69. The activities of medical representatives are subject to the Code of Practice for the Pharmaceutical Industry mentioned earlier. This code covers such activities as the training and ethical conduct, the proper basis for claims for products and the frequency, timing and duration of calls on doctors and the security of medical products. The code also recommends that representatives are paid a fixed basic salary and that commission on sales should not constitute an undue portion of their remuneration. An important aspect of the training of medical representatives is that detailed briefing
material must be provided on the technical aspects of any product that is to be promoted and that a copy of such material must be available to the Licensing Authority on request.

70. Medical representatives undergo a training programme and examination under the auspices of the ABPI. Examinations take place twice yearly. There are currently about 3000 medical representatives employed by the various pharmaceutical companies operating in the United Kingdom, one for every 25-30 doctors compared with one for every two doctors in Japan.

The supply of samples

71. The Code of Practice for the Pharmaceutical Industry (ABPI) also gives specific guidance on the supply of samples to the medical profession.

72. Samples should be provided to a doctor only in response to a signed request unless intended solely for identification or demonstration purposes. Wherever practical, an individual sample should not represent more than four days' treatment for an individual patient. Samples of products restricted to supply on prescription must be handed direct to the doctor or his authorized representative and a strict system of accountability should be established. In addition, distribution of samples in hospitals should comply with any individual hospital regulations.

Holding of symposia

73. The holding of symposia is a recognized part of the promotion of a new drug. Many such symposia are held in Postgraduate Medical Centres situated in hospital grounds. The Association of the British Pharmaceutical Industry, the National Association of Clinical Tutors and the Advisory Committee of Deans of the Council for Postgraduate Medical Education have agreed that meetings sponsored by a pharmaceutical company may be allowed in a Postgraduate Medical Centre at the discretion of and arranged through the Clinical Tutor or Local Postgraduate Medical Education Committee. It is recommended that some vetting of lecture material or films be undertaken and that a doctor sufficiently experienced in the topic should always be available at such meetings to give an independent opinion. Publicity by the pharmaceutical company is allowed but it is recommended that this should be separate from the educational content of the meeting. Sponsorship by the pharmaceutical company should be limited to the provision of light refreshments and the printing of programmes.

SUMMARY

74. The clinical trial and marketing of new drugs in the United Kingdom first came under voluntary control when the Committee on Safety of Drugs was established in 1964. A statutory system now operates through the Medicines Act (1968) which was implemented in 1971 and, for biological substances, through the Biological Standards Act (1975) via the National Biological Standards Board and its executive arm, the National Institute for Biological Standards and Control. So far as safety, quality and efficacy of medicines
are concerned, the United Kingdom has a comprehensive set of controls, consistent with those of other members of the European Community and most other developed countries, governing the import, manufacture, testing, labelling, advertising, distribution and retail sale of medicines. A well developed system for the reporting of adverse reactions feeds information to WHO and to other regulatory authorities. The export of medicines is not controlled under United Kingdom medicines legislation. Progress continues towards harmonization with the European Community, but there is some way to go before this process can be completed.

75. Medicines are available to the population of the United Kingdom either through over-the-counter purchase of approved medicines or by supply through the National Health Service. For the most part doctors are free to prescribe under the NHS medicines of their choice. A recent development, however, has been the introduction of a selected list of medicines prescribable mainly for relatively minor ailments. Except for a standard prescription charge, from which there are extensive exemptions, prescribed medicines are supplied free of charge. Prices to the NHS are controlled under a non-statutory scheme agreed between the government and the industry. The way in which companies may promote their medicines is regulated by a mixture of statutory controls, self-regulation by the industry and by financial pressures exerted through the price control scheme. The United Kingdom government seeks in various ways to encourage doctors to prescribe effectively and economically, including the prescribing of generic forms of branded medicines.
THE ROLE OF THE WHO ACTION PROGRAMME ON ESSENTIAL DRUGS AND VACCINES

Introduction

1. The period following the discovery and development of antibiotics has seen the development of the pharmaceutical industry as it exists today. Numerous new and effective pharmaceutical products have become available and make for a more rational approach to diagnosis and therapy. Tens of thousands of proprietary drugs have appeared on the market in countless combinations of active ingredients.

2. Governments and their drug control authorities have reacted differently to this massive proliferation of pharmaceutical products. The Nordic countries held the number of drugs in their national formularies to some 2000 to 3000, Norway continuing to apply a needs principle it laid down early, admitting new drugs only when medically justified and eliminating older drugs as newer and more effective drugs were submitted for registration. Most industrialized countries, however, in particular those with large pharmaceutical industries, allowed new drugs to enter the market when they satisfied their regulations on quality, safety and efficacy. As many as 5 000 – 10 000 or more prescription drugs appeared on the market, often accompanied by thousands of over-the-counter drugs.

3. Before gaining their independence most developing countries had little access to modern drugs. Now, little attention being paid to public health needs and the economic situation, the demand for drugs in them has escalated and the pharmaceutical industry has marketed ever-increasing numbers of brand-name and combination products. In the 1950s and 1960s developing countries had – and many still have – huge national formularies. Bangladesh had 4000 preparations, Brazil 52 000, Egypt 22 000, Mexico 40 000, Mozambique about 13 000, the Philippines 15 000, Thailand 25 000. (For comparison, the United Kingdom had about 17 000, while Norway had no more than 1900 formulations of about 900 specific chemical entities.) National drug bills soared, often consuming 20%-40% of the meagre national health budgets in developing countries.

4. Paradoxically, in spite of the huge number of different proprietary drugs, there were insufficient basic drugs at prices that the rural and urban poor could afford. The private sector catered, as it still does, to an urban elite, while government health services fought an uphill struggle against the weaknesses of their inherited drug procurement, storage, and distribution infrastructure.

5. A few developing countries (Afghanistan, Pakistan, Papua New Guinea, Sri Lanka, and others) made serious attempts to remedy the situation, but most attempts failed for lack of political will and internal or external pressure, or both. Some countries, however, adopted limited drug lists and reported good acceptance as well as favourable medical and economic results. In the developed countries many hospitals started to experiment with restricted formularies.
6. It was in response to this situation that the Director-General of WHO, in a report to the Twenty-eighth World Health Assembly in 1975, reviewed the main drug problems facing the developing countries and outlined possible new drug policies.

The WHO model list of essential drugs

7. A WHO expert committee met in 1977\(^1\) to answer the pressing question of which basic drugs are necessary for the health needs of a population. It established guidelines and criteria for the establishment of lists of essential drugs and vaccines. The most important were:

(a) the selection of the drugs should be unbiased and be based on the best available scientific information, yet allow for variations to take local needs and requirements into account

(b) the selection should be based on the results of benefit and safety evaluations obtained in controlled clinical trials and/or epidemiological studies

(c) international nonproprietary (generic) names for drugs or pharmaceutical substances should be used whenever available

(d) in cost comparisons between drugs the cost of the total treatment and not only the unit cost must be considered, as well as the cost of non-pharmaceutical therapeutic modalities

(e) consideration should be given to the competence of the personnel to make a correct diagnosis

(f) when several drugs are available for the same purpose, the pharmaceutical product and dosage form should be selected that provide the greatest benefit in relation to risk

(g) When two or more drugs are therapeutically equivalent, preference should be given to:

   (i) the drug that has been most thoroughly investigated

   (ii) the drug with the most favourable pharmacokinetic properties, e.g., one that improves compliance and minimizes risk to health

   (iii) the drug for which reliable local pharmaceutical manufacturing facilities exist

   (iv) the drug and dosage form with the greatest stability or for which adequate storage facilities exist

Fixed-ratio combinations should be accepted only if the following criteria are met:

(i) clinical literature justifies the concomitant use of more than one drug

(ii) the therapeutic effect is greater than the sum of the effect of each drug separately

(iii) the cost of the combination product is less than the sum of the cost of the individual products

(iv) patient compliance is improved

(v) sufficient drug ratios are provided to permit dosage adjustments to meet the needs of the majority of the population.

8. The expert committee in its 1977 report listed as a model about 220 drugs, vaccines, diagnostic agents, and solutions in 26 major categories. The establishment of a WHO model list does not imply that no other drugs are useful but simply that, in a given situation, these drugs are those most needed for the health care of the majority of the population and those, therefore, that should be available at all times in adequate amounts and in the proper dosage forms.

9. The 1977 model list of essential drugs has stood the test of time. It met with initial surprise and resistance from both the medical establishment and the pharmaceutical industry, but it has since gained guarded acceptance from both. The list has been revised three times since 1977 but with only a limited number of additions, changes, and deletions. Given the global investment in research and development for new drugs, it is surprising, disconcerting even, that so few new chemical entities have been added to the list.

Action programme on essential drugs and vaccines

10. After the establishment of the 1977 WHO model list of essential drugs, many developing, but no industrialized, countries made attempts to establish national lists suited to their own needs. Today the number of countries with lists of essential drugs or national formularies containing chiefly essential drugs exceeds 80.

11. The establishment of a national list, however, does not necessarily lead to implementation of the concept of essential drugs. In some developing countries the new list of essential drugs became just another list added to the many existing lists. The importation, distribution, and use of expensive non-essential drugs continued as before in the growing private sector and the drugs appeared in the national formularies. In other countries (Afghanistan, Kenya, Mozambique, Tanzania, etc.) the list was applied with some vigour to the primary health care system or (Peru) to
reimbursable social insurance schemes. From 1977 to 1982 WHO collaborated in about 30 country studies with a view to analysing the drug supply situation and drug policy and management.

12. The WHO Action Programme on Essential Drugs was formally established in 1981 as an operational programme to support countries in the establishment of essential drug policies. Its aim is to help assure the regular availability of essential drugs of good quality and at the lowest possible prices. In 1981 WHO also joined forces with UNICEF to support the provision of essential drugs for primary health care in developing countries.

13. No more than modest progress was reported by the Action Programme in 1982, only a few countries having formulated national drug policies. In fact, populations that had gone unserved with essential drugs before 1977 continued to go unserved, populations that numbered — and still number — tens, if not hundreds, of millions. To remedy this deplorable situation and accelerate a hitherto slow-moving process, a global strategy that could be applied in Member States was needed. A plan of action was presented in 1982 to the Thirty-fifth World Health Assembly, which endorsed it and its principles. It contained the following major components:

(a) identifying therapeutic needs
(b) selecting essential drugs
(c) estimating the quantities needed
(d) improving the drug supply system
(e) ensuring the proper use of essential drugs
(f) providing the public with information and education
(g) achieving local production or formulation wherever technically and economically feasible
(h) ensuring quality control
(i) monitoring adverse reactions
(j) introducing appropriate legislation
(k) meeting manpower requirements
(l) ensuring coordinated multisectoral action
(m) establishing monitoring and evaluation procedures.

14. According to the plan, WHO has two mutually supporting roles: coordination and technical cooperation. It is exercising that dual role on the basis of a well-consolidated plan of action and on a policy and strategy
that have been proved to be intrinsically sound and economically feasible for most developing countries, with or without international support.

15. Much progress has been achieved since 1982 at the global, regional and country level, as reported to the Health Assembly in 1984.

**WHO's coordinating role**

16. WHO is now recognized as the lead agency in essential drugs. It coordinates, directly or indirectly, international efforts in support of country programmes. Most development agencies in the health field have officially adopted the concept of essential drugs or apply it in practice in support of primary health care. Nongovernmental agencies such as the League of Red Cross Societies have officially adopted the concept. The International Organization of Consumer Unions and its informal network, Health Action International, are strong and often vocal advocates of an essential drugs policy for both developing and developed countries.

17. UNICEF has widespread operational activities in most developing countries, not least in distribution and training, making it an obvious partner for the WHO Action Programme on Essential Drugs and Vaccines. WHO and UNICEF work closely together in countries, and at regional and global levels. UNICEF concentrates mainly on procurement, kit-packaging, distribution and, in some countries, technical support to programme development, while WHO's role consists of programme development, coordination, monitoring, and evaluation, as well as technical and scientific support to countries and international organizations. Both WHO and UNICEF actively mobilize resources on behalf of national essential drug programmes.

18. UNIDO supports technology transfer for the local production of essential drugs and has developed an inventory of suppliers of 26 different raw materials for the formulation of essential drugs. UNHCR has developed a system of essential drug supplies applicable to refugee situations. UNCTAD and the United Nations Office of Transnational Corporations have devoted several studies to the global pharmaceutical situation in relation to pricing, transfer of technology, local production, patents, etc. The World Bank supports an essential drugs component for primary health care programmes in several countries.

19. The technology-based pharmaceutical industry cooperates with both WHO and UNICEF in commercial transactions with least developed countries for the supply of low-cost essential drugs. Several industry associations and groups of drug companies support training in quality control, distribution systems, and the supply of essential drugs for developing countries. Numerous generic manufacturers, as well as generic subsidiaries of multinational companies, supply essential drugs at low prices and of good quality via UNICEF or directly to developing countries.

20. The advocacy role of the Action Programme has led to wide, although perhaps not yet sufficiently wide, knowledge of the concept of essential
drugs. In addition to WHO's official publications on this subject, an ever-increasing literature deals with a range of issues on the production, pricing, marketing, advertising, prescription and use of drugs. More than 250 documents and papers are listed in the Action Programme's annotated bibliography. Numerous TV films, slide shows, newspaper articles, and public debates have highlighted the advantages of an essential drugs policy. The Action Programme is now issuing a newsletter and a brochure on the progress and components of the programme. These are intended to reach wider audiences in both the developed and the developing countries. Seminars, workshops and international conferences aimed at reaching both present and future decision-makers and providers of health care are continuous features of the programme.

21. Financial, political, and technical support has been mobilized and WHO continues to play a strong role in mobilizing support for national essential drugs programmes.

22. The Action Programme stores and distributes a wide range of documents: teaching and learning material for schools of medicine, pharmacy and public health; guidelines, manuals, and therapeutic guides; principles of drug legislation; price lists and names of suppliers of essential drugs; documents on experience in countries and evaluation procedures and reports. Draft drug information sheets are available for adaptation to needs in countries. Most documents are available in more than one language.

23. With the acceleration of national essential drugs programmes, it is envisaged that the WHO coordinating and advocacy role will increase in the coming years. It serves to align policies and strategies so as to facilitate the implementation at the country level of internationally agreed approaches to improving the supply and use of essential drugs. It serves countries directly in the application and adaptation of global policies and strategies to national needs.

The technical cooperation role

24. The technical support role to countries now takes up most of the Action Programme's manpower and financial resources. With increased experience, WHO has moved from an initial rather orthodox approach, advocating policy formulation, legislation, quality control, planning, and implementation, to a more flexible pragmatic approach to problems taken if possible in order of priority.

25. Most existing national drug legislation permits initial experiment with essential drug lists, distribution and training and later expansion into primary health care coverage with a national essential drugs programme. Policy formulation can evolve as experience is gained and legislation be drafted and adopted according to needs. It makes little or no sense to establish a more rational drug procurement scheme if the distribution infrastructure is a major constraint. Training in better patient management may prove futile if drugs are not actually available. A well-developed implementation plan may quickly be shelved if financing is the overwhelming
problem. Technical collaboration on essential drugs now focuses on the fastest possible approach to overcoming the major problems, but always with a view to an eventual consolidated national policy and system of selection, procurement, storage, distribution, training, and use of essential drugs. The project approach has long since been abandoned and a national programme approach is systematically advocated. Isolated projects, however well designed and well executed, tend to fizzle out when they ignore the wider context in which they operate; too many pilot projects move from initial enthusiasm to complete abandonment because they have never formed part of an overall policy and strategy.

26. Global guidelines, manuals, etc. take second place to nationally developed material. This can be shared with other countries and can often be adapted to their specific needs.

National lists of essential drugs

27. WHO collaborates with national drug committees both in the establishment and revision of essential drug lists and in the selection of lists appropriate for different levels of health care. The WHO model list with its 220 drugs and vaccines has proved to be a most useful tool for national drug committees in establishing their own lists. Few countries have less than that number. Several countries operate national lists with 300-400 different generic drugs.

28. For the different levels in the health care system a surprisingly uniform pattern has been evolving, with about 6-12 drugs at the village level, 15-20 at the dispensary level, and 40-45 at the health centre level. District hospitals need about 100-120, specialist hospitals rarely more than 250 different drugs and vaccines. Many hospital formularies in developed countries satisfy the needs of sophisticated medical care with some 400 different drugs. A recent study in the United Kingdom has demonstrated the positive results of using a limited formulary in general practice: a diverse group of general practitioners showed over a one-year period that a formulary with only 137 drugs could provide adequate treatment for 90% of general practice patients.1

29. In its collaboration with countries WHO advises a phased reduction in the number of drugs and a gradual change to generic drug procurement and prescription. Objective information on drugs and, in particular, fixed-ratio combinations that are harmful, dangerous, or without proven therapeutic value is available in WHO and in many drug regulatory agencies in developed countries. This information can assist developing countries to determine which drugs should be removed from the market. The Bangladesh Drugs (Control) Ordinance 1982 took such an approach and removed more than 1500 inappropriate products from the market in a very short period of time. A reduction in the number of drugs after careful selection of essential drugs provides initial and lasting advantages in procurement, storage, quality control, and distribution.

30. Quantification of drug needs poses a far more complex problem than the selection of drugs. It is frequently based on past consumption rather than on present and anticipated morbidity patterns, attendance rates, and the diagnostic competence of the health staff. Since past consumption is an aggregate reflection of numerous and often irrational factors, it is a poor basis for forecasting requirements. This is clear in many developing countries; some drugs are far in excess of what can or should be used before the date of expiry, while others are in short supply.

31. The Action Programme has collaborated with several countries in the quantification of drug needs at the primary health care level. A reasonable degree of accuracy has been achieved over a number of years, wastage has been reduced, smaller inventories can be drawn up, and drugs can be used within less than 6-12 months after the date of manufacture. A methodology for projecting estimates of national essential drugs needs has been developed, based fundamentally on morbidity patterns and health services statistics. It is being field-tested in a number of countries, and training in its application will start in 1986 for national health authorities concerned with drug procurement and supply. With successful application, it is expected that considerable savings can be achieved and supply and needs be better balanced. However, operational research may be required in each country to determine the morbidity, attendance rates, skill levels, and the relation of demand to need.

National legislation

32. Most developing countries have inherited their drug legislation from the colonial period. It was in principle designed for a completely different socioeconomic and health situation and has proved ill suited to the present public health situation. Many countries have revised and updated, but few have radically overhauled, their legislation. A few bigger countries (India and Mexico) have enacted radical and progressive legislation only to end up in protracted and complex court battles. A few other countries have achieved legislative reform that has had a profound effect on the pharmaceutical sector (Bangladesh, the Gambia, Iran, and Mozambique).

33. Although essential drugs programmes can be implemented without elaborate legislative reform, most countries must face the hard challenge of bringing about such reform. There is no substitute for national efforts to create the legal basis for a drug sector that is suited to the particular needs and circumstances of the country. WHO provides guidelines for such national legislation. The Action Programme has collaborated in the drafting of national legislation and can provide technical and legal expertise to countries that wish to benefit from experience elsewhere.

Financial and economic issues

34. People, particularly in rural areas, in many countries have little or no access to reasonably priced drugs. Paradoxically, the government policy
of providing free health services, including drugs, has often resulted in no
drugs being available in government health facilities, especially in rural
areas, leaving the private sector as the sole source. The cost of the drugs
is often prohibitive, especially when added to the time and effort necessary
to travel to where drugs can be purchased. Thus people delay seeking care
until the situation deteriorates into an emergency, when they are obliged to
pay whatever the price demanded for drugs.

35. With the implementation of an essential drugs programme drugs can
become more accessible, both financially and geographically, to even the
poorest income groups. The share of a family's income devoted to the
purchase of drugs should remain the same or even decline, thereby freeing
income for other purposes. Most importantly, when drugs are both reasonably
priced and available people are usually willing to bear some or all of the
cost.

36. While the implementation of an essential drugs programme cannot solve a
country's foreign exchange problem, it can help to reduce it to manageable
proportions as far as drug purchases are concerned. This is achieved by
careful estimation of drug requirements, improved procurement, better
prescribing, better consumption habits, and so on. Most countries are
spending at least $1 per capita on drug imports, which has been shown to be
sufficient to supply essential drugs in primary health care. In Kenya the
cost of drugs per outpatient visit to a health centre was only $0.19, and at
a dispensary only $0.29. In fact, following the implementation of the
essential drugs programme (1980-1984), Kenya's total drug bill increased by
only 1.2% taking inflation into account, despite the fact that the
population increased by over 20% during that period. Yet drugs are now
widely available in rural health facilities. This is partly explained by
the fact that losses on the way from the central store to consumers were
reduced from around 25% to an estimated 5% through the implementation of a
strict control system using ration kits and other control measures.

37. Once people are confident that drugs are available the attendance may
increase at health facilities and the overall cost per patient will decline
with more efficient use of existing personnel and facilities. In both Kenya
and Tanzania it appears that attendance may indeed have increased. Another
benefit is that people who come to the health facilities for curative care
can then be reached by preventive health measures and health education,
provided that the health personnel are trained to take advantage of the
opportunity.

38. A number of less tangible benefits with economic implications can be
expected. Patients have greater confidence in health care providers and in
the health care system as a whole. This in turn improves the morale and
productivity of the health personnel at all levels and they are better able
to meet the expectations of the community. And the availability of
essential drugs should go a long way towards improving health in general, to
the economic benefit of the community.

39. Experience in Kenya and Tanzania has shown that the cost of
implementing an essential drugs programme can be relatively low. The main
A major question is the maintenance of an essential drugs programme. Not only are the populations of most developing countries increasing at 2.5-4% annually but the health budgets have also been stagnant or even decreasing in real terms over the past five years. Clearly many countries may not be able to continue to finance essential drug programmes in a system of free access to health care. One solution to this dilemma is some form of cost recovery. People in virtually all parts of the world have demonstrated their willingness to pay for drugs, even where drugs and health services are supposed to be provided free. In fact, in many countries with government health services private purchases of drugs are twice those of the government. Costs can be recovered in many different ways to fit the economic and cultural circumstances of a country, and selectively either as direct payment for drugs received or as part of a fee for service. Subsidies can be used to make the more expensive essential drugs affordable. Many different options are available for the recovery of costs.

Once funds have been recovered from the sale of drugs one problem arising is how they can be used to replenish the stock of drugs. Another is that in many countries the local currency recovered through cost recovery schemes cannot easily be converted into the foreign exchange needed to import drugs. One solution to the first problem that has had some success in several countries is a revolving drug fund. The principle is relatively simple: after an initial amount of capital or stock of drugs is provided (often by an external donor) the funds are collected and deposited in the revolving fund, which in turn is used to replenish the stock of drugs on a regular basis. A manual on drug supply management published by WHO and Management Sciences for Health, a consulting group, points out, however, a number of pitfalls in the operation of revolving funds: underestimation of the initial stock; unanticipated price increases (although prices of many essential drugs have been declining in recent years, local inflation or exchange rate fluctuations may nullify the decreases); rapid programme expansion; prices fixed too low to recover costs; failure to collect established fees; and theft and other losses. It is important to note, however, that all of these possibilities can be planned for and minimized, if not entirely eliminated.

The main obstacle in many countries to the successful implementation of a cost recovery scheme is the shortage of foreign exchange. Unfortunately there is no easy solution to this problem. However, the implementation of an essential drugs programme should reduce to a minimum the need for foreign exchange for drug purchases, and in many cases the amount needed will be below what is currently spent on drugs. A ministry of health that has done all it can to reduce its need for foreign exchange by implementing an essential drugs programme should receive a sympathetic hearing from a ministry of finance or central bank in its request for foreign exchange for

drugs. Typically the amount requested represents a relatively tiny percentage of the country's need for foreign exchange - and drugs are surely at least as essential as petrol.

Procurement and prices of essential drugs

43. Analysis of prices demonstrates all too clearly that many developing countries, particularly the less populous LDCs, have been singularly unsuccessful in obtaining good quality generic essential drugs at prevailing international prices. Many countries year in and year out pay from three to ten times too much for drugs. Fragmented procurement, poor payment records, complicated specifications, and irrational tendering or ordering systems are among the main reasons for this unacceptable situation.

44. The WHO Action Programme, in close cooperation with the UNICEF Packing and Assembly Centre (UNIPAC), collaborates with countries to improve procurement procedures. Tender documents, price lists, and names of reputable suppliers are available on request. UNIPAC has expanded its procurement activities and, through international competitive bidding for standardized essential drugs, has managed to achieve considerable reductions in the prices of about 140 essential drugs. Countries can obtain essential drugs at these low prices through a reimbursable scheme which, however, requires prepayment in hard currency. A financing arrangement is being developed whereby countries with essential drugs programmes will be provided with credit for drug procurement. In some instances local currency may be accepted in part payment.

45. With the objective of obtaining the lowest possible prices for good quality generic drugs, WHO will continue to work with UNICEF/UNIPAC to procure drugs in sufficiently large quantities to establish reference prices for commodity generic drugs. The prices will be monitored and supplied on a regular basis to countries that need price and market information for their own procurement system.

46. Pooled procurement schemes between countries, particularly smaller countries, provide obvious advantages in terms of economies of scale. However, practical difficulties have so far prevented such schemes from materializing. Several countries do pool their national requirements to obtain good prices, and the Action Programme advocates this approach for most situations.

Local production and formulation

47. Self-sufficiency or self-reliance in the supply of the most important drugs is a declared goal in many developing countries. In fact, however, no country in the world has achieved complete self-sufficiency; even industrialized countries with large pharmaceutical industries rely in part on the importation of raw materials and intermediate and finished products. A number of large developing countries (notably Argentina, Brazil, China, Egypt, India, and Mexico) have gradually built up drug industries, including
the production of good-quality raw materials. Often subsidiaries of multinational companies and indigenous factories combine.

48. Many less developed countries have experienced prolonged difficulties in establishing an economically viable local industry. In the absence of supporting industries (packing material, labels, starch, sugar, etc.), the value added component in the formulation of essential drugs is rather small and the technology required to produce good quality products complicated. Smaller quantities of raw material cannot always be procured at a good price and local taxes may add to the cost of the finished product. Irregular power and water supplies, periodic shortages of necessary ingredients, the breakdown of machinery, and competition from imported finished products often lead to low plant utilization. In several LDCs a 20-40% capacity utilization is the rule rather than the exception, so that domestic prices exceed international competitive prices and state subsidies are needed to ensure marketing at reasonably fair prices.

49. Packaging from bulk drugs and the production of intravenous solutions and water for injection may provide a sound first step with a potentially reasonable capital return. More than 40 developing countries formulate part of their requirements for oral rehydration salts at or close to international price levels. With increased experience and knowhow a gradual increase in their activities can be considered.

50. UNIDO is the United Nations agency entrusted with technology transfer in the pharmaceutical area. It has supported a number of developing countries and has increasingly gained experience in this field.

51. It is generally accepted today that the establishment of formulation plants to produce essential drugs at competitive prices requires careful study of technical and economic feasibility.

Storage and distribution

52. Problems of storage and distribution are more easily identified than solutions are. Inappropriate buildings, insufficiency or absence of shelf space to store drugs and equipment, lack of staff trained in modern storage and distribution management, shortage of fuel, poor roads, long distances to health care facilities, etc. often appear to be insurmountable obstacles, leading to waste and frustration.

53. Experience in a few countries has, however, showed that it is possible to improve both storage and distribution. Essential drugs are, in fact, reaching the most distant units in several countries on a regular basis and with a minimum of wastage. The ration kit system used in Kenya and Tanzania appears to be a feasible approach. Drug quantities tailored to the needs of a health unit and designed for a specific number of patients are prepacked in sealed boxes. New kits are supplied on the basis of attendance rates rather than on monthly or quarterly schedules that ignore the number of patients treated.
54. Kit packaging adds to the cost of procurement because of the packing material and labour needed. The additional cost appears, however, to be more than offset by the reduction in wastage and diversion of drugs.

55. The Action Programme, together with UNICEF, collaborates with several countries in improving storage and distribution systems and training store managers in better techniques. Manuals and teaching material on storage and logistics have been developed and the first few workshops have taken place. WHO will continue to collaborate with countries in the improvement of storage and distribution as part of national essential drugs programmes.

56. Research to determine the stability of drugs stored under tropical conditions is under way. Operational research is planned to devise better packaging and presentation forms for the individual patient in the public health sector.

Quality control

57. The question is often raised of the quality and quality control of imported or locally manufactured drugs. The degree and extent of the problem are unknown; the evidence ranges from the purely anecdotal to actual demonstration of substandard drug supplies. Clearly governments need to take steps to ensure the quality of all drugs marketed in their country, in both the public and the private sector. WHO provides guidelines for good manufacturing practices and quality control laboratories, including testing methodologies; it also provides technical support and training in quality control.

58. In the absence of a national quality control laboratory and a supporting inspection and enforcement system, countries can nevertheless take important steps to assure good drug quality. Selection of reputable manufacturers is the most important first step to ensuring the continuous supply of good quality products. In addition, countries can insist on assurance of quality through the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce (Working Paper 2.6). WHO also provides for the testing of samples at independent collaborating quality control laboratories.

59. Another problem is how to assure the quality of drugs actually supplied to the patient. No tests or certification schemes can prevent the gradual deterioration of products passing through a storage and distribution system and subjected to prolonged heat, humidity, rough handling and careless dispensing. Tropical packing material, careful ordering, and a fast first in first out storage and distribution system can go a long way towards ensuring the arrival of freshly produced products, as has been recently demonstrated in both Kenya and Tanzania. A systems approach is advocated including in-service training of the staff actually handling drugs all the way from the producer to the consumer.
Training, education, and other information transfer

60. Training at various levels, education, and information transfer are integral components of the WHO Action Programme in support of national programmes. They are dealt with more specifically on pages 109-141 and 299-317.

Monitoring and evaluation

61. Essential drug programmes, like other programmes, need monitoring to provide decision makers and managers with information to determine to what degree approaches and activities contribute towards the achievement of stated targets. Financial control is needed to keep within budgetary limits and to ensure that cost effectiveness is maintained. Since national essential drugs programmes are relatively recent, it is not surprising that problems have arisen in the monitoring of programme progress. A methodology based on the experience so far gained is currently being developed by the Action Programme in collaboration with a university centre.

62. Two national essential drug programmes in primary health care have now been evaluated. Evaluation procedures and manuals are available from the Action Programme. They can be used to evaluate essential drug programmes and be applied to present supply systems as part of a process for the development of new approaches.

Conclusion

63. The WHO Action Programme on Essential Drugs has over the few years of its existence emerged as a means of improving not only the availability but also the rational use of essential drugs. In less than a decade it has moved from drawing up a model list of essential drugs towards working systematically on the complex range of issues that every country must address to ensure both the supply and the correct use of good quality medicines. Its implementation by countries constitutes a most important approach towards the rational use of drugs at all levels of health care. It has so far mainly tackled problems in the public sector, with emphasis on primary health care. In countries with a large public sector, it may, with time, demonstrate the feasibility of changing existing patterns of drug use to achieve a more rational use of drugs. In countries with a large private sector the problem of excessive use of drugs is likely to continue or worsen unless concerted action is taken to remedy the situation.
THE WHO CERTIFICATION SCHEME ON THE QUALITY
OF PHARMACEUTICAL PRODUCTS MOVING IN INTERNATIONAL COMMERCE

OBJECTIVES OF THE SCHEME

1. Countries lacking a comprehensive and fully independent system of drug control are limited in their capability to assure the quality, safety and efficacy of pharmaceutical products marketed under their aegis. Where there is no independent quality control laboratory, sub-standard, degraded or even spurious products will remain undetected, and where there is no effective system of drug registration the sale of unlicensed and mislabelled products will remain unchallenged.

2. These deficiencies can be corrected in locally manufactured products only by upgrading national control mechanisms. When a product is imported, however, the regulatory authority in the country of origin should be in a position to provide an assurance on the conditions under which it is manufactured together with information on whether, and for what purposes, it is available in the domestic market.

3. Such assurances are important because in some countries drugs intended for export are not necessarily subjected to the same control procedures as those produced for domestic use. In general, more comprehensive assurances can be offered for products that are both registered and sold in the country of origin, than for unregistered products or supplies manufactured to the specification of the importing agent. Moreover, a valid assurance is obtainable only when the product is exported from the manufacturer directly to the importing agent.

4. The WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce (Appendix 1, pages 296-297), which was adopted in its present form in 1975 by the Twenty-eighth World Health Assembly, extends and unifies various schemes previously operated by some drug-exporting countries which issued so-called "free-sale" certificates on request to foreign importers in respect of registered products that had been subjected to control. It provides a simple administrative mechanism whereby importing countries can:

(i) ascertain whether a given product has been registered for marketing in the exporting country and, when appropriate, request an explanation of the reason registration has not been accorded

(ii) obtain assurance that the manufacturing plant in which the product is produced is:

- subject to periodic inspection and

- conforms to requirements for good practices in the manufacture and quality control of drugs as recommended by WHO
(iii) obtain details of the inspection and control procedures exercised by the authority in the exporting country and request relevant inquiries to be instituted by the exporting authority should a certified product be found to be of unacceptable quality.

5. Whereas the Scheme imposes specific obligations and responsibilities on governmental authorities in exporting countries in connection with inspection of manufacturing premises, sampling of finished products, and enforcement of internationally recognized standards of manufacturing practice, countries that do not export drugs are invited to notify their participation in the Scheme exclusively as importers without such commitment.

OTHER UN INITIATIVES BEARING UPON THE EXPORT OF PHARMACEUTICAL PRODUCTS

6. Coincidentally with the promulgation of the WHO Certification Scheme the United Nations General Assembly became engaged in a protracted and, as yet, ongoing debate on products harmful to health and the environment with special reference to exported pharmaceutical products. One of the consequential resolutions, GA37/137 (Appendix 2, page 298), addresses two practices that the Certification Scheme is intended to prevent, namely:

- "the continued production and export of products that have been banned and/or permanently withdrawn on grounds of human health and safety from domestic markets."

- "the export of pharmaceutical products ultimately intended also for consumption and/or sale in the home market of the exporting country, but which have not yet been approved for use there."

7. The resolution calls upon countries to ensure:

- that products banned from domestic consumption and/or sale on grounds of safety are sold abroad only upon the request of the importing country or when the consumption of such products is officially permitted in the importing country

- that full information, including clear labelling in a language acceptable to the importing country, is provided for products that are either severely restricted or not approved for domestic consumption and/or sale.

8. In addition the Secretary-General is requested to strengthen the national capabilities of developing countries to identify such products by ensuring the provision of the necessary information and assistance by the United Nations system and, in particular, by preparing and regularly updating a consolidated list of products that have been banned, withdrawn, severely restricted or, in the case of pharmaceuticals, not approved by governments.
9. The first of these consolidated lists(1) was prepared in English by the UN Secretariat in December 1983. It will now be issued in six of the working languages of the UN system and regularly updated in a biennial cycle. Formal responsibility for the listing and annotation of pharmaceutical substances is now accorded to WHO which will rely for notifications primarily on its network of designated national information officers. The list will thus derive from and complement the monthly compendia of regulatory decisions currently issued by WHO to all national drug regulatory authorities (see pages 109-141).

IMPLEMENTATION OF THE CERTIFICATION SCHEME

Participation in the Scheme

10. In 1980, five years after the promulgation of the Scheme, less than one-third of the Member States of WHO had formally notified the Organization of their intention to participate. The World Health Assembly in that year approved a Secretariat proposal to review its operation.(2) Since then a questionnaire has been issued to governments, consultants have visited 13 representative countries in four regions, recommendations for extension of the Scheme have been formulated by the Third International Conference of Drug Regulatory Authorities,(3) an informal consultation has been convened to discuss these recommendations and guidelines on the implementation of the Scheme are being drafted. These activities have themselves stimulated interest in the Scheme to the extent that, to date, 110 Member States have advised WHO that they are actively participating.

11. The questionnaire, which was issued to all governments in 1983, elicited 87 replies.(4) These showed that more countries utilized the Scheme than had formally acceded to it. Others, nominally participating, had apparently never used it. A total of 116 countries were reported to have requested certificates from the 47 exporting countries that provided relevant information.

12. Although the original intention of the Scheme was to assist the flow of information to developing countries it was most extensively used between countries within the European region. Countries within Europe, the Americas and the Eastern Mediterranean region had generated between them about 65% of the requests for certificates.

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(1) Consolidated list of products whose consumption and/or sale have been banned, withdrawn, severely restricted or not approved by governments. UN, New York, 30 December 1983.
(4) Slight perturbations in the size of the samples cited arise because some governments did not respond to all items in the questionnaire.
13. In contrast, countries within the African region used the Scheme least. It is relevant that six of the 22 countries from this region that responded to the questionnaire had yet to introduce a national drug registration system. In others, there was an apparent dissociation between the agencies responsible, respectively, for drug procurement and drug control.

14. Overall, however, more certificates were issued year by year. The aggregate of requests received by the 47 exporting countries contained within the sample increased from 15,000 in 1978 to 27,000 in 1982. This trend may be expected to continue because several countries are committed to introduce statutory provisions for certification of imported drugs. Seventeen countries from four regions indicated that they had already introduced such requirements or were in the process of promulgating them. Among these are five developed countries from the European region.

Circumstances in which certificates are provided

15. Only 27 of 51 exporting countries that responded to the questionnaire explicitly confirmed that they issued certificates in full conformity with the WHO Scheme. Six others acknowledged that their procedures differed from those proposed but in only one instance were details offered. In this case the attestation related only to the registration status of the product and not to inspection of manufacturing premises. It remains uncertain in what particulars certificates issued by the remaining countries differed from the WHO format.

16. A majority of exporting countries (36 of 51) did not require drugs intended exclusively for export to be submitted to a registration procedure. However, at least some of these authorities assessed and registered such products at the request of the manufacturer, in which case full certificates were issued. Among the 13 countries that did make specific provision in this regard, the regulations were varied:

- In one instance registration was limited to preparations that differ only in strength from products registered domestically.

- In another, registration was conditional upon receipt of a specific order from an importing country; lack of any reason to believe that the product would have been refused registration for domestic sale on grounds of quality, efficacy or safety; and adequate assurance that the product satisfied required pharmacopoeial specifications and any other criteria imposed by the importing country.

17. Although the Scheme refers to the issuance of batch certificates providing the results of a full, independent analysis of a sample of a specific consignment and offering an attestation that the consignment conforms to the declared specification, most exporting countries find this commitment impracticable and place the responsibility for these analyses on the manufacturer. However, a few countries newly entering into an export trade in pharmaceutical products have accepted to implement this provision,
at least in selected circumstances, to provide additional independent assurance on the performance of manufacturers attempting to establish a reputation internationally.

Circumstances in which certificates are requested

18. Twelve countries among 72 that used the Scheme primarily for importation required a certificate on each occasion an order was placed for a consignment of a product. A more common requirement, operative in more than half of these countries, was to request certification (either routinely or on a selective basis) on the first occasion that a product is imported. Among these, seven countries required recertification as a condition of renewal of product registration. The period of validity of product licences within these countries ranged from three to 15 years. Ten countries cited special situations in which certificates were required on a non-routine basis, and 21 had occasionally requested additional information as provided for within the Scheme. Several authorities in exporting countries commented that they occasionally received requests for information on manufacturers that they considered to be extraneous to the implementation of the Scheme.

19. Only eight of the 72 importing countries routinely requested product certificates directly from the regulatory authority in the country of manufacture. The remainder obtained them either through the importing agent or the manufacturer. However, returns from exporting countries suggested that a higher proportion of requests was submitted directly to the competent regulatory authority.

20. Batch certificates were requested on a routine or selective basis by more than half (41 of 71) of the importing countries within the sample. A higher proportion (46 of 71) commissioned independent laboratory analyses of products on or prior to importation and, of these, 10 authorities arranged for this work to be undertaken abroad. Thirty-seven drug exporting countries were prepared to arrange for these analyses to be performed in independent quality control laboratories at the request of the importing countries on a charge for service basis.

THE PERFORMANCE OF THE SCHEME

21. The results of the questionnaire, the country visits, and discussions within the Third International Conference of Drug Regulatory Authorities (ICDRA 3) and within informal consultations, have resulted in a consensus on broad issues of principle. It has been generally accepted that a system of independent certification of pharmaceutical products moving in international commerce is of value to all countries, and not only those lacking comprehensive administrative and laboratory facilities for drug control. It is evident, however, that the Scheme is not functioning effectively in all countries. Moreover, reports of the alleged infiltration of counterfeit drugs, commonly labelled as antibiotics, into some developing countries, underscores the need for substantial improvement in current standards of control. The reasons are manifold.
22. Some countries still lack the prerequisite administrative infrastructure for drug control. Some have no national registration system for pharmaceutical products. Others do not coordinate drug procurement with drug control. Sustained promotion of the Scheme is evidently necessary — even where it may previously have been operated to useful effect — particularly in countries with small national regulatory authorities and a high turnover of staff.

23. The formal language of the Scheme requires interpretation in simplified guidelines that are now in preparation and that will discuss not only the provisions of the Scheme but also the administrative structure required for its implementation, the circumstances in which certificates are of greatest value, the arrangements now in operation internationally for independent analyses of samples, the value of a national quality control laboratory, and the relationship between the Scheme and other systems of exchange of information operated under the aegis of WHO.

24. Some exporting countries that have formally notified WHO of their intention to participate have, on occasion, issued certificates that make no allusion to the WHO Scheme. Certificates have sometimes been difficult to interpret and, on occasion, they have proven to be unreliable in so far, for example, as they have provided no explicit assurance regarding inspection of manufacturing premises.

25. Ambiguities and misunderstandings have arisen because drug registration or licensing differs conceptually and operationally in different countries. Moreover, communications between competent national authorities have sometimes failed, either because the names and addresses of competent authorities are published in the official working languages of WHO rather than in the relevant national language, or because exporting countries with a federal structure do not identify the competent authority of each constituent state.

26. Competent authorities in importing countries are either reluctant to challenge an apparent misrepresentation or uncertain how to resolve a consequential dispute. The Scheme envisages resolution of disputes by direct negotiation, but countries have felt obliged, on occasion, to refer to WHO as an adviser or mediator.

27. Regulatory authorities in exporting countries are evidently best placed to provide information on products that are both registered and sold in the country of origin. When a product is not registered under their aegis they may be able to offer little more than an attestation that the manufacturer is regularly inspected and is permitted to manufacture products of the nature specified in the certificate. However, two categories of unregistered products are of particular importance and merit further consideration:
- generic products commissioned to be manufactured in response to a tender issued by, or on behalf of, a foreign agency

- products for which no market and/or no indication exists in the country of origin.

28. A product manufactured on commission in response to an international tender is made to the express specification and requirement of the importing agency. The same item may be available in the manufacturer's normal product range, but this is not necessarily so. Moreover, the packaging and labelling requested by the importer may differ from those specified in the product licence. In this case it is for the authority in the exporting country to detail in the certificate those respects in which the product, as ordered, differs from its licensed counterpart. By the same token, it is for the competent authority in the importing country to determine, on the basis of this information, whether to commission an independent analysis of the product, and to review any discrepancies in packaging and labelling requirements, and associated product literature. It is also important for the authority in the importing country to realize that the Certification Scheme provides an assurance on a product or a consignment only up to the moment that it leaves the safe keeping of the manufacturer. Once a third party becomes involved as a broker or procurement agency, the transaction has to be undertaken on the basis of trust rather than attestation, in that the reputation of the immediate supplier becomes the decisive consideration for the importing country.

29. The apportionment of responsibility between the competent authorities in the exporting and importing countries raises more complex considerations in the case of a catalogued product offered for export by a manufacturer, and for which no market exists in the country of origin. Legislative approaches to the export of such products differ among the major drug exporting countries. These range from debarring from export products not registered for use on the domestic market, through various provisions for the export of unlicensed products (subject to various safeguards particularly in relation to attestation of quality and provision of information), to registration of products specifically and exclusively for export markets. In exercising the last of these options a national regulatory authority is faced with a conflict of interest in so far as the certifying authority is acting at the behest of the exporting company rather than the importing authority, in which case the resulting certificate might reasonably be perceived as promotional rather than regulatory in concept.

30. There are, none the less, situations - exemplified by the regulatory status of piperazine and injectable contraceptives - in which a preparation withdrawn or unregistered in the country of origin on grounds of safety may be regarded by other countries as having important utility.\(^1\) Less

\(^1\) Piperazine and nitrosation. WHO Drug information bulletin, 83.1, pp. 5-7.

\(^2\) Injectable contraceptives. WHO Drug information bulletin, 84.2, pp. 7-11 and 84.3, pp. 7-12.
developed countries thus need to have recourse to authoritative, independent, internationally representative advice. This falls within the constitutional mandate of WHO. In creating its major research-based programmes concerned with tropical and diarrhoeal diseases and human reproduction, the World Health Assembly has cast the Organization in the role of an impartial technical adviser on certain categories of drugs and vaccines, and particularly those of strategic importance in developing countries. The practical significance of WHO's international status in this regard has been indelibly established in the elimination of smallpox. Unless its counsel is heeded on the registration and use of drugs crucial to the control of the major transmissible diseases, as now in the case of the new antimalarial compound mefloquine, the prodigious effort involved in bringing such substances into medicinal use could be rapidly and irretrievably dissipated.

POSSIBILITIES FOR FURTHER DEVELOPMENT OF THE SCHEME

31. The WHO Certification Scheme is dependent upon acceptance by exporting countries of the obligations they incur as participants. It can operate effectively only if trust is developed between the authorities of the importing and exporting countries. It is inevitable that, occasionally, the quality of an imported product will be called into question. An explicit obligation is placed on the responsible authority of the exporting country to institute appropriate inquiries on request.

32. An essential distinction between the WHO Scheme and, for instance, the Pharmaceutical Inspection Convention (1) operated under the auspices of the European Free Trade Association, is that the capacity of a country to meet the stated requirements for exportation is determined autonomously by its own administration, rather than by an international body. The Scheme thus devolves directly from the existing legal and administrative powers and responsibilities of national drug regulatory authorities. There is no provision, either within the Scheme itself or within the mandate of WHO, to create an international inspectorate force or independent arbitration procedures to supervise its implementation. Nor does the Scheme create or anticipate any mechanism for external inspection of manufacturing facilities by officials from importing countries. Any such arrangements, should they materialize, must evolve from bilateral or multilateral agreements and undertakings outside the ambit of the WHO Scheme.

33. The prime responsibility of the competent authority in the exporting country is to attest that a given product has been produced in accordance with internationally accepted standards of manufacturing practice. As yet, although a declaration is also required as to whether or not the product is registered in the exporting country, no details are specifically requested of any attendant conditions or restrictions. At the time the Scheme was conceived in the early 1970s few national regulatory authorities had

developed a system of approving product information including labelling, prescribing information and promotional material.

34. Now, most highly evolved authorities include within the licence of newly registered products details of the indications, dosage, contraindications, warnings, precautions and known adverse reactions to which all product-related information, including advertising material and promotional activities, should conform. The Third International Conference of Drug Regulatory Authorities (ICDRA 3) consequently recommended that the Scheme be extended, by formal amendment, if necessary, to include provision of product information approved in the country of origin. Since most countries have yet to review all longer established pharmaceutical products currently marketed under their aegis, an effective system of attestation of information would need to confirm that the information had been approved by the certifying authority and to indicate the date of approval.

35. ICDRA 3 also stressed the importance of complementing the certification procedure with:

- more systematic exchange of information on the results of formal reviews of marketed drugs undertaken by national regulatory authorities

- periodic status reports on the categories of drugs that have been reviewed by each national authority and on those that are pending for assessment.

Effective international exchange of this information will directly assist regulatory authorities in their responsibility of revising labelling requirements and removing from national markets products that do not conform with prevailing standards of efficacy and safety. It could also relieve many national authorities of a substantial technical and administrative burden by reducing the need for independent and duplicative reviews.

36. The Certification Scheme, as it now stands, is concerned exclusively with finished pharmaceutical products. As a consequence of the growth of local manufacturing capability in many developing countries the feasibility of extending the Scheme to embrace active ingredients has been raised within several countries. Whereas a start has been made in some countries to license ingredients as well as finished products, this remains the exception rather than the rule. Indeed, in some major exporting countries the relevant enabling legislation makes no provision for licensing anything other than the finished pharmaceutical products. At present, therefore, local manufacturers need to place reliance in the reputation of their suppliers, in the published pharmacopoeial specifications, and in their own responsibility of ascertaining through full analyses the compliance of all active ingredients with stated specifications. None the less, independent certification of these materials, in so far as it proves to be feasible, could offer an important contribution to quality assurance and the possibility of extending the Scheme in this context will remain under review.
Appendix 1*

2. CERTIFICATION SCHEME ON THE QUALITY OF PHARMACEUTICAL PRODUCTS MOVING IN INTERNATIONAL COMMERCE

Part I — Certification of Pharmaceutical Products

1. For the purpose of this Certification Scheme "pharmaceutical product" means any medicine in its finished dosage form, intended for human use, that is subject to control by legislation in the exporting Member State and in the importing Member State.

2. A pharmaceutical product exported or imported under this Certification Scheme would be certified by the competent authority of the exporting Member State on a Certificate of Pharmaceutical Products, issued at the request of the interested party, to be sent to the competent authority of the importing Member State, which would decide to grant or to refuse the authorization for sale or distribution of the certified product, or to make the authorization conditional on the submission of supplementary data.

3. The issue of the Certificate of Pharmaceutical Products would be subject to the conditions required by the competent authority of the exporting Member State in order to certify that:

(a) the product is authorized for sale or distribution within the exporting Member State (if not, the reasons therefore would be stated on the certificate); and

(b) the manufacturing plant in which the product is produced is subject to inspections at suitable intervals to show that the manufacturer conforms to requirements for good practices in manufacture and quality control, as recommended by the World Health Organization, in respect of products to be sold or distributed within the country of origin or to be exported.

A suggested layout of a Certificate of Pharmaceutical Products with explanatory notes is attached.

4. If certificates of individual batches of products covered by a Certificate of Pharmaceutical Products are required, such certificates could be issued either by the manufacturer or by the competent authority of the exporting Member State, according to the nature of the product and the requirements of the exporting Member State or of the importing Member State. The batch certificate would indicate the name and dosage form of the product, the batch number, the expiry date and storage conditions, a reference to the Certificate of Pharmaceutical Products, and a statement that the batch conforms either to the requirements of the competent authority for sale or distribution within the exporting Member State (with reference to the authorization) or, as the case may be, to published specifications, or to established specifications to be provided by the manufacturer. The certificate could also include data on packaging, labelling, nature of the container, the date of manufacture, results of analysis, and other data.

Part II — Exchange of Information

1. Upon the request of the competent authority of the Member State into which a pharmaceutical product covered by this Certification Scheme is to be or has been imported, the competent authority of the exporting Member State should provide:

(a) information on the implementation of the Requirements for Good Practices in the Manufacture and Quality Control of Drugs as recommended by the World Health Organization;*

(b) information on controls of the product as exercised by the competent authority of the exporting Member State;

(c) the names and functions of the persons designated to sign certificates of individual batches of the product to be exported.

Information on general and specific standards of quality control of the product to be exported, in so far as they are required to comply with legislative provisions of the importing Member State, could also be supplied with the consent of the manufacturer.

2. In the case of quality defects of products imported under this Certification Scheme that are considered to be of a serious nature by the importing country, not attributable to local conditions and circumstances, and appearing after the introduction of a particular batch into the Importing Member State, the competent authority should notify the occurrence, together with the relevant facts, to the competent authority of the exporting Member State that had issued the Certificate for the product concerned, with a request to institute inquiries. Conversely, if the competent authority of the exporting Member State ascertains serious quality defects, that competent authority should notify the competent authority of the importing Member State.

Part III — Participating Member States

1. Each Member State agreeing to participate in the Certification Scheme shall communicate (a) the name and address of its principal authority to be considered as competent within the meaning of the

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*It is realized that in some countries this may require the consent of the manufacturer.
Certification Scheme, and (b) any significant reservations relating to its participation, to the Director-General of the World Health Organization, who would notify all other Member States.

2. Exporting Member States participating in the Certification Scheme shall ensure that:

(a) authorization for sale or distribution of pharmaceutical products is subject to appropriate testing measures, by the competent authority, designed to ensure their quality, and that adequate laboratory facilities are available for this purpose;

(b) the pharmaceutical industry is obliged to conform to requirements for good practices in the manufacture and quality control of drugs as recommended by the World Health Organization;

(c) the competent authority is empowered to conduct appropriate investigations to ensure that manufacturers conform to the requirements referred to in (b), including, for example, the examination of records and the taking of samples;

(d) the inspectors of the services of its competent authority have appropriate qualifications and experience.

3. Exporting Member States participating in the Certification Scheme should, whenever possible, ensure that the international nonproprietary names, whenever available, are used in the description of the composition of the product on the Certificates and, as far as possible, appear on the labelling of pharmaceutical products to be exported under the Certification Scheme.

**CERTIFICATE OF PHARMACEUTICAL PRODUCT(S)**

Name and dosage form of product: .................................................................

Name and amount of each active ingredient: ² ............................................

Manufacturer, and/or when applicable, the person responsible for placing the product on the market: ..........................................................

Address(es): .................................................................................................

It is certified that:

☐ This product has been authorized to be placed on the market for use in this country.

Number of permit and date of issue (if applicable): ........................................

☐ This product has not been authorized to be placed on the market for use in this country for the following reasons:

..................................................................................................................

It is also certified that (a) the manufacturing plant in which the product is produced is subject to inspections at suitable intervals, and (b) the manufacturer conforms to requirements for good practices in the manufacture and quality control, as recommended by the World Health Organization, in respect of products to be sold or distributed within the country of origin or to be exported. (See Explanatory Notes.)

........................................... .........................................

(Signature of designated authority) ..........................................................

(Place and date) ..........................................................................................

**Explanatory Notes**

*Certificate of Pharmaceutical Product(s)*

This certificate is intended to define the status of the pharmaceutical product and its manufacturer in the exporting country. It is issued by the competent authority in the exporting country in accordance with the requirements of the competent authority of the importing country. It may be required by the importing country at the time of the first importation and subsequently if confirmation or updating is required.

The requirements for good practices in the manufacture and quality control of drugs mentioned in the certificate refer to the text adopted by the Twenty-eighth World Health Assembly in its resolution WHA28.65 (see Official Records No. 226, Annex 12, Part I).

**Batch certificates**

If certificates of individual batches of products covered by a Certificate of Pharmaceutical Products are required, such certificates could be issued either by the manufacturer or by the competent authority of the exporting Member State, according to the nature of the product and the requirements of the exporting Member State or of the importing Member State. The batch certificate would indicate the name and dosage form of the product, the batch number, the expiry date and storage conditions, a reference to the Certificate of Pharmaceutical Products and a statement that the batch conforms either to the requirements of the competent authority for sale or distribution within the exporting Member State (with reference to the authorization) or, where appropriate, to published specifications or to established specifications to be provided by the manufacturer. The certificate could also include data on packaging, labelling, nature of the container, the date of manufacture, results of analysis, and other data.

¹ This form may be adapted to cover several products of the same manufacturer.

² Use, whenever possible, international nonproprietary names (INN) or national nonproprietary names.
37/137. Protection against products harmful to health and the environment

The General Assembly,

Aware of the damage to health and the environment that the continued production and export of products that have been banned and/or permanently withdrawn on grounds of human health and safety from domestic markets is causing in the importing countries,

Aware that some products, although they present a certain usefulness in specific cases and/or under certain conditions, have been severely restricted in their consumption and/or sale owing to their toxic effects on health and the environment,

Aware of the harm to health being caused in importing countries by the export of pharmaceutical products ultimately intended also for consumption and/or sale in the home market of the exporting country, but which have not yet been approved there,

Considering that many developing countries lack the necessary information and expertise to keep up with developments in this field,

Considering the need for countries that have been exporting the above-mentioned products to make available the necessary information and assistance to enable the importing countries to protect themselves adequately,

Cognizant of the fact that almost all of these products are at present manufactured and exported from a limited number of countries,

Taking into account that the primary responsibility for consumer protection rests with each State,

Recalling its resolution 36/166 of 16 December 1981 and the report on transnational corporations in the pharmaceutical industry of developing countries,¹ and acting in pursuance of Economic and Social Council resolution 1981/62 of 23 July 1981,

Bearing in mind in this context the work of the Food and Agriculture Organization of the United Nations, the World Health Organization, the International Labour Organization, the United Nations Environment Programme, the General Agreement on Tariffs and Trade, the United Nations Centre on Transnational Corporations and other relevant intergovernmental organizations,

1. Agrees that products that have been banned from domestic consumption and/or sale because they have been judged to endanger health and the environment should be sold abroad by companies, corporations or individuals only when a request for such products is received from an importing country or when the consumption of such products is officially permitted in the importing country;

2. Agrees that all countries that have severely restricted or have not approved the domestic consumption and/or sale of specific products, in particular pharmaceuticals and pesticides, should make available full information on these products with a view to safeguarding the health and environment of the importing country, including clear labelling in a language acceptable to the importing country;

3. Requests the Secretary-General to continue to ensure the provision of the necessary information and assistance by the United Nations system in order to strengthen the national capacities of developing countries to protect themselves from the consumption and/or sale of banned, withdrawn, severely restricted or, in the case of pharmaceuticals, non-approved products;

4. Requests the Secretary-General, based upon the work already being done within the Food and Agriculture Organization of the United Nations, the World Health Organization, the International Labour Organization, the United Nations Environment Programme, the General Agreement on Tariffs and Trade, the United Nations Centre on Transnational Corporations and other relevant intergovernmental organizations, to the maximum extent possible within existing resources, to prepare and regularly update a consolidated list of products whose consumption and/or sale have been banned, withdrawn, severely restricted or, in the case of pharmaceuticals, not approved by Governments, and to make this list available as early as possible and, in any case, not later than December 1983;

5. Agrees that the consolidated list referred to in paragraph 4 above should be easy to read and understand and should contain both generic/chemical and brand names in alphabetical order, as well as the names of all manufacturers and a short reference to the grounds and the decisions taken by Governments that have led to the banning, withdrawal or severe restriction of such products;

6. Decides, on the basis of the above-agreed criteria, to keep under review the format of the consolidated list with a view to its possible improvement;

7. Requests Governments and the relevant organs, organizations and bodies of the United Nations system to provide all the information and assistance necessary for the prompt and effective fulfilment of the task entrusted to the Secretary-General.

109th plenary meeting
17 December 1982

¹ E/C.10/85.

1. The rational use of drugs requires that patients receive medicines appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and the community. Rational use implies balancing benefit against risk and cost and is the joint responsibility of policy-makers and drug regulatory authorities, the pharmaceutical industry, health care professionals, and patients and the general public as consumers.

2. Rational drug use concerns equally the developed and the developing countries. In developed countries inappropriate and unnecessary prescribing is placing a severe strain on the health care budget as well as increasing the burden of iatrogenic disease. In developing countries the unnecessary use of inessential medicines and the relatively high cost of many essential ones impedes the delivery of health care (1,2). Irrational drug use is therefore a matter of major concern for all countries.

EDUCATIONAL AND INFORMATION REQUIREMENTS FOR RATIONAL DRUG USE

3. If policy-makers are to formulate coherent strategies to promote rational drug use they require information about their community's pharmaceutical needs, the cost of meeting them, and the utilization of pharmaceutical products. Requirements for essential medicines can be estimated from the prevalence of diseases for which effective drugs are available. An adequate epidemiological data base is therefore an essential prerequisite for planning rational drug use. In developing countries without adequate epidemiological information a service-based or demand-morbidity method can be successfully adopted (3). Projections of drug consumption must also take into account the community's desire for self-medication; policy-makers should draw up realistic self-medication strategies (4).

4. Health care budgets are under severe constraints in both developed and developing countries, and policy-makers therefore need reliable estimates of the cost of medicines. In countries with a substantial indigenous pharmaceutical industry reasonable pharmaceutical price stability can usually be achieved. In countries without a significant national pharmaceutical industry prices may fluctuate widely because of changes in exchange rates or interruptions in supply.

The Director-General acknowledges with appreciation the contribution to the preparation of this paper of Professor Michael D. Rawlins, Professor of Clinical Pharmacology, Wolfson Unit of Clinical Pharmacology, University of Newcastle-upon-Tyne, England.
5. Information about drug utilization is as important for developed countries as for less developed ones. Drug utilization data can be used to identify areas of wasteful and unnecessary prescribing, alert policy-makers and regulatory authorities to any increase in iatrogenic disease, and form a basis for monitoring the performance of health care professionals. They can be obtained from the sales figures of individual pharmaceutical companies, the purchases made by pharmacies and hospitals, and analysis of prescriptions. Yet, even where reasonably accurate drug utilization data are available to governments and policy-makers, there is little evidence that appropriate action is taken on them. For example, in developed countries problems associated with dependence on benzodiazepines (5) could have been anticipated by the health authorities during the 1970s when they began to be used widely and excessively (6).

6. In addition to providing policy-makers and administrators with the necessary information for planning the rational use of pharmaceutical resources, there is a need for training them in reaching appropriate decisions. One particular approach, pioneered by WHO in collaboration with the Harvard Business School, has been the use of case histories designed specifically for health administrators in less developed countries. Extension of this scheme could probably improve the quality of decision-making by health administrators in developed and developing countries.

7. The staff of national drug regulatory authorities have the responsibility of ensuring that pharmaceutical products are of satisfactory quality, effective for the indications claimed by their manufacturers, and safe in relation to their efficacy. The professional and scientific staff of regulatory authorities have backgrounds in pharmacy, medicine, pharmacology, toxicology and statistics. The professional skills required of a member of a regulatory authority, however, are broader than those acquired during conventional training programmes in pharmacy, medicine, or science. In-service training of the professional staff of regulatory authorities in developed and developing countries therefore requires closer attention than it has been given in the past.

8. The inferior quality of some pharmaceutical products, particularly imported generic preparations and drugs manufactured locally, has generated concern in both affluent and poor countries (7,8). Quality assurance and quality control are the responsibility of pharmaceutical assessors in regulatory authorities. The WHO Certification Scheme, which attempts to provide relevant information, does not, however, provide a substitute for proper local control of quality and stability. Quality assurance requires the establishment of an appropriately trained inspectorate. Training schemes for plant inspectors have been arranged by UNIDO. The necessity for quality control laboratories has been accepted in developed countries, but the lack of equipment and trained staff has prevented their establishment in many less developed countries. Facilities for the training of quality control personnel from developing countries have been made available through IFPMA. This training, however, will be of little value if policy-makers do not accept the importance of adequate arrangements for quality assurance and quality control and make appropriate financial provision. Pharmacists in
regulatory authorities therefore have the special responsibility of educating policy-makers about the importance of those aspects of drug regulation and of the consequences to public health of any deficiencies.

9. Medical staff in regulatory authorities are responsible for assessing the efficacy and safety of new and marketed pharmaceutical products. In addition to their general medical training, medical assessors also require experience in clinical pharmacology or pharmaceutical medicine. In developed countries the recruitment of appropriately trained individuals has not been easy, in part at least because of the scarcity of clinical pharmacologists outside northern Europe. In developing countries recruitment of appropriately trained medical assessors is often extremely difficult; urgent action is required to provide suitable in-service training for new recruits with previous experience in medical disciplines other than clinical pharmacology. Given the small number of trained clinical pharmacologists in developing countries, local in-service training will often be impracticable. Consideration should therefore be given to establishing training courses on a supranational basis.

10. Assessment of the efficacy and safety of new pharmaceutical products will generally be based on submissions from individual pharmaceutical companies. Proper assessment of animal toxicology findings, clinical trial data, and human safety data demands expertise in a wide range of disciplines as well as knowledge of contemporary medical and scientific literature and good judgement. Information about the pharmacological and toxicological properties of the class to which the preparation belongs should be available to the medical assessor in standard works of reference. Decisions reached by other regulatory authorities may also be relevant.

11. In evaluating the continuing efficacy and safety of marketed products the medical assessor will depend particularly on reports in the medical literature, post-marketing experience gained by other regulatory authorities and, most particularly, post-marketing surveillance in his own country. The medical literature provides an important source of scientific data to support (or refute) further indications for a particular product. It may also provide the first reports (alerts) of suspected adverse reactions (9). Other regulatory authorities may provide additional information about suspected adverse reactions. Every regulatory authority, however, needs its own mechanisms for post-marketing surveillance. Geographical and racial differences in disease patterns, pharmacogenetic polymorphisms, and environmental influences on drug action make it unwise to extrapolate drug safety from one population to another.

12. Medical assessors therefore require information if they are to fulfil their responsibilities adequately. In developed countries library facilities and an informal network of regulatory authorities facilitate information retrieval and exchange. In developing countries limited access to the current medical literature and the absence of an informal information network may be a bar to effective drug regulation. Within national regulatory authorities WHO has contact with nominated information officers who act as recipients for WHO information bulletins containing brief reports of important regulatory decisions and current drug problems. These
bulletins should help ensure that medical assessors in regulatory authorities remain in touch with international developments. The suggestion that the WHO newsletter should be issued more frequently and include data sheets on new products from the country of first registration requires further examination (10).

13. Information about the safety of marketed pharmaceutical products requires the establishment of local post-marketing surveillance schemes. The cheapest and simplest system is that of voluntary adverse reaction reporting by prescribers (11). Voluntary reporting systems are capable of detecting new adverse reactions and play an important role in the evaluation of known adverse effects (12). They are relatively easy to establish, requiring only the enthusiasm and goodwill of the health care professions. They do not, at least in their early stages, require computer facilities, and they are appropriate for use in both developed and developing countries.

14. To exercise proper professional judgement in prescribing drugs for their patients, doctors need basic background knowledge and understanding of pharmacology, clinical pharmacology, and therapeutics. They also need accurate information about the properties, benefits, risks, and cost of all the pharmaceutical products available to them for prescribing.

15. Pharmacology is an essential component of the modern undergraduate medical curriculum. There is, however, a large gap between the basic science of pharmacology and its application to practical therapeutics. In northern Europe and Australasia clinical pharmacology has developed both as an academic and as a service discipline to fill this gap; formal instruction in clinical pharmacology has become a permanent feature of the medical curricula in those countries and is an integral component of their qualifying examination systems. Even in the United Kingdom, however, where almost every medical school has established a department or subdepartment of clinical pharmacology, a recent government inquiry into effective prescribing urged that more attention be given to this area (13). Many developed countries and most developing countries have failed to recognize clinical pharmacology as a service specialty and neglected its potential contribution to undergraduate training. Although the impact on rational drug use will be long-term, improved undergraduate education in clinical pharmacology is likely to be one of the most cost-effective ways of improving prescribing.

16. Undergraduate teaching programmes in clinical pharmacology should seek to provide students with a knowledge of the scientific basis of therapeutics. This means instruction in the actions, therapeutic effects, toxicity, and fate of the major drugs. Students should also be taught about the relative importance of various sources of information and be introduced at an early stage to their national formulary. They need to know how to evaluate published claims of efficacy and safety, understand the sociology and economics of prescribing, and be adequately prepared for their role as educators of other health care professionals and patients.

17. Advances in clinical pharmacology and therapeutics and the influx of new pharmaceutical products make it essential for practising doctors to have
access to appropriate prescribing information. To prescribe a drug safely and effectively, doctors need to know its pharmacological action, the preparations available, and the therapeutic indications for which it is effective. They also need to know the usual range of effective doses, whether dosage titration is necessary, what dosages are recommended for special patient groups (e.g., the young, the elderly, the malnourished), and what monitoring is necessary both during and after treatment. Prescribers must be provided with information about the adverse reactions and interactions that may be encountered, their type and frequency, their relationship to dosage, their prognosis, and their management or prevention. Finally, they need to be aware of the likely effects of the drug if given during pregnancy. This information should be provided by national formularies which, when properly prepared, can play an extremely important role in encouraging rational drug use. They can provide better comparative data on safety and efficacy than the literature of pharmaceutical companies. Publications of pharmaceutical companies (e.g., *Data sheet compendium, Physician's desk reference*) are potentially useful adjuncts to national formularies in providing prescribing information on individual products. They must, however, be factually accurate and should undergo some form of review to ensure that they are, such as approval by the regulatory authority before they are distributed. Data sheets should contain not only full prescribing information but also details of excipients, and should carry the date of the last review by the regulatory authority.

18. National and local drug bulletins and newsletters are distributed in many developed countries to encourage rational prescribing. These have been produced in response to perceived local or national needs by government health departments, consumer organizations, academic units of clinical pharmacology, and local hospitals. WHO headquarters issues a quarterly *Drug information bulletin* and a number of regional offices issue similar publications. The influence of bulletins and newsletters in encouraging rational drug usage is presumed rather than proven. While it is inherently likely that they have beneficial effects, further work is needed to establish the most appropriate scope, format, and style for different readerships.

19. Meetings, lectures, and seminars on clinical pharmacology and therapeutics are important ways for doctors to maintain their competence as prescribers. In most countries, however, public funding for these educational activities is limited and many such meetings are organized and financed by the pharmaceutical industry. There is a real danger that, by relying on the pharmaceutical industry for the financing of continuing education in rational drug use, policy-makers and health administrators will not achieve overall control of the use of drugs.

20. The traditional role of pharmacists in dispensing prescriptions has become less important with the wide availability of finished pharmaceutical products. They have therefore increasingly become involved in counselling patients about the use of prescribed medicines, advising about medicines for self-medication, and providing other health care professionals (including doctors) with information about drugs. In developed countries these
extensions of the traditional role of the pharmacist have become institutionalized in the subspecialties of clinical pharmacy, ward pharmacy, and information pharmacy. In developed countries there has also been some increase in the range of over-the-counter products that a pharmacist may offer patients, on his own responsibility, for self-medication. These changes have not invariably been accompanied by appropriate changes in the undergraduate education of pharmacists. The training must provide students with the necessary skills and attitudes that will enable them to meet their newer responsibilities.

21. Practising pharmacists also need information about both the pharmaceutical and the clinical aspects of the products they dispense. They require information about quality and stability; they must have available to them the clinical indications that have been accepted by the regulatory authority; they should be aware of a product's important adverse effects and its potential interactions with other drugs; and they must be able to confirm that the prescribed dosages are appropriate. This information should be available in national formularies and pharmacopoeias.

22. Nurses are involved in administering drugs to patients and in counselling them about their safe use. They also have some prescribing responsibilities, although the range varies in different countries.

23. The education of student nurses needs to reflect accurately their responsibilities for promoting rational drug use within the context of their future nursing practice. Moreover, irrespective of the type of health care delivery system within which they will be working, nurses must be adequately prepared for their role as educators and counsellors. They should be able to explain to patients why the medicines they are receiving are necessary, how they should use them most effectively, and how they should undertake self-medication for themselves and their families.

24. Nurses need information about the medicines they administer and prescribe. This information should include the indications, the preparations available, the route(s) of administration, the dosages, and the likely adverse reactions. They also need to know how the drug should be taken in relation to meals. For drugs that they themselves prescribe nurses need additional advice on the duration of treatment regimens, the need for dosage adjustments in special patient groups, and the precautions to be adopted when giving drugs to pregnant women.

25. The format in which information on drug administration and prescribing can be best provided for nurses needs to be tailored to meet their diverse roles and responsibilities. A national formulary is very useful for nurses working in most clinical situations, and formularies should be constructed with the needs of nurses in mind. Additional material may be necessary for midwives and for those working in specialized fields such as cancer, intensive therapy, renal dialysis, and psychiatry. Specially prepared material is also likely to be required by nurses working in rural communities, and by others with responsibilities for supervising community health workers, as well as by those providing contraceptive services.
26. **Community health workers** (variously described as rural health workers, health guides, barefoot doctors, village health workers, health promoters, health kadars, etc.) are playing an increasingly important part in the delivery of primary health care in developing countries (14). It is the experience of WHO that community health workers can be trained to use a limited number of drugs with skill and judgement. To do this, however, they require appropriate instruction and written information to support their prescribing in practice. To use their limited range of drugs most effectively, community health workers require information on storage, clinical indications, dosages, precautions, contra-indications, and adverse reactions. They also need adequate training in explaining to patients about the medicines they prescribe and about appropriate self-medication.

27. **Consumers** in both developed and developing countries have a right to know about the drugs they are prescribed by health care professionals. They also require advice about self-medication. Patients need to know the name of the drug they have been given and the reasons why it has been prescribed (15). They also need to know how to take their medicine, what to do if they forget a dose, for how long the course of treatment is to last, and why it is necessary to continue it even though their symptoms may have disappeared. Patients can also expect advice about the adverse reactions they may encounter while taking the drug; the occurrence of some adverse reactions requires immediate action by the patient, whereas others may disappear with continued administration of the drug. Unless patients are provided with such information they cannot take appropriate action. Patients are unlikely to remember all the information they need during a single consultation and reminders by the dispensing pharmacists are therefore important. The provision of written information, specific for the drug, is probably the most effective way of communicating this essential information (16,17). Policy-makers, health care professionals, and the pharmaceutical industry should be encouraged to provide written information routinely specifically designed for patients (patient package inserts).

28. In those countries in which self-medication is encouraged, or at least accepted, the public needs adequate information about safe and effective self-medication. In these countries the development of an appropriate national self-medication policy is desirable. Regulatory authorities have the same responsibility for ensuring that medicines available for self-medication are safe and that the advertising claims made by their manufacturers are clear, unambiguous, and precise as they have for prescription drugs. Regulatory authorities should also ensure that medicines available for self-medication are labelled with appropriate advice on indications, dosages, warnings, and adverse reactions.

29. Consumers must also have confidence in the ability of health care professionals to use drugs safely and effectively. They can reasonably expect to know that prescribers are adequately trained and have sufficient and appropriate information about the drugs they use.
EDUCATION AND TRAINING FOR RATIONAL DRUG USE

30. Education and training to encourage the rational use of drugs must take into account the historical, cultural, and structural features of society that encourage irrational drug use. Irrational use is historically ancient and geographically universal. The voluminous pharmacopoeias of ancient civilizations (18) demonstrate that man's insatiable appetite for medicines is no recent aberration. Unquestioning faith in the ability of drugs to prevent or cure disease, improve athletic or sexual powers, or provide psychological pleasure, is universal among wealthy urban populations in developed countries as well as the poor in developing countries. This faith renders ordinary people susceptible to the marketing pressures of manufacturers and retailers of medicines and medicinal products. As a result, the promotion of drugs for self-medication (either overtly or covertly) may result in the use of products that are ineffective or dangerous, and may also squander individual financial resources that could be put to better use. The promotion of prescription drugs to the general public occurs in both developed (19) and developing (1) countries, creating a demand for supplies from health care professionals that may be irresistible.

31. Attempts to change public attitudes towards the use of medicines require a concerted approach that has not been seriously attempted in either developed or developing countries. Although health education programmes have tried, with varying degrees of success, to modify behaviour in certain specific areas such as drug abuse, the attempts are unlikely to succeed unless a more fundamental approach is adopted, involving changing public attitudes to the use of drugs for both therapeutic and non-therapeutic purposes. Such an approach to the misuse of drugs needs to be accompanied by a proper understanding of how to use self-medication where that is accepted practice.

32. The paucity of training opportunities in clinical pharmacology for health care professionals, together with exaggerated public expectations of the benefits of drug therapy, has resulted in a vacuum that has to a considerable degree been filled by the pharmaceutical industry in many parts of the world. The sophisticated promotional and information techniques of the pharmaceutical industry could, if appropriately applied, substantially influence public attitudes. The industry rightly claims credit for the discovery and development of many medicinal products that have had a major beneficial impact on health; effective vaccines, anaesthetic agents, and drugs to treat a wide range of microbial, cardiovascular, respiratory, and psychiatric disorders have made a crucial contribution to medical care in developed countries and, to a lesser extent, in developing countries. These positive features, however, have too often been accompanied by over-zealous marketing and promotional techniques that have encouraged the extravagant use of drugs. The exaggerated promotion of medicines among an over-optimistic and unquestioning public and inadequately educated health care professionals leads inevitably to irrational drug use. Measures designed to curb extravagant drug promotion must, however, be accompanied by attempts both to change public attitudes and to increase knowledge amongst health care professionals.
Whose responsibility?

33. The responsibility for promoting the rational use of drugs does not lie with any single group. Policy-makers and health administrators, health care professionals, the pharmaceutical industry, and consumers must all play their part.

34. Identifying the goals of rational drug usage and providing the necessary financial and human resources to achieve them are the responsibility of policy-makers and health administrators. In achieving the goals policy-makers need the advice and support of health care professionals, the pharmaceutical industry, patients, and the public. The potential for conflict, however, is substantial; health care professionals tend to be suspicious of political attempts to interfere with clinical freedom as they perceive it; pharmaceutical companies resent measures which they fear could reduce their profits; patients understandably demand that what they perceive to be the most effective medicines should be available to them, irrespective of cost; and the public desires open and easy access to safe medicinal products for self-medication. The resolution of these conflicts requires great political skill.

35. Policy-makers and health administrators also need to ensure that the training of health care professionals is adequate and that there is a coherent strategy for continuing education. In addition, they should ensure that doctors, pharmacists, and nurses can continually educate themselves by having easy access to reliable sources of unbiased information such as a properly prepared national formulary. In producing national formularies some developing countries may wish to draw on those already available in developed countries, at least in part. However, it is important to recognize that local factors usually require each country to aim at producing its own national formulary. A similar formulary is needed by community health workers, modified to meet their own special needs. Excellent examples have already been produced by some developing countries (20,21). Policy-makers and regulatory authorities should also be concerned to ensure that prescribing information published by pharmaceutical companies is accurate and complete. The methods by which this is accomplished will vary, but unless the authenticity of the manufacturers' promotional claims is assured rational prescribing will not be possible.

36. The responsibility for ensuring that the information given to health care professionals is accurate and unbiased rests with the regulatory authorities. In fulfilling that responsibility, regulatory authorities need the advice and support of the health care professionals themselves, particularly those with special knowledge and expertise in particular areas of medicine; clinical pharmacologists in hospitals and academic institutions are a particularly valuable source of advice. Health care professionals also have individual and collective responsibility for ensuring correct use of the medicines they prescribe and for the education and counselling of their patients.
37. It is the responsibility of consumers to act on the information they have been given for the safe and effective use of medicines. Consumer organizations in some countries contribute greatly to ensuring that health care professionals have access to unbiased information on therapeutics generally and prescribing in particular and that people have access to such information in a language they can understand. Consumer organizations play an important role in representing the interests of patients and the public at the boundary between politics and medical practice, although in maintaining their independence of vested interests they sometimes come into conflict with policy-makers, regulatory authorities, health care professionals, and the pharmaceutical industry. They are, however, an important ingredient in the social control of health systems, including ensuring the proper use of drugs.

CONCLUSIONS

38. It can be seen that the rational use of drugs in both developed and developing countries requires the cooperation of policy-makers, health administrators, health care professionals, and consumers. For such cooperation to be fruitful, proper understanding of the many factors involved is required by all concerned. Education and training can make a valuable contribution to this understanding. It is the responsibility of individual countries to find the political, financial, and practical means for that purpose.
REFERENCES


WHO'S ROLE IN TRAINING, EDUCATION AND OTHER INFORMATION TRANSFER

The scope of WHO's training activities

1. Self-reliance in virtually every sphere of government activity is built upon sound management and technical competence. Training and education have consequently long been recognized as staple elements in WHO's supportive role to countries concerned to develop their health care infrastructure. These activities have several distinct foci. On the one hand emphasis is placed upon the development of planning and managerial skills as key elements in the elaboration and implementation of national health policies. On the other hand, with a view to extending the coverage of medical care particularly within developing countries, much attention is now directed to establishing primary health care systems and creating a cadre of community health workers. Thirdly, the strengthening of research capability has been accorded priority in selected areas both in an administrative context, as in the planning of health services, and in a technical context, as in the provision of institutional support and the promotion of research programmes of high social relevance.

2. Each of these elements of training and education is represented within WHO's drug-related activities. Over the years training programmes have been developed to subserve and to promote national regulatory capability, the concept of essential drugs particularly in relation to the development of primary health care, and the evolution of clinical pharmacology and epidemiological approaches to drug monitoring as disciplines concerned with the rationalization as well as the advancement of therapeutic management.

The development of national regulatory capability

3. Comprehensive national approaches to drug control are very largely a phenomenon of the post-thalidomide era. In most of the highly developed countries attention was initially directed primarily to the assessment of newly developed products. The review of pre-existing drugs was regarded as a collateral activity, subordinate in importance to preventing the accession of unacceptably hazardous new drugs to the market. Ten years ago few national administrations had compiled comprehensive catalogues of drugs available on their national markets. Many had still to embark upon a systematic review of products marketed prior to the implementation of statutory registration procedures. Even now very few countries have completed this initial survey. Virtually everywhere products can still be found that are promoted on the basis of advertising that has not yet been subjected to control, and the number of countries exploring administrative options for rationalizing the structure of their drug markets is increasing.

4. The regulatory basis of drug control is thus still evolving in developed as well as in developing countries. Indeed, the adequacy of WHO's Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce, which was introduced in 1975 as a basis for
exchanging information on drugs between governments, is also now frequently called into question.

5. Against this background of evolution and reappraisal and of differing national philosophies and needs, an exclusively didactic approach to training and education in drug regulation at international level would be inappropriate. Over the past five years, therefore, WHO has placed emphasis on providing a forum for discussion of administrative strategies and major technical issues between senior officials from regulatory authorities on a worldwide basis. As a result of a joint initiative by the United States Food and Drug Administration and WHO in 1980, the biennial International Conference of Drug Regulatory Authorities (ICDRA) has become an influential yet informal mechanism for the exchange of ideas and for upgrading collaboration between national authorities.

6. The support and patronage that the ICDRA receives from many governments of developed and developing countries alike has created a better appreciation on every side of the need for an effective flow of information between national authorities, and it has highlighted both the strengths and the shortcomings of the Certification Scheme. It has given national officials an insight at first hand into how other countries at all levels of development approach their tasks and how they respond to common problems. It is also providing opportunity for an exchange of views on unresolved and innovative aspects of drug control including such varied topics as the labelling of pharmaceutical products, the development of orphan drugs and the impact of recombinant DNA technology on the regulatory process. To ensure that Conference programmes are responsive to regional requirements, a planning meeting is convened in the alternate years in accordance with agreed terms of reference (see Appendix, page 318) both in order to settle the agenda for the forthcoming Conference and to follow up the implementation of previous recommendations.

7. Whereas the International Conference is of value to countries wishing to refine or extend their existing regulatory operations, its existence has also underscored the fact that many countries have yet to create a system of drug control appropriate to their particular circumstances. Indeed, the model provided by many highly developed countries - centred, as it is, around multidisciplinary technical assessments of drug safety and performance - may well serve to deter rather than to encourage these authorities from embarking upon a systematic approach to regulation. Many countries are inherently dependent upon externally-generated information in formulating their decisions in this technically complex field. Their prime need is to create an operative framework within which information available internationally can be used to best advantage.

8. Much is already in place to provide the basis of a simplified registration procedure, including the WHO Certification Scheme, the Model List of Essential Drugs, the International pharmacopoeia, the model quality control laboratory and the technical information generated both by national regulatory authorities and WHO which is circulated through the network of designated national information officers. Work is already in hand within WHO on a manual that describes and interrelates these resources with a view
to demonstrating how they can be utilized to develop a simple, yet effective, national registration system which, in turn, might provide the administrative basis for a statutory system of control.

9. Meanwhile, informed advice about the planning and organization of a national control facility has been available to many developing countries on a consultancy basis, both within the context of bilateral collaboration and under the auspices of the WHO Fellowships programme. The Organization has also attracted the collaboration of governments, interested nongovernmental organizations and universities in providing individual or group training in specific aspects of drug control, notably in laboratory management and drug analysis as it relates to quality control, and in drug selection and procurement.

Training in drug quality control and drug assessment

10. Since 1947 WHO has provided fellowships as one means of helping Member States to train selected individuals for responsible positions in health administrations. The financial assistance that is provided enables individuals to follow an advanced programme of study, usually abroad, with the understanding that the nominating governments will employ the returning fellows in appropriate capacities. Whereas a retrospective study undertaken in one region of WHO\(^1\) suggests that both the value and the subsequent utilization of this training in career development is high, the total number of fellows that can be accepted for training is limited, and the scheme is open to nomination of candidates in every field of health. Thus the proportion of pharmacists contained within the sample of more than 400 fellowships subjected to review was less than 3%.

11. In order to satisfy the demand for training in drug regulation, WHO has consequently needed to seek financial sponsorship from other interested parties including governments, the pharmaceutical industry, professional organizations and universities. Opportunities for using government facilities, including national quality control laboratories for training purposes, are infrequent and at the Thirty-second World Health Assembly in May 1979 the International Federation of Pharmaceutical Manufacturers Associations (IFPMA) made an offer of training places in drug quality control within the pharmaceutical industry. The offer is open to nationals of developing countries employed in governmental control laboratories (not connected with the manufacture of pharmaceuticals) and from pharmaceutical inspection services. Training is directed at individuals who have completed their formal education in pharmacy or chemistry and who have at least a basic knowledge of analytical work. It is carried out in the analytical laboratories or quality control departments of pharmaceutical companies and it is directed, according to individual needs, to chemical, microbiological, or biological control. The training normally extends over a period of

3-6 months with a possibility of more limited training for trainees from countries that are concerned only with dosage forms of pharmaceuticals, and of combined training in all three areas where a demand exists.

12. The companies concerned operate in many countries thereby offering the prospect that training can be carried out in a neighbouring country and efforts are made to tailor the training to individual needs using facilities and equipment available in the applicant's national control laboratory.

13. As of May 1985, 66 applications had been received from 28 countries, half of which are in the African region, and 33 applicants had completed their training. An analogous offer from the World Federation of Proprietary Medicine Manufacturers to train individuals as inspectors of manufacturing premises and distribution facilities is now also under consideration.

14. These arrangements for individual training have long been complemented by shorter periods of group training which provide larger numbers of candidates with an overview of the basics of quality control, and an understanding of how their work relates to the broader responsibility of drug control. A three-week course for 15 to 20 candidates now costs some US$ 200 000 if it is run on a global basis. Costs are appreciably lower if courses are arranged on a regional or interregional basis, and this also holds advantage in that the course content and the facilities provided are more likely to approximate to candidates' needs and working conditions.

15. Financial and organizational support for these courses has been, and continues to be, generously provided by governments and governmental agencies - notably the Danish International Development Agency and the United States Food and Drug Administration - and by professional organizations including the International Pharmaceutical Federation, the Commonwealth Pharmaceutical Association and - in connection with drug evaluation - by the International Union of Pharmacology.

Training in drug selection and procurement

16. Teaching and training at country and intercountry level supports the development of national capability to plan, implement, and monitor national essential drugs programmes. WHO's role is best illustrated by examples of past activities and its plans for the future.

17. In the early eighties the Action Programme identified the need for a series of workshops for senior managers and decision-makers. The purpose was to demonstrate actual country experience and to discuss ways and means of improving delivery and use of essential drugs. The workshops have proved useful in exposing participants both to the concepts and the country application of essential drugs but have not aimed at the development of specific skills.

18. WHO has now moved towards supporting a more skills-oriented, "hands-on" type of workshop addressing specific elements of a national essential drugs programme. Examples include drug logistics and distribution, revision of
essential drugs lists, drug legislation, quality control, application of microcomputers, and methodologies for estimating national drug requirements.

19. These workshops have and will continue to provide material which can be adapted for use by countries in their own situations. WHO's role thus becomes a supporting one for the development of relevant training material and its dissemination to interested countries.

20. All countries embarking on essential drugs programmes have identified at an early stage the need for training and retraining of health workers in improved diagnosis and patient management. WHO will continue to support national training programmes with training of trainers as well as consultants to assist in the development of appropriate teaching and learning materials. Well tested materials, such as: Managing Drug Supply, Management Sciences for Health, USA; Manual for Rural Health Workers, Ministry of Health, Kenya; Handbook for Health Workers, United Republic of Tanzania; logistics modules, computer software for an essential drugs management system; and methodologies for estimating drug requirements, etc., are now available in several languages.

The development of clinical pharmacology

21. Over the years WHO has repeatedly underscored the potential of clinical pharmacologists to further the socioeconomic implications of drug therapy as well as the innovative aspects. It has defined a role for the specialty in drug usage studies;¹ in promoting the notification of suspected adverse drug reactions in hospital practice;² and in broader aspects of drug control. A series of symposia on clinical pharmacological evaluation in drug control, convened annually since 1972 by the WHO Regional Office for Europe, with sponsorship by the Federal Republic of Germany,³ provides a forum for scientific discussion of clinical issues associated with drug control and with defining a role for the specialty of clinical pharmacology within this context.

22. As a more direct service to doctors and scientists working in drug regulation WHO has produced a series of technical reports over the years that provide normative guidelines on the various aspects of drug assessment and much of this material has recently been consolidated in a monograph


directed primarily to practising clinical pharmacologists entitled "Safety
requirements for the first use of new drugs and diagnostic agents in man".1

Education

23. Much of WHO's normative technical material is also inherently
educational in character. The series of technical reports promulgating the
WHO Model List of Essential Drugs2 thus provides information that can be
used as effectively for training purposes as for the development of national
policies and strategies. Moreover, the model drug data sheets that are
referred to in these reports — and particularly those for community health
workers — are intended primarily as an educational tool.

24. Nonetheless, WHO has not yet clearly defined its mandate in the area of
education on the rational use of drugs, and schools of medicine, pharmacy
and public health have been slow or reluctant to introduce the concept of
essential drugs in their regular teaching programmes. Until a well-designed
and well-defined curriculum on the rational use of drugs becomes an integral
part of training we cannot reasonably hope for sustained improvement in the
use of present and future pharmaceutical products.

25. Successful although limited initiatives have been taken by WHO to
introduce the essential drugs concept at least in postgraduate training.
Case material illustrating a range of issues on essential drugs has been
developed in collaboration with the Harvard School of Public Health, Boston,
USA. This material, after testing and use in six to eight schools of public
health in both developed and developing countries, will be made generally
available.

26. Draft curricula on essential drugs for schools of medicine and schools
of pharmacy have also been developed; initial trials in a few institutions
will determine to what degree such teaching institutions will be willing and
able to introduce in their teaching and research activities these new
concepts on the use of drugs.

Information transfer

27. Each of the various systematized approaches developed within WHO for
transferring information between national authorities is described in
extenso on pages 109-141. However, a considerable proportion of the
technical information provided by WHO to governments on issues concerned
with drug safety and drug use is given in response to ad hoc requests.

1 Safety requirements for the first use of new drugs and diagnostic

28. Information transfer has so far been a rather limited activity of the WHO Action Programme on Essential Drugs. It has mainly been restricted to responding to requests for specific information on prices of drugs, suppliers, quality control, and to general information on essential drug programmes. The Action Programme is planning a more active and targetted approach, initially through the distribution of a newsletter and an information brochure on the Programme.

29. The number and variety of requests that WHO receives from governments for technical information suggests that the time is fast approaching when the compilation and maintenance of a computerized data bank of technical and economic information on drugs, which can be interrogated on-line by all national authorities, will constitute a cost-effective approach to informational needs.
APPENDIX

ADVISORY GROUP OF REPRESENTATIVES OF DRUG REGULATORY AUTHORITIES

TERMS OF REFERENCE

Objectives

The group will be convened, insofar as budgetary allocations allow:

- during the year preceding each International Conference of Drug Regulatory Authorities and, in any case, at least twelve months before the projected Conference

- immediately on the closure of each Conference.

These meetings will be held with a view to:

- planning Conference agendas and canvassing presentations

- preparing formal reports on Conference proceedings

- monitoring the implementation of Conference decisions

- reviewing implementation of activities concerned with the exchange of information between drug regulatory authorities within the framework of relevant World Health Assembly and United Nations General Assembly resolutions.

Composition

The group will consist of:

- a representative of the host country who will also serve as Chairman

- the immediate past Chairman

- a representative of a national authority within each of the six regions of WHO.

To the extent that is consonant with equitable regional representation, members will be selected having regard to their previous experience of, and contribution to, conference proceedings.

No member shall serve for a period exceeding three years.

One-third of the regional representatives shall be replaced each year. Their successors will be appointed following consultation between WHO headquarters and the interested WHO regional office.
Annex 1

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Professor L. A. Kaprio, Executive Secretary, WHO, Geneva


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