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Model List of Essential Drugs
(Seventh List)

Fifth report of the
WHO Expert Committee

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1. Introduction

The WHO Expert Committee on the Use of Essential Drugs met in Geneva from 18 to 22 November 1991. The meeting was opened on behalf of the Director-General by Dr J. F. Dunne, Director of the Division of Drug Management and Policies, who emphasized that the concept of essential drugs was fundamental both to WHO's revised drug strategy (*1*), as endorsed by the World Health Assembly in resolution WHA39.27 in 1986 (*2*), and to the development of comprehensive national drug policies. Regular updating of WHO's Model List of Essential Drugs sustained the momentum of the revised drug strategy and was a basic element of the validated information required by most of WHO's Member States for optimal rationalization of drug procurement and supply.

The Expert Committee decided to prepare its report as a self-contained document and to incorporate into it those parts of the previous report (*3*) that require no modification or merely bringing up to date. The seventh list will be found in section 15 of this report, and explanations of the changes in section 16.

In a report (*4*) to the Twenty-eighth World Health Assembly in 1975, the Director-General reviewed the main drug problems facing the developing countries and outlined possible new drug policies. The Director-General also referred to the experience gained in some countries where schemes of basic or essential drugs had been implemented. Such schemes were intended to extend the accessibility of the most necessary drugs to populations whose basic health needs could not be met by the existing supply system. The Director-General pointed out that the selection of these essential drugs would depend on the health needs and on the structure and development of the health services of each country. Lists of essential drugs should be drawn up locally, and periodically updated, with the advice of experts in public health, medicine, pharmacology, pharmacy and drug management. He also considered that adequate information on the properties, indications and use of the drugs listed should be provided. By resolution WHA28.66 (*5*), the Health Assembly requested the Director-General to implement the proposals contained in his report and, in particular, to advise Member States on the selection and procurement, at reasonable cost, of essential drugs of established quality corresponding to their national health needs.

Following wide consultation, an initial Model List of Essential Drugs was included in the first report of the Expert Committee on the Selection of Essential Drugs (*6*). This has subsequently been revised and updated in five further reports (*3*, *7-10*).

In undertaking a further review of the list at its present meeting, the Expert Committee has been guided throughout by the following statement contained in the previous reports:

Because of the great differences between countries, the preparation of a drug list of uniform, general applicability is not feasible or possible. Therefore, each country has the direct responsibility of evaluating and adopting a list of essential drugs, according to its own policy in the field of health.

The list of essential drugs based on the guidelines put forward in this report is a model which can furnish a basis for countries to identify their own priorities and to make their own selection.

The Committee also draws attention to the following guidelines set out in the initial report:

1. The extent to which countries implement schemes or establish lists of essential drugs is a national policy decision of each country.
2. As far as health services in developing countries are concerned, the organized procurement and use of essential drugs have many advantages in terms of economy and effectiveness. However, the concept of "essential drug lists" must accommodate a variety of local situations if the lists are ever to meet the real health needs of the majority of the population.
3. There are convincing justifications for WHO to propose "model" or "guiding" lists of essential drugs as a contribution to solving the problems of Member States whose health needs far exceed their resources and who may find it difficult to initiate such an endeavour on their own.
4. Such "guiding" or "model" lists should be understood as a tentative identification of a "common core" of basic needs which has universal relevance and applicability. In certain situations, there is a need to make available additional drugs essential for rare diseases. The further local needs move away from the core, the more the health authorities or specific sectors of the health services will have to adjust the lists. However, any list proposed by WHO should set out to indicate priorities in drug needs, with the full understanding that exclusion does not imply rejection. A list of essential drugs does not imply that no other drugs are useful, but simply that in a given situation these drugs are the most needed for the health care of the majority of the population and, therefore, should be available at all times in adequate amounts and in the proper dosage forms.
5. The selection of essential drugs is a continuing process, which should take into account changing priorities for public health action and epidemiological conditions, as well as progress in pharmacological and pharmaceutical knowledge. It should be accompanied by a concomitant effort to supply information and give education and training to health personnel in the proper use of the drugs.
6. Finally, the WHO Action Programme on Essential Drugs should be a focal point for organized and systematic investigation of this approach.

Thus it will identify plans of action and research at the national and international level to meet unsatisfied basic health needs of populations which, at present, are denied access to the most essential prophylactic and therapeutic substances.

2. Guidelines for establishing a national programme for essential drugs

Since the first report on the selection of essential drugs was published in 1977, the concept of essential drugs has been widely applied. It has provided a rational basis not only for drug procurement at national level but also for establishing drug requirements at various levels within the health care system. In fact, many developing countries have already selected essential drugs according to their needs and the related programmes are, in some cases, at an advanced stage of implementation.

In order to ensure that an essential drugs programme is adequately instituted at national level, several steps are recommended:

1. The establishment of a list of essential drugs, based on the recommendations of a committee, is the starting-point of the programme. The committee should include individuals competent in the fields of medicine, pharmacology and pharmacy, as well as peripheral health workers. Where individuals with adequate training are not available within the country, cooperation from WHO could be sought.
2. The international nonproprietary (generic) names for drugs or pharmaceutical substances (*11*) should be used whenever available, and prescribers should be provided with a cross-index of non-proprietary and proprietary names.
3. Concise, accurate and comprehensive drug information should be prepared to accompany the list of essential drugs.
4. Quality, including drug content, stability and bioavailability, should be assured through testing or regulation, as discussed in section 5. Where national resources are not available for this type of control, the suppliers should provide documentation of the product's compliance with the required specifications.
5. Competent health authorities should decide the level of expertise required to prescribe individual drugs or a group of drugs in a therapeutic category. Consideration should be given, in particular, to the competence of the personnel to make a correct diagnosis. In some instances, while individuals with advanced training are necessary to prescribe initial therapy, individuals with less training could be responsible for maintenance therapy.
6. The success of the entire essential drugs programme is dependent upon the efficient administration of supply, storage and distribution at every

point from the manufacturer to the end-user. Government intervention may be necessary to ensure the availability of some drugs in the formulations listed, and special arrangements may need to be instituted for the storage and distribution of drugs that have a short shelf-life or require refrigeration.

7. Efficient management of stocks is necessary to eliminate waste and to ensure continuity of supplies. Procurement policy should be based upon detailed records of turnover. In some instances, drug utilization studies may contribute to a better understanding of true requirements.
8. Research, both clinical and pharmaceutical, is sometimes required to settle the choice of a particular drug product under local conditions. Facilities for such research must be provided.
9. A national drug regulatory authority should be established along the lines recommended in the guiding principles for small national drug regulatory authorities presented in Annex 1. The authority should interact with other interested bodies, including organizations responsible for drug procurement in the public and private sectors and the committee referred to in item 1.

3. Criteria for the selection of essential drugs

Essential drugs are those that satisfy the health care needs of the majority of the population; they should therefore be available at all times in adequate amounts and in the appropriate dosage forms.

The choice of such drugs depends on many factors, such as the pattern of prevalent diseases; the treatment facilities; the training and experience of the available personnel; the financial resources; and genetic, demographic and environmental factors.

Only those drugs should be selected for which sound and adequate data on efficacy and safety are available from clinical studies and for which evidence of performance in general use in a variety of medical settings has been obtained.

Each selected drug must be available in a form in which adequate quality, including bioavailability, can be assured; its stability under the anticipated conditions of storage and use must be established.

Where two or more drugs appear to be similar in the above respects, the choice between them should be made on the basis of a careful evaluation of their relative efficacy, safety, quality, price and availability.

In cost comparisons between drugs, the cost of the total treatment, and not only the unit cost of the drug, must be considered. The cost/benefit ratio is a major consideration in the choice of some drugs for the list. In some cases the choice may also be influenced by other factors, such as comparative pharmacokinetic properties, or by local considerations such as the availability of facilities for manufacture or storage.

Most essential drugs should be formulated as single compounds. Fixed-ratio combination products are acceptable only when the dosage of each ingredient meets the requirements of a defined population group and when the combination has a proven advantage over single compounds administered separately in therapeutic effect, safety or compliance.

4. Guidelines for the selection of pharmaceutical dosage forms

The purpose of selecting dosage forms and strengths for the drugs in the model list is to provide guidance to countries wishing to standardize or minimize the number of preparations in their own drug lists. As a general rule, pharmaceutical forms are selected on the basis of their general utility and their wide availability internationally. In many instances, a choice of preparations is provided, particularly in relation to solid dosage forms. Tablets are usually less expensive than capsules, but, while cost should be taken into account, the selection should also be based on a consideration of pharmacokinetics, bioavailability, stability under ambient climatic conditions, availability of excipients, and established local preference.

In a few instances where there is no uniformity of tablet strength, for example acetylsalicylic acid and paracetamol, a dosage range is provided from within which suitable tablet strengths should be selected on the basis of local availability and need. When precise dosage is not mandatory, the use of scored tablets is recommended as a simple method of making dosage more flexible if so required and, in some instances, to provide a convenient paediatric dose. Specific paediatric dosages and formulations are included in the list only when indicated by special circumstances. In many instances, dosage is specified in terms of a selected salt or ester, but in others – for example chloroquine – it is calculated, in accordance with common practice, in terms of the active moiety.

5. Quality assurance

Quality assurance of drugs, as embodied in good manufacturing practice and subsequent monitoring of quality throughout the distribution chain to utilization, is a crucial element in any essential drugs programme. All aspects of these procedures have been dealt with at length in the twenty-sixth to thirty-first reports of the WHO Expert Committee on Specifications for Pharmaceutical Preparations (*12-17*).

Priority should be given to ensuring that the available drugs have been made according to good manufacturing practices (*18*) and are of generally recognized quality. This requires knowledge of and confidence in the origin of the product. The risks of procuring drugs from anonymous sources cannot be overstressed. It is recommended that drugs are

purchased directly from known manufacturers, their duly accredited agents, or recognized international agencies known to apply high standards in selecting their suppliers.

Developing countries with inadequate laboratory facilities for drug analysis may be unable to carry out the process of quality control. In this connection, the Committee would emphasize the importance of WHO's Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce. This has been available since 1975 as a means of exchanging information between regulatory authorities in importing and exporting countries. Its purposes are:

1. To provide assurance that a given product has been authorized to be placed on the market in the exporting country and, if not, to explain why authorization has been withheld.
2. To provide assurance that the plant in which the product is manufactured is subject to inspections at suitable intervals and conforms to the requirements for good practices in the manufacture and quality control of drugs, as recommended by WHO.
3. To provide for exchange of information on the implementation of inspections and controls by the authorities in the exporting country. In the case of serious quality defects inquiries may also be made.

In 1988 the scope of the certification scheme was extended, in accordance with World Health Assembly resolution WHA41.18 (*17*), to provide for a more comprehensive exchange of information between governments. Drug substances as well as finished dosage forms were included within the scheme and provision was made for the exchange of officially approved, product-specific prescribing information on the safety and efficacy of finished products.

The Committee wishes to encourage national authorities to issue certificates in precise conformity with the format proposed by WHO in order to ensure that clear details are given about a product's place of manufacture or assembly and whether WHO's standards of good manufacturing practice have been applied. Countries that have not already done so are urged to extend the system of licensing to manufacturers of pharmaceutical products destined exclusively for export. The licensing system should ensure that these manufacturers are subject to inspection, that they comply with internationally recognized requirements for good manufacturing practices, and that every reasonable precaution is taken to ensure that the quality of their products meets pharmacopoeial specifications.

Poor bioavailability is a particular problem for products of low solubility or narrow therapeutic index. It can result in inadequate drug absorption and thus treatment failure just as readily as products deficient in active ingredients. The bioavailability of essential drugs should continue to receive consideration since it is a key factor in quality assurance.

The Committee appreciates that the development of the Model List of Essential Drugs has provided a natural focus for the third edition of *The international pharmacopoeia* (*19*), thus enhancing its potential value to developing countries. Essential drugs are accorded priority and all quality specifications are supported by classical methods of testing and analysis. A plan for a small quality-control laboratory in which most of these tests can be performed has been available since 1984 (*15*). Since quality assurance of essential drugs is so important, the Committee recommends to national governments the setting up of such laboratories and the adoption of *The international pharmacopoeia* by those currently lacking the means to confirm independently the quality of the supplies they procure. In this context, attention is also drawn to the WHO publication *Basic tests for pharmaceutical substances* (*20*), which enables the identity of drug substances to be verified and gross degradation to be excluded when laboratory facilities for full pharmacopoeial analyses are not available.

The Committee emphasizes the need to extend the coverage of *The international pharmacopoeia* to include not only essential drug substances, but also the dosage forms specified in the Model List of Essential Drugs, together with additional information on bioavailability, stability and recommended packaging and storage conditions.

6. Reserve antimicrobials and monitoring resistance

The increasing prevalence of strains of common pathogenic bacteria resistant to widely available, relatively cheap antimicrobials included in the model list is, in many cases, dangerously eroding their effectiveness. The need for more systematic and coordinated international approaches to laboratory monitoring of antimicrobial sensitivity is important and urgent. It has already been emphasized that reference laboratories need to be established in developing as well as developed countries in order to monitor the resistance of important bacterial pathogens (*21*, *22*). Each Member country should have a national reference laboratory to monitor the local resistance patterns of important microorganisms. Knowledge of prevailing sensitivity patterns is vital to the proper selection and use of antimicrobials and to the development of appropriate prescribing policies. Without these data the health of seriously ill patients could be jeopardized. Knowledge of sensitivity patterns should come from proper laboratory investigations. However, in countries with inadequate facilities for monitoring resistance, clinical evidence of lack of efficacy of a particular antimicrobial against a particular infectious disease should be utilized to modify the drug treatment for the particular disease in the community concerned.

It is becoming increasingly common for important pathogens to emerge in a country or locality that are shown, on sensitivity testing, to have developed resistance to all normally appropriate essential drugs. In these

circumstances a reserve antimicrobial is needed. A reserve antimicrobial is an antimicrobial that is useful for a wide range of infections, but because of the need to reduce the risk of development of resistance and because of its relatively high cost, it would be inappropriate to recommend its unrestricted use.

The concept of reserve antimicrobials is of practical relevance only when information is available on the prevailing sensitivities of important bacterial pathogens. Within this context the second- and third-generation cefalosporins, the fluoroquinolones and vancomycin are most important.

There are many third-generation cefalosporins. Some are suitable for the treatment of bacterial meningitis or severe pneumonia, particularly in children, where there is evidence that strains of *Haemophilus influenzae* type b are resistant to chloramphenicol.

Some will also cure gonorrhoea and chancroid. For example, a single intramuscular dose of 250 mg of the third-generation cefalosporin ceftriaxone will cure both of these diseases. However, this should be used for gonorrhoea only where strains resistant to penicillin and spectinomycin are prevalent, and for chancroid only where there is a high prevalence of *Haemophilus ducreyi* strains resistant to tetracyclines and trimethoprim/sulfamethoxazole.

Ciprofloxacin is an example of a member of the quinolone family of antimicrobial agents. Although this is now listed as an essential drug, the comparative costs of alternative broad-spectrum products will be an important determinant of selection. Ciprofloxacin and certain other fluoroquinolones are of value as reserve agents, particularly in the following circumstances:

- For typhoid fever and other systemic salmonella infections where there are strains of *Salmonella* resistant to chloramphenicol, amoxicillin and trimethoprim/sulfamethoxazole.
- For severe shigellosis where *Shigella* spp. strains exist that are resistant to the above three antimicrobials and to tetracyclines. In such cases, nalidixic acid, an older and cheaper fluoroquinolone, may be used.
- For gonorrhoea and chancroid, as alternatives to cefalosporins, when oral administration is appropriate.
- For hospital-acquired infections due to Gram-negative bacilli, including *Escherichia coli, Klebsiella* spp. and *Pseudomonas aeruginosa,* that are resistant to essential drugs such as amoxicillin, tetracyclines, piperacillin, chloramphenicol and gentamicin.

Meticillin-resistant *Staphylococcus aureus* strains are resistant to all ß-lactam antimicrobials and usually also to unrelated drugs such as erythromycin, clindamycin, chloramphenicol, the tetracyclines and the aminoglycosides. The only effective reserve drug for infections due to these multiresistant organisms is vancomycin, which is expensive and must be administered intravenously.

7. Applications of the essential drugs concept

The concept of essential drugs has been endorsed unanimously by the World Health Assembly. It is intended to be flexible and adaptable to many different situations; exactly which drugs are regarded as essential remains a national responsibility.

The concept of essential drugs has been disseminated and promoted extensively at the country level by WHO's Action Programme on Essential Drugs as well as by bilateral agencies. The wide applicability of the concept is now evident from experience gained in many countries. Most national lists of essential drugs are stratified to reflect requirements at different levels within the health care infrastructure. Typically, a very short list has been compiled for community health workers while the most comprehensive lists have been reserved for large urban and regional hospitals. Many countries have also successfully applied the concept to teaching hospitals and facilities providing specialized care. The concept has also been applied in the dissemination of drug information.

The model list has been adopted by numerous international and bilateral agencies that now include drug supply and the rationalization of drug use in their health care programmes. Adoption of the list has resulted in greater international coordination in health care development, and it is also being used to evaluate whether drug donations are appropriate in a given situation.

A shorter, adapted list has proved to be of particular value in emergency situations. It is contained in an emergency health kit (*23*), designed to cover the basic needs of a population of 10 000 for a period of about 3 months, which has been developed and updated by WHO, the Office of the United Nations High Commissioner for Refugees, UNICEF, *Médecins sans frontières,* the International Federation of Red Cross and Red Crescent Societies, the Christian Medical Commission and several other nongovernmental organizations. Many non-profit suppliers maintain a stock of most of the drugs on the list, which allows a rapid response to demand.

8. Essential drugs and primary health care

It cannot be emphasized too strongly that, in practice, the selection of drugs for primary health care must be determined nationally since the training and responsibilities of the personnel charged to administer this care vary considerably. Highly trained workers are able to use a wide range of drugs appropriate to their diagnostic skills with acceptable safety, and decisions about the availability of specific drugs can be made only when all relevant local factors have been taken into account. The following considerations will inevitably influence the compilation of such drug lists.

8.1 Existing systems of medicine

The establishment of primary health care services in developing countries should not result in abrupt disruption of prevailing cultural patterns in rural communities. The work of traditional healers, for example, should be adapted and supplemented so as to ensure that innovation is successfully integrated into existing systems of care.

8.2 The national health infrastructure

The type of primary health care service that a country requires is dependent upon the proximity and nature of the first referral facilities. It is still not unusual in some countries for the nearest permanently staffed health post to be a day's travelling time or more from isolated villages in its catchment area.

8.3 Training and supplies

The numbers of trained personnel, the facilities placed at their disposal, and the supplies entrusted to them determine both the scope and the limitations of the primary health care system. Workers with one or more years' vocational training can obviously accomplish more than personnel reliant upon an intensive course of practical instruction lasting only a few weeks. But, whatever the circumstances, little can be accomplished unless continuity of essential supplies and information is assured.

8.4 The pattern of endemic disease

The prevalence of major endemic infections and parasitic diseases may vary from region to region within a country in conformity with climatic, geographical, topographical, social, economic and occupational factors. Careful planning and, in some cases, epidemiological surveys are required to ensure that the most effective drugs are provided and to obtain full benefit from limited resources.

9. Drugs used in displaced communities

As already stated on page 4, essential drugs are those that satisfy the health care needs of the majority of the population; they should therefore be available at all times in adequate amounts and in the appropriate dosage forms. This is especially important in the case of displaced populations.

It has been estimated by the United States Committee for Refugees (*24*) that more than 30 million people are currently seeking refuge outside their country of origin (refugees). This figure is rapidly increasing and does not take account of the much larger numbers who are forced by extreme hardship, and often by famine, to migrate long distances within their own national boundaries (internally displaced people).

During the period in which new communities are being established in new sites, mortality rates, particularly among children up to 14 years of age, can

be as high as 5-15 per 10 000 people per day. Later, mortality rates within established displaced communities gradually tend to approximate to those of the surrounding populations.

In virtually every setting the first infections likely to strike, which are often fatal, are measles, diarrhoeal diseases and acute respiratory infections. In endemic areas malaria may be comparably devastating, particularly when the population does not have adequate immunity. Epidemics of other potentially fatal diseases including meningitis, cholera and typhoid fever also occur less commonly. Once the displaced persons have been living for several months in their new site, the prevalence rate of all these diseases becomes similar to that prevailing within the communities from which they originate; at this stage, serious outbreaks of tuberculosis may occur.

In order to reduce mortality rates in displaced communities, priority must be accorded to satisfying the following needs.

9.1 Nutrition

Malnutrition is the single most important predisposing factor in the development of infectious disease. Culturally appropriate food rations should ideally contain at least 8.0 MJ (1900 kcal) of energy per adult per day. Emphasis should be placed on the protective value of breast-feeding and the use of feeding bottles and infant formulae should be discouraged.

Supplemental vitamin A should be given to all adults and children at the first contact and every 3 months thereafter according to guidelines published by WHO (25). Priority should be given to severely malnourished children. Women should not be given supplements of vitamin A during pregnancy; however, a supplement should be given during the first 4 weeks after delivery. Consideration should also be given to the administration of vitamin C, iron and folate and, in certain areas, iodine and vitamin B.

9.2 Immunization

Priority should be accorded to immunization against measles. All the necessary equipment for vaccination and the vaccine itself should be immediately available. Ideally, all children aged between 9 months and 5 years should be immunized against measles upon entering a refugee camp or similar setting, as should those between 6 and 9 months whose immunization status is not known. Children who receive their first immunization under 9 months of age should be reimmunized as soon as possible after they reach 9 months. Vitamin A should be given concurrently.

In facilities where families might stay for prolonged periods, a routine immunization programme should be started as soon as possible. This should include all six childhood vaccines currently recommended by

WHO, as listed in the WHO document *Immunization policy* (*26*). It is essential that a fully operational cold chain is in place before immunization begins. Guidance on its establishment can be found in the WHO document *Immunization in practice – a guide for health workers who give vaccines* (*27*). Immunization against diseases other than those recommended above (e.g. meningococcal disease or typhoid fever) should be undertaken only if justified by surveillance data.

9.3 Protection from infectious diseases

Many factors, including overcrowding, contaminated and inadequate water supply, poor sanitation, and physical and mental stress also contribute to the vulnerability of displaced people to infectious disease. It has been estimated by the United Nations High Commissioner for Refugees (*28*) that a minimum of 15 litres of clean water per person per day is necessary to reduce the incidence of disease in a displaced population.

Pneumonia is a major cause of mortality in displaced communities, particularly in young children. Specific measures that can help to prevent it include: improved nutrition, particularly for pregnant women; promotion of breast-feeding; immunization against measles and pertussis; and protection of young children, especially infants under 2 months, from exposure to cold. Other measures that reduce overcrowding may also contribute to diminishing the transmission of pneumonia, as well as other respiratory infections. Prompt recognition and treatment are essential to prevent mortality from pneumonia. Essential antimicrobials for the treatment of pneumonia in children are sulfamethoxazole/trimethoprim for non-severe cases and benzylpenicillin, gentamicin and chloramphenicol for severe cases; these should be administered according to the guidelines provided in the WHO document *Acute respiratory infections in children: case management in small hospitals in developing countries* (*29*). The use of pharmaceutical preparations for treating coughs and colds is not essential and therefore should not be a priority.

Diarrhoeal diseases are another major cause of mortality. Specific measures that can help to prevent diarrhoea include: breast-feeding; proper weaning practices; hand-washing; proper use of water for hygiene and drinking; use of latrines; and safe disposal of sewage. All patients with acute diarrhoea should be assessed for dehydration and treated according to guidelines published by WHO (*30*). Emphasis should be placed on the use of oral rehydration therapy. The use of antidiarrhoeal preparations should be discouraged. Antimicrobials should only be given to patients with dysentery, suspected cholera, or confirmed amoebiasis or giardiasis. Priority should be given to immunization against measles. In contrast, the currently available cholera and typhoid vaccines are of little value; indeed, their use in this situation may create a false sense of protection, which may promote the spread of these diseases.

Malaria is an important consideration in areas where it is endemic, particularly when non-immune people arrive in such an area. It is essential

that appropriate drugs and adequate facilities for diagnosis by microscopy be made available for prompt treatment of malaria. Treatment should follow the recommendations of the national malaria control programme. Guidelines for the use of antimalarials are given in *WHO model prescribing information: drugs used in parasitic diseases* (*31*).

Emphasis should be placed upon health education of the population regarding personal protection (e.g. use of insect repellents, long-sleeved clothing, and impregnated bednets or protective curtains), recognition of malaria symptoms and the importance of prompt medical care. Pregnant women and children require special consideration. Health workers should be trained to diagnose and treat malaria, and to implement those vector control measures that are feasible.

9.4 Drugs

A list of essential drugs should be drawn up for each individual situation and should reflect the particular health needs of the targeted populations. The emergency health kit referred to in section 7 (*23*) lists drugs and equipment that can be used in the early phase of large-scale emergencies and disasters.

When drugs are donated, the following principles should be observed by donors:

- No drug should be provided that is not on the national list of essential drugs or, if no such list exists, the Model List of Essential Drugs.
- All drugs provided should be obtained from a reliable source. The WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce (*17*) should be used.
- All drugs should have a remaining shelf-life of at least one year.
- Labelling should be in a language that is understood locally and should include the generic name of the drug. Labelling of the outside of boxes is advised.
- Drugs should be packaged in large-quantity units, if possible.
- No drugs should be donated that have already been issued to patients and returned to a pharmacy in the donor country.
- A financial contribution should be considered instead of a drug donation since it may be cheaper to buy the drugs locally.

If the above requirements are not observed, drugs may have to be destroyed.

9.5 Surveillance

A health information system should be established for storing and evaluating data on the displaced population, including patterns of mortality and morbidity, vaccination coverage and data on drug stock and use. Such data will assist in determining policies concerning the major diseases.

In the post-emergency phase, consideration must also be given to the development of programmes for the control of tuberculosis, human immunodeficiency virus (HIV) infection and other sexually transmitted infections, as well as programmes for maternal and child health care, including family planning.

10. Post-registration drug studies

Clinical studies for the development of new drugs take place, for the most part, in major medical centres with extensive facilities and highly trained staff. The patients entering the clinical trials in these centres will usually have received full medical evaluations.

Often, certain groups of patients such as pregnant women, young children and old people will have been excluded from the trials. For this reason, the patients receiving the new drug prior to registration will not represent the full range of patients who will be receiving the drug after registration. In addition, the genetic and environmental factors influencing populations in other parts of the world may differ from those that characterize the populations in which the drug was studied and cause differences in population dose–response relationships.

Little is known about the clinical consequences of different prescribing patterns between countries or between regions within a country. There are few systematic and comprehensive data on the utilization of drugs after they have been marketed, but it is recognized that they are frequently not used to their full potential or in accordance with generally accepted criteria. Moreover, data on overdose effects and uncommon or longer-term adverse effects are usually not available at the time of registration. It is important, whenever feasible, to quantify these risks in order to identify the safest available products and to remove from the market those that are unacceptably dangerous. Such information is essential if drug selection committees are to function optimally.

Other information that can be obtained when a drug is used in practice relates to unanticipated uses discovered when the drug is given to patients who have both the accepted indication and another illness. Furthermore, when used in practice a drug may fail to produce the benefit that was expected on the basis of the pre-registration studies. This may be because the results of the pre-registration clinical trials cannot be generalized to the entire population of patients with the indication for the drug or because the dosage form being used contains less than the labelled amount of the drug or contains the labelled amount, but not in a bioavailable form. These latter factors could result from poor manufacturing practices or from intentional counterfeiting of legitimate dosage forms.

In order to obtain all the additional information needed for the fully rational use of essential drugs, post-registration drug surveillance or surveys are needed.

Depending on their purpose and the facilities available, drug surveys can be carried out at various levels. Their value is enhanced by using standard procedures (common drug classification systems and units of measurement) in different regions and countries. These procedures should be used to provide data on all relevant drugs in a particular therapeutic class, paying attention to both cost and quantities prescribed, and taking differences in therapeutic practice into consideration.

The main purpose of drug surveys is to quantify present usage and estimate future demands. Studies can be designed simply to quantify the drug inventory only or to evaluate drug utilization. Data can also be used: (a) to measure the effects of informational and regulatory measures, price policy, etc.; (b) to define areas for further investigation on the absolute and relative efficacy and safety of drug therapy; (c) to aid in the determination of benefit/risk ratios and cost-effectiveness; and (d) when properly interpreted, to indicate the overuse, underuse or misuse of individual drugs or therapeutic classes of drugs.

Highly evolved national drug regulatory authorities are increasing their investment in post-marketing surveillance. This is expensive and calls for sustained international collaboration. For many years the WHO Collaborating Centre on International Drug Monitoring has collated the reports of the national monitoring schemes of developed and developing countries and, more recently, WHO has collaborated with the Council for International Organizations of Medical Sciences to promote epidemiologically based methods of monitoring.

The ability of most developing countries to carry out such studies is limited by cost. Nevertheless, when concern arises over the safety of a drug used exclusively for a tropical disease, the need for post-marketing surveillance is as great as in any other situation. Such a matter is already being addressed by WHO in the instance of the use of ivermectin in community-based mass treatment programmes for onchocerciasis. Such surveillance may also require the establishment of special reporting facilities and, exceptionally, small follow-up studies of people exposed to specific drugs may be necessary.

If the detection of longer-term adverse sequelae to drug use is to become more efficient, reliable methods of linking prescribing information to hospital records will need to be more widely introduced. This, in turn, will require a means of assuring the confidentiality and privacy of personal information. Until these methods are developed, the application of epidemiological principles to the assessment of drug-induced effects will remain difficult to explore. WHO possesses the appropriate consultative capacity to promote debate of the issues, to promote the most suitable methods, and to monitor the results of their application.

These general principles apply not only to the detection and assessment of adverse drug effects but to all other indicators of drug performance. In

particular, the Committee wishes to emphasize the need for access to microbiological reference laboratories as a mandatory prerequisite for the rational use of the expensive reserve antimicrobials.

The opportunities to advance therapeutics through post-registration drug studies will be only partially utilized until all health care professionals accept their responsibility to report on the effects of drugs in actual use.

11. Research and development

If the establishment of a list of essential drugs is to succeed in improving health and in reducing drug costs in developing countries, use of the list should be either preceded by, or developed together with, adequate supply and distribution systems and procurement procedures. To hasten the self-reliance of countries, research and development should be undertaken in the following broad areas.

11.1 Pharmaceutical aspects

1. Development of local or regional capability in quality assurance in order to ensure that drug quality is maintained.
2. Development of procurement procedures to take advantage of the benefits of purchasing large quantities of drugs.
3. Development of facilities for processing and packaging simple dosage forms, and ensuring the quality of the product.
4. Development of an efficient countrywide distribution system with suitably trained personnel.

11.2 Clinical aspects

Development of facilities and expertise to carry out therapeutic trials in order to assess:

- the relative efficacy and safety of new candidate compounds for inclusion in an essential drugs list;
- the benefits and safety of traditional medicines, including medicinal plants;
- the effects of genetic and environmental differences among populations on pharmacokinetic, pharmacodynamic and therapeutic parameters.

11.3 Educational aspects

1. Development of simple, concise labels for each dosage form.
2. Development of training programmes in policy formulation, quality control, pharmaceutical information systems, and drug procurement, production, storage and distribution procedures.
3. Development of appropriate public education and information programmes in diagnosis and self-medication for conditions for which early recognition of symptoms and prompt self-medication are crucial.

12. Nomenclature

The need to identify each pharmaceutical substance by a unique, globally recognized generic name is of critical importance in facilitating communication as well as in the labelling and advertising of medicinal products in international commerce.

This is the objective of the WHO programme on the selection of international nonproprietary names, whose activities have led to the publication of names for roughly 6000 new pharmaceutical products since 1950. Its role is to coordinate and harmonize the activities of existing national drug nomenclature commissions, which now follow a common set of conventions for devising generic names. Officially assigned generic names now rarely differ from the international nonproprietary names (INNs), and some countries have disestablished their national commissions and automatically accept all recommended INNs.

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

The Expert Committee consequently recommends, as a matter of urgency, that:

- international organizations discourage the use of trade marks that are derived from INNs;
- manufacturers refrain from applying for such trade marks;
- drug regulatory authorities disallow the use of such trade marks.

While INNs are widely used in reference books and journals, they are not always identified as such or even accorded preference, particularly in the case of older substances that may have several different generic names. Editors are urged to give preference to INNs in reference works, journals and data banks and to allow the use of a code for a new substance (pending the assignment of an INN) rather than an unofficial name.

13. Drug information and educational activities

For the safe, effective and prudent use of essential drugs, relevant and reliable drug information should be available. In order to provide this, a

series of publications entitled *WHO model prescribing information* is being prepared. The first three titles in this series, *Drugs used in anaesthesia* (*32*), *Drugs used in parasitic diseases* (*31*) and *Drugs used in mycobacterial diseases* (*33*) have already been published. Further titles are in preparation. The Committee supports with great enthusiasm the provision of model prescribing information and considers that the documents published to date are clear, useful and well written. The Committee urges that this activity receive high priority within WHO and that the distribution of the information be as wide as possible.

Health care professionals should receive education about the use of drugs not only during their initial professional training but throughout their entire professional careers. The more highly trained individuals should assume a responsibility to educate those with less training. Pharmacists and other health care workers responsible for dispensing drugs should accept every opportunity to inform consumers about the rational use of these products at the time they are dispensed.

Drug information sheets

The following is an example of a format for supplying information to facilitate the safe and effective use of drugs to prescribers and consumers. The content should be adjusted to the needs, knowledge and responsibilities of the prescriber.

1. International nonproprietary name (INN) of each active substance.
2. Pharmacological data: a brief description of pharmacological effects and mechanism of action.
3. Clinical information:
   (a) Indications: whenever appropriate, simple diagnostic criteria should be provided.
   (b) Dosage regimen and relevant pharmacokinetic data:
      - average and range for adults and children;
      - dosing interval;
      - average duration of treatment;
      - special situations, e.g. renal, hepatic, cardiac or nutritional insufficiencies that require either an increased or a reduced dosage.
   (c) Contraindications.
   (d) Precautions and warnings (reference to pregnancy, lactation, etc.).
   (e) Adverse effects (quantify by category, if possible).
   (f) Drug interactions (include only if clinically relevant; drugs used for self-medication should be included).
   (g) Overdosage:
      - brief clinical description of symptoms;
      - non-drug treatment and supportive therapy;
      - specific antidotes.

4. Pharmaceutical information:
   (a) Dosage forms.
   (b) Strength of dosage form.
   (c) Excipients.
   (d) Storage conditions and shelf-life (expiry date).
   (e) Pack sizes.
   (f) Description of the product and package.
   (g) Legal category (narcotic or other controlled drug, prescription or non-prescription).
   (h) Name and address of manufacturer(s) and importer(s).

14. Updating of lists of essential drugs

An essential drug list must be flexible enough to accommodate, as necessary, new drugs, new information on established drugs and changes in the status of internationally controlled substances. Experience with the original model list and the subsequent revisions, as well as with regional and national lists of essential drugs, has confirmed the need for regular review and updating. Revision is necessary not only because of advances in drug therapy but also in order to meet the needs of practice in the light of experience. Frequent and extensive changes are clearly undesirable since they result in disruption of channels of procurement and distribution and may have implications for the training of health personnel. For this reason a number of drugs have been retained on the model list that have been largely superseded in countries where there is a more extensive range of new medicaments, but that are still used widely and successfully elsewhere.

Applications for the addition of drugs to the model list will always receive full consideration by WHO. An application form can be found in Annex 2.

15. Model List of Essential Drugs (seventh list)

Explanatory notes[1]

Many drugs included in the list are preceded by a square symbol (□) to indicate that they represent an *example of a therapeutic group* and that various drugs could serve as alternatives. It is imperative that this is understood when drugs are selected at national level, since choice is then influenced by the comparative cost and availability of equivalent products. Examples of acceptable substitutions include:

□ Codeine: other drugs for the symptomatic treatment of diarrhoea in

[1] The numbers preceding the drug sections and subsections in the model list have, in general, been allocated in accordance with English alphabetical order; they have no formal significance.

adults, such as loperamide or, when indicated for treatment of cough, dextromethorphan.

- ☐ Hydrochlorothiazide: any other thiazide-type diuretic currently in broad clinical use.
- ☐ Hydralazine: any other peripheral vasodilator having an anti-hypertensive effect.
- ☐ Senna: any mild stimulant laxative (either synthetic or of plant origin).
- ☐ Sulfadimidine: any other short-acting, systemically active sulfonamide unlikely to cause crystalluria.

Numbers in parentheses following the drug names indicate:

(1) Drugs subject to international control under: (a) the Single Convention on Narcotic Drugs, 1961 (*34*); (b) the Convention on Psychotropic Substances, 1971 (*35*); or (c) the Convention on Illicit Traffic in Narcotic Drugs and Psychotropic Substances, 1988 (*36*).
(2) Specific expertise, diagnostic precision or special equipment required for proper use.
(3) Greater potency or efficacy.
(4) In renal insufficiency, contraindicated or dosage adjustments necessary.
(5) To improve compliance.
(6) Special pharmacokinetic properties.
(7) Adverse effects diminish benefit/risk ratio.
(8) Limited indications or narrow spectrum of activity.
(9) For epidural anaesthesia.

Letters in parentheses after the drug names indicate the reasons for the inclusion of *complementary drugs*:

(A) When drugs in the main list cannot be made available.
(B) When drugs in the main list are known to be ineffective or inappropriate for a given individual.
(C) For use in rare disorders or in exceptional circumstances.

Certain pharmacological effects have many therapeutic uses. Drugs with these effects could be listed in many different therapeutic categories in the model list. However, the inclusion of such drugs in more than one therapeutic category has been limited to circumstances that the Committee wished to emphasize. Drugs in the model list are therefore not necessarily listed in each of the therapeutic categories in which they are of value. Information on therapeutic use is (or will be) available in the *WHO model prescribing information* publications. In addition, essential drugs could be categorized by whether their use is to treat a life-threatening illness, to minimize or prevent a disability, or to improve the quality of life. This system is not used here, however, since the Committee considered all of these uses to be essential for proper therapeutics.

Drug	*Route of administration, dosage forms and strengths*[a]
1. Anaesthetics	
1.1 *General anaesthetics and oxygen*	
diazepam (1b, 2)	injection, 5 mg/ml in 2-ml ampoule
ether, anaesthetic (2)	inhalation
halothane (2)	inhalation
ketamine (2)	injection, 50 mg (as hydrochloride)/ml in 10-ml vial
nitrous oxide (2)	inhalation
oxygen	inhalation (medicinal gas)
□ thiopental (2)	powder for injection, 0.5 g, 1.0 g (sodium salt) in ampoule
1.2 *Local anaesthetics*	
□ bupivacaine (2, 9)	injection, 0.25%, 0.5% (hydrochloride) in vial
	injection for spinal anaesthesia, 0.5% (hydrochloride) in 4-ml ampoule to be mixed with 7.5% glucose solution
□ lidocaine	injection, 1%, 2% (hydrochloride) in vial
	injection, 1%, 2% (hydrochloride) + epinephrine 1:200000 in vial
	injection for spinal anaesthesia, 5% (hydrochloride) in 2-ml ampoule to be mixed with 7.5% glucose solution
	topical forms, 2–4% (hydrochloride)
	dental cartridge, 2% (hydrochloride) + epinephrine 1:80000
1.3 *Preoperative medication*	
atropine	injection, 1 mg (sulfate) in 1-ml ampoule

[a] When the strength is specified in terms of a selected salt or ester, this is mentioned in brackets; when it refers to the active moiety, the name of the salt or ester in brackets is preceded by the word "as".

Drug	*Route of administration, dosage forms and strengths*[a]
1. Anaesthetics *(continued)*	
1.3 *Preoperative medication* (continued)	
chloral hydrate	syrup, 200 mg/5 ml
□ diazepam (1b)	injection, 5 mg/ml in 2-ml ampoule
□ morphine (1a)	injection, 10 mg (sulfate or hydrochloride) in 1-ml ampoule
□ promethazine	elixir or syrup, 5 mg (hydrochloride)/5 ml
2. Analgesics, antipyretics, non-steroidal anti-inflammatory drugs and drugs used to treat gout	
2.1 *Non-opioids*	
acetylsalicylic acid	tablet, 100–500 mg
	suppository, 50–150 mg
allopurinol (4)	tablet, 100 mg
colchicine (7)	tablet, 500 µg
□ ibuprofen	tablet, 200 mg
□ indometacin	capsule or tablet, 25 mg
paracetamol	tablet, 100–500 mg
	suppository, 100 mg
	syrup, 125 mg/5 ml
2.2 *Opioid analgesics*	
□ codeine (1a)	tablet, 30 mg (phosphate)
□ morphine (1a)	injection, 10 mg (sulfate or hydrochloride) in 1-ml ampoule
	oral solution, 10 mg/5 ml
	tablet, 10 mg (sulfate)
Complementary drug	
□ pethidine (A) (1a, 4)	injection, 50 mg (hydrochloride) in 1-ml ampoule
	tablet, 50 mg, 100 mg (hydrochloride)

[a] When the strength is specified in terms of a selected salt or ester, this is mentioned in brackets; when it refers to the active moiety, the name of the salt or ester in brackets is preceded by the word "as".

Drug	*Route of administration, dosage forms and strengths*[a]
3. Antiallergics and drugs used in anaphylaxis	
□ chlorphenamine	tablet, 4 mg (hydrogen maleate)
	injection, 10 mg (hydrogen maleate) in 1-ml ampoule
□ dexamethasone	tablet, 500 µg, 4 mg
	injection, 4 mg (as sodium phosphate) in 1-ml ampoule
epinephrine	injection, 1 mg (as hydrochloride) in 1-ml ampoule
hydrocortisone	powder for injection, 100 mg (as sodium succinate) in vial
□ prednisolone	tablet, 5 mg
4. Antidotes and other substances used in poisonings	
4.1 *General*	
□ charcoal, activated	powder
ipecacuanha	syrup, containing 0.14% ipecacuanha alkaloids calculated as emetine
4.2 *Specific*	
atropine	injection, 1 mg (sulfate) in 1-ml ampoule
deferoxamine	powder for injection, 500 mg (mesilate) in vial
dimercaprol (2)	injection in oil, 50 mg/ml in 2-ml ampoule
□ methionine	tablet, 250 mg (racemate)
methylthioninium chloride (methylene blue)	injection, 10 mg/ml in 10-ml ampoule
naloxone	injection, 400 µg (hydrochloride) in 1-ml ampoule
penicillamine (2)	capsule or tablet, 250 mg
potassium ferric hexacyanoferrate(II) · $2H_2O$ (Prussian blue)	powder for oral administration

[a] When the strength is specified in terms of a selected salt or ester, this is mentioned in brackets; when it refers to the active moiety, the name of the salt or ester in brackets is preceded by the word "as".

Drug	*Route of administration, dosage forms and strengths*[a]
4. Antidotes and other substances used in poisonings *(continued)*	
4.2 *Specific* (continued)	
sodium calcium edetate (2)	injection, 200 mg/ml in 5-ml ampoule
sodium nitrite	injection, 30 mg/ml in 10-ml ampoule
sodium thiosulfate	injection, 250 mg/ml in 50-ml ampoule
5. Antiepileptics	
carbamazepine	scored tablet, 100 mg, 200 mg
□ diazepam (1b)	injection, 5 mg/ml in 2-ml ampoule (intravenous or rectal)
ethosuximide	capsule or tablet, 250 mg
	syrup, 250 mg/5 ml
phenobarbital (1b)	tablet, 15–100 mg
	elixir, 15 mg/5 ml
phenytoin	capsule or tablet, 25 mg, 100 mg (sodium salt)
	injection, 50 mg (sodium salt)/ml in 5-ml vial
valproic acid (7)	enteric coated tablet, 200 mg, 500 mg (sodium salt)
6. Anti-infective drugs	
6.1 *Anthelminthics*	
6.1.1 Intestinal anthelminthics	
levamisole (8)	tablet, 50 mg, 150 mg (as hydrochloride)
□ mebendazole	chewable tablet, 100 mg
niclosamide	chewable tablet, 500 mg
piperazine	tablet, 500 mg hydrate (as adipate or citrate)
	elixir or syrup (as citrate) equivalent to 500 mg hydrate/5 ml
praziquantel	tablet, 150 mg, 600 mg
pyrantel	chewable tablet, 250 mg (as embonate)
	oral suspension, 50 mg (as embonate)/ml
tiabendazole	chewable tablet, 500 mg
	lotion, 500 mg/5 ml

[a] When the strength is specified in terms of a selected salt or ester, this is mentioned in brackets; when it refers to the active moiety, the name of the salt or ester in brackets is preceded by the word "as".

Drug	*Route of administration, dosage forms and strengths*[a]
6. Anti-infective drugs *(continued)*	
6.1 *Anthelminthics* (continued)	
6.1.2 Specific anthelminthics	
albendazole	chewable tablet, 200 mg
6.1.3 Antifilarials	
diethylcarbamazine	tablet, 50 mg (dihydrogen citrate)
ivermectin	scored tablet, 6 mg
suramin sodium (2, 7)	powder for injection, 1 g in vial
6.1.4 Antischistosomals	
metrifonate	tablet, 100 mg
oxamniquine	capsule, 250 mg
	syrup, 250 mg/5 ml
praziquantel	tablet, 600 mg
6.2 *Antibacterials*	
6.2.1 Penicillins	
□ amoxicillin (4)	capsule or tablet, 250 mg, 500 mg (anhydrous)
	powder for oral suspension, 125 mg (anhydrous)/5 ml
ampicillin (4)	powder for injection, 500 mg (as sodium salt) in vial
benzathine benzylpenicillin (5)	powder for injection, 1.44 g benzylpenicillin (= 2.4 million IU) in 5-ml vial
benzylpenicillin	powder for injection, 600 mg (= 1 million IU), 3 g (= 5 million IU) (as sodium or potassium salt) in vial
□ cloxacillin	capsule, 500 mg (as sodium salt)
	powder for oral solution, 125 mg (as sodium salt)/5 ml
	powder for injection, 500 mg (as sodium salt) in vial
phenoxymethylpenicillin	tablet, 250 mg (as potassium salt)
	powder for oral suspension, 250 mg (as potassium salt)/5 ml

[a] When the strength is specified in terms of a selected salt or ester, this is mentioned in brackets; when it refers to the active moiety, the name of the salt or ester in brackets is preceded by the word "as".

Drug	*Route of administration, dosage forms and strengths*[a]
6. Anti-infective drugs *(continued)*	
6.2 *Antibacterials* (continued)	
6.2.1 Penicillins (continued)	
□ piperacillin	powder for injection, 1 g, 2 g (as sodium salt) in vial
procaine benzylpenicillin	powder for injection, 1 g (= 1 million IU), 3 g (= 3 million IU)
6.2.2 Other antibacterials	
□ chloramphenicol (7)	capsule, 250 mg
	oral suspension, 150 mg (as palmitate salt)/5 ml
	powder for injection, 1 g (as sodium succinate) in vial
□ erythromycin	capsule or tablet, 250 mg (as stearate or ethyl succinate)
	powder for oral suspension, 125 mg (as stearate or ethyl succinate)
	powder for injection, 500 mg (as lactobionate) in vial
□ gentamicin (2, 4, 7)	injection, 10 mg, 40 mg (as sulfate)/ml in 2-ml vial
□ metronidazole	tablet, 200–500 mg
	injection, 500 mg in 100-ml vial
	suppository, 500 mg, 1 g
	oral suspension, 200 mg (as benzoate)/5 ml
spectinomycin (8)	powder for injection, 2 g (as hydrochloride) in vial
□ sulfadimidine (4)	tablet, 500 mg
	oral suspension, 500 mg/5 ml
	injection, 1 g (sodium salt) in 3-ml ampoule
□ sulfamethoxazole + trimethoprim (4)	tablet, 100 mg + 20 mg, 400 mg + 80 mg
	oral suspension, 200 mg + 40 mg/5 ml
□ tetracycline	capsule or tablet, 250 mg (hydrochloride)

[a] When the strength is specified in terms of a selected salt or ester, this is mentioned in brackets; when it refers to the active moiety, the name of the salt or ester in brackets is preceded by the word "as".

Drug	*Route of administration, dosage forms and strengths*[a]
6. Anti-infective drugs *(continued)*	
6.2 *Antibacterials* (continued)	
6.2.2 Other antibacterials (continued)	
Complementary drugs	
ciprofloxacin (B)	tablet, 250 mg (as hydrochloride)
clindamycin (B)	injection, 150 mg (as phosphate)/ml
doxycycline (B) (5, 6)	capsule or tablet, 100 mg (as hyclate)
	powder for injection, 100 mg (as hyclate) in ampoule
nitrofurantoin (B) (4, 7)	tablet, 100 mg
trimethoprim (B)	tablet, 100 mg, 200 mg
Additional reserve antimicrobials are discussed in section 6 of the text.	
6.2.3 Antileprosy drugs	
clofazimine	capsule, 50 mg, 100 mg
dapsone	tablet, 50 mg, 100 mg
rifampicin	capsule or tablet, 150 mg, 300 mg
6.2.4 Antituberculosis drugs	
ethambutol (4)	tablet, 100–400 mg (hydrochloride)
isoniazid	tablet, 100–300 mg
pyrazinamide	tablet, 500 mg
rifampicin	capsule or tablet, 150 mg, 300 mg
rifampicin + isoniazid	tablet, 150 mg + 100 mg, 300 mg + 150 mg
streptomycin (4)	powder for injection, 1 g (as sulfate) in vial
Complementary drug	
thioacetazone + isoniazid (A) (7)	tablet, 50 mg + 100 mg, 150 mg + 300 mg
6.3 *Antifungal drugs*	
amphotericin B (4)	powder for injection, 50 mg in vial
griseofulvin	capsule or tablet, 125 mg, 250 mg

[a] When the strength is specified in terms of a selected salt or ester, this is mentioned in brackets; when it refers to the active moiety, the name of the salt or ester in brackets is preceded by the word "as".

Drug	*Route of administration, dosage forms and strengths*[a]
6. Anti-infective drugs *(continued)*	
6.3 *Antifungal drugs* (continued)	
□ ketoconazole (2)	tablet, 200 mg
	oral suspension, 100 mg/5 ml
nystatin	tablet, 100 000 IU, 500 000 IU
	lozenge, 100 000 IU
	pessary, 100 000 IU
Complementary drug	
flucytosine (B) (4, 8)	capsule, 250 mg
	infusion, 2.5 g in 250 ml
6.4 *Antiprotozoal drugs*	
6.4.1 Antiamoebic and antigiardiasis drugs	
□ diloxanide	tablet, 500 mg (furoate)
□ metronidazole	tablet, 200–500 mg
	injection, 500 mg in 100-ml vial
	oral suspension, 200 mg (as benzoate)/5 ml
Complementary drug	
chloroquine (B)	tablet, 150 mg (as phosphate or sulfate)
6.4.2 Antileishmaniasis drugs	
□ meglumine antimoniate	injection, 30%, equivalent to approx. 8.5% antimony, in 5-ml ampoule
pentamidine (5)	powder for injection, 200 mg (isetionate) in vial
6.4.3 Antimalarial drugs	
(a) For curative treatment	
□ chloroquine	tablet, 150 mg (as phosphate or sulfate)
	syrup, 50 mg (as phosphate or sulfate)/5 ml
primaquine	tablet, 7.5 mg, 15 mg (as diphosphate)

[a] When the strength is specified in terms of a selected salt or ester, this is mentioned in brackets; when it refers to the active moiety, the name of the salt or ester in brackets is preceded by the word "as".

Drug	*Route of administration, dosage forms and strengths*[a]
6. Anti-infective drugs *(continued)*	
6.4 *Antiprotozoal drugs* (continued) *6.4.3 Antimalarial drugs* (continued)	
□ quinine	tablet, 300 mg (as bisulfate or sulfate)
	injection, 300 mg (as dihydrochloride)/ml in 2-ml ampoule
Complementary drugs	
mefloquine (B)	tablet, 250 mg (as hydrochloride)
□ sulfadoxine + pyrimethamine (B)	tablet, 500 mg + 25 mg
□ tetracycline (B)	capsule or tablet, 250 mg (hydrochloride)
(b) For prophylaxis	
chloroquine	tablet, 150 mg (as phosphate or sulfate)
	syrup, 50 mg (as phosphate or sulfate)/5 ml
proguanil[b]	tablet, 100 mg (hydrochloride)
Complementary drug	
mefloquine (B)	tablet, 250 mg (as hydrochloride)
6.4.4 Antitrypanosomal drugs	
(a) African trypanosomiasis	
melarsoprol (5)	injection, 3.6% solution
pentamidine (5)	powder for injection, 200 mg (isetionate) in vial
suramin sodium	powder for injection, 1 g in vial
Complementary drug	
eflornithine (C)	injection, 200 mg (hydrochloride)/ml in 100-ml bottles
(b) American trypanosomiasis	
benznidazole (7)	tablet, 100 mg
nifurtimox (2, 8)	tablet, 30 mg, 120 mg, 250 mg

[a] When the strength is specified in terms of a selected salt or ester, this is mentioned in brackets; when it refers to the active moiety, the name of the salt or ester in brackets is preceded by the word "as".

[b] For use only in combination with chloroquine.

Drug	*Route of administration, dosage forms and strengths*[a]
6. Anti-infective drugs *(continued)*	
6.5 *Insect repellents*	
diethyltoluamide	topical solution, 50%, 75%
7. Antimigraine drugs	
7.1 *For treatment of acute attack*	
acetylsalicylic acid	tablet, 300–500 mg
ergotamine (7)	tablet, 2 mg (tartrate)
paracetamol	tablet, 300–500 mg
7.2 *For prophylaxis*	
□ propranolol	tablet, 10 mg, 20 mg (hydrochloride)
8. Antineoplastic and immunosuppressant drugs and drugs used in palliative care	
8.1 *Immunosuppressant drugs*	
□ azathioprine (2)	tablet, 50 mg
	powder for injection, 100 mg (as sodium salt) in vial
ciclosporin (2)[b]	capsule, 25 mg
	concentrate for injection, 50 mg/ml in 1-ml ampoule
8.2 *Cytotoxic drugs*	
bleomycin (2)	powder for injection, 15 mg (as sulfate) in vial
cisplatin (2)	powder for injection, 10 mg, 50 mg in vial
cyclophosphamide (2)	tablet, 25 mg
	powder for injection, 500 mg in vial
cytarabine (2)	powder for injection, 100 mg in vial
dacarbazine (2)	powder for injection, 100 mg in vial
dactinomycin (2)	powder for injection, 500 µg in vial

[a] When the strength is specified in terms of a selected salt or ester, this is mentioned in brackets; when it refers to the active moiety, the name of the salt or ester in brackets is preceded by the word "as".

[b] For organ transplantation.

Drug	*Route of administration, dosage forms and strengths*[a]
8. Antineoplastic and immunosuppressant drugs and drugs used in palliative care *(continued)*	
8.2 *Cytotoxic drugs* (continued)	
□ doxorubicin (2)	powder for injection, 10 mg, 50 mg (hydrochloride) in vial
etoposide (2)	capsule, 100 mg
	injection, 20 mg/ml in 5-ml ampoule
fluorouracil (2)	injection, 50 mg/ml in 5-ml ampoule
mercaptopurine (2)	tablet, 50 mg
methotrexate (2)	tablet, 2.5 mg (as sodium salt)
	powder for injection, 50 mg (as sodium salt) in vial
procarbazine	capsule, 50 mg (as hydrochloride)
vinblastine (2)	powder for injection, 10 mg (sulfate) in vial
vincristine (2)	powder for injection, 1 mg, 5 mg (sulfate in vial)
Complementary drug	
calcium folinate (C) (2)[b]	tablet, 15 mg
	injection, 3 mg/ml in 10-ml ampoule
8.3 *Hormones and antihormones*	
□ dexamethasone	tablet, 500 µg, 4 mg
	injection, 4 mg (as sodium phosphate) in 1-ml ampoule
□ ethinylestradiol	tablet, 50 µg
□ prednisolone	tablet, 5 mg
	injection, 20 mg, 25 mg (as sodium phosphate or sodium succinate) in vial
tamoxifen	tablet, 10 mg, 20 mg (as citrate)

8.4 *Drugs used in palliative care*

The Committee recommended that all the drugs mentioned in the WHO publication *Cancer pain relief* (*37*) be considered essential. The drugs are included in the relevant sections of the model list, according to their therapeutic use, e.g. analgesics.

[a] When the strength is specified in terms of a selected salt or ester, this is mentioned in brackets; when it refers to the active moiety, the name of the salt or ester in brackets is preceded by the word "as".

[b] For "rescue therapy" with methotrexate.

Drug	*Route of administration, dosage forms and strengths*[a]
9. Antiparkinsonism drugs	
□ biperiden	tablet, 2 mg (hydrochloride)
	injection, 5 mg (lactate) in 1-ml ampoule
levodopa + □ carbidopa (5, 6)	tablet, 100 mg + 10 mg, 250 mg + 25 mg
10. Drugs affecting the blood	
10.1 ***Antianaemia drugs***	
ferrous salt	tablet, equivalent to 60 mg iron
	oral solution, equivalent to 25 mg iron (as sulfate)/ml
ferrous salt + folic acid[b]	tablet, 60 mg + 250 µg
folic acid (2)	tablet, 1 mg, 5 mg
	injection, 1 mg (as sodium salt) in 1-ml ampoule
hydroxocobalamin (2)	injection, 1 mg in 1-ml ampoule
Complementary drug	
□ iron dextran (B) (5)	injection, equivalent to 50 mg iron/ml in 2-ml ampoule
10.2 ***Drugs affecting coagulation***	
desmopressin (8)	injection, 4 µg (acetate)/ml in 1-ml ampoule
heparin	injection, 1000 IU/ml, 5000 IU/ml, 20000 IU/ml in 1-ml ampoule
phytomenadione	injection, 10 mg/ml in 5-ml ampoule
	tablet, 10 mg
protamine sulfate	injection, 10 mg/ml in 5-ml ampoule
□ warfarin (2, 6)	tablet, 1 mg, 2 mg, 5 mg (sodium salt)

[a] When the strength is specified in terms of a selected salt or ester, this is mentioned in brackets; when it refers to the active moiety, the name of the salt or ester in brackets is preceded by the word "as".

[b] Nutritional supplement for use during pregnancy.

Drug	*Route of administration, dosage forms and strengths*[a]
11. Blood products and plasma substitutes	
11.1 *Plasma substitutes*	
□ dextran 70	injectable solution, 6%
□ polygeline	injectable solution, 3.5%
11.2 *Plasma fractions for specific uses*[b]	
albumin, human (2, 8)	injectable solution, 5%, 25%
Complementary drugs	
□ factor VIII concentrate (C) (2, 8)	dried
□ factor IX complex (coagulation factors II, VII, IX, X) concentrate (C) (2, 8)	dried
12. Cardiovascular drugs	
12.1 *Antianginal drugs*	
glyceryl trinitrate	tablet (sublingual), 500 µg
□ isosorbide dinitrate	tablet (sublingual), 5 mg
□ nifedipine	capsule or tablet, 10 mg
□ propranolol	tablet, 10 mg, 40 mg (hydrochloride)
	injection, 1 mg (hydrochloride) in 1-ml ampoule
Complementary drug	
atenolol (B)	tablet, 50 mg, 100 mg
12.2 *Antidysrhythmic drugs*	
lidocaine	injection, 20 mg (hydrochloride)/ml in 5-ml ampoule
□ propranolol	tablet, 10 mg, 40 mg (hydrochloride)
	injection, 1 mg (hydrochloride) in 1-ml ampoule
verapamil (8)	tablet, 40 mg, 80 mg (hydrochloride)
	injection, 2.5 mg (hydrochloride)/ml in 2-ml ampoule

[a] When the strength is specified in terms of a selected salt or ester, this is mentioned in brackets; when it refers to the active moiety, the name of the salt or ester in brackets is preceded by the word "as".

[b] All plasma fractions should comply with the Requirements for the Collection, Processing, and Quality Control of Blood, Blood Components, and Plasma Derivatives (Revised 1988). *WHO Expert Committee on Biological Standardization.* Thirty-ninth report (WHO Technical Report Series, No. 786, 1989, Annex 4).

Drug	*Route of administration, dosage forms and strengths*[a]
12. Cardiovascular drugs *(continued)*	
12.2 *Antidysrhythmic drugs* (continued)	
Complementary drugs	
atenolol (B)	tablet, 50 mg, 100 mg
□ procainamide (B)	tablet, 250 mg, 500 mg (hydrochloride)
	injection, 100 mg (hydrochloride)/ml in 10-ml ampoule
□ quinidine (A)	tablet, 200 mg (sulfate)
12.3 *Antihypertensive drugs*	
□ hydralazine	tablet, 25 mg, 50 mg (hydrochloride)
	powder for injection, 20 mg (hydrochloride) in ampoule
□ hydrochlorothiazide	tablet, 25 mg
□ nifedipine	capsule or tablet, 10 mg
□ propranolol	tablet, 40 mg, 80 mg (hydrochloride)
Complementary drugs	
atenolol (B)	tablet, 50 mg, 100 mg
□ captopril (B)	scored tablet, 25 mg
methyldopa (B) (7)	tablet, 250 mg
□ reserpine (A)	tablet, 100 µg, 250 µg
	injection, 1 mg in 1-ml ampoule
□ sodium nitroprusside (C) (2, 8)	powder for infusion, 50 mg in ampoule
12.4 *Cardiac glycosides*	
digoxin (4)	tablet, 62.5 µg, 250 µg
	oral solution, 50 µg/ml
	injection, 250 µg/ml in 2-ml ampoule
Complementary drug	
digitoxin (B) (6)	tablet, 50 µg, 100 µg
	injection, 200 µg in 1-ml ampoule

[a] When the strength is specified in terms of a selected salt or ester, this is mentioned in brackets; when it refers to the active moiety, the name of the salt or ester in brackets is preceded by the word "as".

Drug	*Route of administration, dosage forms and strengths*[a]
12. Cardiovascular drugs *(continued)*	
12.5 *Drugs used in vascular shock*	
dopamine	injection, 40 mg (hydrochloride)/ml in 5-ml vial
12.6 *Antithrombotic drugs*	
acetylsalicylic acid	tablet, 100 mg
Complementary drug	
streptokinase (C)	powder for injection, 100 000 IU in vial
13. Dermatological drugs	
13.1 *Antifungal drugs (topical)*	
benzoic acid + salicylic acid	ointment or cream, 6% + 3%
□ miconazole	ointment or cream, 2% (nitrate)
nystatin	ointment or cream, 100 000 IU/g
sodium thiosulfate	solution, 15%
Complementary drug	
selenium sulfide (C)	detergent-based suspension, 2%
13.2 *Anti-infective drugs*	
□ methylrosanilinium chloride (gentian violet)	aqueous solution, 0.5% tincture, 0.5%
mupirocin	cream, 2%
□ neomycin + □ bacitracin	ointment, 5 mg neomycin sulfate + 500 IU bacitracin zinc/g
silver sulfadiazine	cream, 1%, in 500-g container
13.3 *Anti-inflammatory and antipruritic drugs*	
□ betamethasone (3)	ointment or cream, 0.1% (as valerate)
□ calamine lotion	lotion
□ hydrocortisone	ointment or cream, 1% (acetate)

[a] When the strength is specified in terms of a selected salt or ester, this is mentioned in brackets; when it refers to the active moiety, the name of the salt or ester in brackets is preceded by the word "as".

Drug	*Route of administration, dosage forms and strengths*[a]
13. Dermatological drugs *(continued)*	
13.4 *Astringent drugs*	
aluminium diacetate	solution, 13% for dilution
13.5 *Keratoplastic and keratolytic agents*	
benzoyl peroxide	lotion or cream, 5%
coal tar	solution, topical, 5%
dithranol	ointment, 0.1–2%
fluorouracil	ointment, 5%
□ podophyllum resin (7)	solution, topical, 10–25%
salicylic acid	solution, topical, 5%
13.6 *Scabicides and pediculicides*	
benzyl benzoate	lotion, 25%
permethrin	lotion, 1%
13.7 *Ultraviolet-blocking agents*	
Complementary drugs	
p-aminobenzoic acid, sun protection factor 15 (C)	cream, lotion or gel
□ benzophenones, sun protection factor 15 (C)	cream, lotion or gel
□ zinc oxide (C)	cream or ointment
14. Diagnostic agents	
14.1 *Ophthalmic drugs*	
fluorescein	eye drops, 1% (sodium salt)
□ tropicamide	eye drops, 0.5%
14.2 *Radiocontrast media*	
□ amidotrizoate	injection, 140–420 mg iodine (as sodium or meglumine salts)/ml in 20-ml ampoule
barium sulfate	aqueous suspension

[a] When the strength is specified in terms of a selected salt or ester, this is mentioned in brackets; when it refers to the active moiety, the name of the salt or ester in brackets is preceded by the word "as".

Drug	*Route of administration, dosage forms and strengths*[a]
14. Diagnostic agents *(continued)*	
14.2 *Radiocontrast media* (continued)	
□ iopanoic acid	tablet, 500 mg
□ propyliodone	oily suspension, 500–600 mg/ml in 20-ml ampoule[b]
Complementary drug	
□ meglumine iotroxate (C)	injectable solution, 5–8 g iodine (as meglumine salt) in 100–250 ml
15. Disinfectants and antiseptics	
15.1 *Antiseptics*	
□ chlorhexidine	solution, 5% (digluconate) for dilution
hydrogen peroxide	solution, 3%
□ iodine	solution, 2.5%
15.2 *Disinfectants*	
□ calcium hypochlorite	powder (70% available chlorine) for solution
glutaral	solution, 2%
16. Diuretics	
□ amiloride (4, 7, 8)	tablet, 5 mg (hydrochloride)
□ furosemide	tablet, 40 mg
	injection, 10 mg/ml in 2-ml ampoule
□ hydrochlorothiazide	tablet, 25 mg, 50 mg
Complementary drugs	
□ mannitol (C)	injectable solution, 10%, 20%
spironolactone (C)	tablet, 25 mg

[a] When the strength is specified in terms of a selected salt or ester, this is mentioned in brackets; when it refers to the active moiety, the name of the salt or ester in brackets is preceded by the word "as".

[b] For administration only into the bronchial tree.

Drug	*Route of administration, dosage forms and strengths*[a]
17. Gastrointestinal drugs	
17.1 *Antacids and other antiulcer drugs*	
aluminium hydroxide	tablet, 500 mg
	oral suspension, 320 mg/5 ml
□ cimetidine	tablet, 200 mg
	injection, 200 mg in 2-ml ampoule
magnesium hydroxide	oral suspension, equivalent to 550 mg magnesium oxide/10 ml
17.2 *Antiemetic drugs*	
metoclopramide	tablet, 10 mg (as hydrochloride)
	injection, 5 mg (as hydrochloride)/ml in 2-ml ampoule
□ promethazine	tablet, 10 mg, 25 mg (hydrochloride)
	elixir or syrup, 5 mg (hydrochloride)/5 ml
	injection, 25 mg (hydrochloride)/ml in 2-ml ampoule
17.3 *Antihaemorrhoidal drugs*	
□ local anaesthetic, astringent and anti-inflammatory drug	ointment or suppository
17.4 *Anti-inflammatory drugs*	
hydrocortisone	suppository, 25 mg (acetate)
sulfasalazine (2)	tablet, 500 mg
17.5 *Antispasmodic drugs*	
□ atropine	tablet, 1 mg (sulfate)
	injection, 1 mg (sulfate) in 1-ml ampoule

[a] When the strength is specified in terms of a selected salt or ester, this is mentioned in brackets; when it refers to the active moiety, the name of the salt or ester in brackets is preceded by the word "as".

Drug	*Route of administration, dosage forms and strengths*[a]

17. Gastrointestinal drugs *(continued)*

17.6 *Cathartic drugs*

□ senna	tablet, 7.5 mg (sennosides) (or traditional dosage forms)

17.7 *Drugs used in diarrhoea*

17.7.1 Oral rehydration

oral rehydration salts (for glucose–electrolyte solution)	powder, 27.9 g/l

Components	*g/litre*
sodium chloride	3.5
trisodium citrate dihydrate[b]	2.9
potassium chloride	1.5
glucose	20.0

17.7.2 Antidiarrhoeal (symptomatic) drugs

□ codeine (1a)	tablet, 30 mg (phosphate)

18. Hormones, other endocrine drugs and contraceptives

18.1 *Adrenal hormones and synthetic substitutes*

□ dexamethasone	tablet, 500 µg, 4 mg
	injection, 4 mg (as sodium phosphate) in 1-ml ampoule
hydrocortisone	powder for injection, 100 mg (as sodium succinate) in vial
□ prednisolone	tablet, 1 mg, 5 mg

Complementary drug

fludrocortisone (C)	tablet, 100 µg (acetate)

18.2 *Androgens*

Complementary drug

testosterone (C) (2)	injection, 200 mg (enantate) in 1-ml ampoule

[a] When the strength is specified in terms of a selected salt or ester, this is mentioned in brackets; when it refers to the active moiety, the name of the salt or ester in brackets is preceded by the word "as".

[b] Trisodium citrate dihydrate may be replaced by sodium hydrogen carbonate (sodium bicarbonate) 2.5 g/l. However, as the stability of the latter formulation is very poor under tropical conditions, it is recommended only when manufactured for immediate use.

Drug	*Route of administration, dosage forms and strengths*[a]
18. Hormones, other endocrine drugs and contraceptives *(continued)*	
18.3 *Contraceptives*	
18.3.1 Hormonal contraceptives	
□ ethinylestradiol + □ levonorgestrel	tablet, 30 µg + 150 µg, 30 µg + 250 µg
□ ethinylestradiol + □ norethisterone	tablet, 35 µg + 1.0 mg
Complementary drugs	
depot medroxyprogesterone acetate (B) (7, 8)	injection, 150 mg/ml in 1-ml vial, 50 mg/ml in 3-ml vial
□ norethisterone (B)	tablet, 350 µg
norethisterone enantate (B) (7, 8)	oily solution, 200 mg/ml in 1-ml ampoule
18.3.2 Intrauterine devices	
copper-containing device	
18.3.3 Barrier methods	
condoms with or without spermicide (nonoxinol)	
diaphragms with spermicide (nonoxinol)	
18.4 *Estrogens*	
□ ethinylestradiol	tablet, 50 µg
18.5 *Insulins and other antidiabetic agents*	
insulin injection (soluble)	injection, 40 IU/ml in 10-ml vial, 80 IU/ml in 10-ml vial, 100 IU/ml in 10-ml vial
intermediate-acting insulin	injection, 40 IU/ml in 10-ml vial, 80 IU/ml in 10-ml vial, 100 IU/ml in 10-ml vial (as compound insulin zinc suspension or isophane insulin)
□ tolbutamide	tablet, 500 mg

[a] When the strength is specified in terms of a selected salt or ester, this is mentioned in brackets; when it refers to the active moiety, the name of the salt or ester in brackets is preceded by the word "as".

Drug	*Route of administration, dosage forms and strengths*[a]
18. Hormones, other endocrine drugs and contraceptives *(continued)*	
18.6 *Ovulation inducers*	
Complementary drug	
□ clomifene (C) (2, 8)	tablet, 50 mg (citrate)
18.7 *Progestogens*	
norethisterone	tablet, 5 mg
18.8 *Thyroid hormones and antithyroid drugs*	
levothyroxine	tablet, 50 µg, 100 µg (sodium salt)
potassium iodide	tablet, 60 mg
□ propylthiouracil	tablet, 50 mg
19. Immunologicals	
19.1 *Diagnostic agents*	
tuberculin,[b] purified protein derivative (PPD)	injection
19.2 *Sera and immunoglobulins*[c]	
anti-D immunoglobulin (human)	injection, 250 µg in single-dose vial
antiscorpion sera	injection
□ antitetanus immunoglobulin (human)	injection, 500 IU in vial
antivenom sera	injection
diphtheria antitoxin	injection, 10 000 IU, 20 000 IU in vial
immunoglobulin, human normal (2)	injection
□ rabies immunoglobulin	injection, 150 IU/ml in vial

[a] When the strength is specified in terms of a selected salt or ester, this is mentioned in brackets; when it refers to the active moiety, the name of the salt or ester in brackets is preceded by the word "as".

[b] All tuberculins should comply with the Requirements for Tuberculins (Revised 1985). *WHO Expert Committee on Biological Standardization.* Thirty-sixth report (WHO Technical Report Series, No. 745, 1987, Annex 1).

[c] All plasma fractions should comply with the Requirements for the Collection, Processing, and Quality Control of Blood, Blood Components, and Plasma Derivatives (Revised 1988). *WHO Expert Committee on Biological Standardization.* Thirty-ninth report (WHO Technical Report Series, No. 786, 1989, Annex 4).

Drug	*Route of administration, dosage forms and strengths*[a]
19. Immunologicals *(continued)*	
19.3 *Vaccines*[b]	
19.3.1 For universal immunization	
BCG vaccine (dried)	injection
diphtheria–pertussis–tetanus vaccine	injection
diphtheria–tetanus vaccine	injection
measles–mumps–rubella vaccine	injection
measles vaccine	injection
poliomyelitis vaccine (inactivated)	injection
poliomyelitis vaccine (live attenuated)	oral solution
tetanus vaccine	injection
19.3.2 For specific groups of individuals	
hepatitis B vaccine	injection
influenza vaccine	injection
meningococcal vaccine	injection
rabies vaccine	injection
rubella vaccine	injection
typhoid vaccine	injection
yellow fever vaccine	injection

[a] When the strength is specified in terms of a selected salt or ester, this is mentioned in brackets; when it refers to the active moiety, the name of the salt or ester in brackets is preceded by the word "as".

[b] All vaccines should comply with the following Requirements for Biological Substances, as published in the reports of the WHO Expert Committee on Biological Standardization. Dried BCG Vaccine (Revised 1985) (WHO Technical Report Series, No. 745, 1987) and Amendment 1987 (WHO Technical Report Series, No. 771, 1988); Diphtheria, Tetanus, Pertussis and Combined Vaccines (Revised 1989) (WHO Technical Report Series, No. 800, 1990); Measles Vaccine (Live) (Revised 1987) (WHO Technical Report Series, No. 771, 1988); Mumps Vaccine (Live) (WHO Technical Report Series, No. 760, 1987); Rubella Vaccine (Live) (WHO Technical Report Series, No. 610, 1977) and Addendum 1980 (WHO Technical Report Series, No. 658, 1981); Poliomyelitis Vaccine (Oral) (Revised 1989) (WHO Technical Report Series, No. 800, 1990); Poliomyelitis Vaccine (Inactivated) (Revised 1981) (WHO Technical Report Series, No. 673, 1982) and Addendum 1985 (WHO Technical Report Series, No. 745, 1987); Hepatitis B Vaccine Prepared from Plasma (Revised 1987) (WHO Technical Report Series, No. 771, 1988); Influenza Vaccine (Inactivated) (Revised 1990) (WHO Technical Report Series, No. 814, 1991); Meningococcal Polysaccharide Vaccine (WHO Technical Report Series, No. 594, 1976) and Addendum 1980, incorporating Addendum 1976 and Addendum 1977 (WHO Technical Report Series, No. 658, 1981); Rabies Vaccine for Human Use (Revised 1980) (WHO Technical Report Series, No. 658, 1981); Typhoid Vaccine (Live, Attenuated, Ty 21a, Oral) (WHO Technical Report Series, No. 700, 1984); Yellow Fever Vaccine (Revised 1975) (WHO Technical Report Series, No. 594, 1976) and Addendum 1987 (WHO Technical Report Series, No. 771, 1988).

Drug	*Route of administration, dosage forms and strengths*[a]
20. Muscle relaxants (peripherally acting) and cholinesterase inhibitors	
□ gallamine (2)	injection, 40 mg (triethiodide)/ml in 2-ml ampoule
□ neostigmine	tablet, 15 mg (bromide)
	injection, 500 µg, 2.5 mg (metilsulfate) in 1-ml ampoule
suxamethonium (2)	injection, 50 mg (chloride)/ml in 2-ml ampoule
	powder for injection (chloride)
Complementary drugs	
pyridostigmine (B) (2, 8)	tablet, 60 mg (bromide)
	injection, 1 mg (bromide) in 1-ml ampoule
vecuronium bromide (C)	powder for injection, 10 mg in vial
21. Ophthalmological preparations	
21.1 *Anti-infective agents*	
□ gentamicin	solution (eye drops), 0.3%
□ idoxuridine	solution (eye drops), 0.1%
	eye ointment, 0.2%
silver nitrate	solution (eye drops), 1%
□ tetracycline	eye ointment, 1% (hydrochloride)
21.2 *Anti-inflammatory agents*	
□ prednisolone	solution (eye drops), 0.5%
21.3 *Local anaesthetics*	
□ tetracaine	solution (eye drops), 0.5% (hydrochloride)

[a] When the strength is specified in terms of a selected salt or ester, this is mentioned in brackets; when it refers to the active moiety, the name of the salt or ester in brackets is preceded by the word "as".

Drug	*Route of administration, dosage forms and strengths*[a]
21. Ophthalmological preparations *(continued)*	
21.4 *Miotics and antiglaucoma drugs*	
acetazolamide	tablet, 250 mg
□ pilocarpine	solution (eye drops), 2%, 4% (hydrochloride or nitrate)
□ timolol	solution (eye drops), 0.25%, 0.5% (maleate)
21.5 *Mydriatics*	
atropine	solution (eye drops), 0.1%, 0.5%, 1% (sulfate)
Complementary drug	
epinephrine (A)	solution (eye drops), 2% (as hydrochloride)
22. Oxytocics and antioxytocics	
22.1 *Oxytocics*	
□ ergometrine	tablet, 200 µg (hydrogen maleate)
	injection, 200 µg (hydrogen maleate) in 1-ml ampoule
oxytocin	injection, 10 IU in 1-ml ampoule
22.2 *Antioxytocics*	
□ salbutamol (2)	tablet, 4 mg (as sulfate)
	injection, 50 µg (as sulfate)/ml in 5-ml ampoule
23. Peritoneal dialysis solution	
intraperitoneal dialysis solution (of appropriate composition)	parenteral solution

[a] When the strength is specified in terms of a selected salt or ester, this is mentioned in brackets; when it refers to the active moiety, the name of the salt or ester in brackets is preceded by the word "as".

Drug	*Route of administration, dosage forms and strengths*[a]
24. Psychotherapeutic drugs	
□ amitriptyline	tablet, 25 mg (hydrochloride)
□ chlorpromazine	tablet, 100 mg (hydrochloride)
	syrup, 25 mg (hydrochloride)/5 ml
	injection, 25 mg (hydrochloride)/ml in 2-ml ampoule
□ diazepam (1b)	scored tablet, 2 mg, 5 mg
□ fluphenazine (5)	injection, 25 mg (decanoate or enantate) in 1-ml ampoule
□ haloperidol	tablet, 2 mg, 5 mg
	injection, 5 mg in 1-ml ampoule
lithium carbonate (2, 4)	capsule or tablet, 300 mg
25. Drugs acting on the respiratory tract	
25.1 *Antiasthmatic drugs*	
□ aminophylline (2)	tablet, 100 mg, 200 mg
	injection, 25 mg/ml in 10-ml ampoule
beclometasone	inhalation (aerosol), 50 µg (dipropionate) per dose
epinephrine	injection, 1 mg (as hydrochloride) in 1-ml ampoule
□ salbutamol	tablet, 2 mg, 4 mg (as sulfate)
	inhalation (aerosol), 100 µg (as sulfate) per dose
	syrup, 2 mg (as sulfate)/5 ml
	injection, 50 µg (as sulfate)/ml in 5-ml ampoule
	respirator solution for use in nebulizers, 5 mg (as sulfate)/ml

[a] When the strength is specified in terms of a selected salt or ester, this is mentioned in brackets; when it refers to the active moiety, the name of the salt or ester in brackets is preceded by the word "as".

Drug	*Route of administration, dosage forms and strengths*[a]
25. Drugs acting on the respiratory tract *(continued)*	
25.1 *Antiasthmatic drugs* (continued)	
Complementary drugs	
□ cromoglicic acid (B)	inhalation (aerosol), 20 mg (sodium salt) per dose
ephedrine (A)	tablet, 30 mg (hydrochloride)
	elixir, 15 mg (hydrochloride)/5 ml
	injection, 50 mg (sulfate) in 1-ml ampoule
25.2 *Antitussives*	
□ codeine (1 a)	tablet, 10 mg (phosphate)
26. Solutions correcting water, electrolyte and acid–base disturbances	
26.1 *Oral rehydration*	
oral rehydration salts (for glucose–electrolyte solution)	for composition see 17.7.1 (p. 39)
potassium chloride	powder for solution
26.2 *Parenteral*	
glucose	injectable solution, 5% isotonic, 50% hypertonic
glucose with sodium chloride	injectable solution, 4% glucose, 0.18% sodium chloride (equivalent to Na^+ 30 mmol/l, Cl^- 30 mmol/l)
potassium chloride (2)	11.2% solution in 20-ml ampoule (equivalent to K^+ 1.5 mmol/ml, Cl^- 1.5 mmol/ml)
sodium chloride	injectable solution, 0.9% isotonic (equivalent to Na^+ 154 mmol/l, Cl^- 154 mmol/l)
sodium hydrogen carbonate	injectable solution, 1.4% isotonic (equivalent to Na^+ 167 mmol/l, HCO_3^- 167 mmol/l)
	8.4% solution in 10-ml ampoule (equivalent to Na^+ 1 mol/l, HCO_3^- 1 mol/l)
□ compound solution of sodium lactate	injectable solution

[a] When the strength is specified in terms of a selected salt or ester, this is mentioned in brackets; when it refers to the active moiety, the name of the salt or ester in brackets is preceded by the word "as".

Drug	*Route of administration, dosage forms and strengths*[a]
26. Solutions correcting water, electrolyte and acid–base disturbances *(continued)*	
26.3 *Miscellaneous*	
water for injection	2-ml, 5-ml, 10-ml ampoules
27. Vitamins and minerals	
□ ergocalciferol	capsule or tablet, 1.25 mg (50 000 IU)
	oral solution, 250 µg/ml (10 000 IU/ml)
iodine	iodized oil, 1 ml (480 mg iodine), 0.5 ml (240 mg iodine) in ampoule (oral or injectable)
	capsule, 200 mg
□ nicotinamide	tablet, 50 mg
pyridoxine	tablet, 25 mg (hydrochloride)
□ retinol	sugar-coated tablet, 10 000 IU (as palmitate) (5.5 mg)
	capsule, 200 000 IU (as palmitate) (110 mg)
	oral oily solution, 100 000 IU/ml in multidose dispenser (as palmitate)
	water-miscible injection, 100 000 IU (as palmitate) (55 mg) in 2-ml ampoule
riboflavin	tablet, 5 mg
sodium fluoride (8)	tablet, 500 µg
	solution, 2% (for professional dental use only)
thiamine	tablet, 50 mg (hydrochloride)
Complementary drugs	
ascorbic acid (C)	tablet, 50 mg
calcium gluconate (C) (2, 8)	injection, 100 mg/ml in 10-ml ampoule

[a] When the strength is specified in terms of a selected salt or ester, this is mentioned in brackets; when it refers to the active moiety, the name of the salt or ester in brackets is preceded by the word "as".

16. Considerations and changes made in revising the model list

Amendments to the individual entries in the list are detailed below.

Section 1. Anaesthetics

1.1 *General anaesthetics and oxygen*

The Committee considered other, more expensive, formulations of diazepam for injection but decided not to include them at this time.

Section 2. Analgesics, antipyretics, non-steroidal anti-inflammatory drugs and drugs used to treat gout

2.2 *Opioid analgesics*

A toxic metabolite of pethidine, norpethidine, accumulates during therapy and can cause central nervous system excitation, including myoclonus and seizures. Morphine or alternatives including hydromorphone and levorphanol are preferred when they are available.

The emergency health kit referred to in section 7 (*23*) contains pentazocine as the strong analgesic even though it is considered inferior to morphine by the Committee. The reason given for its inclusion in the kit is the administrative and regulatory difficulties of including an opioid drug for immediate distribution to sites of emergencies. The Committee rejects the request to add pentazocine to the model list for this reason, since it would be endorsing the use of an inferior analgesic for victims of large-scale emergencies or disasters because of regulatory requirements. Rather, the Committee strongly urges that administrative and regulatory requirements be modified to permit the use of the essential drug morphine in emergency health care.

Section 3. Antiallergics and drugs used in anaphylaxis

Antihistamines with less sedative action are currently available. It is, however, considered premature to include one of these.

Section 6. Anti-infective drugs

6.1.2 *Specific anthelminthics*

For albendazole the footnote restricting use to patients with echinococcosis or cysticercosis is deleted, since this drug is useful in other parasitic diseases.

6.2.1 *Penicillins*

Oral amoxicillin is preferred to oral ampicillin because it is better absorbed and causes fewer adverse effects.

6.2.2 *Other antibacterials*

The numbers (2) and (7) after gentamicin are retained in order to discourage its indiscriminate use. Dosage must always be calculated according to the weight and renal clearance of the patient.

Ciprofloxacin is added to the complementary list with the letter (B) for use in patients with infections resistant to drugs in the main list.

Clindamycin is added to the complementary list with the letter (B) for use in patients who are allergic to penicillin and have infections resistant to drugs in the main list.

6.2.4 *Antituberculosis drugs*

It is essential that all products containing rifampicin are shown to have adequate bioavailability.

The frequency of severe adverse reactions to thioacetazone appears to be much higher in tuberculosis patients who are infected with human immunodeficiency virus (HIV) than in those who are HIV-negative. Because of the high frequency of these adverse reactions, the combination tablets containing thioacetazone are moved to the complementary list with the letter (A) and the number (7), to be used when the drugs in the main list are unavailable.

6.3 *Antifungal drugs*

Nystatin tablets, 100 000 IU, are added for use in children. Nystatin lozenges, 100 000 IU, are added for use in patients with oral candidiasis.

6.4.3 *Antimalarial drugs*

(a) For curative treatment

The square symbol preceding chloroquine is retained solely to accommodate hydroxychloroquine.

The Committee considers that the experience with halofantrine to date does not warrant its inclusion as an essential drug at this time.

(b) For prophylaxis

Mefloquine is added to the complementary list with the letter (B).

Proguanil should be used only in combination with chloroquine.

It should be noted that no antimalarial drug can guarantee 100% protection. Prophylaxis should be restricted to pregnant women, non-immune visitors to endemic areas, and special groups such as labour teams and military personnel living in closed communities.

6.4.4 *Antitrypanosomal drugs*

Eflornithine is added to the complementary list with the letter (C) for the treatment of late-stage African trypanosomiasis due to *Trypanosoma brucei gambiense.*

Antiviral drugs

A subsection on antiviral drugs was considered because the Committee recognizes the importance of viral illnesses and the need for effective antiviral drugs. However, because of their limited efficacy, toxicity and high cost, none of those currently available is considered to qualify for inclusion. Aciclovir is, none the less, accepted as being of value in the treatment of severe herpes infections, and zidovudine is acknowledged to suppress the progression of HIV infection temporarily. Neither is considered essential, however, for the reasons given above.

Section 8. Antineoplastic and immunosuppressant drugs and drugs used in palliative care

8.1 *Immunosuppressant drugs*

Ciclosporin is added to the main list. Immunosuppressant drugs are essential for use in organ transplant programmes. They are not considered essential, however, where no such programmes exist.

8.4 *Drugs used in palliative care*

This new subsection is added because the Committee recognizes the importance of palliative care in patients with cancer and wishes to emphasize the essential nature of the drugs used for this purpose.

Section 10. Drugs affecting the blood

10.1 *Antianaemia drugs*

For folic acid, a 5-mg tablet is added.

10.2 *Drugs affecting coagulation*

For phytomenadione, a 10-mg tablet is added.

Desmopressin intravenous preparation is added to the main list with the number (8) in view of its usefulness in reducing the need for blood and blood products in the treatment of haemophilia and von Willebrand disease.

Section 11. Blood products and plasma substitutes

11.2 *Plasma fractions for specific uses*

The square symbol preceding factor VIII is retained to accommodate cryoprecipitate and that preceding factor IX is retained to accommodate plasma and cryoprecipitate-poor plasma.

Section 12. Cardiovascular drugs

Atenolol is added to sections 12.1, 12.2 and 12.3 since cardioselective ß-adrenoreceptor antagonists may be advantageous in some patients.

12.3 *Antihypertensive drugs*

For hydrochlorothiazide the 50-mg tablet is deleted, since the optimum antihypertensive effect can usually be achieved with a dosage of 25 mg per day.

Methyldopa in the complementary list refers to the L isomer only.

12.4 *Cardiac glycosides*

The role of cardiac glycosides in the treatment of heart failure is diminishing because of their small margin of safety and their replacement by other classes of drugs.

12.6 *Antithrombotic drugs*

Streptokinase is added to the complementary list with the letter (C) for the treatment of patients presenting within a few hours of acute coronary thrombosis.

Section 13. Dermatological drugs

13.1 *Antifungal drugs*

Sodium thiosulfate 15% solution is added for the treatment of pityriasis versicolor.

13.2 *Anti-infective drugs*

The concentration of methylrosanilinium chloride is reduced from 1% to 0.5% to minimize adverse effects. The square symbol is retained to accommodate other dyes, in particular brilliant green.

13.6 *Scabicides and pediculicides*

Lindane is deleted since it is toxic to the environment and humans, and safer alternatives are available.

13.7 *Ultraviolet-blocking agents*

Sun-blocking agents are included because of their importance in preventing ultraviolet-induced skin cancers in people whose occupations expose them to sun for long periods of time. Zinc oxide (cream or ointment) is added to the list because it is cheap and effective.

Section 15. Disinfectants and antiseptics

This section is divided into two subsections because antiseptics are for use on skin while disinfectants are for use on inanimate objects. Most of the drugs listed are included in the booklet, *Guidelines on sterilization and disinfection methods effective against human immunodeficiency virus (HIV)* (*38*).

15.1 *Antiseptics*

These include chlorhexidine 5%, hydrogen peroxide 3% and iodine 2.5% solution. Hydrogen peroxide 1.5% is replaced by hydrogen peroxide 3.0% for the removal of debris and as a mouthwash in dental practice.

15.2 *Disinfectants*

These include activated glutaral 2%, and calcium hypochlorite (70% available chlorine) powder for solution.

Calcium hypochlorite may be used in exceptional circumstances to disinfect water in reservoirs. An available chlorine concentration of 0.5 ppm should be maintained.

Section 16. Diuretics

A square symbol is added to mannitol to indicate that sorbitol could serve as an alternative.

Section 17. Gastrointestinal drugs

17.1 *Antacids and other antiulcer drugs*

Sodium citrate solution is deleted because it is no longer widely used.

Bismuth salts are being evaluated for treatment of peptic ulcer in the context of their effect on *Helicobacter pylori,* but it is considered premature to include them.

Section 18. Hormones, other endocrine drugs and contraceptives

18.3 *Contraceptives*

Ethinylestradiol 50 μg in contraceptive tablets also containing levonorgestrel or norethisterone is replaced by ethinylestradiol 30 μg and 35 μg respectively, since the Committee considers this strength to be safer.

Section 19. Immunologicals

19.1 *Diagnostic agents*

The Committee recognizes the importance of patch testing for occupationally acquired contact dermatitis, but is unable to recommend specific products for use at this time.

19.2 *Sera and immunoglobulins*

A square symbol is added to antitetanus immunoglobulin to accommodate tetanus antitoxin (equine), which is deleted. Antirabies hyperimmune serum is replaced by rabies immunoglobulin with a square symbol. The Committee considers these products improvements in therapy.

Section 20. Muscle relaxants (peripherally acting) and cholinesterase inhibitors

The square symbol preceding gallamine is retained to indicate that alcuronium chloride can be used in its place. Vecuronium bromide is added to the complementary list with the letter (C) in view of its relatively short duration of action and its lack of vagolytic activity.

Section 21. Ophthalmological preparations

A square symbol is added to gentamicin and prednisolone to indicate that other aminoglycosides or corticosteroids could serve as alternatives.

Section 25. Drugs acting on the respiratory tract

For salbutamol, 5 mg (as sulfate) per ml respirator solution is added for use in nebulizers.

Section 26. Solutions correcting water, electrolyte and acid–base disturbances

26.1 ***Oral rehydration***

For potassium chloride, the oral solution is replaced by a powder, which should be dissolved in water to make a 1 mmol/ml solution for dispensing.

Section 27. Vitamins and minerals

For sodium fluoride, a 2% solution is added for professional dental use only.

17. Glossary of terms used in the report

In the course of its work, the Expert Committee used certain terms with the meanings given below:

Benefit/risk ratio	The ratio of benefit to risk in the use of a drug; a means of expressing a judgement concerning the role of the drug in the practice of medicine, based on efficacy and safety data along with consideration of misuse potential, severity and prognosis of the disease, etc. The concept may be applied to a single drug or in comparisons between two or more drugs used for the same condition.
Bioavailability	The rate and extent of absorption of a drug from a dosage form as determined by its concentration/time curve in the systemic circulation or by its excretion in urine.
Compliance	Faithful adherence by the patient to the prescriber's instructions.

Dosage form	The form of the completed pharmaceutical product, e.g. tablet, capsule, elixir, suppository.
Drug	Any substance in a pharmaceutical product that is used to modify or explore physiological systems or pathological states for the benefit of the recipient.
Drug formulation	The composition of a dosage form, including the characteristics of its raw materials and the operations required to process it.
Drug utilization	The marketing, distribution, prescription and use of drugs in a society, with special emphasis on the resulting medical, social and economic consequences.
Efficacy	The ability of a drug to produce the purported effect as determined by scientific methods.
Excipient	Any component of a finished dosage form other than the claimed therapeutic ingredient or ingredients.
Pharmaceutical product	Synonymous with dosage form.
Pharmacokinetics	The study of the rate of drug action, particularly with respect to: – the variation of drug concentrations in tissues with time, and – the absorption, distribution, metabolism and excretion of drugs and metabolites.

18. Alphabetical list of essential drugs

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Annex 1

Guiding principles for small national drug regulatory authorities[1]

1. General considerations

Small countries which have yet to introduce comprehensive legal provisions for drug regulation can draw from a diversity of national systems in determining their own requirements. None the less, problems in establishing drug control in developing countries have too often resulted from the adaptation of provisions successful elsewhere but of a complexity

[1] The elaboration of guiding principles for small national drug regulatory authorities is a component of WHO's revised drug strategy, which was adopted by the Thirty-ninth World Health Assembly following the WHO Conference of Experts on the Rational Use of Drugs held in Nairobi, Kenya in November 1985. This consultative document, which has been circulated to Member States, is based extensively on the report of a meeting convened in Geneva in November 1987, and was subsequently reviewed in November–December 1988 by the WHO Expert Committee on Specifications for Pharmaceutical Preparations. It has also been published in WHO Technical Report Series, No. 790: 64–79 (1990) and *WHO drug information*, 3:43–50 (1989).

that precludes their effective implementation in the country of adoption. It is of paramount importance that legislation and administrative practices are attuned to available resources and that every opportunity is taken to obtain and use information provided by regulatory authorities in other countries on pharmaceutical products and substances moving in international commerce.

Channels of communication between national regulatory authorities are improving, as is evident from the information contained in WHO's monthly *Pharmaceuticals newsletter*, the quarterly journal *WHO drug information*, and the United Nations *Consolidated list of products whose consumption and/or sale have been banned, withdrawn, severely restricted or not approved by governments* (*1*). Moreover, many difficulties inherent in storing, retrieving and analysing data that subserve the many facets of the regulatory process can now be overcome by the use of microcomputers and commercial software packages.

1.1 *The scope of drug control*

To be effective, a small drug regulatory authority needs to operate within the context of a defined national drugs policy and to interrelate with other interested bodies, including organizations responsible for drug procurement in the public sector and the national formulary committee, where such exists.

1.2 *Basic responsibilities*

The responsibilities of the regulatory authority are to ensure that all products subject to its control conform to acceptable standards of quality, safety and efficacy; and that all premises and practices employed to manufacture, store and distribute these products comply with requirements to ensure the continued conformity of the products to these standards until such time as they are delivered to the end-user.

1.3 *Licensing functions*

These objectives can be accomplished effectively only if a mandatory system of licensing products, manufacturers, importing agents and distributors is in place. A small authority has strictly limited capacity to undertake these tasks. For the assurances it requires in relation to imported pharmaceutical products and drug substances, it is vitally dependent on authoritative, reliable, and independent information generated in the exporting country. This information is most effectively obtained through the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce.

Before a formal licensing system can become operative, it is necessary:

- to adopt a precise definition of a drug product and of the various categories of licence-holders;

- to determine the content and format of licences, both for products and for licence-holders;
- to detail the criteria on which licence applications will be assessed; and
- to provide guidance to interested parties on the content and format of licence applications, and on the circumstances in which an application for renewal, extension or variation of a licence will be required.

The definition of a drug product is commonly contingent upon the claims that are made for it. Ideally, controls need to be applied to any product that is offered for sale for administration to human beings for treating, preventing and diagnosing disease, for anaesthesia, for contraception, and for otherwise altering normal physiological functions.[1] In practice, exemptions may need to be granted to various specific categories of products in order to address priorities effectively. It might be decided as an interim measure, for example, to require licences only for products listed in a national formulary. Ultimately, however, control needs to be extended not only to all products moving in the major distribution channels, but to those formulated in pharmacies and hospital dispensaries, to herbal preparations, and to other traditional medicines entering into local commerce.

Analogous priorities may also need to be accorded to the registration of licence-holders, although the ultimate objective should be to embrace all manufacturers, importing agents, wholesalers involved in repackaging, pharmacies and hospital dispensaries in a system that imposes upon them relevant statutory obligations.

1.4 *Product licences*

The issuance of product licences is pivotal to any system of drug control. The licence is a legal document that establishes the detailed composition and formulation of the product, the pharmacopoeial or other officially recognized specifications of its ingredients, its clinical interchangeability (in the case of multisource products), and its packaging, shelf-life and labelling. Of itself, this goes a long way towards establishing the assurances of quality, efficacy and safety to which the system is directed. However, without a viable pharmaceutical inspectorate or access to an independent quality-control laboratory operating to standards that will ensure its credibility in the event of dispute, licensing provisions cannot be effectively enforced.

1.5 *Manufacturers' and distributors' licences*

The pharmaceutical inspectorate is responsible for ensuring that pharmaceutical products comply with conditions set out in the licence up to the time that they are delivered to the end-user. Its functions are:

[1] Veterinary products administered to food-producing animals may also fall into this category; see the revised WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce (*2*).

- to establish, through periodic formal inspections and spot-checks, that all categories of licence-holder are operating in accordance with their licensed activities, prevailing standards of good manufacturing practice, and other prescribed regulations;
- to maintain oversight of distribution channels, either by inspection and monitoring or by arranging for pharmacopoeial analysis of selected samples, with a view to ensuring that products are not subject to unacceptable degradation during transit and storage at the periphery.

1.6 *New drug assessments*

Within highly evolved national drug regulatory authorities much effort is directed to establishing the efficacy and safety of new drug entities through pharmaceutical, biological and clinical assessment and through subsequent surveillance of their performance in routine use after marketing. Pre-marketing assessment is dependent upon detailed multidisciplinary technical review, and post-marketing surveillance requires a highly developed health care infrastructure. Only in exceptional circumstances should a small regulatory authority contemplate allocation of scarce resources to these ends. Reliance must be placed primarily on information notified by other countries through the network of national information officers established by WHO.

1.7 *Authorization of clinical trials*

A small authority may occasionally need to consider an application to conduct a clinical trial of an unregistered drug in the treatment of a condition that has a high local prevalence. To provide for this contingency, the registration system should include provision for the importation of the necessary materials, subject to appropriate controls. Such trials should only take place after formal clearance has been obtained from the competent registration authority and after assurances have been obtained that they will be conducted in conformity with the principles contained in the World Medical Association's Declaration of Helsinki and the *Proposed international guidelines for biomedical research involving human subjects* issued by the Council for International Organizations of Medical Sciences (*3*). WHO stands ready to offer independent technical advice to national authorities in these circumstances.

1.8 *Terms of reference of the regulatory authority*

The formal terms of reference of a national drug regulatory authority are determined by statute and regulation. Legislation relating to pharmaceutical products has developed piecemeal in many countries, and there are obvious advantages in bringing matters concerned with their regulation under one law. For example, it is important to correlate laws relating to the control of narcotic and psychotropic substances with requirements for product registration. If comprehensive overhaul of the legal system is impracticable, control within the existing

framework through regulations specifically related to the registration of pharmaceutical products offers advantages of economy and time-saving. Whichever option is chosen, regulatory authorities require the flexibility to respond to changing circumstances imposed by the evolution of pharmaceutical science.

In general terms, the authority should be vested with legal powers to:

- issue, vary and revoke licences for pharmaceutical products on grounds of quality, safety and efficacy;
- secure the subsequent safe and effective use of each product by controlling, through the terms of the licence, the content of all labelling (including package inserts, associated prescribing information and advertising) and the channels through which the product may legitimately be supplied; and
- inspect and license all manufacturing premises, importing agents, wholesalers and distributors, hospital dispensaries, independent pharmacies and other retail outlets to ensure that they comply with prevailing regulations and guidelines.

1.9 *Powers of enforcement*

In order to implement these responsibilities the authority must command powers of enforcement backed by legal provision for penal sanction against offenders.

In establishing administrative mechanisms for decision-making, the regulatory authority should not lose necessary flexibility. In particular, it should make provision for:

- implementing decisions regarded as urgent in the interest of public safety; and
- formal consultation (usually through representative bodies) with pharmaceutical companies and other interested parties, including pharmacists, doctors, nurses and patients.

1.10 *Technical competence*

A small licensing authority will rarely, if ever, undertake comprehensive independent assessment of the safety and efficacy of individual products. The administrative and technical responsibilities that fall within its ambit are essentially of a pharmaceutical nature and they are directed primarily to quality assurance. The professional staff must include members with a thorough understanding and practical experience of the different facets of this work.

The responsible officer is accountable for the professional validation and assessment of licence applications and for the administrative aspects of licensing and, as such, should be involved in determining priorities and

developing a timetable for implementation of controls. These activities require administrative and clerical support and premises sufficient to handle the large volume of documentation involved with appropriate confidentiality. Efficiency of operation is enhanced when the required information can be retrieved rapidly from a computerized database.

1.11 *Advisory bodies*

The responsible officer must also have access to a standing advisory committee or board of independent experts (including academic and practising health care professionals) for advice on technical issues. Consideration should also be given to the need for a multidisciplinary commission to advise on matters of general policy and administration and to ensure effective relations with bodies responsible for drug procurement in the public sector and with the national formulary committee.

1.12 *Independence of operation*

To retain public confidence and respect, the authority must be seen to undertake its tasks in an independent, authoritative and impartial manner. It should be concerned exclusively with the determination of standards and the implementation of controls. Although it will need to work closely with the authority responsible for drug procurement within the public sector, it should not itself be responsible for procurement and it should remain independent and autonomous in its operational activities and decisions.

2. Administrative aspects of the licensing process

2.1 *Provisional registration of existing medicinal products*

Before any system of control can become effective, it is necessary to identify and catalogue all products already sold or otherwise supplied on the domestic market, in both the public and the private sectors, that qualify for control. To this end, all manufacturers and importing agencies must be given reasonable notice through official gazettes, the trade press and other media of their obligation to notify the authority by a specific date of all medicinal products that they currently distribute within the jurisdiction of the authority and that they intend to continue to supply after a duly appointed day, on which licensing requirements enter into operation. After the appointed day no medicinal product may lawfully be distributed or supplied unless its existence has been notified to the authority, and no new product may be introduced until a request for a product licence has been granted by the authority.

Effective administration of the provisional registration procedure is dependent upon:

- prior identification of all interested manufacturers and importers;
- a precise definition of a notifiable medicinal product based primarily

on the labelled claims and the indications for use;
- the issuance of guidelines on the procedure to be followed.

Each notified product must be identified by name (either brand or generic), the names and full addresses of the manufacturer and importing agent, a description of the dosage form, its composition – including active and inactive ingredients (using international nonproprietary names where appropriate) – the therapeutic class, the indications, a copy of all labelling, including any package insert, and a copy of any relevant certificates and warranties relating to the product or its components.

2.2 *Screening of provisionally registered products*

A rapid screening of notified products should be undertaken at the earliest opportunity with a view to securing the withdrawal of any products which, simply on the basis of a review of their ingredients and indications, are judged not to meet admissible standards of safety. This may be achieved by the withdrawal of permission to trade in specific notified products or the issuance of regulations imposing specified restrictions on precisely defined groups of products.

After this preliminary review, a set of longer-term priorities needs to be set for the definitive assessment of provisionally registered products. Consideration needs to be given to the resources required, both in personnel and information, if the review is to be adapted to a proposed time-schedule. Standards must be maintained and calls to accelerate the speed of implementation must be recognized as having resource implications.

In planning priorities, consideration must be given to:

- the number of provisionally registered products to be processed;
- the number of staff and/or consultants to be allocated to the task;
- the amount of relevant information available from other national authorities;
- the extent to which products can be reviewed in groups rather than individually;
- the extent to which a *laissez-faire* disposition can be adopted towards such products as herbal remedies and tonics that are without potent pharmacological activity and carry imprecise claims, but which satisfy an acknowledged public demand.

Considerations of safety require that particular attention be accorded to:

- products that either have been withdrawn or are the subject of restrictive regulatory action in other countries as notified in the United Nations *Consolidated list of products whose consumption and/or sale have been banned, withdrawn, severely restricted or not approved by governments*, and in WHO's *Pharmaceuticals newsletter* to national drug regulatory authorities;
- products representing examples of irrational poly-pharmacy; and

– products for which exaggerated or spurious promotional claims are made in the labelling.

Subsequently, the review needs to be extended in a phased manner, giving priority to drugs that are widely used, listed in nationally recognized formularies, or of a particularly important therapeutic class. An adequate documentation and information retrieval system is vital for this purpose.

Some traditional products and particularly herbal preparations, because of their complexity, do not lend themselves to licensing on a product-specific basis. Control is then more readily applied through consideration of individual ingredients. Several regulatory authorities have devised administrative approaches to their licensing which are based on a three-category system of classification:

(a) all herbal ingredients, save for those items classified under (b) below, which may be dispensed for a specific, named patient by practitioners of herbal medicine who do not possess a formal medical qualification;
(b) ingredients such as digitalis leaf and atropine which, because of their pharmacological potency or their toxicity, need to be subjected to prescription control; and
(c) ingredients which, as a result of widespread, long-established and apparently innocuous traditional usage, are included, often within defined permissible limits, in labelled products for which limited claims are made and which are sold directly to the public from retail outlets other than pharmacies.

2.3 *New product licences*

No product that is first proposed for authorization after the appointed day (see section 2.1 above) should be accorded a product licence without first having been submitted to technical assessment. Such products may not necessarily contain a new active ingredient: they may constitute a new combination of two or more established substances or they may merely represent a new dosage strength, a new dosage form, or a generic version of a pre-existing, nominally equivalent licensed product. In no case should the requirement for assessment be waived. A rationale for the formulation of every new product should invariably be provided, but the extent of the required review will vary considerably according to circumstances.

The normal procedure for the authorization of a product is accomplished in three stages:

– the application is received from the manufacturer and is checked and assessed for completeness by the authority's technical staff;
– it is submitted to the competent standing committee for advice on whether or not to authorize marketing of the product;
– the formal administrative action to grant or refuse a licence and to settle its content is then taken by the authority.

The assessment of the product must be based primarily on its safety, quality and efficacy, with regard to its intended use. In accordance with locally determined requirements, the assessment might also impinge upon comparative efficacy and/or safety and embrace economic factors, including price, cost-effectiveness and other considerations determined by national policy.

For administrative convenience, the product licence should be as simple as possible. It should always describe the product by name, manufacturer and importing agent, identify the ingredients (preferably by their international nonproprietary names) and provide full details of the dosage form. It should also contain a serial number, the date of issuance of the licence, its date of expiry and any special conditions to be observed. It is advisable to cite certain additional items in the licence for easy reference, such as shelf-life and sales category; but in other particulars it should refer to the information submitted by the licence-holder in the dated product application.

2.4 *Renewal and variation of licences*

Licences should never be regarded as immutable. Ideally, they should be reviewed at, say, five-year intervals. However, many national authorities do not have the capacity to undertake this task, particularly for as long as they remain engaged in the initial review of provisionally licensed products. In these circumstances many products fall to review on an ad hoc basis. Sometimes this is inspired by recently generated concern regarding safety. More frequently, a product attracts attention because the licence-holder has altered the formulation in some way – by changing, for instance, the source of the starting materials, the nature of the excipients, the route of synthesis of an active ingredient, or the claims made in labelling and promotional material. The precise circumstances in which licence-holders are required to apply for variations in a product licence differ from country to country. These circumstances should be clearly defined in all product licence documents, including provisional licences.

Licence-holders should be required, in all circumstances, to inform regulatory authorities immediately of unanticipated adverse effects that could possibly be associated with a licensed product and that might call for restrictive licensing action or the withdrawal of the product licence.

3. Technical aspects of the licensing process

3.1 *General considerations*

Although countries vary in their resources and priorities, advantage accrues from harmonizing documentary requirements to the fullest possible extent, since this simplifies registration procedures and reduces costs.

The most important starting-point for imported products is the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce (*2*). This gives basic information on composition, an assurance that the product is manufactured in accordance with good manufacturing practices in premises subject to inspection, and information on the regulatory status of the product in the country of export. A certificate, issued in compliance with the model format recommended by WHO, should be required whenever application is made to license an imported product.

3.2 *Products containing long-established chemical entities*

For products indicated for standard uses and that contain established ingredients, the following elements of information usually suffice as the basis both for a product licence and for a computerized data retrieval system:

- name of the product
- active ingredient(s) [by international nonproprietary name(s)]
- type of formulation
- therapeutic category
- quantitative formula (including excipients)
- quality control specifications
- indications, dosage, method of use
- contraindications, warnings, precautions
- bioavailability data (*in vitro/in vivo*)
- stability data, shelf-life
- container, packaging, labelling
- intended method of distribution:
  controlled drug; prescription item
  pharmacy sale; general sale
- manufacturer
- importer/distributor
- regulatory status in the exporting country.

If the dosage form is a novel one, such as a delayed-release tablet, or if a new route of administration is proposed, supporting data from clinical studies will be required.

3.3 *Products containing new chemical entities*

Considerably more extensive information is required to support a marketing application for a new drug substance in order to provide assurance of efficacy and safety as well as of quality. In particular, detailed accounts are required of:

- chemistry (structure, physical properties, synthesis, specification, impurities, stability characteristics);
- pharmacological properties (in animals and humans);
- toxicological data (short and long-term studies in animals, including carcinogenicity studies);

- reproductive and teratological studies in animals;
- clinical studies.

Small regulatory authorities need to adopt caution in licensing newly developed products because they are likely not to possess the capacity to undertake the multidisciplinary assessment applied to them within large, highly evolved authorities, or to monitor their performance in use through post-marketing surveillance.

In general, a small authority is best advised to wait until this information has been generated and assessed elsewhere before authorizing such a product for use.

In the case of products intended exclusively for tropical parasitic diseases, much of this evidence may need to be built up in countries with limited resources. The expertise of the World Health Organization is at hand to offer advice in these circumstances. Once a decision is taken to authorize such a product for general use, the regulatory authority and the manufacturer share a responsibility to ensure that a monitoring mechanism is put in place to detect unanticipated reactions. A mutually acceptable plan for post-marketing surveillance should be settled in advance and included in the product licence as a condition of approval.

3.4 *Herbal products*

The use of herbal and other naturally occurring substances is part of the fabric of traditional medicine. Because of the complex, and sometimes imprecise nature of the ingredients they contain and the paucity of scientific information on their properties, products containing these substances, often in combination, can rarely be reviewed on a rigorously scientific basis. Where time-honoured practices do no apparent harm, there is no urgency for regulatory intervention other than to set up a system for provisional registration.

However, prolonged and apparently uneventful use of a substance offers insecure testimony of its safety. In a few instances, recently commissioned investigations of the potential toxicity of naturally occurring substances widely used as ingredients in these preparations have revealed a previously unsuspected potential for systemic toxicity, carcinogenicity and teratogenicity. Small regulatory authorities need to be quickly and reliably informed of these findings. They should also have the authority to respond promptly to such alerts, either by withdrawing or varying the licences of registered products containing the suspect substance, or by rescheduling the substance in order, for instance, to disallow its use by practitioners who are not medically qualified.

All regulatory authorities should also be alert to the practice of incorporating potent pharmacologically active compounds, such as steroids, into herbal preparations. When this is done clandestinely, it is a manifestly dangerous practice which demands immediate withdrawal of the products and a review of the manufacturer's licence.

3.5 *Combinations of potent, therapeutically active substances*

The justifications for formulating fixed combinations of potent, therapeutically active substances are few. All biologically active substances have a potential to induce harm as well as therapeutic benefit. The administration of two or more such substances, rather than one, increases the potential for adverse effects. Fixed-ratio combination products are consequently acceptable only when the dosage of each ingredient meets the requirements of a defined population group and when use of the combination provides a clear advantage over separate administration of the individual active compounds, in either therapeutic effect or compliance, or when it enhances safety – as in the case of multiple chemotherapy intended to reduce the emergence of resistant pathogens.

3.6 *Generic products*

In many countries, for reasons of economy, drugs destined for use in the public sector are purchased on open tender. This favours the use of generic products, and the practice in some countries is for tenders to be issued, bids examined, and contracts offered by the procurement authority without reference to the drug regulatory authority.

The licensing of generic products poses a challenge to all regulatory authorities, particularly when the product to be supplied is not registered in the country of origin. The need for expert assessment is accentuated because not all drug-exporting countries submit drugs intended exclusively for export to the same rigorous controls as drugs intended for the domestic market. Nominally equivalent generic products should contain the same amount of the same therapeutically active ingredients in the same dosage form and they should meet required pharmacopoeial standards. However, they are not necessarily identical and in some instances their clinical interchangeability may be in question. Differences in colour, shape and flavour, while obvious and sometimes disconcerting to the patient, are often inconsequential to the performance of the product, but differences in sensitizing potential due to the use of different excipients and differences in stability and bioavailability have obvious clinical implications. Regulatory authorities consequently need to consider not only the quality, efficacy and safety of such products, but also their interchangeability one with another and with the original innovative product. This concept of interchangeability applies not only to the dosage form but also to the instructions for use and even to the packaging specifications, when these are critical to stability and shelf-life.

Some highly evolved authorities require that every generic product must satisfy three sets of criteria of therapeutic equivalence. These relate to:

- manufacturing and quality control;
- product characteristics and labelling; and
- bioequivalence.

Others adopt a more pragmatic approach to the need for experimental demonstration of bioequivalence. Study of the bioavailability of a dosage form is a costly undertaking that is demanding of human resources. It is clearly not a cost-effective requirement for highly water-soluble substances, when neither precise dosage nor consistency of response is a critical consideration. In developing countries the *in vivo* bioavailability testing of all domestically manufactured products would be impracticably costly. The regulatory authority should be in a position to help local manufacturers by advising them on drugs that pose potential bioavailability problems.

In the case of imported products, assurance should be obtained through the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce that the product has been produced in accordance with WHO's standards of good manufacturing practices and that, in the light of a full assessment, it has been authorized to be placed on the market in the country of origin.

References

1. *Consolidated list of products whose consumption and/or sale have been banned, withdrawn, severely restricted or not approved by governments,* 4th ed. New York, United Nations, 1990.
2. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-first report.* Geneva, World Health Organization, 1990 (WHO Technical Report Series, No. 790), Annex 5.
3. Council for International Organizations of Medical Sciences. *Proposed international guidelines for biomedical research involving human subjects.* Geneva, 1982 (also contains the Declaration of Helsinki as revised by the 29th World Medical Assembly, Tokyo, 1975).

Annex 2

Application form for inclusion in the Model List of Essential Drugs[1]

Submitted by:

Name of responsible officer:

Address:

Contact person (if submitted by an organization):

Telephone No.: Fax No.:

We hereby request the World Health Organization to consider the following pharmaceutical product for inclusion in the Model List of Essential Drugs

Signature _____ *Date* _____

Name of drug (INN and trade name):

Dosage form and strength:

Why is this drug being proposed for inclusion in the list?

Please state how it conforms to the criteria for inclusion as an essential drug:

If a therapeutic class for this drug already exists in the list, please summarize the advantages of this product:

Describe the drug's pharmacokinetics:

List any contraindications, precautions and toxic effects:

Is this drug available as a generic product?

Please state any restrictions on the use of this drug. Should a note be included in the list regarding its use?

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[1] A summary (maximum 3 pages) of relevant background information should be attached, together with relevant literature to support the therapeutic use.

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* Prices in developing countries are 70% of those listed here.